Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-155727- -00000-0000

Fecha: 2013-07-02 16:30:22 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 5

SOLICITUD DE PATE

INVENCIÓN

TITULO: MODULADORES DE LA VÍA DEL COMPLEMENTO Y USOS DE LOS MISMOS.

SOLICITANTE: Novartis AG.

DIRECCIÓN: Lichtstrasse 35, CH-4056 Basel, Suiza

APODERADO: CARLOS R. OLARTE

BOGOTÁ: 02 de Julio de 2013

P2013/000120

OLARTEMOURE

OLARTE MOURE & ASC

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-155727- -00000-0000

Fecha: 2013-07-02 16:30:22 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 5

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2013/000120**

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
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: Carrera 5 No 34-03 Bogotá D.C.
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olartemoure.com

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

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA
Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/EP2012/050005 Fecha Enero 2, 2012

Publicación Internacional No. WO 2012/093101 A1 Fecha Julio 12, 2012

(6) **Título (54)** **MODULADORES DE LA VÍA DEL COMPLEMENTO Y USOS DE LOS MISMOS.**

Clasificación Internacional (51) C07D 401/14; C07D 403/12; C07D 403/14; C07D 405/14; C07D 409/14; C07D 417/12; C07D 417/14; C07D 471/04; A61K 31/403; A61K 31/407; A61K 31/416; A61P 27/02.

Prioridad **SI** [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Enero 4, 2011	61/429,730

(9) **Comprobante de pago No.** 13- **Fecha** _____

ANEXOS

[x]	Comprobante de pago de la tasa de presentación de la solicitud.
[x]	Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
[x]	Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 08-102.832
[ ]	Documento de cesión del inventor al solicitante o a su causante.
[x]	Declaraciones. Declaración bajo la regla 4.17 (ii) del PCT.
[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.
[x]	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

LISTA DE INVENTORES

PCT/EP2012/050005

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Switzerland

Citizen: Switzerland

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Citizen: Germany

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Citizen: Italy

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68220 Hésingue

France

Citizen: France

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 13 - 0060149

Bogotá D.C., Junio 19 de 2013 - 12:49:07

RECIBIDO DE : OLARTE MOURE & ASOCIADOS NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	559321044	18/06/2013	5.808.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	500.000.00	500.000.00
				$500.000.00

SON: **QUINIENTOS MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-155727- -00000-0000

Fecha: 2013-07-02 16:30:22 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 5

Industria y Comercio SUPERINTENDENCIA	PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA ***RELACIÓN DE ANEXOS***	
Dependencia: 2020	Fecha: 2013 / 07 / 02 AAAA MM DD	Recorrido:
Tipo de Radicación: Entrada: ✓ Salida: ☐ Traslado: ☐ Convenio: ☐		
Radicador:		Planilla:

ID	*No. Radicación*	*Consecutivo*	*Item*
1	13-155727-	0	
2			
3			
4			
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11			
12			
13			
14			
15			
16			
17			

Item	*Unidad de Conservación*
1	Bolsa
2	Caja
3	Libro
4	Sobre
5	Tomo
6	**Otro**
Item	***Soporte Documental***
7	CD
8	Disquete
9	DVD
10	Folleto
11	Foto
12	Periódico
13	Plano
14	Publicación Periódica
15	USB
16	**Otro**

Observaciones:

Anexan CD

Ruth

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-155727- -00000-0000

Fecha: 2013-07-02 16:30:22 Dep: 2020 DIR.NUEVASCR
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Act: 411 PRESENTACION Folios: 5

PATENTE DE INVENCIÓN [ ] MODELO DE

- [ ] Indicación que se solicita 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 (De ser el caso formato de descuento)

Completa [ ] Incompleta [ ]

PATENTE DE INVENCIÓN PCT [x] MODELO DE UTILIDAD PCT [ ] Art.33 Decisión 486/00, Circular Única

- [x] Indicación que se solicita una PCT
- [x] Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- [x] Dibujos de ser estos pertinentes
- [x] Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa [x] Incompleta [ ]

DISEÑO INDUSTRIAL [ ] (Art. 119 Decisión 486/00)

- [ ] Indicación que se solicita 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 [ ] (Art. 92 Decisión 486/00)

- [ ] Indicación que se solicita un esquema de trazado
- [ ] Datos de identificación del solicitante o de la persona que presenta la solicitud
- [ ] Representación gráfica de un esquema de trazado
- [ ] Comprobante de pago de las tasas establecidas

Completa [ ] Incompleta [ ]

TRADUCCIÓN OFICIAL DE UN DOCUMENTO QUE ESTÁ ORIGINALMENTE EN INGLÉS

Nota del traductor:

El documento adjunto de poder de Novartis AG a Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana Maria Frieri y/o Juan Guillermo Moure y/o Natalia Castro lleva los siguientes datos en inglés.

CERTIFICACIÓN NOTARIAL

1. En esta fecha, día 30 de Agosto de 2006, yo, el suscrito Notario Público certifico por medio del presente la autenticidad de las firmas del señor Arthur Canonica, ciudadano de Corticiasca, Suiza, residente en Wisen/SO, Suiza, y del Sr. Pascal Traub, ciudadano de Riehen, Suiza, residente en Basilea, Suiza, ambos personas mayores de edad y con dirección comercial en Lichstrasse 35, 4056, Basilea, Suiza. La autenticidad de la firmas fue establecida por medio de la comparación.
2. Además, yo, el Notario Público, certifico por el presente que las anteriores personas han ejecutado el anterior documento como apoderados de Novartis AG.
3. Además, yo, el Notario Público certifico por el presente que Novartis AG, con su principal lugar de negocios en Basilea, Suiza, está debidamente constituida, está actualmente vigente y que los propósitos para los cuales se otorgó el Documento de Poder están dentro del alcance de sus propósitos corporativos.

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Miniusticia

4. Además, yo, el Notario Público, certifico por el presente que las anteriores personas tienen la autoridad para ejecutar el documento de Poder y que por este instrumento, su representación es legal.

La base para mis certificaciones de los puntos 2, 3 y 4 fue la exhibición de los siguientes documentos auténticos:

- Documento de Poder de Novartis AG fechado el 19 de junio de 2006 y
- Extracto del Registro de Comercio del Cantón de la ciudad de Basilea para Novartis AG, en Basilea, fechado el 25 de enero de 2006.

Basilea, Suiza, este día 30 de Agosto de 2006.

(Firmado) Dr. Matthias Staehelin, Notario Público del Cantón de la ciudad de Basilea, Suiza.

Mi licencia vence el 11 de Marzo de 2009.

Hay una Apostilla de Suiza, firmada por Heidi Fischer, bajo el No. 8049/13584.

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

Certificación:

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Novartis"

Fecha: 12 de Septiembre de 2006.

Traductor: Jorge Enrique Sierra Reyes.

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

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

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

E-mail: treseser1@yahoo.com. No. 8346

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olarte
J. Ian Raisbeck
Ana María Frieri
Juan Guillermo Moure
Natalia Castro

Zayde Chahin
Jacqueline Chaparro
José Luis Londoño
Felipe Mendoza
Simón Salinas

Of Counsel
Guillermo Chahin
Graciela Melo

Power of Attorney

Poder

The undersigned,

El suscrito,

NOVARTIS AG

domiciled in

domiciliado en

Lichtstrasse 35, CH-4056 Basel / Switzerland

by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Ana María Frieri and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer's Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana María Frieri y/o Juan Guillermo Moure y/o Natalia Castro** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las **Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:

Arthur Canonica

Pascal Traub

Date/Fecha: June 27, 2006

City,Country/Ciudad,País: Basel, Switzerland

Attestation

1 On this date, the 30th (thirtieth) day of August 2006 (two thousand and six), I, the undersigned Notary Public certify herewith the authenticity of the signatures of **Mr. Arthur Canonica**, citizen of Corticiasca, Switzerland, residing in Wisen/SO, Switzerland and of **Mr. Pascal Traub**, citizen of Riehen, Switzerland, residing in Basel, Switzerland, both of legal age and with business address at, Lichtstrasse 35, 4056 Basel, Switzerland. The authenticity of the signatures was established by means of comparison.

2 Further, I, the Notary Public certify herewith that the foregoing persons have executed the foregoing document as proxy holders for Novartis AG.

3 Further, I, the Notary Public certify herewith that Novartis AG, having its principal place of business located in Basel / Switzerland, is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4 Further, I, the Notary Public certify herewith that the foregoing persons have the authority to execute the Power of Attorney and that for this instrument their representation is legal.

The foundation for my certifications contained in points 2 (two), 3 (three) and 4 (four) was the exhibition of the following authentic documents:

- Power of Attorney by Novartis AG dated June 19 (nineteen), 2006 (two thousand and six); and
- Extract from the Register of Commerce of the Canton of Basel-City for Novartis AG, in Basel, dated January 25 (twenty-five), 2006 (two thousand and six).

BASEL, Switzerland, this 30th (thirtieth) day of August 2006 (two thousand and six)

M. Staehelin Notar

Dr. Matthias Staehelin, Notary Public
in the Canton of Basel-City, Switzerland

My license expires on March 11 (eleven), 2009 (two thousand and nine).

Leg.Prot.Nr. 975 /2006

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz / Suisse)

This official document

2. is signed by .....

.....

3. in his / her function as .....

4. and certified by the seal of the .....

.....

Certified 30. Aug. 2006

5. in Basel (Bâle) 6. on .....

7. by the State Chancery of the Canton of Basel-Stadt .....

8. no. 8'049 / 13'584

9. Seal / stamp: 10. Signature:

.....

Heidi Fischer

STATE CHANCERY * BASLE · CITY *

Sheet No. .....

Box No. VIII (ii) DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT

The declaration must conform to the standardized wording provided for in Section 212; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (ii). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51*bis*.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

in relation to the international application PCT/EP2012/050005,

Novartis AG, is entitled to apply for and be granted a patent by virtue of the following:

an assignment from:
Eva ALTMANN, Novartis Pharma AG, Postfach, 4002 Basel, Switzerland,
dated 09.12.2011
Ulrich HOMMEL, Novartis Pharma AG, Postfach, 4002 Basel, Switzerland,
dated 16.12.2011
Edwige Liliane Jeanne LORTHIOIS, Novartis Pharma AG, Postfach, 4002 Basel,
Switzerland, dated 09.12.2011
Juergen Klaus MAIBAUM, Novartis Pharma AG, Postfach, 4002 Basel, Switzerland,
dated 09.12.2011
Nils OSTERMANN, Novartis Pharma AG, Postfach, 4002 Basel, Switzerland,
dated 09.12.2011
Jean QUANCARD, Novartis Pharma AG, Postfach, 4002 Basel, Switzerland,
dated 09.12.2011
Stefan Andreas RANDL, Karl-Stieler-Straße 9, 60320 Frankfurt am Main , Germany,
dated 24.11.2011
Oliver SIMIC, Novartis Pharma AG, Postfach, 4002 Basel, Switzerland, dated 09.12.2011
Anna VULPETTI, Novartis Pharma AG, Postfach, 4002 Basel, Switzerland,
dated 12.12.2011

to Novartis Pharma AG.

an assignment from Novartis Pharma AG, Lichtstrasse 35, 4056 Basel, Switzerland,
dated 21.12.2011

to Novartis AG.

an assignment from:
Olivier ROGEL, Novartis Pharma AG, Postfach, 4002 Basel, Switzerland,
dated 26.01.2012 *

to Novartis Pharma AG.

an assignment from Novartis Pharma AG, Lichtstrasse 35, 4056 Basel, Switzerland,
dated 31.01.2012

to Novartis AG.

* inventor Oliver ROGEL passed away. Assignment has been signed by his wife!

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (ii)".

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 July 2012 (12.07.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/093101 A1

(51) International Patent Classification:
C07D 401/14 (2006.01) *C07D 417/14* (2006.01)
C07D 403/12 (2006.01) *C07D 471/04* (2006.01)
C07D 403/14 (2006.01) *A61K 31/403* (2006.01)
C07D 405/14 (2006.01) *A61K 31/407* (2006.01)
C07D 409/14 (2006.01) *A61K 31/416* (2006.01)
C07D 417/12 (2006.01) *A61P 27/02* (2006.01)

(21) International Application Number:
PCT/EP2012/050005

(22) International Filing Date:
2 January 2012 (02.01.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/429,730 4 January 2011 (04.01.2011) US

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

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **ALTMANN, Eva** [CH/CH]; Novartis Pharma AG, Postfach, CH-4002 Basel (CH). **HOMMEL, Ulrich** [DE/CH]; Novartis Pharma AG, Postfach, CH-4002 Basel (CH). **LORTHIOIS, Edwige Liliane Jeanne** [FR/CH]; Novartis Pharma AG, Postfach, CH-4002 Basel (CH). **MAIBAUM, Juergen Klaus** [DE/CH]; Novartis Pharma AG, Postfach, CH-4002 Basel (CH). **OSTERMANN, Nils** [DE/CH]; Novartis Pharma AG, Postfach, CH-4002 Basel (CH). **QUANCARD, Jean** [FR/CH]; Novartis Pharma AG, Postfach, CH-4002 Basel (CH). **RANDL, Stefan Andreas** [DE/DE]; Karl-Stieler-Straße 9, 60320 Frankfurt am Main (DE). **SIMIC, Oliver** [DE/CH]; Novartis Pharma AG, Postfach, CH-4002 Basel (CH). **VULPETTI, Anna** [IT/CH]; Novartis Pharma AG, Postfach, CH-4002 Basel (CH). **ROGEL, Olivier** [FR/CH]; Novartis Pharma AG, Postfach, CH-4002 Basel (CH).

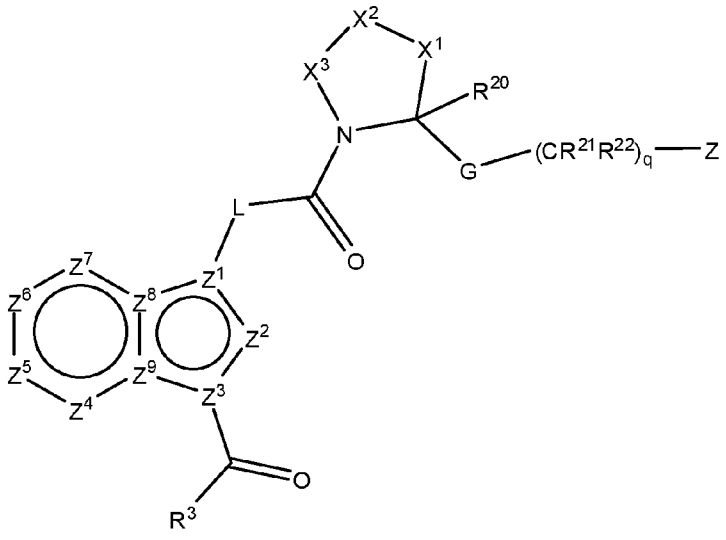
(74) Agent: **VON SPRECHER, Georg**; Novartis Pharma AG, Patent Department, CH-4002 Basel (CH).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: INDOLE COMPOUNDS OR ANALOGUES THEREOF USEFUL FOR THE TREATMENT OF AGE-RELATED MACULAR DEGENERATION (AMD)



(I)

(57) Abstract: The present invention provides a compound of formula (I): a method for manufacturing the compounds of the invention, and its therapeutic uses. The present invention further provides a combination of pharmacologically active agents and a pharmaceutical composition.

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INDOLE COMPOUNDS OR ANALOGUES THEREOF USEFUL FOR THE TREATMENT OF AGE-RELATED MACULAR DEGENERATION (AMD)

FIELD OF THE INVENTION

The invention relates to the inhibition of the complement alternative pathway and particularly to inhibition of Factor D, in patients suffering from conditions and diseases associated with complement alternative pathway activation such as age-related macular degeneration, diabetic retinopathy and related ophthalmic diseases.

BACKGROUND OF THE INVENTION

The complement system is a crucial component of the innate immunity system and comprises a group of proteins that are normally present in an inactive state. These proteins are organized in three activation pathways: the classical, the lectin, and the alternative pathways (V. M. Holers, In Clinical Immunology: Principles and Practice, ed. R.R. Rich, Mosby Press; 1996, 363-391). Molecules from microorganisms, antibodies or cellular components can activate these pathways resulting in the formation of protease complexes known as the C3-convertase and the C5-convertase. The classical pathway is a calcium/magnesium-dependent cascade, which is normally activated by the formation of antigen-antibody complexes. It can also be activated in an antibody-independent manner by the binding of C-reactive protein complexed to ligand and by many pathogens including gram-negative bacteria. The alternative pathway is a magnesium-dependent cascade which is activated by deposition and activation of C3 on certain susceptible surfaces (e.g., cell wall polysaccharides of yeast and bacteria, and certain biopolymer materials).

Factor D may be a suitable target for the inhibition of this amplification of the complement pathways because its plasma concentration in humans is very low (about 1.8 µg/mL), and it has been shown to be the limiting enzyme for activation of the alternative complement pathway (P.H. Lesavre and H.J. Müller-Eberhard. J. Exp. Med., 1978; 148: 1498-1510; J.E. Volanakis et al., New Eng. J. Med., 1985; 312:395-401).

Macular degeneration is a clinical term that is used to describe a family of diseases that are characterized by a progressive loss of central vision associated with abnormalities of Bruch's membrane, the choroid, the neural retina and/or the retinal pigment epithelium. In the center of the retina is the macula lutea, which is about 1/3 to ½ cm in diameter. The macula provides detailed vision, particularly in the center (the fovea), because the cones are higher in density and because of the high ratio of ganlion cells to photoreceptor cells. Blood vessels, ganglion cells, inner nuclear layer and cells, and the plexiform layers are all displaced to the side (rather than resting above the photoreceptor cells), thereby allowing light a more direct

path to the cones. Under the retina is the choroid, a part of the uveal tract, and the retinal pigmented epithelium (RPE), which is between the neural retina and the choroid. The choroidal blood vessels provide nutrition to the retina and its visual cells.

Age-related macular degeneration (AMD), the most prevalent form of macular degeneration, is associated with progressive loss of visual acuity in the central portion of the visual field, changes in color vision, and abnormal dark adaptation and sensitivity. Two principal clinical manifestations of AMD have been described as the dry, or atrophic, form and the neovascular, or exudative, form. The dry form is associated with atrophic cell death of the central retina or macula, which is required for fine vision used for activities such as reading, driving or recognizing faces. About 10-20% of these AMD patients progress to the second form of AMD, known as neovascular AMD (also referred to as wet AMD).

Neovascular AMD is characterized by the abnormal growth of blood vessels under the macula and vascular leakage, resulting in displacement of the retina, hemorrhage and scarring. This results in a deterioration of sight over a period of weeks to years. Neovascular AMD cases originate from intermediate or advanced dry AMD. The neovascular form accounts for 85% of legal blindness due to AMD. In neovascular AMD, as the abnormal blood vessels leak fluid and blood, scar tissue is formed that destroys the central retina.

The new blood vessels in neovascular AMD are usually derived from the choroid and are referred to as choroidal neovascularizaton (CNV). The pathogenesis of new choroidal vessels is poorly understood, but such factors as inflammation, ischemia, and local production of angiogenic factors are thought to be important. A published study suggests that CNV is caused by complement activation in a mouse laser model (Bora P.S., J. Immunol. 2005;174; 491-497).

Human genetic evidence implicates the involvement of the complement system, particularly the alternative pathway, in the pathogenesis of Age-related Macular Degeneration (AMD). Significant associations have been found between AMD and polymorphisms in complement factor H (CFH) (Edwards AO, et al. Complement factor H polymorphism and age-related macular degeneration. Science. 2005 Apr 15;308(5720):421-4; Hageman GS, et al Acommon haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. Proc Natl Acad Sci U S A. 2005 May 17;102(20):7227-32; Haines JL, et al. Complement factor H variant increases the risk of age-related macular degeneration. Science. 2005 Apr 15;308(5720):419-21; Klein RJ, et al Complement factor H polymorphism in age-related macular degeneration. Science. 2005 Apr 15;308(5720):385-9; Lau LI, et al. Association of the Y402H polymorphism in complement factor H gene and neovascular age-related macular degeneration in Chinese patients. Invest Ophthalmol Vis Sci. 2006 Aug;47(8):3242-6; Simonelli F, et al. Polymorphism p.402Y>H in the complement factor H protein is a risk factor for age related macular degeneration in an Italian

population.Br J Ophthalmol. 2006 Sep;90(9):1142-5; and Zareparsi S, et al Strong association of the Y402H variant in complement factor H at 1q32with susceptibility to age-related macular degeneration. Am J Hum Genet. 2005 Jul;77(1):149-53.), complement factor B (CFB) and complement C2 (Gold B, et al. Variation in factor B (BF) and complement component 2 (C2) genes is associated with age-related macular degeneration. Nat Genet. 2006 Apr;38(4):458-62 and Jakobsdottir J, et al. C2 and CFB genes inage-related maculopathy and joint action with CFH and LOC387715 genes. PLoS One. 2008 May 21;3(5):e2199), and most recently in complement C3 (Despriet DD, et al Complement component C3 and risk of age-related macular degeneration. Ophthalmology. 2009 Mar;116(3):474-480.e2; Maller JB, et al Variation in complement factor 3 is associated with risk of age-related macular degeneration. Nat Genet. 2007 Oct;39(10):1200-1 and Park KH, et al Complement component 3 (C3) haplotypes and risk of advanced age-related macular degeneration. Invest Ophthalmol Vis Sci. 2009 Jul;50(7):3386-93. Epub 2009 Feb 21.). Taken together, the genetic variations in the alternative pathway components CFH, CFB, and C3 can predict clinical outcome in nearly 80% of cases.

Currently there is no proven medical therapy for dry AMD and many patients with neovascular AMD become legally blind despite current therapy with anti-VEGF agents such as Lucentis. Thus, it would be desirable to provide therapeutic agents for the treatment or prevention of complement mediated diseases and particularly for the treatment of AMD.

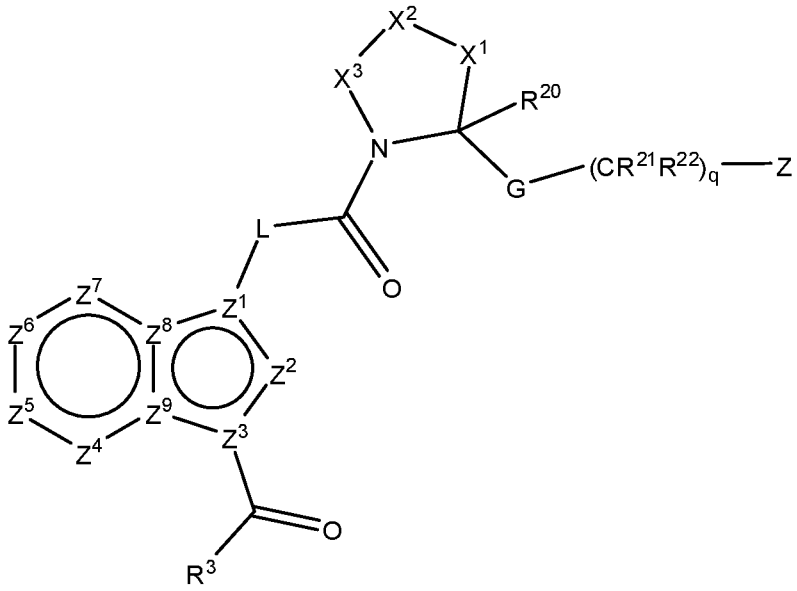
SUMMARY OF THE INVENTION

The present invention provides compounds that modulate, and preferably inhibit, activation the alternative complement pathway. In certain embodiments, the present invention provides compounds that modulate, and preferably inhibit, Factor D activity and/or Factor D mediated complement pathway activation. Such Factor D modulators are preferably high affinity Factor D inhibitors that inhibit the catalytic activity of complement Factor D, such as primate Factor D and particularly human Factor D.

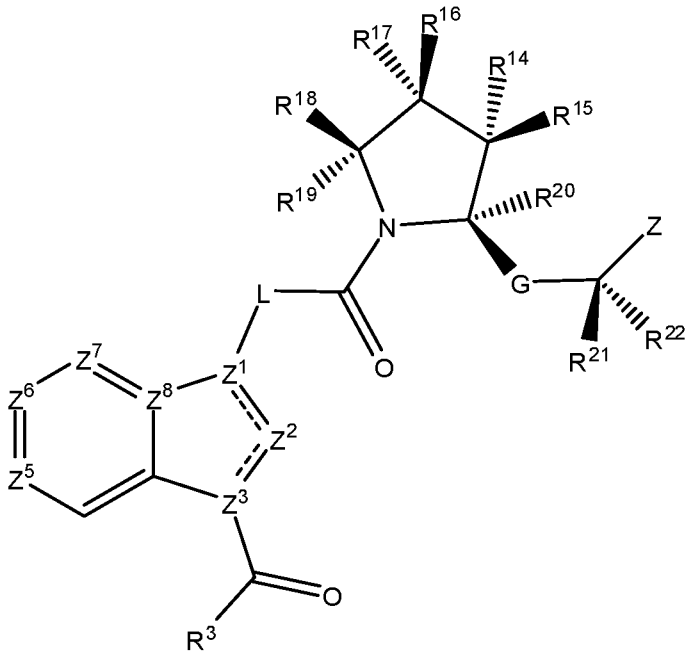
The compounds of the present invention inhibit or suppress the amplification of the complement system caused by C3 activation irrespective of the initial mechanism of activation (including for example activation of the classical, lectin or ficolin pathways).

Various embodiments of the invention are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments.

Within certain aspects, Factor D modulators provided herein are compounds of Formula I and salts thereof:



Within certain other aspects, Factor D modulators provided herein are compounds of Formula VII and salts thereof:



(VII),

In another embodiment, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound according to the definition of formula (I) or subformulae thereof and one or more pharmaceutically acceptable carriers.

In another embodiment, the invention provides a combination, in particular a pharmaceutical combination, comprising a therapeutically effective amount of the compound according to the definition of formula (I) or subformulae thereof and one or more therapeutically active.

The invention further provides methods of treating or preventing complement mediated diseases, the method comprising the steps of identifying a patient in need of complement modulation therapy and administering a compound of Formula (I) or a subformulae thereof.

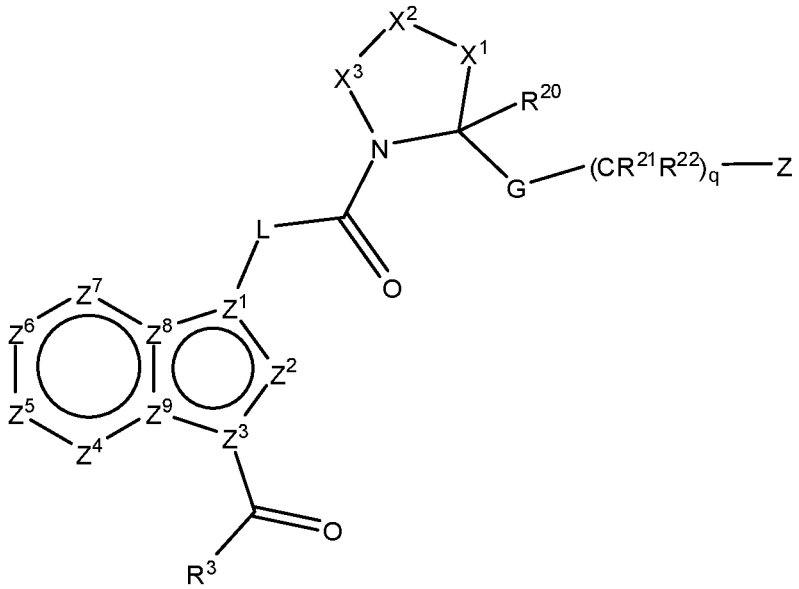
Complement mediated diseases include ophthalmic diseases (including early or neovascular age-related macular degeneration and geographic atrophy), autoimmune diseases (including arthritis, rheumatoid arthritis), Respiratory diseases, cardiovascular diseases.

Other aspects of the invention are discussed *infra*.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention provides compounds that modulate Factor D activation and/or Factor D-mediated signal transduction of the complement system. Such compounds may be used *in vitro* or *in vivo* to modulate (preferably inhibit) Factor D activity in a variety of contexts.

In a first embodiment, the invention provides compounds of Formula I and pharmaceutically acceptable salts thereof, which modulate the alternative pathway of the complement system. Compounds of Formula I are represented by the structure:



(I)

or a pharmaceutically acceptable salt thereof, wherein

Z^1 is C and L is a divalent residue selected from the group consisting of –N(H)– and –C(H)(R^1)–, or

Z^1 is N and L is CH_2;

R^1 is hydrogen, hydroxy, or amino;

Z^2 is C(R^2) or N;

Z^3 is C or N,

Z^4 is C(R^4) or N;

Z^5 is C(R^5) or N, or an N-oxide thereof;

Z^6 is C(R^6) or N, or an N-oxide thereof;

Z^7 is C(R^7) or N, or an N-oxide thereof;

Z^8 is C or N;

Z^9 is C or N;

wherein one of Z^1, Z^3, Z^8 and Z^9 is N and three of Z^1, Z^3, Z^8 and Z^9 are C;

wherein 0, 1, or 2 or 3 of Z^2, Z^4, Z^5, Z^6 and Z^7 are N;

R^2 is hydrogen or C_1-C_6alkyl;

R^3 is selected from the group consisting of hydrogen, C_1-C_4alkyl, hydroxyC_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl, haloC_1-C_4alkyl, amino or methylamino;

R^4 is selected from the group consisting of hydrogen, halogen, and C_1-C_6alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, halogen, hydroxy, NR^8R^9, cyano, CO_2H, $CONR^{10}R^{11}$ SO_2C_1-C_6alkyl, and SO_2NH_2, $SO_2NR^{10}R^{11}$, C_1-C_6alkoxycarbonyl, $-C(NR^{10})NR^8R^9$, C_1-C_6alkyl, haloC_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, C_2-C_6alkenyloxy, wherein each alkyl, alkenyl, alkoxy and alkenyloxy is unsubstituted or substituted with up to 4 substitutents independently selected from halogen, hydroxy, tetrazole, C_1-C_4alkoxy, C_1-C_4haloalkoxy, CO_2H, C_1-C_6alkoxycarbonyl, $C(O)NR^{10}R^{11}$, NR^8R^9, optionally substituted phenyl, heterocycle having 4 to 7 ring atoms and 1, 2, or 3 ring heteroatoms selected from N, O or S, heteroaryl having 5 or 6 ring atoms and 1 or 2 ring heteroatoms selected from N, O or S, and wherein optional phenyl substituents are selected from halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy and CO_2H;

R^5 and $R^{6'}$ taken in combination with the atoms to which they are attached, form a cycle having 4 to 7 ring atoms and 0, 1 or 2 additional ring N, O or S atoms;

R^7 is selected from the group consisting of hydrogen, halogen, C_1-C_6alkyl, C_1-C_6alkoxy, haloC-C_6alkyl, haloC-C_6alkoxy C_1-C_6alkoxycarbonyl, CO_2H and $C(O)NR^{10}R^{11}$;

R^8 and R^9 are independently selected from the group consisting of hydrogen, and C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, hydroxyC_1-C_6alkyl, or NR^8R^9, taken in combination, form a heterocycle having 4 to 7 ring atoms and 0 or 1 additional ring N, O or S atoms, which heterocycle is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_1-C_4alkyl, halogen, hydroxy, C_1-C_4alkoxy;

R^{10} and R^{11}, are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, or hydroxyC_1-C_6alkyl;

X^1 is $CR^{14}R^{15}$ or sulfur;

X^2 is $CR^{16}R^{17}$, oxygen sulfur, N(H) or N(C_1-C_6alkyl), wherein at least one of X^1 and X^2 is carbon; or

X^1 and X^2, in combination, forms an olefin of the formula $-C(R^{16})=C(H)-$ or $-C(R^{16})=C(C_1$-C_4alkyl)-, wherein the $C(R^{16})$ is attached to X^3;

X^3 is $(CR^{18}R^{19})_m$ or N(H) wherein m is 0,1 or 2, wherein X^3 is $CR^{18}R^{19}$ or $(CR^{18}R^{19})_2$ when either X^1 or X^2 is sulfur or X^2 is oxygen; or

X^2 and X^3, taken in combination, are $-N=C(H)-$ or $-N=C(C_1$-C_4alkyl)– in which the C(H) or $C(C_1$-C_4alkyl) is attached to X^1;

R^{14} is selected from the group consisting of hydrogen, halogen, hydroxy, amino and C_1-C_6alkyl;

R^{15} is selected from the group consisting of hydrogen, hydroxy, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, NR^8R^9, N(H)C(O)C_1-C_6alkyl, N(H)C(O)OC_1-C_6alkyl and OC(O)$NR^{10}R^{11}$ each of alkyl, alkoxy, alkenyl, and alkynyl substituents may be substituted with 0, 1, or 2 groups independently selected at each occurrence from the group consisting of halogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, and NR^8R^9;

R^{16} is hydrogen, halogen, hydroxy, azide, cyano, COOH, C_1-C_6alkoxycarbonyl, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, NR^8R^9, N(H)C(O)C_1-C_6alkyl, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, or C_1-C_6alkyl substituted with NR^8R^9, N(H)C(O)H or N(H)C(O)(C_1-C_4alkyl);

R^{17} is hydrogen, halogen, hydroxy, cyano, C_1-C_6alkyl, C_1-C_6alkoxy, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, haloC_1-C_6alkyl, or C_1-C_6haloalkoxy;

R^{18} is selected from the group consisting of hydrogen, phenyl and C_1-C_6alkyl, which alkyl group is unsubstituted or substituted with hydroxy, amino, azide, and NHC(O)C_1-C_6alkyl;

R^{19} and R^{20} are each independently selected from hydrogen and C_1-C_6alkyl; or

$CR^{16}R^{17}$, taken in combination forms a spirocyclic 3 to 6 membered carbocycle which is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen and methyl; or

R^{16} and R^{17}, taken in combination, form an exocyclic methylidene (=CH_2);

R^{15} and R^{16} taken in combination form an epoxide ring or a 3 to 6 membered carbocyclic ring system which carbocyclic ring is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen, methyl, ethyl, hydroxyC_1-C_4alkyl, C_1-C_6alkoxyC_1-C_4alkyl, C_1-C_4alkoxycarbonyl, CO_2H, and C_1-C_4alkyl substituted with NR^8R^9; or

R^{16} and R^{18} or R^{17} and R^{19}, taken in combination, form a fused 3 membered carbocyclic ring system which is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen, methyl, ethyl, hydroxyC_1-C_4alkyl, C_1-C_6alkoxyC_1-C_4alkyl, C_1-C_4alkoxycarbonyl, CO_2H, and C_1-C_4alkyl substituted with NR^8R^9; or

R^{14} and R^{20} taken in combination form a fused 3 carbocyclic ring system;

R^{14} and R^{19} taken in combination form a form 1 to 3 carbon alkylene linker;

R^{17} and R^{20} taken in combination form 1 to 3 carbon alkylene linker;

G is a divalent residue selected from C(O)-N(H), CH_2-N(H)–$S(O)_2$–, CH_2–N(H)–C(O), CH_2-N(H)-C(O)-O, CH_2N(H), CH_2-N(H)-C(O)-N(H), CH_2-N(H)-C(O)-N(Me), CH_2N(H)-$S(O)_2$-N(H)-, and CH_2N(H)-$S(O)_2$-N(Me)-, wherein the right most residue is attached to –$(CR^{21}R^{22})_q$;

q is 0, 1, 2, 3 or 4;

R^{21} is independently selected at each occurrence from the group consisting of hydrogen, hydroxy, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, phenyl, CO_2H, C_1-C_6alkoxy carbonyl, $C(O)NH_2$, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, C_1-C_6alkyl substituted with NR^8R^9, imidazoylC_1-C_6alkyl heterocycleC_1-C_6alkyl, where the heterocycle is selected from azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, 1-oxa-6-aza-spiro[3.3]heptane, 2-oxa-6-aza-spiro[3.3]heptane, piperazinyl, 1,6-diaza-spiro[3.3]heptane, and 2,6-diaza-spiro[3.3]heptane each of which is optionally substituted by 1 or 2 substituent selected from fluoro, hydroxy, C_1-C_4alkyl or C_1-C_4alkoxy;

R^{22} is independently selected at each occurrence from hydrogen or C_1-C_6alkyl; or

when q is 1, 2, 3 or 4, R^{21} and a R^{22} substituent, taken in combination with the carbon atoms to which they are attached, form a 3 to 6 membered carbocycle or 4 to 6 membered heterocyle having a ring oxygen or nitrogen; or

when q is 2, 3 or 4, two R^{21} or R^{22} residues, located on adjacent carbon atoms, form, together with the carbon atoms to which they are attached, a 3 to 6 membered carbocycle; and

Z is C_1-C_6alkyl, C_1-C_6haloalkyl, phenyl, phenoxy, naphthyl, naphthyloxy, C_3-C_7cycloalkyl, indanyl, a 5, 6, 9 or 10 membered saturated or partially unsaturated, monocyclic or bicyclic heterocycle having 1, 2, or 3 ring heteroatoms selected from N, O, or S, or a 5 or 6 membered heteroaryl or heteroaryloxy, which heteroaryl has 1 or 2 ring heteroatoms selected from N, O or S provided that the ring does not have 2 O or S atoms, each residue is unsubstituted or substituted with 1, 2, 3, or 4 substituents which are independently selected from the group consisting of substituted or unsubstituted C_1-C_6alkyl, C_1-C_6haloalkyl, halogen, CN, hydroxy, CO_2H, tetrazolyl, $C(O)R^{25}$, $S(O)_2R^{26}$, substituted or unsubstituted C_1-C_6alkoxy, haloC_1-C_6alkoxy, phenoxy, $NR^{23}R^{24}$, $CH_2NR^{23}R^{24}$, 5 or 6 membered heteroaryl and unsubstituted or substituted phenyl, which substituted phenyl has 1 or 2 substituents independently selected from the group consisting of cyano, halo, C_1-C_6alkyl or C_1-C_6haloalkyl, OH, COOH, COR^{25}, $S(O)_2R^{26}$, amino, and CH_2NH_2, and which substituted alkyl or alkoxy has a substituent selected from hydroxy, C_1-C_4alkoxy, cyano, CO_2H, tetrazole or $NR^{23}R^{24}$;

R^{23} is hydrogen or C_1-C_6alkyl;

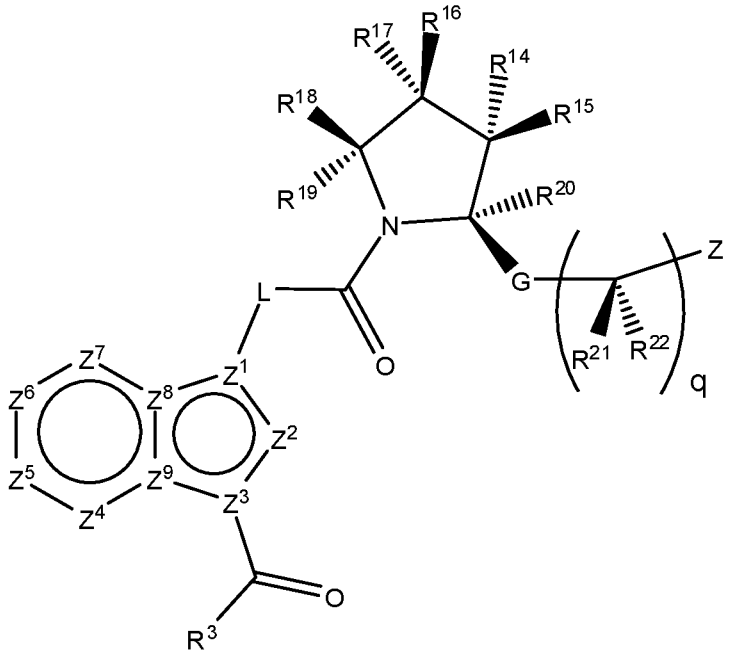
R^{24} is hydrogen, C_1-C_6alkyl, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, aminoC_1-C_6alkyl, mono- and di-C_1-C_6alkylaminoC_1-C_6alkyl; or

$NR^{23}R^{24}$, taken in combination form a 4, 5 or 6 membered heterocycle having 0 or 1 additional ring heteroatoms selected from the group consisting of N, O or S, and which is substituted with 0, 1 or 2 substituents independently selected from fluoro, hydroxy, C_1-C_4alkyl or C_1-C_4alkoxy;

R^{25} is independently selected at each occurrence from the group consisting of C_1-C_6alkoxy and $NR^{23}R^{24}$; and

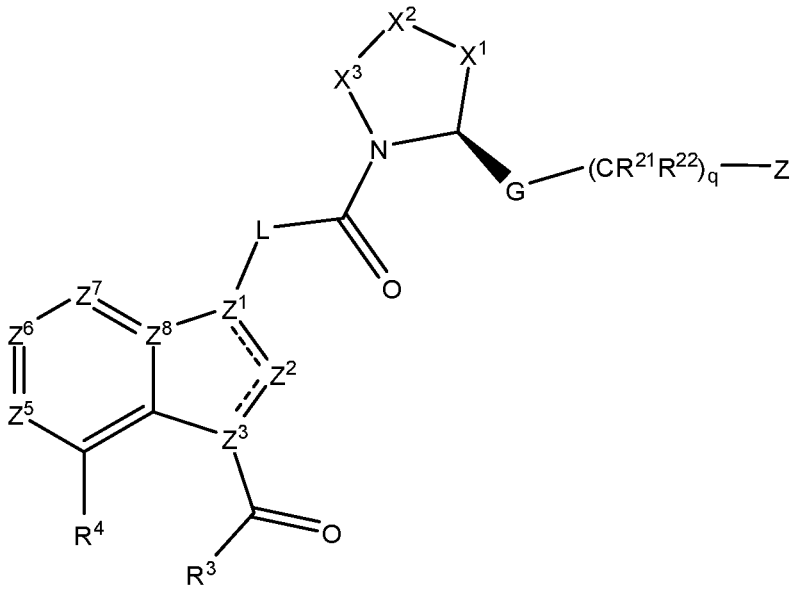
R^{26} is selected from the group consisting of amino, hydroxy, C_1-C_6alkyl, and, mono- and di-C_1-C_6alkylamino.

In certain aspects, the compounds of formula (I) preferably have the stereochemistry of compounds represented by formula (Ia):



(Ia),

In one aspect, compounds of formula (I) include those compounds represented by formula (II):



(II)

wherein:

Z^2 is CH or N;

X^1 is CHR^{15} or S;

X^2 is $CR^{16}R^{17}$ or S, wherein at least one of X^1 and X^2 is not sulfur;

X^3 is $CR^{18}R^{19}$ or N(H);

R^{15} is selected from the group consisting of hydrogen, hydroxy, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, NR^8R^9, N(H)C(O)C_1-C_4alkyl, N(H)C(O)OC_1-C_4alkyl and OC(O)$NR^{10}R^{11}$, each alkyl and alkoxy may be substituted with 0, 1, or 2 groups independently selected at each occurrence from the group consisting of hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, and NR^8R^9;

R^{16} is hydrogen, halogen, hydroxy, amino, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, heterocycleC_0-C_4alkyl, NR^8R^9, N(H)C(O)C_1-C_4 alkyl, hydroxyC_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl or C_1-C_4alkyl substituted with NR^8R^9;

R^{17} is hydrogen, halogen, hydroxy, C_1-C_4alkyl, hydroxyC_1-C_4alkyl or C_1-C_2alkoxyC_1-C_4alkyl;

R^{18} is selected from the group consisting of hydrogen, phenyl and C_1-C_6alkyl, which alkyl group is unsubstituted or substituted with hydroxy, amino, NHC(O)C_1-C_6alkyl, amide or mono- or di-C_1-C_4alkyl-amide;

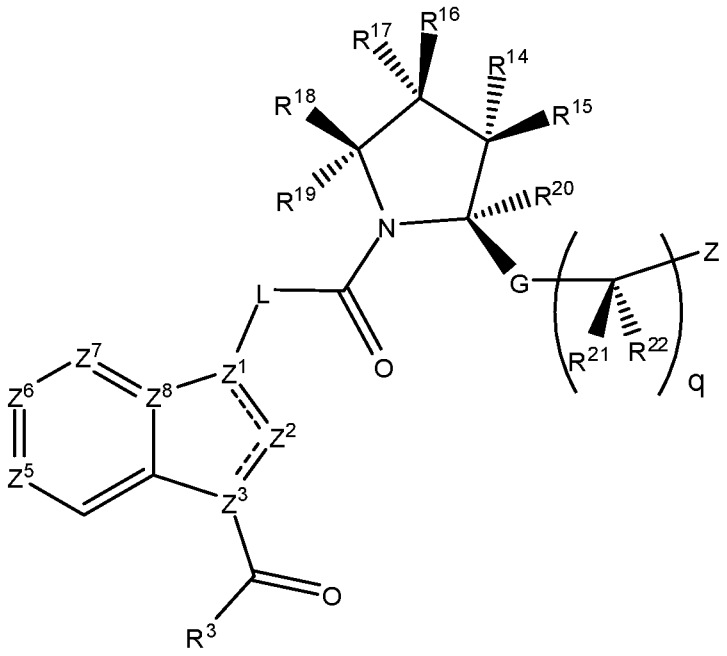
R^{19} is hydrogen; or

$CR^{16}R^{17}$, taken in combination, forms a spirocyclic 3 to 6 membered carbocycle; or

R^{15} and R^{16}, taken in combination, form a cyclopropyl ring which is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen, methyl, ethyl, hydroxymethyl, hydroxyethyl, methoxymethyl, ; or

R^{17} and R^{19} taken in combination form a cyclopropyl ring.

In another embodiment, the invention provides compounds of Formula (VII):



(VII),

or a pharmaceutically acceptable salt thereof, wherein

L is a divalent residue selected from the group consisting of –N(H)– and –C(H)(R^1)–,

R^1 is hydrogen, hydroxy, or amino;

Z^1 is C or N;

Z^2 is C(H) or N;

Z^3 is C or N,

Z^5 is C(R^5), N or an N oxide thereof;

Z^6 is C(R^6), N or an N oxide thereof;

Z^7 is C(R^7), N or an N oxide thereof;

Z^8 is C or N

wherein one of Z^1 and Z^3 is N and the other is C;

wherein 0, 1, 2 or 3 of Z^2, Z^5, Z^6, Z^7 and Z^8 are N;

R^3 is selected from the group consisting of hydrogen, C_1-C_4alkyl, hydroxyC_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl, haloC_1-C_4alkyl, amino or methylamino;

R^5 and R^6 are independently selected from the group consisting of hydrogen, halogen, hydroxy, NR^8R^9, cyano, CO_2H, $CONR^{10}R^{11}$ SO_2C_1-C_6alkyl, and $SO_2NR^{10}R^{11}$, C_1-C_6alkoxycarbonyl, $C(NR^8)NR^8R^9$, C_1-C_6alkyl, haloC_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, C_2-C_6alkenyloxy, wherein each alkyl, alkenyl, alkoxy and alkenyloxy is unsubstituted or substituted with up to 4 substitutents independently selected from halogen, hydroxy, tetrazole, C_1-C_4alkoxy, C_1-C_4haloalkoxy, CO_2H, C_1-C_6alkoxycarbonyl, $C(O)NR^{10}R^{11}$, NR^8R^9 optionally substituted phenyl, heterocycle having 4 to 7 ring atoms and 1, 2, or 3 ring heteroatoms selected from N, O or S, heteroaryl having 5 or 6 ring atoms and 1 or 2 ring

heteroatoms selected from N, O or S, and wherein optional phenyl substituents are selected from halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy and CO_2H;

R^5 and $R^{6,}$ taken in combination with the atoms to which they are attached, form a cycle having 4 to 7 ring atoms and 0 or 1 additional ring N, O or S atoms;

R^7 is selected from the group consisting of hydrogen, halogen, C_1-C_6alkyl, C_1-C_6alkoxy, haloC-C_6alkyl, haloC-C_6alkoxy C_1-C_6alkoxycarbonyl, CO_2H and $C(O)NR^{10}R^{11}$;R^8 and R^9 are independently selected from the group consisting of hydrogen, and C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, hydroxyC_1-C_6alkyl, or NR^8R^9, taken in combination, form a heterocycle having 4 to 7 ring atoms and 0 or 1 additional ring N, O or S atoms, which heterocycle is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_1-C_4alkyl, halogen, hydroxy, C_1-C_4alkoxy;

R^8 and R^9 are independently selected from the group consisting of hydrogen, and C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, hydroxyC_1-C_6alkyl, or NR^8R^9, taken in combination, form a heterocycle having 4 to 7 ring atoms and 0 or 1 additional ring N, O or S atoms, which heterocycle is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_1-C_4alkyl, halogen, hydroxy, C_1-C_4alkoxy;

R^{10} and R^{11}, are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, or hydroxyC_1-C_6alkyl;

R^{14} is selected from the group consisting of hydrogen, halogen, hydroxy, amino and C_1-C_6alkyl;

R^{15} is selected from the group consisting of hydrogen, hydroxy, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, NR^8R^9, N(H)C(O)C_1-C_6alkyl, N(H)C(O)OC_1-C_6alkyl and $OC(O)NR^{10}R^{11}$ each of alkyl, alkoxy, alkenyl, and alkynyl substituents may be substituted with 0, 1, or 2)groups independently selected at each occurrence from the group consisting of halogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, and $NR^{10}R^{11}$;

R^{16} is hydrogen, halogen, hydroxy, azide, cyano, COOH, C_1-C_6alkoxycarbonyl, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, NR^8R^9, N(H)C(O)C_1-C_6alkyl, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, or C_1-C_6alkyl substituted with NR^8R^9, N(H)C(O)H or N(H)C(O)(C_1-C_4alkyl);

R^{17} is hydrogen, halogen, hydroxy, C_1-C_6alkyl, C_1-C_4alkoxy, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, or C_1-C_6haloalkoxy;

R^{18} is selected from the group consisting of hydrogen, phenyl and C_1-C_6alkyl, which alkyl group is unsubstituted or substituted with hydroxy, amino, azide, and NHC(O)C_1-C_6alkyl;

R^{19} and R^{20} are each independently selected from hydrogen and C_1-C_6alkyl; or

$CR^{16}R^{17}$, taken in combination, form a spirocyclic 3 to 6 membered carbocycle which is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen and methyl; or

R^{16} and R^{17}, taken in combination, form an exocyclic methylidene (=CH_2);

R^{15} and R^{16} or R^{14} and R^{17} taken in combination form an epoxide ring or a 3 to 6 membered carbocyclic ring system which carbocyclic ring is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen, methyl, ethyl, hydroxyC_1-C_4alkyl, C_1-C_6alkoxyC_1-C_4alkyl, C_1-C_4alkoxycarbonyl, CO_2H, and C_1-C_4alkyl substituted with NR^8R^9; or

R^{17} and R^{19} or R^{16} and R^{18}, taken in combination, form a fused 3 membered carbocyclic ring system which is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen, methyl, ethyl, hydroxyC_1-C_4alkyl, C_1-C_4alkoxycarbonyl, CO_2H, and C_1-C_4alkyl substituted with NH^8R^9; or

R^{14} and R^{20} taken in combination form a fused 3 carbocyclic ring system;

R^{14} and R^{19}, taken in combination, form a 1 to 3 carbon alkylene linker; or

R^{17} and R^{20}, taken in combination, form a 1 to 3 carbon alkylene linker;

G is a divalent residue selected from C(O)-N(H), CH_2-N(H)–$S(O)_2$–, CH_2–N(H)–C(O), CH_2-N(H)-C(O)-O, CH_2N(H), CH_2-N(H)-C(O)-N(H), CH_2-N(H)-C(O)-N(Me), CH_2N(H)-$S(O)_2$-N(H)-, and CH_2N(H)-$S(O)_2$-N(Me)-, wherein the right most residue is attached to –$(CR^{21}R^{22})_q$;

q is 0, 1, 2, 3 or 4;

R^{21} is independently selected at each occurrence from the group consisting of hydrogen, hydroxy, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, phenyl, CO_2H, C_1-C_6alkoxy carbonyl, $C(O)NH_2$, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, C_1-C_6alkyl substituted with NR^8R^9, imidazoylC_1-C_6alkyl heterocycleC_1-C_6alkyl, where the heterocycle is selected from azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, 1-oxa-6-aza-spiro[3.3]heptane, 2-oxa-6-aza-spiro[3.3]heptane, piperazinyl, 1,6-diaza-spiro[3.3]heptane, and 2,6-diaza-spiro[3.3]heptane each of which is optionally sustituted by 1 or 2 substituent selected from fluoro, hydroxy, C_1-C_4alkyl or C_1-C_4alkoxy;

R^{22} is independently selected at each occurrence from hydrogen or C_1-C_6alkyl; or

when q is 1, 2, 3 or 4, R^{21} and a R^{22} substituent, taken in combination with the carbon atoms to which they are attached, form a 3 to 6 membered carbocycle or 4 to 6 membered heterocyle having a ring oxygen or nitrogen; or

when q is 2, 3 or 4, two R^{21} or R^{22} residues, located on adjacent carbon atoms, form, together with the carbon atoms to which they are attached, a 3 to 6 membered carbocycle; and

Z is C_1-C_6alkyl, C_1-C_6haloalkyl, phenyl, phenoxy, naphthyl, naphthyloxy, C_3-C_7cycloalkyl, indanyl, a 5, 6, 9 or 10 membered saturated or partially unsaturated, monocyclic or bicyclic heterocycle having 1, 2, or 3 ring heteroatoms selected from N, O, or S, or a 5 or 6

membered heteroaryl or heteroaryloxy, which heteroaryl has 1 or 2 ring heteroatoms selected from N, O or S provided that the ring does not have 2 O or S atoms, each residue is unsubstituted or substituted with 1, 2, 3, or 4 substituents which are independently selected from the group consisting of substituted or unsubstituted C_1-C_6alkyl, C_1-C_6haloalkyl, halogen, CN, hydroxy, CO_2H, tetrazolyl, $C(O)R^{25}$, $S(O)_2R^{26}$, substituted or unsubstituted C_1-C_6alkoxy, haloC_1-C_6alkoxy, phenoxy, $NR^{23}R^{24}$, $CH_2NR^{23}R^{24}$, 5 or 6 membered heteroaryl and unsubstituted or substituted phenyl, which substituted phenyl has 1 or 2 substituents independently selected from the group consisting of cyano, halo, C_1-C_6alkyl or C_1-C_6haloalkyl, OH, COOH, COR^{25}, $S(O)_2R^{26}$, amino, and CH_2NH_2, and which substituted alkyl or alkoxy has a substituent selected from hydroxy, C_1-C_4alkoxy, cyano, CO_2H, tetrazole or $NR^{23}R^{24}$;

R^{23} is hydrogen or C_1-C_6alkyl;

R^{24} is hydrogen, C_1-C_6alkyl, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, aminoC_1-C_6alkyl, mono- and di-C_1-C_6alkylaminoC_1-C_6alkyl; or

$NR^{23}R^{24}$, taken in combination form a 4, 5 or 6 membered heterocycle having 0 or 1 additional ring heteroatoms selected from the group consisting of N, O or S, and which is substituted with 0, 1 or 2 substituents independently selected from fluoro, hydroxy, C_1-C_4alkyl or C_1-C_4alkoxy;

R^{25} is independently selected at each occurrence from the group consisting of C_1-C_6alkoxy and $NR^{23}R^{24}$; and

R^{26} is selected from the group consisting of amino, hydroxy, C_1-C_6alkyl, and, mono- and di-C_1-C_6alkylamino.

In another aspect, compounds of formula (I) or (II) are provided in which X^1 is CHR^{15}; and R^{15} is hydrogen, fluoro, hydroxy, amino, C_1-C_4alkyl, C_1-C_6alkoxy, OCH_2CH_2OMe, or C_2-C_4alkoxy substituted with NR^8R^9;

X^2 is $CR^{16}R^{17}$;

R^{16} is hydrogen, halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, NR^8R^9, hydroxyC_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl, C_1-C_4alkyl substituted with NR^8R^9 or C_2-C_4alkoxy substituted with NR^8R^9;

R^{17} is hydrogen, halogen, hydroxy or C_1-C_4alkyl; or

R^{15} and R^{16} taken in combination form a cyclopropyl ring; or

R^{17} and R^{19} taken in combination form a cyclopropyl ring.

In yet another aspect, compounds of formula (I) or (II) are provided in which X^1 is S; and X^2 and X^3 are CH_2; or

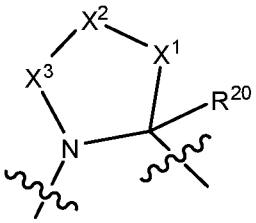
X^1 is CHR^{15}, wherein R^{15} is hydrogen, fluoro, methyl, hydroxy, methoxy, ethoxy, methoxyethoxy or amino; X^3 is CH_2; and X^2 is $CR^{16}R^{17}$, wherein R^{16} is fluoro, amino, hydroxymethyl, methoxymethyl, aminomethyl or methyl and R^{17} is hydrogen or fluoro; or

X^1 is CHR^{15}, X^2 is $CR^{16}R^{17}$, and X^3 is CHR^{19}, wherein R^{17} and R^{19}, taken in combination form a cyclopropyl ring, and R^{16} is hydrogen, hydroxymethyl, or methoxymethyl, and R^{15} is hydrogen; or

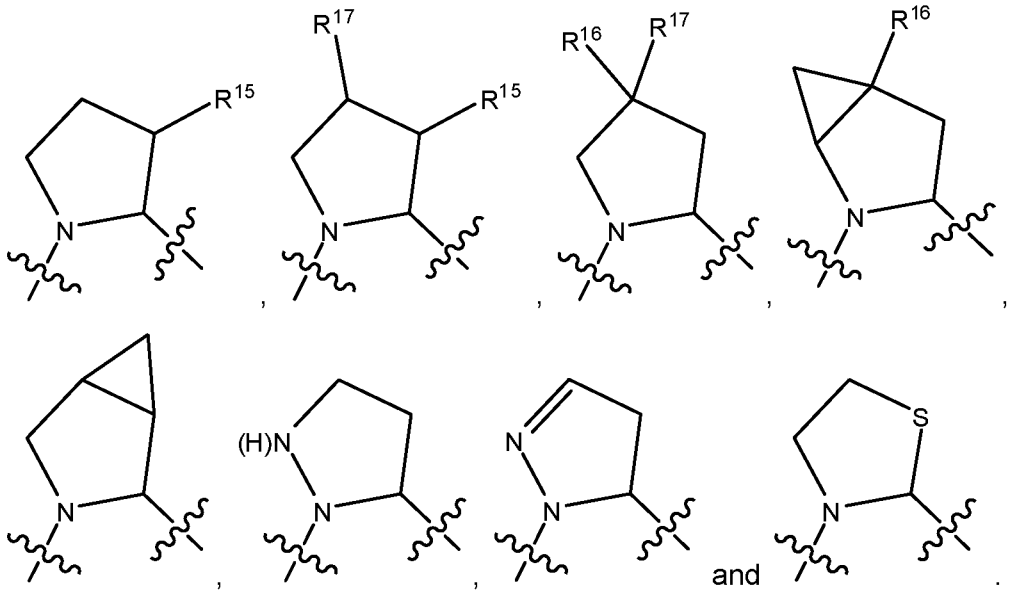
X^1 is CHR^{15}, X^2 is $CR^{16}R^{17}$, and X^3 is CHR^{19}, wherein R^{15} and R^{16}, taken in combination form a cyclopropyl ring, R^{17} and R^{19} are hydrogen; or

X^1 and X^2 are CH_2, and X^3 is N(H).

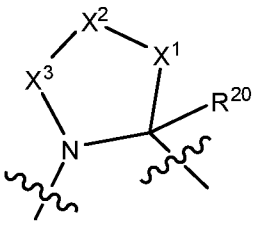
Other compounds of formula (I) or (II) provided herein include those compounds in which the heterocyclic ring of the formula:



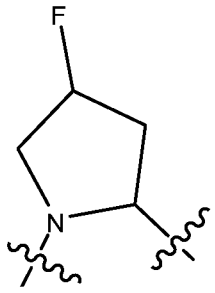
Is selected from the group consisting of:



In certain embodiments, the heterocyclic ring of the compounds of formula (I) and formula (II) of the formula:



Is a 4-fluoro pyrrolidine, e.g., a heterocyle of the formula:



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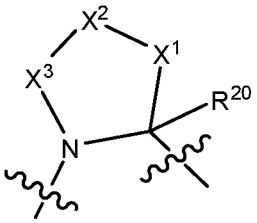
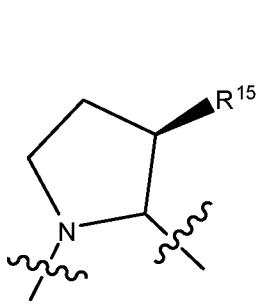
In certain aspects, compounds of formula (I) or (II) include compounds in which the heterocyclic ring of the formula:



is selected from the group consisting of: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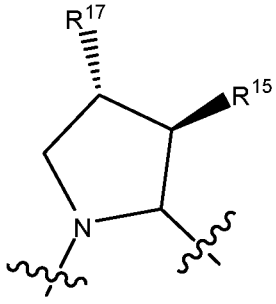
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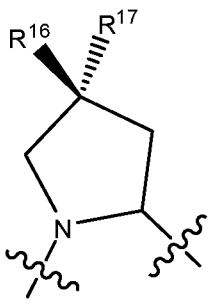
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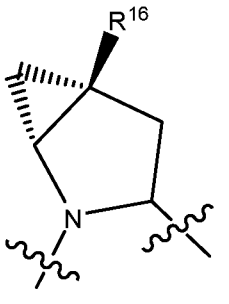
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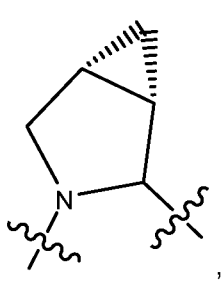
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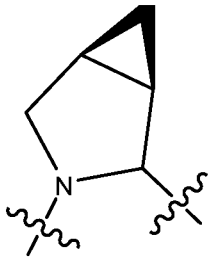
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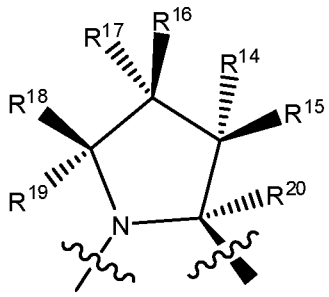
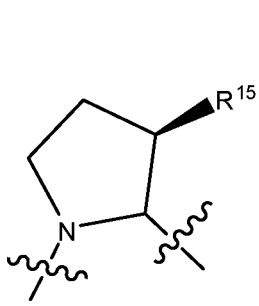
In certain aspects, compounds of formula (VII) include compounds in which the heterocyclic ring of the formula:



is selected from the group consisting of: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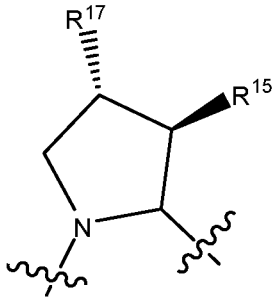
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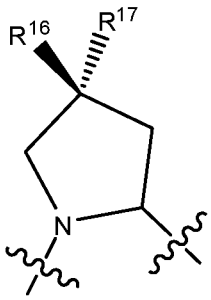
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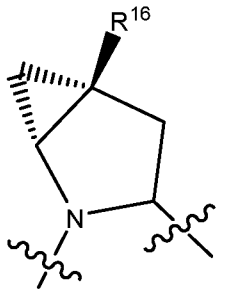
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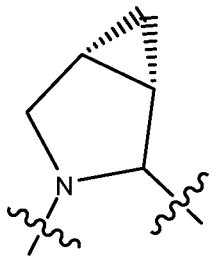
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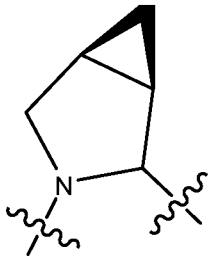
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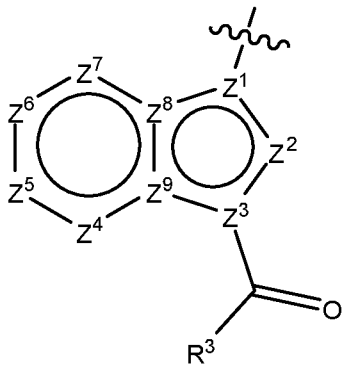
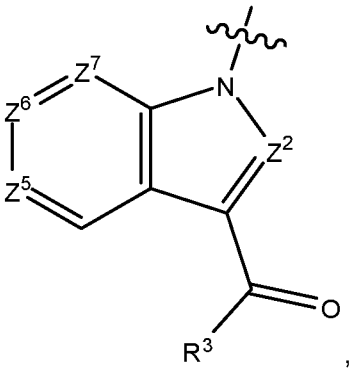
Other compounds of formula (I) provided herein include those compounds in which the bicyclic ring system of the formula:



is selected from the group consisting of:



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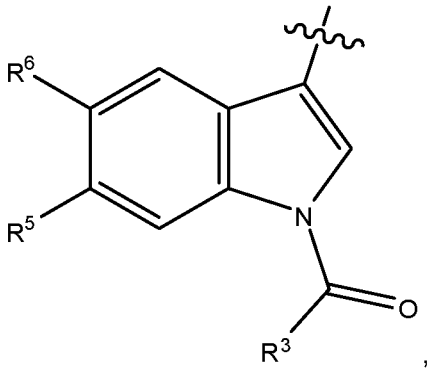

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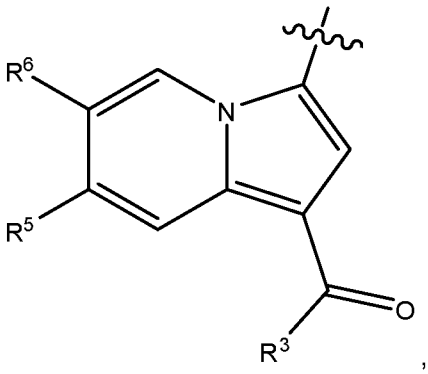

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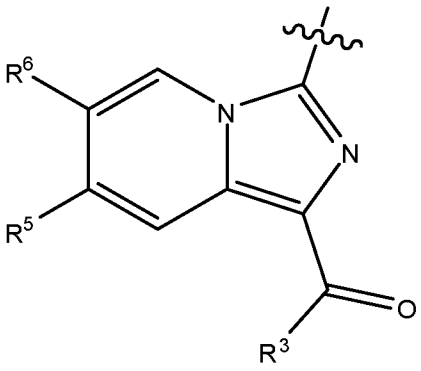

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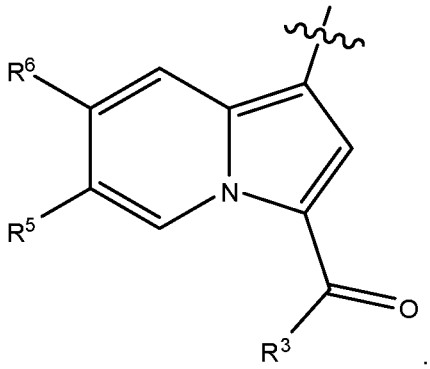

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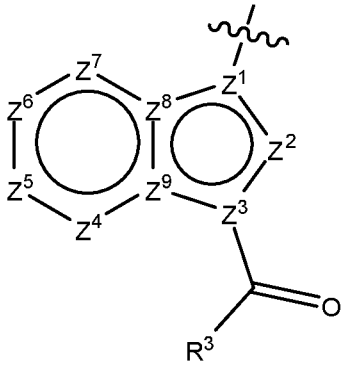
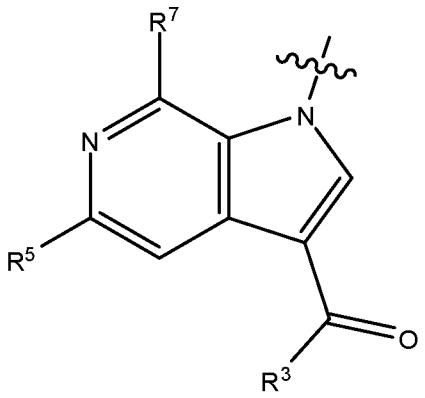
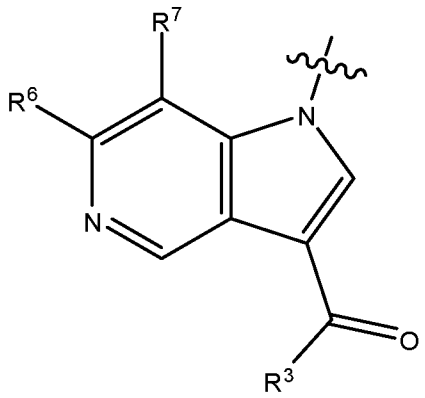
Certain other compounds of formula (I) provided herein include those compounds in which the bicyclic ring system of the formula:



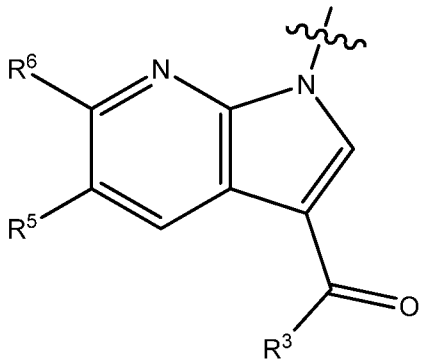
is selected from the group consisting of:


R7
N
N
R5
O
R3

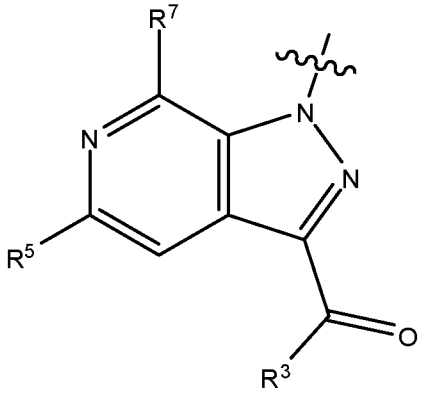
,


R7
R6
N
N
O
R3

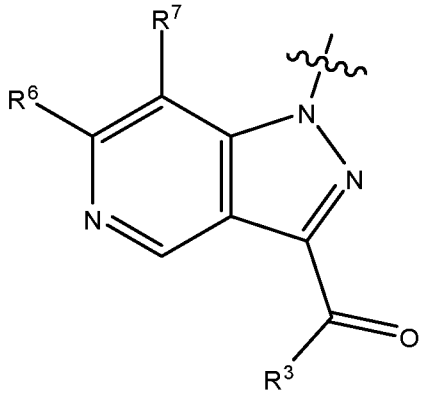
,


R6
N
N
R5
O
R3

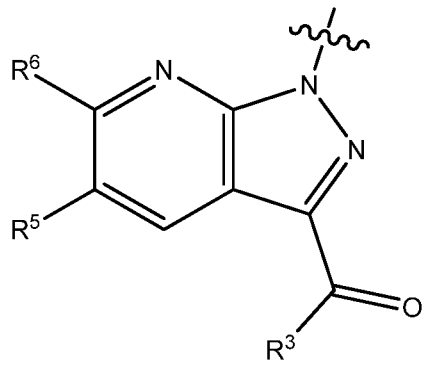
,


R7
N
N
N
R5
O
R3

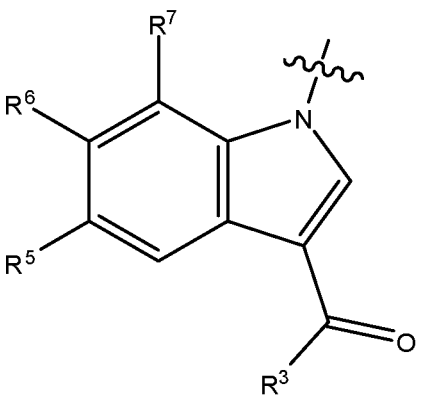
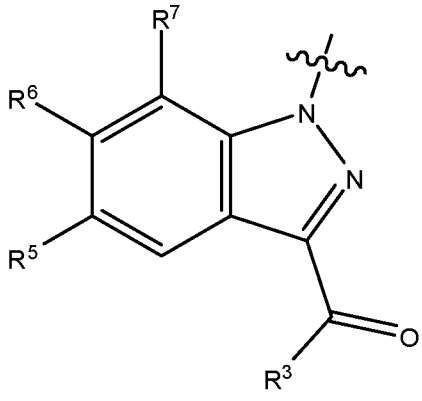
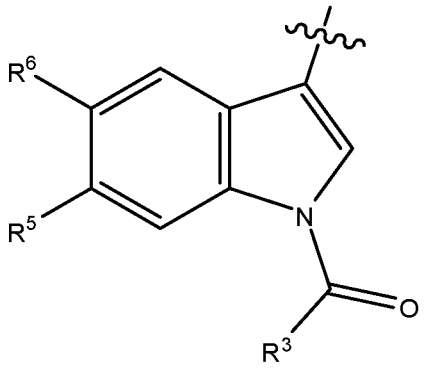
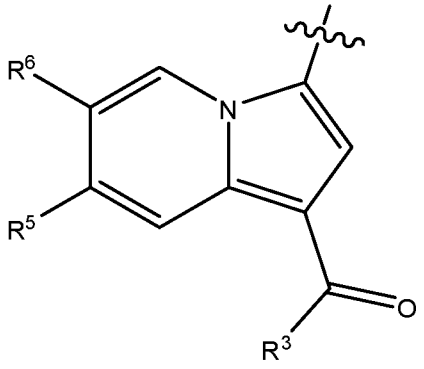
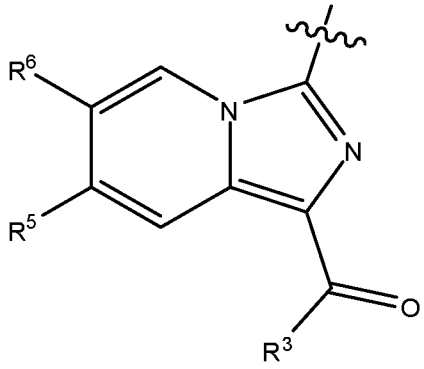
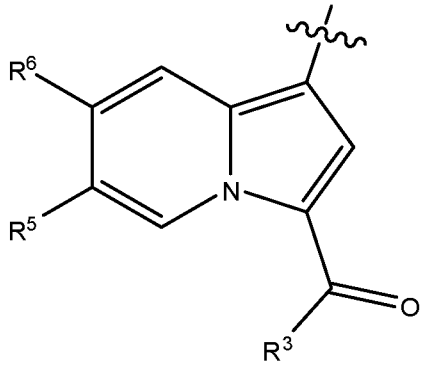
,


R7
R6
N
N
N
O
R3

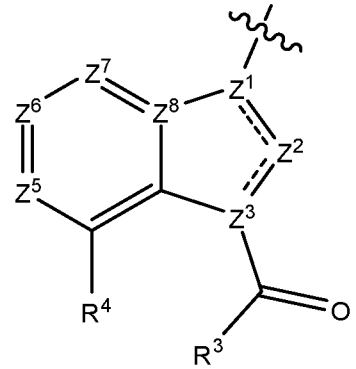
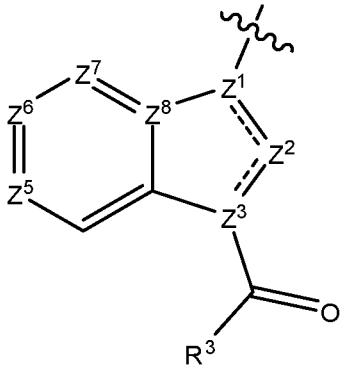
,


R6
N
N
N
R5
O
R3

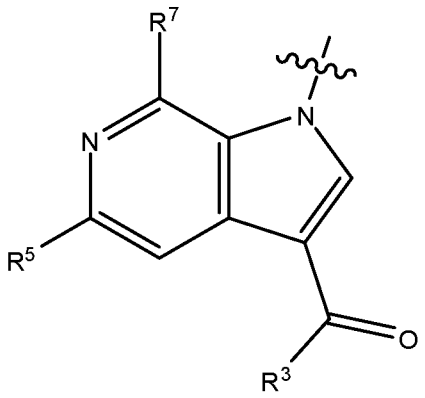
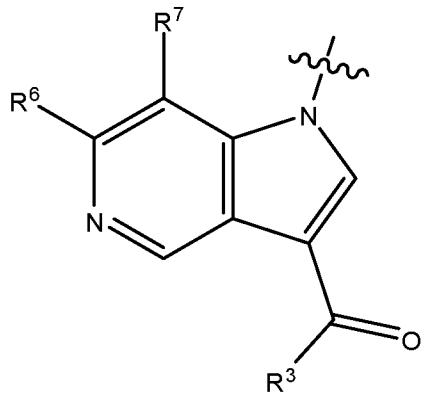
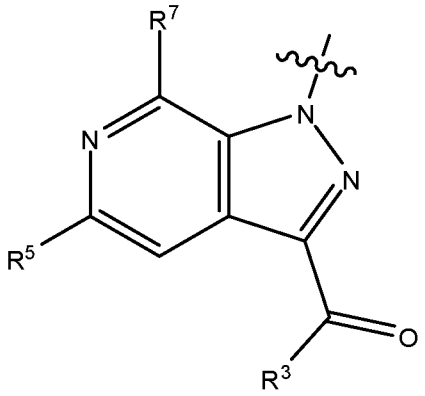
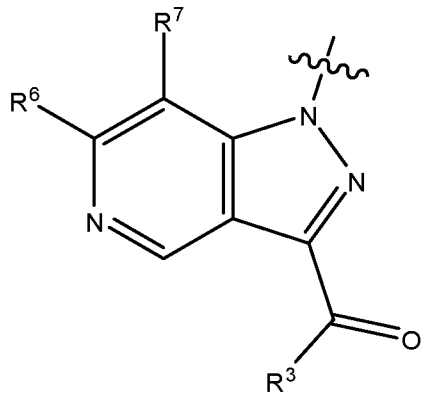
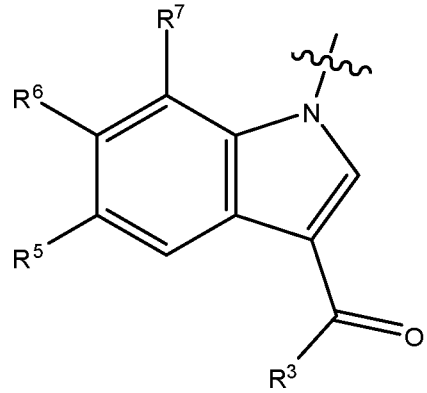
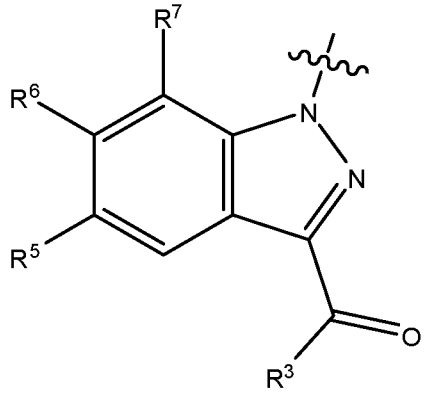
,

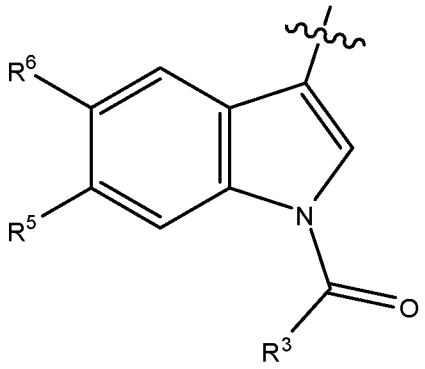







Other compounds of formula (II) or formula (VII) provided herein include those compounds in which the bicyclic ring system of formula (II) or formula (VII)

is selected from the group consisting of:


R7
N
N
R5
O
R3
,

R7
R6
N
N
O
R3
,

R7
N
N
N
R5
O
R3
,

R7
R6
N
N
N
O
R3
,

R7
R6
N
R5
O
R3
,

R7
R6
N
N
R5
O
R3
,



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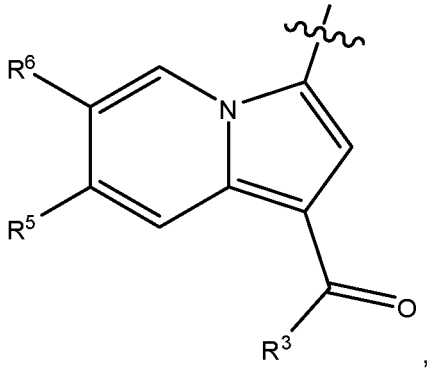

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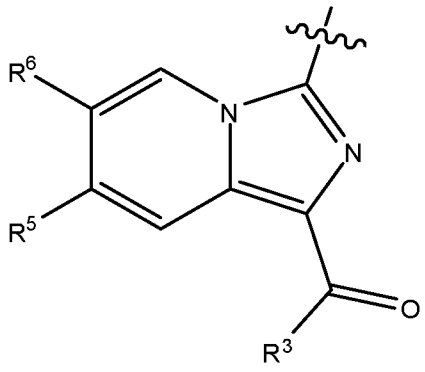
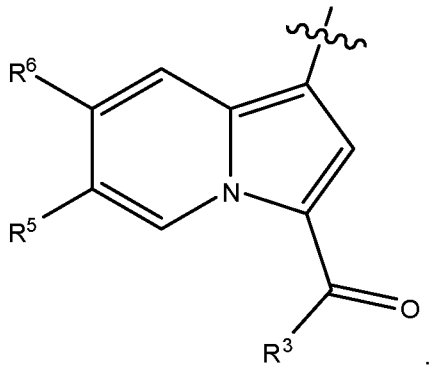


, and


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Certain preferred compounds of formula (I), (Ia), (II), (VII) or any subformula thereof provided herein include those compounds in which L is –N(H)– or $–CH_2–$. Certain other preferred compounds of formula (I), (Ia), (II), (VII) or any subformula thereof provided herein include those compounds in which G is –C(O)-N(H)–.

Still other preferred compounds of formula (I), (Ia), (II) or (VII) or any subformula thereof provided herein include those compounds in which q is 0 or 1;

R^{21} is selected from the group consisting of hydrogen, C_1-C_6alkyl, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl and C_1-C_6alkyl substituted with NR^8R^9;

R^{22} is hydrogen; or

$CR^{21}R^{22}$, taken in combination, form a cyclopropyl ring;

Z is phenyl, pyridyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, thienyl, each of which is unsubstituted or substituted with 1, 2 or 3 substituents, each of which is independently selected from the group consisting of:

halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy, haloC_1-C_4alkyl, haloC_1-C_4alkoxy, $NR^{23}R^{24}$, CO_2H, $C(O)NR^{23}R^{24}$, $CO_2(C_1$-C_4alkyl), tetrazole, piperidinyl, piperazinyl, morpholino, and alkyl substituted with C_1-C_4alkoxy or $NR^{23}R^{24}$.

In still other preferred compounds of formula (I), (Ia), (II), or (VII), or any subformulae thereof provided herein, q is 2;

R^{21} is selected, at each occurrence, from the group consisting of hydrogen, C_1-C_6alkyl, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl and C_1-C_6alkyl substituted with NR^8R^9;

R^{22} is hydrogen; or

$CR^{21}R^{22}CR^{21}R^{22}$, taken in combination, forms a cis or trans cyclopropane ring;

Z is phenyl, pyridyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, thienyl, each of which is unsubstituted or substituted with 1, 2 or 3 substituents, each of which is independently selected from the group consisting of:
halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy, haloC_1-C_4alkyl, haloC_1-C_4alkoxy, $NR^{23}R^{24}$, CO_2H, $C(O)NR^{23}R^{24}$, $CO_2(C_1$-C_4alkyl), tetrazole, piperidinyl, piperazinyl, morpholino, and alkyl substituted with C_1-C_4alkoxy or $NR^{23}R^{24}$.

Still other preferred compounds of formula (I), (Ia), (II) or (VII) or any subformula thereof provided herein include those compounds in which q is 0 or 1;

R^{21} is selected from the group consisting of hydrogen, C_1-C_6alkyl, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, am$_i$noC_1-C_6alkyl, and mono- and di-C_1-C_4alkylaminoC_1-C_6alkyl;

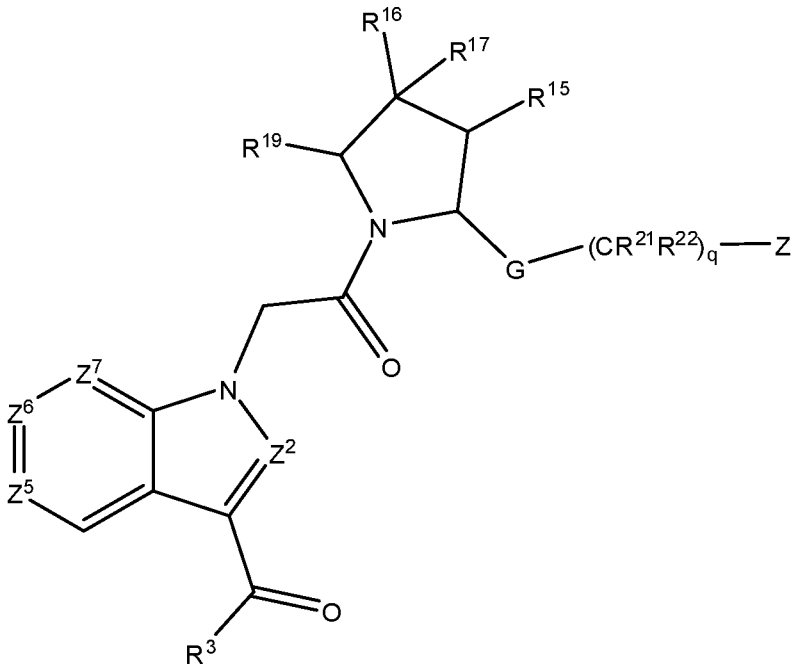
R^{22} is hydrogen; or

$CR^{21}R^{22}$, taken in combination, form a cyclopropyl ring; and

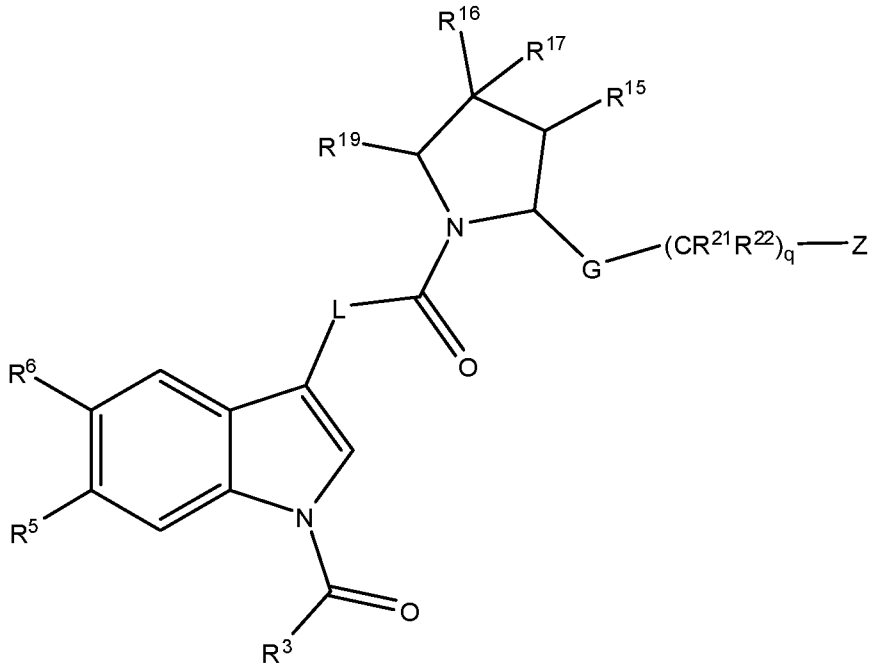
Z is phenyl which is unsubstituted or substituted with 1, 2, or 3 substituents, each of which is independently selected from the group consisting of halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy, haloC_1-C_4alkyl, haloC_1-C_4alkoxy, CO_2H, $C(O)NH_2$, $CO_2(C_1$-C_4alkyl), amino, and mono- and di-C_1-C_4alkylamino, wherein each N-alkyl residue is substituted with 0 or 1 residues selected from the group consisting of hydroxy, C_1-C_4alkoxy, amino, or mono- or di-C_1-C_2alkylamino.

Still other preferred compounds of formula (I), (Ia), (II) or (VII) or any subformula thereof provided herein include those compounds in which q is 0, 1 or 2;
R^{21} is hydrogen;
R^{22} is hydrogen, methyl, or ethyl, which methyl and ethyl are unsubstituted or substituted with hydroxy, methoxy, amino, or mono- or di-methyl amino; or
$CR^{21}R^{22}$, taken in combination, form a cyclopropane ring;
when q is 2, $CR^{21}R^{22}CR^{21}R^{22}$, taken in combination form a cis- or trans- cyclopropane ring;
Z is phenyl which is unsubstituted or substituted with 1, 2, or 3 residues selected from the group consisting of fluoro, chloro, bromo, methyl, trifluoromethyl, methoxy, trifluoromethoxy, amino, mono- and di-C_1-C_2alkylamino, tetrazole or CO_2H; or
Z is pyridyl or thienyl, each of which is unsubstituted or substituted with 1 or 2 substitutents selected from the group consisting of fluoro, chloro, bromo, methyl, trifluoromethyl, methoxy, or trifluoromethoxy.

In another aspect, the invention provides compounds of formula (I) or formula (II) in which the compounds are represented by formulae (III), (IV) or (V):

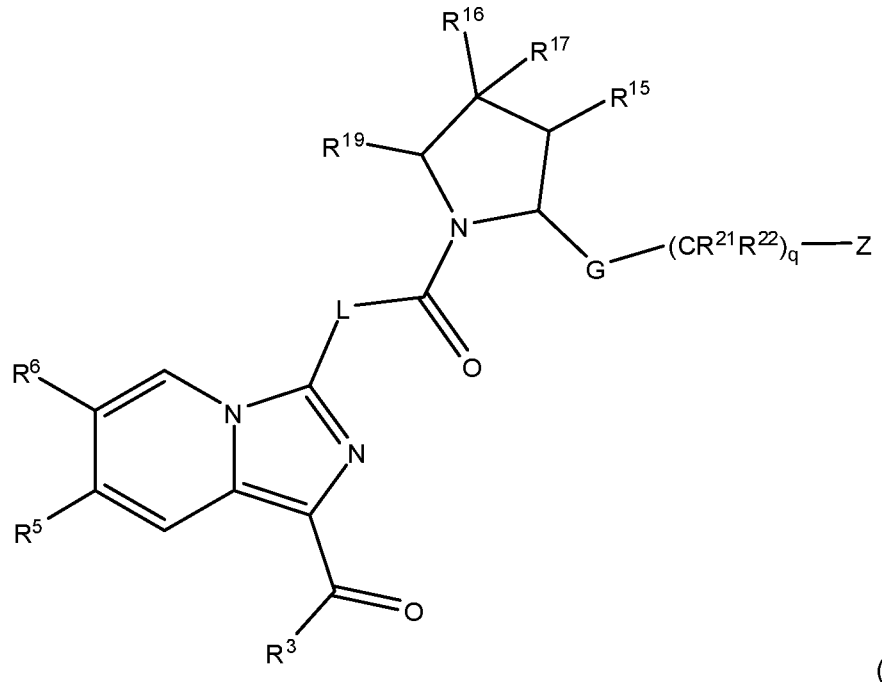


(III)



(IV)

or



(V)

wherein

Z^2 is CH or N;

Z^5 is CR^5 or N;

Z^6 is CR^6 or N;

Z^7 is CH or N, wherein 0, 1 or 2 of Z^5, Z^6 and Z^7 is N;

R^3 is hydrogen, methyl, ethyl, iPr, amino, hydroxymethyl, CH2OMe, or mono-, di- and tri-fluoromethyl, NHMe;

R^5 is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkenyl, C_2-C_4alkenyloxy, hydroxy, CO_2H, tetrazole , C_1-C_4alkoxycarbonyl, cyano, wherein each alkyl or alkoxy group is unsubstituted or substituted with up to 5 halogen atoms and with 0 or 1 additional substituents selected from the group consisting of hydroxy, tetrazole,C_1-C_4alkoxy, CO_2H, C_1-C_4alkoxycarbonyl, optionally substituted phenyl, pyridyl and pyrimidinyl, and wherein the phenyl is unsubstituted or substituted with 1 or 2 substituents independently selected from halogen, hydroxy, methyl, methoxy and CO_2H;

R^6 is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkenyl, C_2-C_4alkenyloxy, hydroxy, CO_2H, C_1-C_4alkoxycarbonyl, cyano, wherein each alkyl or alkoxy group is unsubstituted or substituted with up to 5 halogen atoms and with 0 or 1 additional substituents selected from the group consisting of hydroxy, $NR^{10}R^{11}$, tetrazole, cyano, imidazolyl, C_1-C_4alkoxy, CO_2H, C_1-C_4alkoxycarbonyl, optionally substituted phenyl, pyrrolyl, morpholino, piperidino, piperazino, and pyridyl, and wherein the phenyl is unsubstituted or substituted with 1 or 2 substituents independently selected from halogen, hydroxy, methyl, methoxy, mono- and dimethyl amino, and CO_2H;

L is CH_2 or NH ;

R^{15} is hydrogen, fluoro, methyl, hydroxy, methoxy, ethoxy and OCH_2CH_2OMe, $OCH_2CH_2N(CH_3)_2$, amino or OCH_2CH_2pyrrolyl;

R^{16} is hydrogen, fluoro, methyl, amino, hydroxymethyl, methoxymethyl, or aminomethyl;

R^{17} is hydrogen, fluoro or methyl;

R^{19} is hydrogen or R^{19} and R^{17}, taken in combination, form a cyclopropyl ring; or

R^{15} and R^{16}, taken in combination, form a cyclopropyl ring;

G is -C(O)N(H)-; and

q is 0, 1, or 2;

R^{21} is hydrogen, methyl, or ethyl, which methyl and ethyl are unsubstituted or substituted with hydroxy, methoxy, amino, mono- or di-methyl amino, morpholinomethyl, optionally substituted azetidinomethyl, which azetidino ring is substituted with 0 or 1 fluoro or methoxy; or

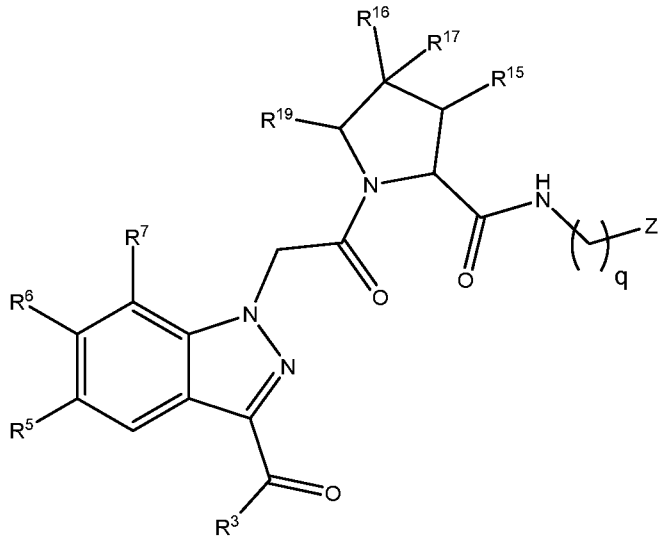
R^{22} is hydrogen;

$CR^{21}R^{22}$, taken in combination, form a cyclopropane ring; or

when q is 2, $CR^{21}R^{22}CR^{21}R^{22}$, taken in combination form a cis- or trans- cyclopropane ring;

Z is phenyl, pyridyl, or thienyl , each of which is unsubstituted or substituted with 1, 2, or 3 residues independently selected at each occurrence from the group consisting of halogen, methyl, methoxy, hydroxy, trifluoromethyl, trifluoromethoxy, CO_2H, tetrazole, and $NR^{23}R^{24}$.

Certain compounds of Formula (III) provided by the invention include compounds represented by formula (IIIa):



(IIIa)

wherein

R^3 is hydrogen, methyl, ethyl, iPr, amino, hydroxymethyl, CH2OMe, or mono-, di- and tri-fluoromethyl, NHMe;

R^5 is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkenyl, C_2-C_4alkenyloxy, hydroxy, CO_2H, tetrazole , C_1-C_4alkoxycarbonyl, cyano, wherein each alkyl or alkoxy group is unsubstituted or substituted with up to 5 halogen atoms and with 0 or 1 additional substituents selected from the group consisting of hydroxy, tetrazole,C_1-C_4alkoxy, CO_2H, C_1-C_4alkoxycarbonyl, optionally substituted phenyl, pyridyl and pyrimidinyl, and wherein the phenyl is unsubstituted or substituted with 1 or 2 substituents independently selected from halogen, hydroxy, methyl, methoxy and CO_2H;

R^6 is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkenyl, C_2-C_4alkenyloxy, hydroxy, CO_2H, C_1-C_4alkoxycarbonyl, cyano, wherein each alkyl or alkoxy group is unsubstituted or substituted with up to 5 halogen atoms and with 0 or 1 additional substituents selected from the group consisting of hydroxy, $NR^{10}R^{11}$, tetrazole, cyano, imidazolyl, C_1-C_4alkoxy, CO_2H, C_1-C_4alkoxycarbonyl, optionally substituted phenyl, pyrrolyl, morpholino, piperidino, piperazino, and pyridyl, and wherein the phenyl is unsubstituted or substituted with 1 or 2 substituents independently selected from halogen, hydroxy, methyl, methoxy, mono- and dimethyl amino, and CO_2H;

R^7 is hydrogen or methyl;

R^{15} is hydrogen, fluoro, methyl, hydroxy, methoxy, ethoxy and OCH_2CH_2OMe, $OCH_2CH_2N(CH_3)_2$, amino or OCH_2CH_2pyrrolyl;

R^{16} is hydrogen, fluoro, methyl, amino, hydroxymethyl, methoxymethyl, or aminomethyl;

R^{17} is hydrogen, fluoro or methyl;

R^{19} is hydrogen or R^{19} and R^{17}, taken in combination, form a cyclopropyl ring; or

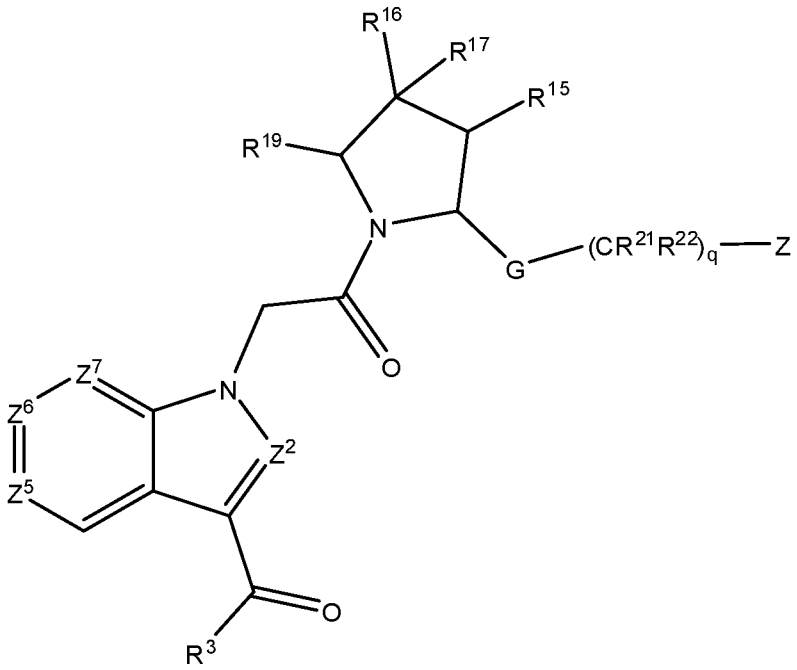
R^{15} and R^{16}, taken in combination, form a cyclopropyl ring;

G is -C(O)N(H)-; and

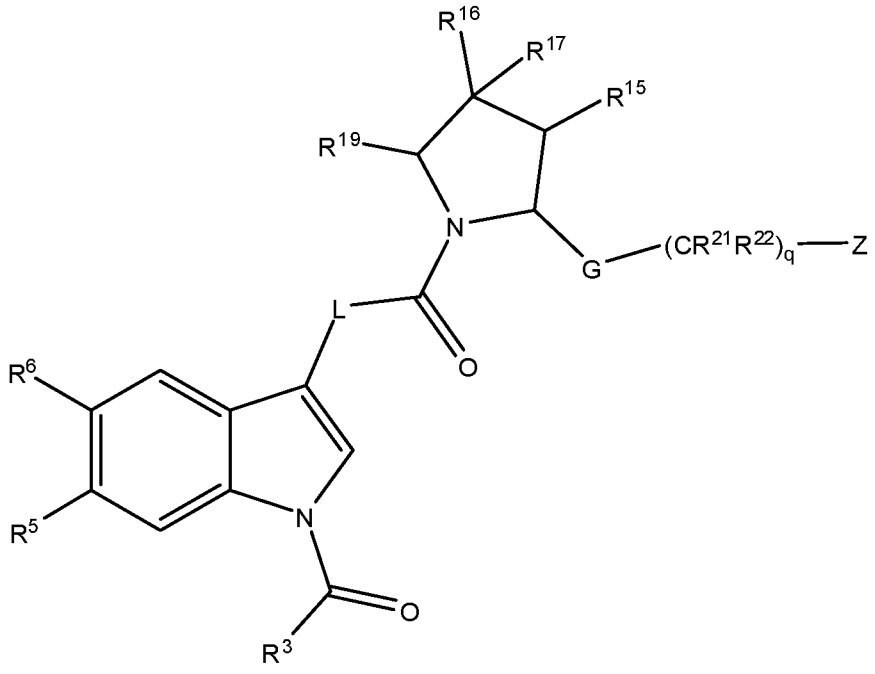
q is 0 or 1;

Z is pyridyl, pyrazinyl, or thienyl , each of which is unsubstituted or substituted with 1, 2, or 3 residues independently selected at each occurrence from the group consisting of halogen, methyl, methoxy, hydroxy, trifluoromethyl, trifluoromethoxy, CO_2H, tetrazole, and $NR^{23}R^{24}$.

In another embodiment, compounds of the first embodiment include those compounds represented by one of the formulae (IIIb) or (IVb):



(IIIb)



(IVb)

wherein

Z^2 is CH or N;

Z^5 is CR^5 or N;

Z^6 is CR^6 or N;

Z^7 is CH, $C(CH_3)$ or N, wherein 0 or 1 or 2 of Z^5, Z^6 and Z^7 is N;

R^3 is hydrogen, methyl, ethyl, iPr, amino, hydroxymethyl, CH2OMe, or mono-, di- and tri-fluoromethyl, NHMe;

R^5 is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkenyl, C_2-C_4alkenyloxy, hydroxy, CO_2H, tetrazole , C_1-C_4alkoxycarbonyl, cyano, wherein each alkyl or alkoxy group is

unsubstituted or substituted with up to 5 halogen atoms and with 0 or 1 additional substituents selected from the group consisting of hydroxy, cyano, tetrazole,C_1-C_4alkoxy, CO_2H, C_1-C_4alkoxycarbonyl, tetrahydrofuranyl, optionally substituted phenyl, pyridyl and pyrimidinyl, and wherein the phenyl is unsubstituted or substituted with 1 or 2 substituents independently selected from halogen, hydroxy, methyl, methoxy and CO_2H;

R^6 is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkenyl, C_2-C_4alkenyloxy, hydroxy, CO_2H, C_1-C_4alkoxycarbonyl, cyano, wherein each alkyl or alkoxy group is unsubstituted or substituted with up to 5 halogen atoms and with 0 or 1 additional substituents selected from the group consisting of hydroxy, $NR^{10}R^{11}$, tetrazole, cyano, imidazolyl, C_1-C_4alkoxy, CO_2H, C_1-C_4alkoxycarbonyl, optionally substituted phenyl, pyrrolyl, morpholino, piperidino, piperazino, and pyridyl, and wherein the phenyl is unsubstituted or substituted with 1 or 2 substituents independently selected from halogen, hydroxy, methyl, methoxy, mono- and dimethyl amino, and CO_2H;

L is CH_2 or NH ;

R^{15} is hydrogen, fluoro, methyl, hydroxy, methoxy, ethoxy and OCH_2CH_2OMe, $OCH_2CH_2N(CH_3)_2$, amino or OCH_2CH_2pyrrolyl;

R^{16} is hydrogen, fluoro, methyl, amino, hydroxymethyl, methoxymethyl, or aminomethyl;

R^{17} is hydrogen, fluoro or methyl;

R^{19} is hydrogen or R^{19} and R^{17}, taken in combination, form a cyclopropyl ring; or

R^{15} and R^{16}, taken in combination, form a cyclopropyl ring;

G is -C(O)N(H)-; and

q is 0 or 1;

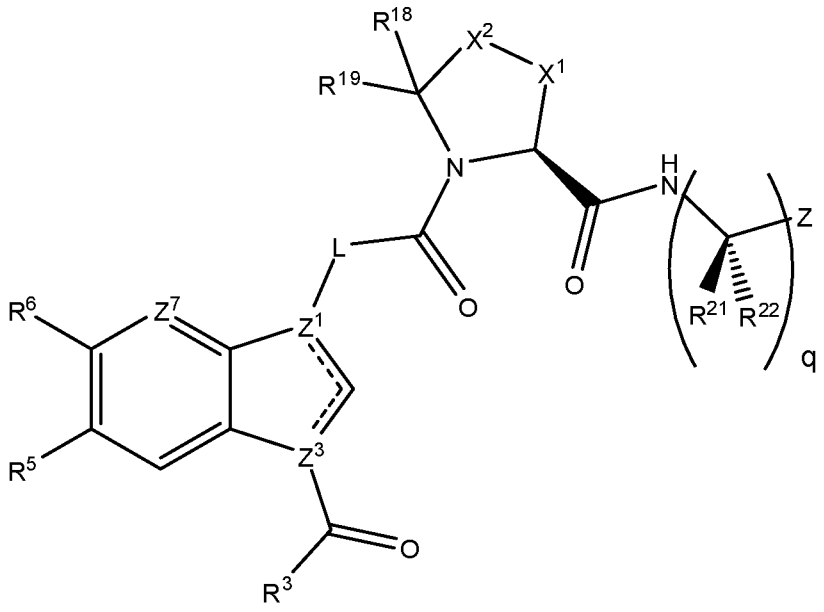
R^{21} is hydrogen, methyl, or ethyl, which methyl and ethyl are unsubstituted or substituted with hydroxy, methoxy, cyano, amino, mono- or di-methyl amino, morpholinomethyl, optionally substituted azetidinomethyl, which azetidino ring is subsituted with 0 or 1 fluoro or methoxy; or

R^{22} is hydrogen;

$CR^{21}R^{22}$, taken in combination, form a cyclopropane ring;

Z is phenyl, pyridyl, pyrazinyl or thienyl , each of which is unsubstituted or substituted with 1, 2, or 3 residues independently selected at each occurrence from the group consisting of halogen, methyl, cyclopropyl, methoxy, hydroxy, trifluoromethyl, trifluoromethoxy, SF_5, CO_2H, tetrazole, and $NR^{23}R^{24}$, unsubstituted or substituted phenyl and unsubstituted or substituted pyridinyl, which substituted phenyl and pyridinyl has 1 or 2 substituents independently selected from the group consisting of halogen and methyl.

Certain compounds, or salts thereof, provided by formula (I) or formula (II) include those compounds which are represented by formula (VI):



(VI)

wherein

q is 0, 1 or 2;

R^{21} is hydrogen;

R^{22} is hydrogen, methyl, or ethyl, which methyl and ethyl are unsubstituted or substituted with hydroxy, methoxy, amino, or mono- or di-methyl amino; or

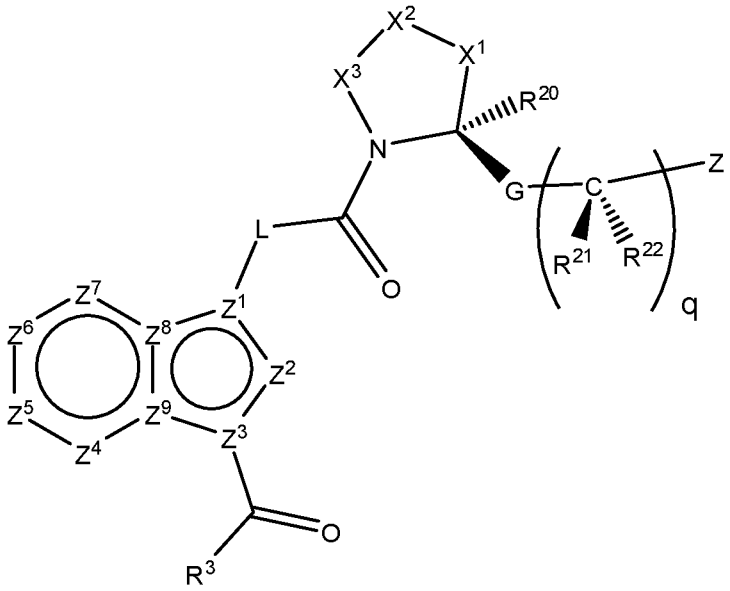
$CR^{21}R^{22}$, taken in combination, form a cyclopropane ring;

when q is 2, $CR^{21}R^{22}CR^{21}R^{22}$, taken in combination form a cis- or trans- cyclopropane ring;

Z is phenyl which is unsubstituted or substituted with 1, 2, or 3 residues selected from the group consisting of fluoro, chloro, bromo, methyl, trifluoromethyl, methoxy, trifluoromethoxy, $NR^{23}R^{24}$, tetrazole or CO_2H; or

Z is pyridyl or thienyl, each of which is unsubstituted or substituted with 1 or 2 substitutents selected from the group consisting of fluoro, chloro, bromo, methyl, trifluoromethyl, methoxy, or trifluoromethoxy.

In certain aspects, the compound of formula (I) is represented by the structure of formula (VI):



(VI).

In another embodiment, individual compounds according to the invention are those listed in the Examples section below. In certain aspects the compound is selected from the group consisting of:

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzylamide 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(pyridin-3-ylmethyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-5-{[(2-methoxy-ethyl)-methyl-amino]-methyl}-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide};

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(pyridin-4-ylmethyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(4-methyl-piperazin-1-yl)-benzylamide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-hydroxy-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(4-methyl-piperazin-1-ylmethyl)-benzylamide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-chloro-thiophen-2-ylmethyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-5-diethylamino-methyl-2-fluoro-benzyl-amide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((S)-2-hydroxy-1-phenyl-ethyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2,3-difluoro-benzylamide);

(2S,3S)-2-{[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-3-methyl-pentanoic acid tert-butyl ester;

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(4-methoxy-piperidin-1-yl)-benzylamide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-5-{[(2-dimethylamino-ethyl)-methyl-amino]-methyl}-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-5-morpholin-4-ylmethyl-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-5-morpholin-4-yl-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(4-methoxy-piperidin-1-ylmethyl)-benzylamide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{3-chloro-2-fluoro-5-[(2-methoxy-ethyl)-methyl-amino]-benzylamide};

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{3-chloro-5-[(2-dimethylamino-ethylamino)-methyl]-2-fluoro-benzylamide};

2-({[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-methyl)-benzoic acid;

2-({[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-3-carbonyl]-amino}-methyl)-benzoic acid;

(2S,3S)-2-{[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-3-methyl-pentanoic acid;

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-phenylamide;

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 2-benzylamide 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide) as a formate salt;

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-methyl-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-trifluoromethyl-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-fluoro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-cyano-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 2-(3-bromo-benzylamide) 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-hydroxy-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-methoxy-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-trifluoromethoxy-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-phenoxy-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 2-[(biphenyl-3-ylmethyl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide] as a formate salt;

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-pyrrol-1-yl-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-(5-chloro-thiophen-2-yl)-benzylamide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(4-methyl-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(4-chloro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(4-trifluoromethyl-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(4-trifluoromethoxy-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(4-hydroxy-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2-hydroxy-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2-fluoro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2-chloro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 2-[(biphenyl-2-ylmethyl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2,3-difluoro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(5-chloro-2-methoxy-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-4-methoxy-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(5-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-4-fluoro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-methyl-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(5-chloro-2-methyl-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-4-methyl-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3,5-dichloro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3,4-dichloro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2,6-difluoro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(naphthalen-2-ylmethyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(naphthalen-1-ylmethyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-methyl-thiazol-2-ylmethyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-chloro-thiophen-2-ylmethyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(4-methyl-pyridin-2-ylmethyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-phenyl)-ethyl]-amide} as a formate salt;

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(R)-1-(3-chloro-phenyl)-ethyl]-amide} as a formate salt;

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[1-(3,5-dichloro-phenyl)-2-hydroxy-ethyl]-amide};

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[1-(3-chloro-phenyl)-3-hydroxy-propyl]-amide};

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(1-phenyl-cyclopropyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 2-benzhydryl-amide 1-[(1-carbamoyl-1H-indol-3-yl)-amide] as a formate salt;

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-cyclohexylmethyl-amide;

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((1R,2S)-2-hydroxy-cyclohexylmethyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((1S,2S)-2-hydroxy-cyclohexylmethyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-cyclohexylamide;

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3-yl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(6-chloro-indan-1-yl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(6-chloro-chroman-4-yl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(phenethyl-amide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-hydroxy-2-phenyl-ethyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((1R,2S)-2-phenyl-cyclopropyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((R)-2-phenyl-propyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((S)-2-phenyl-propyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[2-(3-chloro-phenyl)-ethyl]-amide};

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1Hindol-3-yl)-amide] 2-{[2-(2-chloro-phenyl)-ethyl]-amide};

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1Hindol-3-yl)-amide] 2-{[2-(2-fluoro-phenyl)-ethyl]-amide};

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1Hindol-3-yl)-amide] 2-{[2-(3-fluoro-phenyl)-ethyl]-amide};

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[2-(3-chloro-5-fluoro-phenyl)-ethyl]-amide};

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-phenoxy-ethyl)-amide];

(2S,3S)-2-{[(2S,4S)-4-Amino-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-3-methyl-pentanoic acid methyl ester;

(S)-2-{[(2S,4S)-4-Amino-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-pentanoic acid methyl ester;

(R)-2-{[(2S,4S)-4-Amino-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-3-methyl-butyric acid methyl ester;

(S)-2-{[(2S,4S)-4-Amino-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-4-methyl-pentanoic acid methyl ester;

(S)-2-{[(2S,4S)-4-Amino-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-3-tert-butoxy-propionic acid methyl ester;

(S)-2-{[(2S,4S)-4-Amino-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-3-phenyl-propionic acid methyl ester;

(S)-{[(2S,4S)-4-Amino-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-phenyl-acetic acid methyl ester;

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((1S,2S)-1-carbamoyl-2-methyl-butyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-ethyl-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((1S,2S)-1-hydroxymethyl-2-methyl-butyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-isopropyl-phenyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 2-biphenyl-3-ylamide 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

3-{[(2S,4R)-2-(Benzenesulfonylamino-methyl)-4-fluoro-pyrrolidine-1-carbonyl]-amino}-indole-1-carboxylic acid amide;

3-({(2S,4R)-4-Fluoro-2-[(3-fluoro-benzenesulfonylamino)-methyl]-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide;

3-({(2S,4R)-4-Fluoro-2-[(3-chloro-benzenesulfonylamino)-methyl]-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide;

3-({(2S,4R)-4-Fluoro-2-[(3-bromo-benzenesulfonylamino)-methyl]-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide;

3-({(2S,4R)-4-Fluoro-2-[(3-trifluoromethoxy-benzenesulfonylamino)-methyl]-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide;

3-({(2S,4R)-2-[(3-Chloro-2-fluoro-benzenesulfonylamino)-methyl]-4-fluoro-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide;

3-({(2S,4R)-2-[(5-Chloro-thiophene-2-sulfonylamino)-methyl]-4-fluoro-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide;

3-({(S)-2-[(3-Chloro-benzenesulfonylamino)-methyl]-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide;

3-{[(2S,4R)-4-Fluoro-2-(phenylacetylamino-methyl)-pyrrolidine-1-carbonyl]-amino}-indole-1-carboxylic acid amide;

[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidin-2-ylmethyl]-carbamic acid phenyl ester;

[(1R,3S,5R)-2-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-3-ylmethyl]-carbamic acid 3-chloro-2-fluoro-phenyl ester;

3-({(2S,4R)-2-[(3-Chloro-2-fluoro-benzylamino)-methyl]-4-fluoro-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide;

3-({(S)-2-[(3-Trifluoromethoxy-phenylamino)-methyl]-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide;

1-{2-Oxo-2-[(S)-2-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidin-1-yl]-ethyl}-1H-indole-3-carboxylic acid amide;

(S)-1-[2-(1-Acetyl-1H-indol-3-yl)-acetyl]-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide;

(2S,4R)-1-[2-(1-Acetyl-1H-indol-3-yl)-2-amino-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(3-carbamoyl-indolizin-1-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(3-carbamoyl-indolizin-1-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-indolizin-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(S)-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4S)-4-Cyano-pyrrolidine-1,2 dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,3R)-3-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-6-yl)-acetic acid tert-butyl ester;

(2S,4S)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-acetyl-1H-indol-3-yl)-amide] 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2hydroxy-ethyl]-amide};

(1R,3S,5R)-2-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-(3-chloro-2-fluoro-benzylamide) 2-[(1-methylcarbamoyl-1H-indol-3-yl)-amide];

(2S,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-{[1-carbamoyl-5-(2-methoxy-ethoxy)-1H-indol-3-yl]-amide} 2-(3-chloro-2-fluoro-benzylamide);

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid methyl ester;

(1S,3S,5S)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-trifluoromethoxy-phenyl)-amide];

(1S,2S,5R)-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

2-Aza-bicyclo[2.1.1]hexane-1,2-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 1-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-(3-bromo-2-fluoro-benzylamide) 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,5R)-5-(Acetylamino-methyl)-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(R)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(1S,2S,5R)-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-fluoro-3-trifluoromethoxy-phenyl)-amide];

3-Chloro-5-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-benzoic acid methyl ester;

3-({[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-methyl)-5-chloro-4-fluoro-benzoic acid;

(S)-2,5-Dihydro-pyrrole-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(1R,2S,5S)-6-Oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Trifluoromethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(3-bromo-phenyl)-amide] 2-[(1-carbamoyl-1H-indol-3-yl)-amide];

(1S,5R)-2-Aza-bicyclo[3.1.0]hexane-1,2-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 1-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-[(3-bromo-phenyl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide] ;

(R)-2,2-Dimethyl-thiazolidine-3,4-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 4-[(3-trifluoromethoxy-phenyl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(4'-cyano-biphenyl-3-yl)-amide];

3-Bromo-5-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-benzoic acid methyl ester;

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-5-(2-dimethylamino-ethylcarba-moyl)-2-fluoro-benzylamide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(5-chloro-thiophen-2-ylmethyl)-amide];

2-Bromo-4-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-benzoic acid methyl ester;

(2S,4R)-4-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(6-ethyl-pyridin-2-yl)-amide];

3-Bromo-5-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-benzoic acid;

(S)-Pyrrolidine-1,2-dicarboxylic acid 2-[(4-tert-butyl-thiazol-2-yl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(R)-Thiazolidine-3,4-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 4-[(3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-methoxy-ethoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(6-ethyl-pyridin-2-yl)-amide];

(2S,4S)-4-Hydroxy-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-bromo-4-methyl-pyridin-3-yl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(1R,2S,5S)-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-[(5-bromo-2-methyl-pyridin-3-yl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2,3-difluoro-benzylamide);

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(5-bromo-pyridin-3-yl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-fluoro-pyridin-2-yl)-amide];

(1R,3S,5R)-2-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(2-fluoro-benzylamide);

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(2-fluoro-3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-chloro-2-fluoro-phenyl)-amide] ;

(2S,3R)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide) ;

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,5R)-5-Azidomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(S)-5-Aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-[(1-carbamoyl-1H-indol-3-yl)-amide] 6-(3-chloro-benzylamide);

(2S,4R)-4-Fluoro-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-benzylamide) ;

(1R,3S,5S)-5-Methoxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-fluoro-pyridin-4-yl)-amide];

(2S,3R)-3-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(S)-Piperidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4S)-4-Cyano-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-fluoro-3-trifluoromethoxy-phenyl)-amide];

(2R,3S,4R)-4-Dimethylamino-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2R,3R)-3-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(S)-2-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-chloro-pyridin-3-yl)-amide] ;

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-bromo-pyridin-3-yl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(2,3-difluoro-benzylamide);

(2S,4R)-4-Hydroxy-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1S,2S,5R)-6-Oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

3-Bromo-5-{[(S)-3-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-thiazolidine-2-carbonyl]-amino}-benzoic acid methyl ester;

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-methyl-5-phenyl-2H-pyrazol-3-yl)-amide];

(3S,5S)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-5-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrrolidine-3-carboxylic acid methyl ester;

4,5-Dihydro-pyrazole-1,5-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 5-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Hydroxy-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide};

(2S,3S,4S)-4-Fluoro-3-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,3S,4S)-3-Acetylamino-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1S,2S,5R)-3-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide};

(2R,3S)-3-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-4-morpholin-4-ylmethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1R,2S,5S)-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2R,3S,4R)-4-Acetylamino-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1R,2S,5S)-3-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide};

(2S,3R)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1S,3S,5R)-5-Methoxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-fluoro-pyridin-3-ylmethyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-6-methoxy-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[(S)-1-(3-bromo-phenyl)-2-hydroxy-ethyl]-amide} 2-[(1-carbamoyl-1H-indol-3-yl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(2-fluoro-3-trifluoromethyl-phenyl)-amide];

3-{[(S)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-benzoic acid methyl ester;

(S)-Piperidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-(Acetylamino-methyl)-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2-fluoro-3-trifluoromethyl-benzylamide);

(1R,3S,5R)-2-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-{[(R)-1-(3-chloro-2-fluoro-phenyl)-3-hydroxy-propyl]-amide};

(2S,4S)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2,3-difluoro-4-methoxy-benzylamide);

(1R,3S,5R)-2Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)amide] 3-[(pyridin-3-ylmethyl)-amide];

(2S,3S)-3-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(5-chloro-pyridin-3-ylmethyl)-amide];

(2S,4R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(R)-1-(3-chloro-2-fluoro-phenyl)-3-hydroxy-propyl]-amide};

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-fluoro-pyridin-4-ylmethyl)-amide];

(1R,2S,5S)-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-methoxy-ethyl]-amide};

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-fluoro-2-trifluoromethyl-pyridin-4-ylmethyl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-sulfamoyl-phenyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-difluoromethoxy-phenyl)-amide];

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2,3-difluoro-5-methoxy-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-methoxy-ethyl]-amide};

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-chloro-pyridin-3-ylmethyl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(6-ethyl-pyridin-2-yl)-amide];

(2S,4R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide};

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-5-methylcarbamoyl-benzylamide);

(2S,4S)-4-Fluoro-4-fluoromethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-fluoro-pyridin-2-ylmethyl)-amide];

(2S,4S)-4-Fluoro-4-morpholin-4-ylmethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

3-({[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-methyl)-5-chloro-4-fluoro-benzoic acid methyl ester;

(1S,2S,5R)-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-methoxy-ethyl]-amide};

{[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-(3-chloro-phenyl)-acetic acid;

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(5-chloro-pyridin-3-yl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-dimethylamino-ethyl]-amide};

(2S,4S)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(morpholine-4-carbonyl)-benzylamide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-methoxy-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-5-diethylamino-2-fluoro-benzylamide);

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide};

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-chloro-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(3-methoxy-azetidine-1-carbonyl)-benzylamide];

(2S,4R)-4-Cyano-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,3S)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-benzylamide 2-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,3R)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-chloro-thiophen-2-ylmethyl)-amide];

(2S,4S)-4-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(2-fluoro-3-trifluoromethyl-benzylamide);

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2,3-difluoro-6-methoxy-benzylamide);

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-chloro-thiazol-5-ylmethyl)-amide];

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-5-fluoro-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5S)-5-Hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-(3-chloro-2-fluoro-benzylamide) 2-[(1-methylcarbamoyl-1H-indol-3-yl)-amide];

(S)-4-Methylene-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(5-allyloxy-1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-6-methyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-methoxy-ethyl]-amide} 2-[(1-methylcarbamoyl-1H-indol-3-yl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

3-Bromo-5-{[(1R,3S,5R)-2-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-3-carbonyl]-amino}-benzoic acid methyl ester;

(2S,5R)-5-Phenyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide;

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-fluoro-3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5S)-5-Hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-acetyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-trifluoromethoxy-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-6-yloxy)-acetic acid methyl ester;

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-5-dimethylcarbamoyl-2-fluoro-benzylamide);

2-Bromo-4-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-benzoic acid;

(S)-Pyrrolidine-1,2-dicarboxylic acid 2-[(5-tert-butyl-2-methyl-2H-pyrazol-3-yl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(6-allyloxy-1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-acetyl-1H-indol-3-yl)-amide] 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-dimethylamino-ethyl]-amide};

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-methylcarbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,3R)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-chloro-thiazol-5-ylmethyl)-amide];

(1R,3S,5S)-5-Methoxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-(3-chloro-2-fluoro-benzylamide) 2-[(1-methylcarbamoyl-1H-indol-3-yl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-isopropyl-phenyl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(6-bromo-1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide}2-[(1-methylcarbamoyl-1H-indol-3-yl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-6-ethyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-dimethylamino-ethyl]-amide} 2-[(1-methylcarbamoyl-1H-indol-3-yl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-6-trifluoromethyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-6-chloro-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-5-methoxy-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-chloro-thiophen-2-ylmethyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-5-fluoro-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(2-chloro-thiazol-5-ylmethyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-phenyl)-2,2,2-trifluoro-ethyl]-amide};

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-6-fluoro-1H-indol-3-yl)-amide] 3-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-5-methoxy-1H-indol-3-yl)-amide] 2-[(2-fluoro-3-trifluoromethoxy-phenyl)-amide];

(S)-Azetidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-5-methoxy-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(S)-4,4-Difluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(S)-5,5-Dimethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-{[1-carbamoyl-5-(2-methoxy-ethoxy)-1H-indol-3-yl]-amide} 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-fluoro-4-methyl-pyridin-2-ylmethyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-trifluoromethyl-pyridin-3-ylmethyl)-amide];

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yl)-acetic acid ethyl ester;

(1S,5R)-2-Aza-bicyclo[3.1.0]hexane-1,2-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 1-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-6-difluoromethoxy-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-methoxy-pyridin-4-yl)-amide];

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-chloro-pyridin-3-yl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(6-allyloxy-1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(6-benzyloxy-1-carbamoyl-1H-indol-3-yl)-amide]2-[(3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-dimethylamino-ethyl]-amide};

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-6-yl)-acetic acid ethyl ester;

(2S,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-[(2-tert-butyl-pyridin-4-yl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(1-Carbamoyl-3-{[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidine-1-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid methyl ester;

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(R)-1-(3-chloro-phenyl)-2,2,2-trifluoro-ethyl]-amide};

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-{[(S)-1-(3-chloro-phenyl)-2-hydroxy-ethyl]-amide};

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-bromo-pyridin-3-yl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(4-methyl-piperazine-1-carbonyl)-benzylamide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-fluoro-pyridin-4-yl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-carbamoyl-phenyl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-methanesulfonyl-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(6-chloro-chroman-4-yl)-amide] (mixture of 2 diastereoisomers);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-fluoro-pyridin-2-yl)-amide];

(2S,4S)-4-Dimethylaminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{3-chloro-5-[(2-dimethylamino-ethyl)-methyl-amino]-2-fluoro-benzylamide};

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(3-tert-butyl-phenyl)-amide] 2-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,4S)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(S)-4,4-Difluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

3-Bromo-5-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-4-fluoro-benzoic acid ethyl ester ;

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-trifluoromethoxy-phenyl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(5-allyloxy-1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,5R)-5-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,5S)-5-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,5R)-5-Ethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromthoxy-phenyl)-amide];

3-Chloro-5-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-benzoic acid;

3-Bromo-5-{[(1R,3S,5R)-2-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-3-carbonyl]-amino}-benzoic acid;

3-Bromo-5-{[(S)-3-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-thiazolidine-2-carbonyl]-amino}-benzoic acid;

3-Bromo-5-{[(1R,3S,5R)-2-(1-carbamoyl-5-methoxy-1H-indol-3-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-3-carbonyl]-amino}-benzoic acid;

3-Bromo-5-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-4-fluoro-benzoic acid;

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[3-bromo-5-(1H-tetrazol-5-yl)-phenyl]-amide} 2-[(1-carbamoyl-1H-indol-3-yl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[3-bromo-5-(1-tert-butyl-1H-tetrazol-5-yl)-phenyl]-amide} 2-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(1H-tetrazol-5-yl)-benzylamide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-[5-(1-tert-butyl-1H-tetrazol-5-yl)-3-chloro-2-fluoro-benzylamide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2R,3S)-3-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide);

(2R,3R)-3-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide);

(2S,5R)-5-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,5R)-5-Ethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(3S,5S)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-5-(3-chloro-2,6-difluoro-benzylcarbamoyl)-pyrrolidine-3-carboxylic acid methyl ester;

(3S,5S)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-5-(3-chloro-2,6-difluoro-benzylcarbamoyl)-pyrrolidine-3-carboxylic acid;

(2S,4S)-4-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 2-(3-bromo-2-fluoro-benzylamide) 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,4S)-4-Fluoro-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1S,3S,5R)-5-Hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5S)-5-Hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Difluoromethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,5R)-5-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

4,5-Dihydro-pyrazole-1,5-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 5-(3-chloro-benzylamide);

(S)-4,5-Dihydro-pyrazole-1,5-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 5-(3-chloro-2-fluoro-benzylamide);

(R)-4,5-Dihydro-pyrazole-1,5-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 5-(3-chloro-2-fluoro-benzylamide);

(2S,3R)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(R)-1-(3-chloro-2-fluoro-phenyl)-ethyl]-amide};

(2S,3R)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-ethyl]-amide};

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-{[1-(2-hydroxy-acetyl)-1H-indol-3-yl]-amide} 2-[(3-trifluoromethoxy-phenyl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-6-cyano-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-6-difluoromethoxy-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-6-hydroxy-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-5-hydroxy-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-5-hydroxy-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-5-hydroxy-1H-indol-3-yl)-amide] 3-(2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-5-cyanomethoxy-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid;

(1-Carbamoyl-3-{[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidine-1-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid;

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-6-yloxy)-acetic acid;

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yl)-acetic acid;

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-6-yl)-acetic acid;

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-hydroxy-ethoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide);

(S)-Thiazolidine-2,3-dicarboxylic acid 3-{[1-carbamoyl-5-(2-hydroxy-ethoxy)-1H-indol-3-yl]-amide} 2-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-hydroxy-ethoxy)-1H-indol-3-yl]-amide} 3-[(3-trifluoromethoxy-phenyl)-amide];

(1S,2S,5R)-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[1-carbamoyl-5-(2-hydroxy-ethoxy)-1H-indol-3-yl]-amide} 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-{[1-carbamoyl-5-(2-hydroxy-ethoxy)-1H-indol-3-yl]-amide} 2-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-6-(2-hydroxy-ethyl)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-hydroxy-ethyl)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-hydroxy-2-methyl-propoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-dimethylamino-ethoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-pyrrolidin-1-yl-ethoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-imidazol-1-yl-ethoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide);

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid tert-butyl ester;

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid;

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-6-hydroxy-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-6-hydroxy-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-6-yloxy)-acetic acid methyl ester;

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-6-(2-hydroxy-ethoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,3S,4R)-4-Amino-3-methoxy-pyrrolidine-1,2-dicarboxylicacid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(6-benzyloxy-1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(S)-Piperazine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide);

(S)-Pyrrolidine-1,2-dicarboxylic acid 2-[(4'-aminomethyl-biphenyl-3-yl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 2-[(4'-aminomethyl-2'-fluoro-biphenyl-3-yl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,5R)-5-Aminomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Aminomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4S)-4-Aminomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Aminomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Dimethylaminomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Aminomethyl-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Fluoro-4-formylaminomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2,6-difluoro-benzylamide);

(2S,4S)-4-Aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-{[(S)-1-(3-bromo-phenyl)-2-fluoro-ethyl]-amide} 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,4S)-4-Aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,3S,4S)-3-Amino-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,3R,4S)-4-Amino-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,3R)-3-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,3R)-3-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,3R)-3-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2,2,2-trifluoro-ethyl]-amide};

(2S,3S)-3-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,3S)-3-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide);

(2S,3R)-3-Acetylamino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,3R)-3-(2-Methoxy-ethylamino)-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Fluoro-4-methylaminomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Methylamino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-(2-Methoxy-ethylamino)-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Dimethylamino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(S)-4,4-Dimethoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,3S,4R)-4-Amino-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2R,3S,4R)-4-Amino-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,3S,4S)-3-Amino-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluorobenzylamide);

3-{2-[(S)-5-(3-Chloro-2-fluoro-benzylcarbamoyl)-pyrazolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[(R)-5-(3-Chloro-2-fluoro-benzylcarbamoyl)-pyrazolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

Pyrazolidine-1,5-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 5-(3-chloro-benzylamide);

(3S,5S)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-5-(2-fluoro-3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-3-carboxylic acid methyl ester;

(2S,4S)-4-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2,6-difluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-[(3-bromo-5-carbamoyl-phenyl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(2-methoxy-ethylcarbamoyl)-benzylamide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-isopropyl-isoxazol-5-yl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-phenyl-isoxazol-5-yl)-amide];

3-{2-[(S)-2-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[(2S,4R)-4-Fluoro-2-(2-fluoro-3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-(2-{(1S,2S,5R)-2-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-hydroxy-ethylcarbamoyl]-3-azabicyclo[3.1.0]hex-3-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide;

3-{2-[(2S,3R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-3-hydroxy-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[(2S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-dimethylaminomethyl-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-(2-{(2S,4R)-2-[(R)-1-(3-Chloro-2-fluoro-phenyl)-3-hydroxy-propylcarbamoyl]-4-fluoro-4-methyl-pyrrolidin-1-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide;

3-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-(2-{(1R,3S,5R)-3-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-hydroxy-ethyl carbamoyl]-2-aza-bicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide;

3-{2-[(S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-thiazolidin-3-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-hydroxymethyl-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-methoxy-indole-1-carboxylic acid amide;

3-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-(2-hydroxy-ethoxy)-indole-1-carboxylic acid amide;

3-{2-[(1R,3S,5S)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-5-methoxymethyl-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

5-(2-Hydroxy-ethoxy)-3-{2-oxo-2-[(1R,3S,5R)-3-(3-trifluoromethoxy-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-ethyl}-indole-1-carboxylic acid amide;

3-(2-{(1R,3S,5R)-3-[(5-Chloro-thiophen-2-ylmethyl)-carbamoyl]-2-aza-bicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide;

3-(2-{(1R,3S,5R)-3-[(R)-1-(3-Chloro-2-fluoro-phenyl)-3-hydroxy-propylcarbamoyl]-2-azabicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide;

3-(2-{(1R,3S,5R)-3-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-dimethylamino-ethylcarbamoyl]-2-aza-bicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide;

3-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidin-1-yl]-2-oxo-ethyl}-5-(2-hydroxy-ethoxy)-indole-1-carboxylic acid amide;

3-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-5-fluoro-indole-1-carboxylic acid amide;

3-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-2-methyl-indole-1-carboxylic acid amide;

3-{2-[(S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-thiazolidin-3-yl]-2-oxo-ethyl}-5-(2-hydroxy-ethoxy)-indole-1-carboxylic acid amide;

3-(2-{(1R,2S,5S)-2-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-hydroxy-ethylcarbamoyl]-3-azabicyclo[3.1.0]hex-3-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide;

3-(2-{(1R,3S,5R)-3-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-methoxy-ethylcarbamoyl]-2-aza-bicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide;

3-{2-[(1S,2S,5R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-3-aza-bicyclo[3.1.0]hex-3-yl]-2-oxo-ethyl}-5-(2-hydroxy-ethoxy)-indole-1-carboxylic acid amide;

3-{2-[(2S,3S,4S)-3-Amino-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[(1R,3S,5S)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[(2S,4S)-4-Amino-2-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[5-(3-Chloro-benzylcarbamoyl)-pyrazolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[(2S,4S)-4-Aminomethyl-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[(2S,4S)-4-Aminomethyl-2-(3-chloro-2,6-difluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-(2-dimethylamino-ethoxy)-indole-1-carboxylic acid amide;

(1-Carbamoyl-3-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indol-6-yl)-acetic acid;

3-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-6-(2-hydroxy-ethyl)-indole-1-carboxylic acid amide;

1-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amid;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-7-methoxy-1H-indole-3-carboxylic acid amide;

(S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-piperidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

6-Bromo-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-5-fluoro-1H-indole-3-carboxylic acid amide;

3-[({(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carbonyl}-amino)-methyl]-5-chloro-4-fluoro-benzoic acid methyl ester;

1-{2-[(2S,4R)-2-(3-Bromo-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide;

(2S,4R)-1-[2-(3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (5-chloro-thiophen-2-ylmethyl)-amide;

(2S,3S,4S)-1-[2-(3-Acetyl-5-methoxy-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-phenylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide;

(2S,3S,4S)-1-[2-(3-Acetyl-6-methoxy-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

5-Chloro-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide ;

7-Chloro-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide ;

(1R,3S,5S)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-5-methoxymethyl-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

6-Chloro-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-5,6-difluoro-1H-indole-3-carboxylic acid amide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-trifluoromethoxy-1H-indole-3-carboxylic acid amide;

(1R,3S,5R)-2-[2-(3-Acetyl-5-methoxy-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-{2-[3-(2,2,2-Trifluoro-acetyl)-indol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-5-methoxy-1H-indole-3-carboxylic acid amide;

(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-5-cyano-2-fluoro-benzylamide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-methoxy-1H-indole-3-carboxylic acid amide;

(2S,4R)-1-[2-(3-Acetyl-6-methoxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(S)-1-[2-(3-Acetyl-5-methoxy-indol-1-yl)-acetyl]-piperidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-pyrrolo[3,2-c]pyridin-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

5-Benzyloxy-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide;

(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(R)-1-(3-chloro-2-fluoro-phenyl)-3-hydroxy-propyl]-amide;

(2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,2S,5S)-3-[2-(3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-5-benzyloxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-6-trifluoromethoxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,4S)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[2.2.1]heptane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(S)-3-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-thiazolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid (2-fluoro-3-trifluoromethoxy-phenyl)-amide;

(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [3-bromo-5-(2H-tetrazol-5-yl)-phenyl]-amide;

(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-bromo-2-fluoro-benzylamide;

1-{2-[(2S,4R)-4-Fluoro-2-(2-fluoro-3-trifluoromethyl-phenylcarbamoyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide;

(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid methylamide ;

(2S,3S,4S)-1-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-5-(1H-tetrazol-5-yl)-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-dimethylamino-ethyl]-amide;

3-[({(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carbonyl}-amino)-methyl]-5-chloro-4-fluoro-benzoic acid methyl ester;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[3,2-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-5-(1H-tetrazol-5-yl)-benzylamide;

3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-6-carboxylic acid methyl ester;

(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-5-cyano-2-fluoro-benzylamide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-difluoromethoxy-1H-indole-3-carboxylic acid amide;

6-Benzyloxy-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide ;

(2S,4R)-1-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-6-chloro-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-6-cyano-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-methoxy-ethyl]-amide;

(2S,4R)-1-[2-(3-Acetyl-6-benzyloxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-methoxy-ethyl]-amide;

(1R,3S,5R)-2-[2-(3-Acetyl-6-benzyloxy-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,2S,5S)-3-[2-(3-Acetyl-pyrrolo[3,2-c]pyridin-1-yl)-acetyl]-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,2S,5S)-3-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-5-trifluoromethoxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-5-carboxylic acid methyl ester;

3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluorobenzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-7-carboxylic acid methyl ester;

3-Acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-6-carboxylic acid methyl ester;

(2S,4R)-4-Fluoro-1-{2-[3-(2-hydroxy-acetyl)-indol-1-yl]-acetyl}-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1S,2S,5R)-3-[2-(3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indol-6-yl)-acetic acid methyl ester;

(2S,4R)-4-Fluoro-1-{2-[3-(2,2,2-trifluoro-acetyl)-indol-1-yl]-acetyl}-pyrrolidine-2-carboxylic acid 3-bromo-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

3-Acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-6-carboxylic acid methyl ester;

(3-Acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indol-6-yl)-acetic acid methyl ester;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluorobenzylamide;

(2S,4R)-4-Fluoro-1-{2-[3-(2-hydroxy-acetyl)-indol-1-yl]-acetyl}-pyrrolidine-2-carboxylic acid [(S)-1-(3-bromo-phenyl)-2-fluoro-ethyl]-amide;

(2S,4R)-1-[2-(3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[3,2-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-4-Fluoro-4-methyl-1-{2-[3-(2,2,2-trifluoro-acetyl)-indol-1-yl]-acetyl}-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2R,3S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-dimethylamino-3-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-{2-[3-(2-Hydroxy-acetyl)-indol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(R)-1-(3-chloro-2-fluoro-phenyl)-3-hydroxy-propyl]-amide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (3-trifluoromethoxy-phenyl)-amide;

(S)-1-[2-(3-Formyl-indol-1-yl)-acetyl]-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide;

(2S,4R)-4-Fluoro-1-[2-(3-formyl-5-methoxy-indol-1-yl)-acetyl]-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-4-Fluoro-1-{2-[3-(2,2,2-trifluoro-acetyl)-indol-1-yl]-acetyl}-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (2-fluoro-3-trifluoromethoxy-phenyl)-amide;

(2S,4R)-4-Fluoro-1-{2-[3-(2-hydroxy-acetyl)-indol-1-yl]-acetyl}-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-4-Fluoro-1-{2-[3-(2-hydroxy-acetyl)-indol-1-yl]-acetyl}-pyrrolidine-2-carboxylic acid 3-bromo-2-fluoro-benzylamide;

(2S,4R)-4-Fluoro-1-{2-[3-(2-methoxy-acetyl)-indol-1-yl]-acetyl}-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-hydroxymethyl-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide;

1-{2-[(S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-thiazolidin-3-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide ;

(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-methoxy-ethyl]-amide;

(2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-3-ethoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid [(R)-1-(3-chloro-2-fluoro-phenyl)-ethyl]-amide;

(2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-ethyl]-amide;

(2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid [1-(3-chloro-phenyl)-cyclopropyl]-amide;

(2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid [1-(4-chloro-phenyl)-cyclopropyl]-amide;

1-{2-[(2S,3S,4S)-3-Amino-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide;

(2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-3-amino-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2R,3S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-amino-3-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-5-hydroxy-1H-indole-3-carboxylic acid amide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-hydroxy-1H-indole-3-carboxylic acid amide;

(2S,4R)-1-[2-(3-Acetyl-5-hydroxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-5-hydroxy-indol-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-5-hydroxy-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-6-hydroxy-indol-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-6-hydroxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-6-hydroxy-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-(1H-tetrazol-5-ylmethoxy)-1H-indole-3-carboxylic acid amide;

(2S,4R)-1-{2-[3-Acetyl-6-(1H-tetrazol-5-ylmethoxy)-indol-1-yl]-acetyl}-4-fluoro-yrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-5-methoxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-{2-[3-Acetyl-5-(pyridin-2-ylmethoxy)-indol-1-yl]-acetyl}-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-{2-[3-Acetyl-5-(pyrimidin-2-ylmethoxy)-indol-1-yl]-acetyl}-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-(2-methoxy-ethoxy)-1H-indole-3-carboxylic acid amide;

(3-Carbamoyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indol-6-yloxy)-acetic acid methyl ester;

(3-Carbamoyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indol-6-yloxy)-acetic acid;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-(2-hydroxy-ethoxy)-1H-indole-3-carboxylic acid amide;

(3-Acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indol-6-yl)-acetic acid;

(3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indol-6-yl)-acetic acid;

3-Acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-6-carboxylic acid;

3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-6-carboxylic acid;

3-Acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-6-carboxylic acid;

(2S,3S,4S)-4-Fluoro-3-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-7-carboxylic acid;

4-(3-Acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indol-6-yloxymethyl)-benzoic acid;

3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-5-carboxylic acid;

(2S,4R)-1-[2-(3-Acetyl-6-hydroxymethyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

3-[({(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carbonyl}-amino)-methyl]-5-chloro-4-fluoro-benzoic acid;

3-[({(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carbonyl}-amino)-methyl]-5-chloro-4-fluoro-benzoic acid;

(2S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-aminomethyl-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-methylamino-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-(2-methoxy-ethylamino)-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5S)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5S)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1S,2S,5R)-3-[2-(3-Acetyl-indol-1-yl)-acetyl]-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2hydroxy-ethyl]-amide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide;

(2S,4R)-1-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide;

(1R,3S,5R)-2-{2-[3-Acetyl-5-(N,N-dimethyl-carbamimidoyl)-indol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-{2-[3-Acetyl-6-(N,N-dimethyl-carbamimidoyl)-indol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-{2-[3-Acetyl-6-(1H-tetrazol-5-yl)-indol-1-yl]-acetyl}-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-{2-[3-Acetyl-6-(1H-tetrazol-5-yl)-indol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,3S,4S)-1-[2-(3-Acetyl-*d3*-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-*d3*-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(1-Acetyl-imidazo[1,5-a]pyridin-3-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide; and

{(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hex-3-ylmethyl}-carbamic acid 3-chloro-2-fluoro-phenyl ester.

In another embodiment, pharmaceutical compositions are provided which comprise one or more pharmaceutically acceptable carriers and a therapeutically effective amount of a compound of any one of formulae (I), (Ia), (II), (III), (IV), (V), (VI), (VII), or a subformulae thereof.

In another embodiment, combinations, in particular pharmaceutical combinations, are provided which comprise a therapeutically effective amount of the compound of any one of formulae (I), (Ia), (II), (III), (IV), (V), (VI), (VII), or a subformulae thereof.

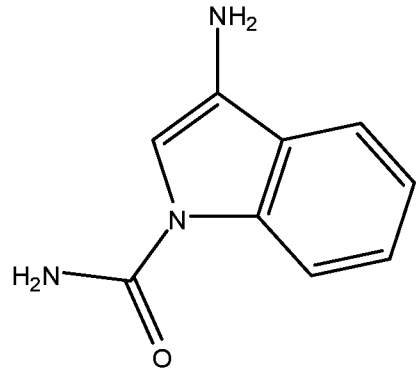
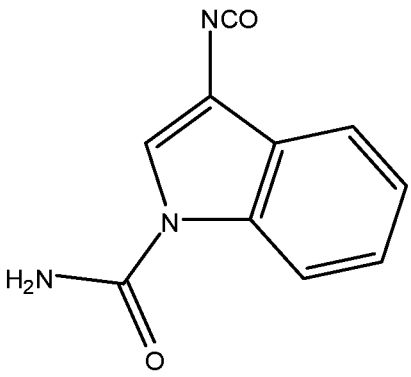
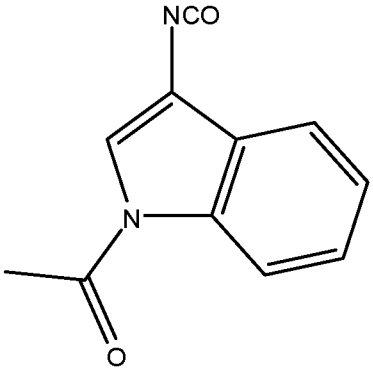
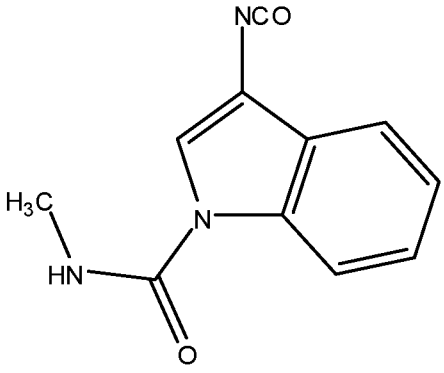
In another embodiment, methods of modulating complement alternative pathway activity in a subject are provided which methods comprise administering to the subject a therapeutically effective amount of the compound of any one of formulae (I), (Ia), (II), (III), (IV), (V), (VI), (VII), or a subformulae thereof.

In yet other embodiments, methods of treating a disorder or a disease in a subject mediated by complement activation, in particular mediated by activation of the complement alternative pathway, are provided, which methods comprise administering to the subject a therapeutically effective amount of the compound of any one of formulae (I), (Ia), (II), (III), (IV), (V), (VI), (VII), or a subformulae thereof.

In another embodiment, methods of treating age related macular degeneration in a subject are provided which methods comprise administering to the subject a therapeutically effective amount of the compound of any one of formulae (I), (Ia), (II), (III), (IV), (V), (VI), (VII), or a subformulae thereof.

In another aspect, the invention provides for the use of compounds of any one of formulae (I), (Ia), (II), (III), (IV), (V), (VI), (VII), or a subformulae thereof for use in the preparation of a medicament and more particularly for use in the manufacture of a medicament for the treatment of a disorder or disease in a subject mediated by complement activation or activation of the complement alternative pathway. In certain other aspects, the invention provides for the use of a compound according to any one of formulae (I), (Ia), (II), (III), (IV), (V), (VI), (VII), or a subformulae thereof in the treatment of age-related macular degeneration.

In another embodiment, compounds which are synthetic intermediates in the preparation of compounds according to any one of formulae (I), (Ia), (II), (III), (IV), (V), (VI), (VII), or a subformulae thereof are provided. In particular, compounds provided herein as synthetic intermediates include the compounds of the formulae:

	
3-amino-1H-indole-1-carboxamide	3-isocyanato-1H-indole-1-carboxamide
	
1-(3-isocyanato-1H-indol-1-yl)ethanone	3-isocyanato-N-methyl-1H-indole-1-carboxamide

In one embodiment, the invention provides a combination, in particular a pharmaceutical combination, comprising a therapeutically effective amount of the compound according to the definition of formula (I), (Ia), (II), (VII) or subformulae thereof or any one of the specifically disclosed compounds of the invention and one or more therapeutically active agents (preferably selected from those listed *infra*).

For purposes of interpreting this specification, the following definitions will apply and whenever appropriate, terms used in the singular will also include the plural and vice versa.

As used herein, the term "alkyl" refers to a fully saturated branched or unbranched hydrocarbon moiety having up to 20 carbon atoms. Unless otherwise provided, alkyl refers to hydrocarbon moieties having 1 to 16 carbon atoms, 1 to 10 carbon atoms, 1 to 7 carbon atoms, or 1 to 4 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, 3-methylhexyl, 2,2- dimethylpentyl, 2,3-dimethylpentyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl and the like.

As used herein, the term "alkylene" refers to divalent alkyl group as defined herein above having 1 to 20 carbon atoms. It comprises 1 to 20 carbon atoms, Unless otherwise provided, alkylene refers to moieties having 1 to 16 carbon atoms, 1 to 10 carbon atoms, 1 to 7 carbon atoms, or 1 to 4 carbon atoms. Representative examples of alkylene include, but are

not limited to, methylene, ethylene, *n*-propylene, *iso*-propylene, *n*-butylene, *sec*-butylene, *iso*-butylene, *tert*-butylene, *n*-pentylene, isopentylene, neopentylene, *n*-hexylene, 3-methylhexylene, 2,2- dimethylpentylene, 2,3-dimethylpentylene, *n*-heptylene, *n*-octylene, *n*-nonylene, *n*-decylene and the like.

As used herein, the term “haloalkyl” refers to an alkyl as defined herein, that is substituted by one or more halo groups as defined herein. The haloalkyl can be monohaloalkyl, dihaloalkyl or polyhaloalkyl including perhaloalkyl. A monohaloalkyl can have one iodo, bromo, chloro or fluoro within the alkyl group. Dihaloalky and polyhaloalkyl groups can have two or more of the same halo atoms or a combination of different halo groups within the alkyl. Typically the polyhaloalkyl contains up to 12, or 10, or 8, or 6, or 4, or 3, or 2 halo groups. Non-limiting examples of haloalkyl include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. A perhaloalkyl refers to an alkyl having all hydrogen atoms replaced with halo atoms.

The term "aryl" refers to an aromatic hydrocarbon group having 6-20 carbon atoms in the ring portion. Typically, aryl is monocyclic, bicyclic or tricyclic aryl having 6-20 carbon atoms.

Furthermore, the term "aryl” as used herein, refers to an aromatic substituent which can be a single aromatic ring, or multiple aromatic rings that are fused together.

Non-limiting examples include phenyl, naphthyl or tetrahydronaphthyl, each of which may optionally be substituted by 1-4 substituents, such as alkyl, trifluoromethyl, cycloalkyl, halogen, hydroxy, alkoxy, acyl, alkyl-C(O)-O-, aryl-O-, heteroaryl-O-, amino, thiol, alkyl-S-, aryl-S-, nitro, cyano, carboxy, alkyl-O-C(O)-, carbamoyl, alkyl-S(O)-, sulfonyl, sulfonamido, phenyl, and heterocyclyl.

As used herein, the term “alkoxy” refers to alkyl-O-, wherein alkyl is defined herein above. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, *tert*-butoxy, pentyloxy, hexyloxy, cyclopropyloxy-, cyclohexyloxy- and the like. Typically, alkoxy groups have about 1-7, more preferably about 1-4 carbons.

As used herein, the term “heterocyclyl” or “heterocyclo” refers to a saturated or unsaturated non-aromatic ring or ring system, *e.g.*, which is a 4-, 5-, 6-, or 7-membered monocyclic, 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic or 10-, 11-, 12-, 13-, 14- or 15-membered tricyclic ring system and contains at least one heteroatom selected from O, S and N, where the N and S can also optionally be oxidized to various oxidation states. The heterocyclic group can be attached at a heteroatom or a carbon atom. The heterocyclyl can include fused or bridged rings as well as spirocyclic rings. Examples of heterocycles include tetrahydrofuran (THF), dihydrofuran, 1, 4-dioxane, morpholine, 1,4-dithiane, piperazine,

piperidine, 1,3-dioxolane, imidazolidine, imidazoline, pyrroline, pyrrolidine, tetrahydropyran, dihydropyran, oxathiolane, dithiolane, 1,3-dioxane, 1,3-dithiane, oxathiane, thiomorpholine, and the like.

The term “heterocyclyl” further refers to heterocyclic groups as defined herein substituted with 1 to 5 substituents independently selected from the groups consisting of the following:

(a) alkyl;
(b) hydroxy (or protected hydroxy);
(c) halo;
(d) oxo, i.e., =O;
(e) amino, alkylamino or dialkylamino;
(f) alkoxy;
(g) cycloalkyl;
(h) carboxyl;
(i) heterocyclooxy, wherein heterocyclooxy denotes a heterocyclic group bonded through an oxygen bridge;
(j) alkyl-O-C(O)-;
(k) mercapto;
(l) nitro;
(m) cyano;
(n) sulfamoyl or sulfonamido;
(o) aryl;
(p) alkyl-C(O)-O-;
(q) aryl-C(O)-O-;
(r) aryl-S-;
(s) aryloxy;
(t) alkyl-S-;
(u) formyl, i.e., HC(O)-;
(v) carbamoyl;
(w) aryl-alkyl-; and
(x) aryl substituted with alkyl, cycloalkyl, alkoxy, hydroxy, amino, alkyl-C(O)-NH-, alkylamino, dialkylamino or halogen.

As used herein, the term "cycloalkyl" refers to saturated or unsaturated monocyclic, bicyclic or tricyclic hydrocarbon groups of 3-12 carbon atoms. Unless otherwise provided, cycloalkyl refers to cyclic hydrocarbon groups having between 3 and 9 ring carbon atoms or between 3 and 7 ring carbon atoms, each of which can be optionally substituted by one, or

two, or three, or more substituents independently selected from the group consisting of alkyl, halo, oxo, hydroxy, alkoxy, alkyl-C(O)-, acylamino, carbamoyl, alkyl-NH-, $(alkyl)_2N$-, thiol, alkyl-S-, nitro, cyano, carboxy, alkyl-O-C(O)-, sulfonyl, sulfonamido, sulfamoyl, and heterocyclyl. Exemplary monocyclic hydrocarbon groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl and cyclohexenyl and the like. Exemplary bicyclic hydrocarbon groups include bornyl, indyl, hexahydroindyl, tetrahydronaphthyl, decahydronaphthyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.1]heptenyl, 6,6-dimethylbicyclo[3.1.1]heptyl, 2,6,6-trimethylbicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl and the like. Exemplary tricyclic hydrocarbon groups include adamantyl and the like.

As used herein, the term “aryloxy” refers to both an --O-aryl and an 0-O-heteroaryl group, wherein aryl and heteroaryl are defined herein.

As used herein, the term "heteroaryl" refers to a 5-14 membered monocyclic- or bicyclic- or tricyclic-aromatic ring system, having 1 to 8 heteroatoms selected from N, O or S. Typically, the heteroaryl is a 5-10 membered ring system (e.g., 5-7 membered monocycle or an 8-10 memberred bicycle) or a 5-7 membered ring system. Typical heteroaryl groups include 2- or 3-thienyl, 2- or 3-furyl, 2- or 3-pyrrolyl, 2-, 4-, or 5-imidazolyl, 3-, 4-, or 5-pyrazolyl, 2-, 4-, or 5-thiazolyl, 3-, 4-, or 5-isothiazolyl, 2-, 4-, or 5-oxazolyl, 3-, 4-, or 5-isoxazolyl, 3- or 5-1,2,4-triazolyl, 4- or 5-1,2, 3-triazolyl, tetrazolyl, 2-, 3-, or 4-pyridyl, 3- or 4-pyridazinyl, 3-, 4-, or 5-pyrazinyl, 2-pyrazinyl, and 2-, 4-, or 5-pyrimidinyl.

The term “heteroaryl” also refers to a group in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include 1-, 2-, 3-, 5-, 6-, 7-, or 8-indolizinyl, 1-, 3-, 4-, 5-, 6-, or 7-isoindolyl, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-indazolyl, 2-, 4-, 5-, 6-, 7-, or 8- purinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, or 9-quinolizinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinoliyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinoliyl, 1-, 4-, 5-, 6-, 7-, or 8-phthalazinyl, 2-, 3-, 4-, 5-, or 6-naphthyridinyl, 2-, 3- , 5-, 6-, 7-, or 8-quinazolinyl, 3-, 4-, 5-, 6-, 7-, or 8-cinnolinyl, 2-, 4-, 6-, or 7-pteridinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-4aH carbazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-carbzaolyl, 1-, 3-, 4-, 5-, 6-, 7-, 8-, or 9-carbolinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenanthridinyl, 1- , 2-, 3-, 4-, 5-, 6-, 7-, 8-, or 9-acridinyl, 1-, 2-, 4-, 5-, 6-, 7-, 8-, or 9-perimidinyl, 2-, 3-, 4-, 5-, 6-, 8-, 9-, or 10-phenathrolinyl, 1-, 2- , 3-, 4-, 6-, 7-, 8-, or 9-phenazinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenothiazinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenoxazinyl, 2-, 3-, 4-, 5-, 6-, or l-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10- benzisoqinolinyl, 2-, 3-, 4-, or thieno[2,3-b]furanyl, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10 -, or 11-7H-pyrazino[2,3-c]carbazolyl,2-, 3-, 5-, 6-, or 7-2H- furo[3,2-b]-pyranyl, 2-, 3-, 4-, 5-, 7-, or 8-5H-pyrido[2,3-d]-o-oxazinyl, 1-, 3-, or 5-1H-pyrazolo[4,3-d]-oxazolyl, 2-, 4-, or 54H-imidazo[4,5-d] thiazolyl, 3-, 5-, or 8-pyrazino[2,3-d]pyridazinyl, 2-, 3-, 5-, or 6- imidazo[2,1-b] thiazolyl, 1-, 3-, 6-, 7-, 8-, or 9-furo[3,4-c]cinnolinyl, 1-, 2-, 3-, 4-, 5-, 6-, 8-, 9-, 10, or 11-4H-pyrido[2,3-c]carbazolyl, 2-, 3-, 6-, or 7-imidazo[1,2-

b][1,2,4]triazinyl, 7-benzo[b]thienyl, 2-, 4-, 5- , 6-, or 7-benzoxazolyl, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, 2-, 4-, 4-, 5-, 6-, or 7-benzothiazolyl, 1-, 2-, 4-, 5-, 6-, 7-, 8-, or 9- benzoxapinyl, 2-, 4-, 5-, 6-, 7-, or 8-benzoxazinyl, 1-, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10-, or 11-1H-pyrrolo[1,2-b][2]benzazapinyl. Typical fused heteroary groups include, but are not limited to 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-benzo[b]thienyl, 2-, 4-, 5- , 6-, or 7-benzoxazolyl, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, and 2-, 4-, 5-, 6-, or 7-benzothiazolyl.

A heteroaryl group may be substituted with 1 to 5 substituents independently selected from the groups consisting of the following:

(a) alkyl;

(b) hydroxy (or protected hydroxy);

(c) halo;

(d) oxo, i.e., =O;

(e) amino, alkylamino or dialkylamino;

(f) alkoxy;

(g) cycloalkyl;

(h) carboxyl;

(i) heterocyclooxy, wherein heterocyclooxy denotes a heterocyclic group bonded through an oxygen bridge;

(j) alkyl-O-C(O)-;

(k) mercapto;

(l) nitro;

(m) cyano;

(n) sulfamoyl or sulfonamido;

(o) aryl;

(p) alkyl-C(O)-O-;

(q) aryl-C(O)-O-;

(r) aryl-S-;

(s) aryloxy;

(t) alkyl-S-;

(u) formyl, i.e., HC(O)-;

(v) carbamoyl;

(w) aryl-alkyl-; and

(x) aryl substituted with alkyl, cycloalkyl, alkoxy, hydroxy, amino, alkyl-C(O)-NH-, alkylamino, dialkylamino or halogen.

As used herein, the term “halogen” or “halo” refers to fluoro, chloro, bromo, and iodo.

As used herein, the term "optionally substituted" unless otherwise specified refers to a group that is unsubstituted or is substituted by one or more, typically 1, 2, 3 or 4, suitable non-hydrogen substituents, each of which is independently selected from the group consisting of:

(a) alkyl;

(b) hydroxy (or protected hydroxy);

(c) halo;

(d) oxo, i.e., =O;

(e) amino, alkylamino or dialkylamino;

(f) alkoxy;

(g) cycloalkyl;

(h) carboxyl;

(i) heterocyclooxy, wherein heterocyclooxy denotes a heterocyclic group bonded through an oxygen bridge;

(j) alkyl-O-C(O)-;

(k) mercapto;

(l) nitro;

(m) cyano;

(n) sulfamoyl or sulfonamido;

(o) aryl;

(p) alkyl-C(O)-O-;

(q) aryl-C(O)-O-;

(r) aryl-S-;

(s) aryloxy;

(t) alkyl-S-;

(u) formyl, i.e., HC(O)-;

(v) carbamoyl;

(w) aryl-alkyl-; and

(x) aryl substituted with alkyl, cycloalkyl, alkoxy, hydroxy, amino, alkyl-C(O)-NH-, alkylamino, dialkylamino or halogen.

As used herein, the term "isomers" refers to different compounds that have the same molecular formula but differ in arrangement and configuration of the atoms. Also as used herein, the term "an optical isomer" or "a stereoisomer" refers to any of the various stereo isomeric configurations which may exist for a given compound of the present invention and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. Therefore, the invention includes enantiomers, diastereomers or racemates of the compound. "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a

"racemic" mixture. The term is used to designate a racemic mixture where appropriate. The asterisk (*) indicated in the name of a compound designate a racemic mixture. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn- Ingold- Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either *R* or *S*. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers or axes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. The present invention is meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (*R*)- and (*S*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. All tautomeric forms are also intended to be included.

As used herein, the term "pharmaceutically acceptable salts" refers to salts that retain the biological effectiveness and properties of the compounds of this invention and, which typically are not biologically or otherwise undesirable. In many cases, the compounds of the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfornate, chloride/hydrochloride, chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, sulfosalicylate, tartrate, tosylate and trifluoroacetate salts. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, and phosphoric acid. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, sulfosalicylic acid, and the like.

Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, cholinate, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

The pharmaceutically acceptable salts of the present invention can be synthesized from a parent compound, a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, e.g., in "Remington's Pharmaceutical Sciences", 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{125}I respectively. The invention includes various isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as ^{3}H, ^{13}C, and ^{14}C , are present. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly desirable for PET or SPECT studies. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the

examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

Further, substitution with heavier isotopes, particularly deuterium (i.e., ^2H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of the formula (I). The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

In certain embodiments, selective deuteration of compounds of Formula (I) include deuteration of R^3, when R^3 is alkanoyl, e.g., $C(O)CD_3$. In other embodiments, certain substitutents on the pyrrole ring are selectively deuterated. For example, when any of R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, or R^{20} are methoxy or ethoxy, the alkyl residue is preferably deuterated, e.g., OCD_3 or OC_2D_5. In certain other compounds, when two substituents of the pyrrole ring are combined to form a cyclopropyl ring, the unsubstituted methylene carbon is selectively deuterated. Certain preferred deuterated compounds are provided in Examples 619 and 620 *infra*.

Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

The compounds of the present invention may inherently or by design form solvates with solvents (including water). Therefore, it is intended that the invention embrace both solvated and unsolvated forms. The term “solvate” refers to a molecular complex of a compound of the present invention (including salts thereof) with one or more solvent molecules. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to a recipient, e.g., water, ethanol, dimethylsulfoxide, acetone and other common organic solvents. The term “hydrate” refers to a molecular complex comprising a compound of the invention and water. Pharmaceutically acceptable solvates in accordance with the

invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

Compounds of the invention, i.e. compounds of formula (I) that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of formula (I) by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of formula (I) with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the invention further provides co-crystals comprising a compound of formula (I).

As used herein, the term "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (*e.g.*, antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drugs, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289- 1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

The term "a therapeutically effective amount" of a compound of the present invention refers to an amount of the compound of the present invention that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc. In one non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the present invention that, when administered to a subject, is effective to (1) at least partially alleviating, inhibiting, preventing and/or ameliorating a condition, or a disorder, or a disease or biological process (e.g., tissue regeneration and reproduction) (i) mediated by Factor D, or (ii) associated with Factor D activity, or (iii) characterized by activity (normal or abnormal) of the complement alternative pathway; or (2) reducing or inhibiting the activity of Factor D; or (3) reducing or inhibiting the expression of Factor D; or (4) reducing or inhibiting activation of the complement system and particularly reducing or inhibiting generation of C3a, iC3b, C5a or the membrane attack complex generated by activation of the complement alternative pathway. In another non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the present invention that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially reducing or inhibiting the activity of Factor D and/or the complement alternative pathway; or at least partially

reducing or inhibiting the expression of Factor D and/or the complement alternative pathway. The meaning of the term “a therapeutically effective amount” as illustrated in the above embodiment for Factor D and/or the complement alternative pathway.

As used herein, the term “subject” refers to an animal. Typically the animal is a mammal. A subject also refers to for example, primates (*e.g.*, humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is a human.

As used herein, the term “inhibit”, "inhibition" or “inhibiting” refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

As used herein, the term “treat”, “treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment “treat”, "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, “treat”, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both. In yet another embodiment, “treat”, "treating" or "treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder.

As used herein, a subject is “in need of” a treatment if such subject would benefit biologically, medically or in quality of life from such treatment.

As used herein, the term "a," "an," "the” and similar terms used in the context of the present invention (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (*e.g.* "such as”) provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed.

Any asymmetric atom (e.g., carbon or the like) of the compound(s) of the present invention can be present in racemic or enantiomerically enriched, for example the (*R*)-, (*S*)- or (*R,S*)- configuration. In certain embodiments, each asymmetric atom has at least 50 % enantiomeric excess, at least 60 % enantiomeric excess, at least 70 % enantiomeric excess, at least 80 % enantiomeric excess, at least 90 % enantiomeric excess, at least 95 % enantiomeric excess, or at least 99 % enantiomeric excess in the (*R*)- or (*S*)- configuration.

Substituents at atoms with unsaturated bonds may, if possible, be present in *cis*- (*Z*)- or *trans*- (*E*)- form.

Accordingly, as used herein a compound of the present invention can be in the form of one of the possible isomers, rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric (*cis* or *trans*) isomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof.

Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, *e.g.*, by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds of the present invention into their optical antipodes, *e.g.*, by fractional crystallization of a salt formed with an optically active acid, *e.g.*, tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-*O,O'-p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, *e.g.*, high pressure liquid chromatography (HPLC) using a chiral adsorbent.

Compounds of the present invention are either obtained in the free form, as a salt thereof, or as prodrug derivatives thereof.

When both a basic group and an acid group are present in the same molecule, the compounds of the present invention may also form internal salts, e.g., zwitterionic molecules.

The present invention also provides pro-drugs of the compounds of the present invention that converts *in vivo* to the compounds of the present invention. A pro-drug is an active or inactive compound that is modified chemically through *in vivo* physiological action, such as hydrolysis, metabolism and the like, into a compound of this invention following administration of the prodrug to a subject. The suitability and techniques involved in making and using pro-drugs are well known by those skilled in the art. Prodrugs can be conceptually divided into two non-exclusive categories, bioprecursor prodrugs and carrier prodrugs. See *The Practice of Medicinal Chemistry*, Ch. 31-32 (Ed. Wermuth, Academic Press, San Diego, Calif., 2001). Generally, bioprecursor prodrugs are compounds, which are inactive or have low activity compared to the corresponding active drug compound, that contain one or more protective groups and are converted to an active form by metabolism or solvolysis. Both the active drug form and any released metabolic products should have acceptably low toxicity.

Carrier prodrugs are drug compounds that contain a transport moiety, *e.g.*, that improve uptake and/or localized delivery to a site(s) of action. Desirably for such a carrier

prodrug, the linkage between the drug moiety and the transport moiety is a covalent bond, the prodrug is inactive or less active than the drug compound, and any released transport moiety is acceptably non-toxic. For prodrugs where the transport moiety is intended to enhance uptake, typically the release of the transport moiety should be rapid. In other cases, it is desirable to utilize a moiety that provides slow release, *e.g.*, certain polymers or other moieties, such as cyclodextrins. Carrier prodrugs can, for example, be used to improve one or more of the following properties: increased lipophilicity, increased duration of pharmacological effects, increased site-specificity, decreased toxicity and adverse reactions, and/or improvement in drug formulation (*e.g.*, stability, water solubility, suppression of an undesirable organoleptic or physiochemical property). For example, lipophilicity can be increased by esterification of (a) hydroxyl groups with lipophilic carboxylic acids (e.g., a carboxylic acid having at least one lipophilic moiety), or (b) carboxylic acid groups with lipophilic alcohols (e.g., an alcohol having at least one lipophilic moiety, for example aliphatic alcohols).

Exemplary prodrugs are, *e.g.*, esters of free carboxylic acids and *S*-acyl derivatives of thiols and *O*-acyl derivatives of alcohols or phenols, wherein acyl has a meaning as defined herein. Suitable prodrugs are often pharmaceutically acceptable ester derivatives convertible by solvolysis under physiological conditions to the parent carboxylic acid, *e.g.*, lower alkyl esters, cycloalkyl esters, lower alkenyl esters, benzyl esters, mono- or di-substituted lower alkyl esters, such as the ω-(amino, mono- or di-lower alkylamino, carboxy, lower alkoxycarbonyl)-lower alkyl esters, the α-(lower alkanoyloxy, lower alkoxycarbonyl or di-lower alkylaminocarbonyl)-lower alkyl esters, such as the pivaloyloxymethyl ester and the like conventionally used in the art. In addition, amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases *in vivo* releasing the free drug and formaldehyde (Bundgaard, *J. Med. Chem.* 2503 (1989)). Moreover, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard, *Design of Prodrugs*, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.

Furthermore, the compounds of the present invention, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

Within the scope of this text, only a readily removable group that is not a constituent of the particular desired end product of the compounds of the present invention is designated a "protecting group", unless the context indicates otherwise. The protection of functional groups by such protecting groups, the protecting groups themselves, and their cleavage reactions are described for example in standard reference works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York

1999, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (Methods of Organic Chemistry), Houben Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jeschkeit, "Aminosäuren, Peptide, Proteine" (Amino acids, Peptides, Proteins), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (Chemistry of Carbohydrates: Monosaccharides and Derivatives), Georg Thieme Verlag, Stuttgart 1974. A characteristic of protecting groups is that they can be removed readily (i.e. without the occurrence of undesired secondary reactions) for example by solvolysis, reduction, photolysis or alternatively under physiological conditions (*e.g.* by enzymatic cleavage).

Salts of compounds of the present invention having at least one salt-forming group may be prepared in a manner known to those skilled in the art. For example, salts of compounds of the present invention having acid groups may be formed, for example, by treating the compounds with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, *e.g.* the sodium salt of 2-ethylhexanoic acid, with organic alkali metal or alkaline earth metal compounds, such as the corresponding hydroxides, carbonates or hydrogen carbonates, such as sodium or potassium hydroxide, carbonate or hydrogen carbonate, with corresponding calcium compounds or with ammonia or a suitable organic amine, stoichiometric amounts or only a small excess of the salt-forming agent preferably being used. Acid addition salts of compounds of the present invention are obtained in customary manner, *e.g.* by treating the compounds with an acid or a suitable anion exchange reagent. Internal salts of compounds of the present invention containing acid and basic salt-forming groups, *e.g.* a free carboxy group and a free amino group, may be formed, *e.g.* by the neutralisation of salts, such as acid addition salts, to the isoelectric point, *e.g.* with weak bases, or by treatment with ion exchangers.

Salts can be converted into the free compounds in accordance with methods known to those skilled in the art. Metal and ammonium salts can be converted, for example, by treatment with suitable acids, and acid addition salts, for example, by treatment with a suitable basic agent.

Mixtures of isomers obtainable according to the invention can be separated in a manner known to those skilled in the art into the individual isomers; diastereoisomers can be separated, for example, by partitioning between polyphasic solvent mixtures, recrystallisation and/or chromatographic separation, for example over silica gel or by *e.g.* medium pressure liquid chromatography over a reversed phase column, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallisation, or by chromatography over optically active column materials.

Intermediates and final products can be worked up and/or purified according to standard methods, *e.g.* using chromatographic methods, distribution methods, (re-) crystallization, and the like.

The following applies in general to all processes mentioned herein before and hereinafter.

All the above-mentioned process steps can be carried out under reaction conditions that are known to those skilled in the art, including those mentioned specifically, in the absence or, customarily, in the presence of solvents or diluents, including, for example, solvents or diluents that are inert towards the reagents used and dissolve them, in the absence or presence of catalysts, condensation or neutralizing agents, for example ion exchangers, such as cation exchangers, *e.g.* in the H+ form, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for example in a temperature range of from about -100 ºC to about 190 ºC, including, for example, from approximately -80 ºC to approximately 150 ºC, for example at from -80 to -60 ºC, at room temperature, at from -20 to 40 ºC or at reflux temperature, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

At all stages of the reactions, mixtures of isomers that are formed can be separated into the individual isomers, for example diastereoisomers or enantiomers, or into any desired mixtures of isomers, for example racemates or mixtures of diastereoisomers, for example analogously to the methods described under "Additional process steps".

The solvents from which those solvents that are suitable for any particular reaction may be selected include those mentioned specifically or, for example, water, esters, such as lower alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofuran or dioxane, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, such as methylene chloride or chloroform, acid amides, such as dimethylformamide or dimethyl acetamide, bases, such as heterocyclic nitrogen bases, for example pyridine or *N*-methylpyrrolidin-2-one, carboxylic acid anhydrides, such as lower alkanoic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, methycyclohexane, or mixtures of those solvents, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

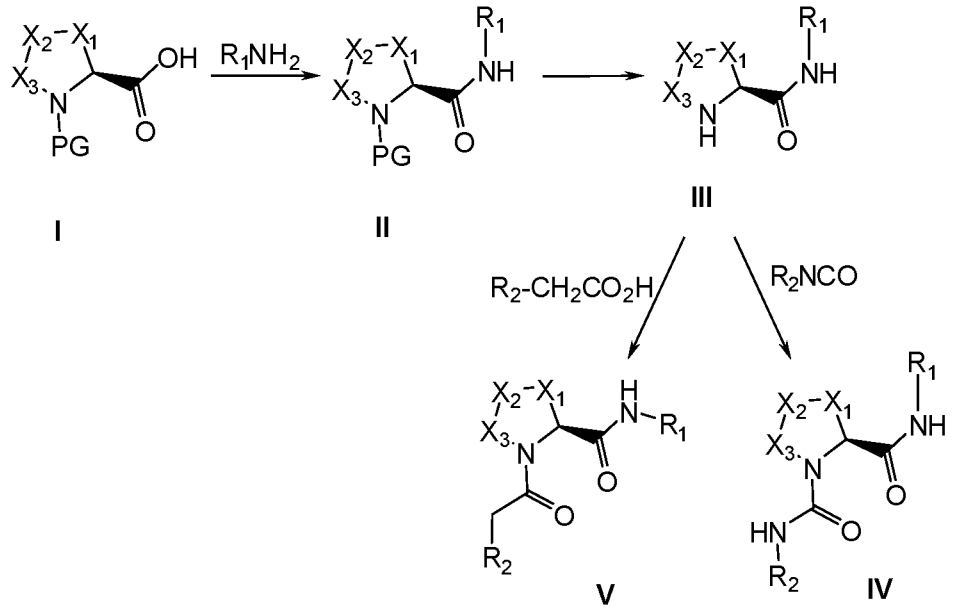
The compounds, including their salts, may also be obtained in the form of hydrates, or their crystals may, for example, include the solvent used for crystallization. Different crystalline forms may be present.

The invention relates also to those forms of the process in which a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in a protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ.

All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents and catalysts utilized to synthesize the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21).

Typically, the compounds of formula (I) can be prepared according to the Schemes provided *infra*.

A compound of the formula IV or V can, for example, be prepared from a corresponding N-protected aminoacid as described below:



By reacting an N-protected aminoacid I wherein PG is a protecting group or a reactive derivative thereof with an amino compound, under condensation conditions to obtain a compound of the formula II. Removing the protecting group and reacting the compound of the formula III with an isocyanate to obtain a compound of the formula IV or with an acid or a reactive derivative thereof under condensation conditions to obtain a compound of the formula V.

The invention further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or in which the starting materials are formed *in situ* under the

reaction conditions, or in which the reaction components are used in the form of their salts or optically pure materials.

Compounds of the invention and intermediates can also be converted into each other according to methods generally known *to those skilled in the art*.

In another aspect, the present invention provides a pharmaceutical composition comprising a compound of the present invention and a pharmaceutically acceptable carrier. The pharmaceutical composition can be formulated for particular routes of administration such as oral administration, parenteral administration, and ophthalmic administration, etc. In addition, the pharmaceutical compositions of the present invention can be made up in a solid form (including without limitation capsules, tablets, pills, granules, powders or suppositories), or in a liquid form (including without limitation solutions, suspensions, emulsions, each of which may be suitable for ophthalmic administration). The pharmaceutical compositions can be subjected to conventional pharmaceutical operations such as sterilization and/or can contain conventional inert diluents, lubricating agents, or buffering agents, as well as adjuvants, such as preservatives, stabilizers, wetting agents, emulsifers and buffers, etc.

Typically, the pharmaceutical compositions are tablets or gelatin capsules comprising the active ingredient together with

a) diluents, *e.g.*, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;

b) lubricants, *e.g.*, silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also

c) binders, *e.g.*, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired

d) disintegrants, *e.g.*, starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or

e) absorbents, colorants, flavors and sweeteners.

Tablets may be either film coated or enteric coated according to methods known in the art.

Suitable compositions for oral administration include an effective amount of a compound of the invention in the form of tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use are prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and

palatable preparations. Tablets may contain the active ingredient in admixture with nontoxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients are, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets are uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

Certain injectable compositions are aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1-75%, or contain about 1-50%, of the active ingredient.

Suitable compositions for transdermal application include an effective amount of a compound of the invention with a suitable carrier. Carriers suitable for transdermal delivery include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Suitable compositions for topical application, *e.g.*, to the skin and eyes, include aqueous solutions, suspensions, ointments, creams, gels or sprayable formulations, *e.g.*, for delivery by aerosol or the like. Such topical delivery systems will in particular be appropriate for ophthalmic application, *e.g.*, for the treatment of eye diseases *e.g.*, for therapeutic or prophylactic use in treating age related macular degeneration and other complement mediated ophthalmic disorders. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

As used herein a topical application may also pertain to an inhalation or to an intranasal application. They may be conveniently delivered in the form of a dry powder (either alone, as a mixture, for example a dry blend with lactose, or a mixed component particle, for example with phospholipids) from a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomizer or nebuliser, with or without the use of a suitable propellant.

Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be desirable.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the active compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

The present invention further provides anhydrous pharmaceutical compositions and dosage forms comprising the compounds of the present invention as active ingredients, since water may facilitate the degradation of certain compounds.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to,

hermetically sealed foils, plastics, unit dose containers (*e. g.*, vials), blister packs, and strip packs.

The invention further provides pharmaceutical compositions and dosage forms that comprise one or more agents that reduce the rate by which the compound of the present invention as an active ingredient will decompose. Such agents, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers, etc.

Prophylactic and Therapeutic Uses

The compounds of formula I in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, e.g. Factor D modulating properties, complement pathway modulating properties and modulation of the complement alternative pathway properties, e.g. as indicated in *in vitro* and *in vivo* tests as provided in the next sections and are therefore indicated for therapy.

The present invention provides methods of treating a disease or disorder associated with increased complement activity by administering to a subject in need thereof an effective amount of the compounds of Formula (I) of the invention. In certain aspects, methods are provided for the treatment of diseases associated with increased activity of the C3 amplification loop of the complement pathway. In certain embodiments, methods of treating or preventing compelment mediated diseases are provided in which the complement activation is induced by antibody-antigen interactions, by a component of an autoimmune disease, or by ischemic damage.

In a specific embodiment, the present invention provides a method of treating or preventing age-related macular degeneration (AMD) by administering to a subject in need thereof an effective amount of the compound of Formula (I) of the invention. In certain embodiments, patients who are currently asymptomatic but are at risk of developing a symptomatic macular degeneration related disorder are suitable for administration with a compound of the invention. The methods of treating or preventing AMD include, but are not limited to, methods of treating or preventing one or more symptoms or aspects of AMD selected from formation of ocular drusen, inflammation of the eye or eye tissue, loss of photoreceptor cells, loss of vision (including loss of visual acuity or visual field), neovascularization (including CNV), retinal detachment, photoreceptor degeneration, RPE degeneration, retinal degeneration, chorioretinal degeneration, cone degeneration, retinal dysfunction, retinal damage in response to light exposure, damage of the Bruch's membrane, and/ or loss of RPE function.

The compound of Formula (I) of the invention can be used, *inter alia*, to prevent the onset of AMD, to prevent the progression of early AMD to advanced forms of AMD including neovascular AMD or geographic atrophy, to slow and/or prevent progression of geographic

atrophy, to treat or prevent macular edema from AMD or other conditions (such as diabetic retinopathy, uveitis, or post surgical or non-surgical trauma), to prevent or reduce the loss of vision from AMD, and to improve vision lost due to pre-existing early or advanced AMD. It can also be used in combination with anti-VEGF therapies for the treatment of neovascular AMD patients or for the prevention of neovascular AMD. The present invention further provides methods of treating a complement related disease or disorder by administering to a subject in need thereof an effective amount of the compound(s) of the invention, wherein said disease or disorder is selected from uveitis, adult macuar degeneration, diabetic retinopathy, retinitis pigmentosa, macular edema, Behcet's uveitis, multifocal choroiditis, Vogt-Koyangi-Harada syndrome, imtermediate uveitis, birdshot retino-chorioditis, sympathetic ophthalmia, ocular dicatricial pemphigoid, ocular pemphigus, nonartertic ischemic optic neuropathy, post-operative inflammation, and retinal vein occlusion.

In some embodiments, the present invention provides methods of treating a complement related disease or disorder by administering to a subject in need thereof an effective amount of the compounds of the invention. Examples of known complement related diseases or disorders include: neurological disorders, multiple sclerosis, stroke, Guillain Barre Syndrome, traumatic brain injury, Parkinson's disease, disorders of inappropriate or undesirable complement activation, hemodialysis complications, hyperacute allograft rejection, xenograft rejection, interleukin-2 induced toxicity during IL-2 therapy, inflammatory disorders, inflammation of autoimmune diseases, Crohn's disease, adult respiratory distress syndrome, thermal injury including burns or frostbite, myocarditis, post-ischemic reperfusion conditions, myocardial infarction, balloon angioplasty, post-pump syndrome in cardiopulmonary bypass or renal bypass, atherosclerosis, hemodialysis, renal ischemia, mesenteric artery reperfusion after aortic reconstruction, infectious disease or sepsis, immune complex disorders and autoimmune diseases, rheumatoid arthritis, systemic lupus erythematosus (SLE), SLE nephritis, proliferative nephritis, liver fibrosis, hemolytic anemia, myasthenia gravis, tissue regeneration and neural regeneration. In addition, other known complement related disease are lung disease and disorders such as dyspnea, hemoptysis, ARDS, asthma, chronic obstructive pulmonary disease (COPD), emphysema, pulmonary embolisms and infarcts, pneumonia, fibrogenic dust diseases, inert dusts and minerals (*e.g.*, silicon, coal dust, beryllium, and asbestos), pulmonary fibrosis, organic dust diseases, chemical injury (due to irritant gases and chemicals, *e.g.*, chlorine, phosgene, sulfur dioxide, hydrogen sulfide, nitrogen dioxide, ammonia, and hydrochloric acid), smoke injury, thermal injury (*e.g.*, burn, freeze), asthma, allergy, bronchoconstriction, hypersensitivity pneumonitis, parasitic diseases, Goodpasture's Syndrome, pulmonary vasculitis, Pauci-immune vasculitis, immune complex-associated inflammation, uveitis (including Behcet's disease and other sub-types of uveitis), antiphospholipid syndrome.

In a specific embodiment, the present invention provides methods of treating a complement related disease or disorder by administering to a subject in need thereof an effective amount of the compounds of the invention, wherein said disease or disorder is asthma, arthritis (*e.g.*, rheumatoid arthritis), autoimmune heart disease, multiple sclerosis, inflammatory bowel disease, ischemia-reperfusion injuries, Barraquer-Simons Syndrome, hemodialysis, systemic lupus, lupus erythematosus, psoriasis, multiple sclerosis, transplantation, diseases of the central nervous system such as Alzheimer's disease and other neurodegenerative conditions, atypicaly hemolytic uremic syndrome (aHUS), glomerulonephritis (including membrane proliferative glomerulonephritis), blistering cutaneous diseases (including bullous pemphigoid, pemphigus, and epidermolysis bullosa), ocular cicatrical pemphigoid or MPGN II.

In a specific embodiment, the present invention provides methods of treating glomerulonephritis by administering to a subject in need thereof an effective amount of a composition comprising a compound of the present invention. Symptoms of glomerulonephritis include, but not limited to, proteinuria; reduced glomerular filtration rate (GFR); serum electrolyte changes including azotemia (uremia, excessive blood urea nitrogen--BUN) and salt retention, leading to water retention resulting in hypertension and edema; hematuria and abnormal urinary sediments including red cell casts; hypoalbuminemia; hyperlipidemia; and lipiduria. In a specific embodiment, the present invention provides methods of treating paroxysmal nocturnal hemoglobinuria (PNH) by administering to a subject in need thereof an effective amount of a composition comprising an compound of the present invention with or without concomitent administration of a complement C5 inhibitor or C5 convertase inhibitor such as Soliris.

In a specific embodiment, the present invention provides methods of reducing the dysfunction of the immune and/or hemostatic systems associated with extracorporeal circulation by administering to a subject in need thereof an effective amount of a composition comprising an compound of the present invention. The compounds of the present invention can be used in any procedure which involves circulating the patient's blood from a blood vessel of the patient, through a conduit, and back to a blood vessel of the patient, the conduit having a luminal surface comprising a material capable of causing at least one of complement activation, platelet activation, leukocyte activation, or platelet-leukocyte adhesion. Such procedures include, but are not limited to, all forms of ECC, as well as procedures involving the introduction of an artificial or foreign organ, tissue, or vessel into the blood circuit of a patient. More particularly, such procedures include, but are not limited to, transplantation procedures including kidney, liver, lung or heart transplant procedures and islet cell transplant procedures.

In other embodiments, the compounds of the invention are suitable for use in the treatment of diseases and disorders associated with fatty acid metabolism, including obesity and other metabolic disorders.

In another embodiment, the compounds of the invention may be used in blood ampules, diagnostic kits and other equipment used in the collection and sampling of blood. The use of the compounds of the invention in such diagnostic kits may inhibit the ex vivo activation of the complement pathway associated with blood sampling.

The pharmaceutical composition or combination of the present invention can be in unit dosage of about 1-1000 mg of active ingredient(s) for a subject of about 50-70 kg, or about 1-500 mg or about 1-250 mg or about 1-150 mg or about 0.5-100 mg, or about 1-50 mg of active ingredients. The therapeutically effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is dependent on the species of the subject, the body weight, age and individual condition, the disorder or disease or the severity thereof being treated. A physician, clinician or veterinarian of ordinary skill can readily determine the effective amount of each of the active ingredients necessary to prevent, treat or inhibit the progress of the disorder or disease.

The above-cited dosage properties are demonstrable *in vitro* and *in vivo* tests using advantageously mammals, *e.g.*, mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. The compounds of the present invention can be applied *in vitro* in the form of solutions, *e.g.*, aqueous solutions, and *in vivo* either enterally, parenterally, advantageously intravenously, *e.g.*, as a suspension or in aqueous solution. The dosage *in vitro* may range between about 10^{-3} molar and 10^{-9} molar concentrations. A therapeutically effective amount *in vivo* may range depending on the route of administration, between about 0.1-500 mg/kg, or between about 1-100 mg/kg.

The activity of a compound according to the present invention can be assessed by the following *in vitro & in vivo* methods.

The compound of the present invention may be administered either simultaneously with, or before or after, one or more other therapeutic agent. The compound of the present invention may be administered separately, by the same or different route of administration, or together in the same pharmaceutical composition as the other agents.

In one embodiment, the invention provides a product comprising a compound of formula (I) and at least one other therapeutic agent as a combined preparation for simultaneous, separate or sequential use in therapy. In one embodiment, the therapy is the treatment of a disease or condition mediated by alternative complement pathway. Products provided as a combined preparation include a composition comprising the compound of formula (I) and the other therapeutic agent(s) together in the same pharmaceutical

composition, or the compound of formula (I) and the other therapeutic agent(s) in separate form, *e.g.* in the form of a kit.

In one embodiment, the invention provides a pharmaceutical composition comprising a compound of formula (I) and another therapeutic agent(s). Optionally, the pharmaceutical composition may comprise a pharmaceutically acceptable excipient, as described above.

In one embodiment, the invention provides a kit comprising two or more separate pharmaceutical compositions, at least one of which contains a compound of formula (I). In one embodiment, the kit comprises means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is a blister pack, as typically used for the packaging of tablets, capsules and the like.

The kit of the invention may be used for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit of the invention typically comprises directions for administration.

In the combination therapies of the invention, the compound of the invention and the other therapeutic agent may be manufactured and/or formulated by the same or different manufacturers. Moreover, the compound of the invention and the other therapeutic may be brought together into a combination therapy: (i) prior to release of the combination product to physicians (*e.g.* in the case of a kit comprising the compound of the invention and the other therapeutic agent); (ii) by the physician themselves (or under the guidance of the physician) shortly before administration; (iii) in the patient themselves, *e.g.* during sequential administration of the compound of the invention and the other therapeutic agent.

Accordingly, the invention provides the use of a compound of formula (I) for treating a disease or condition mediated by the complement alternative pathway, wherein the medicament is prepared for administration with another therapeutic agent. The invention also provides the use of another therapeutic agent for treating a disease or condition mediated by the complement alternative pathway, wherein the medicament is administered with a compound of formula (I).

The invention also provides a compound of formula (I) for use in a method of treating a disease or condition mediated by the complement alternative pathway, wherein the compound of formula (I) is prepared for administration with another therapeutic agent. The invention also provides another therapeutic agent for use in a method of treating a disease or condition mediated by the complement alternative pathway and/or Factor D, wherein the other therapeutic agent is prepared for administration with a compound of formula (I). The invention also provides a compound of formula (I) for use in a method of treating a disease or condition mediated by the complement alternative pathway and/or Factor D, wherein the compound of formula (I) is administered with another therapeutic agent. The invention also provides another

therapeutic agent for use in a method of treating a disease or condition mediated by the complement alternative pathway and/or Factor D, wherein the other therapeutic agent is administered with a compound of formula (I).

The invention also provides the use of a compound of formula (I) for treating a disease or condition mediated by the complement alternative pathway and/or Factor D, wherein the patient has previously (*e.g.* within 24 hours) been treated with another therapeutic agent. The invention also provides the use of another therapeutic agent for treating a disease or condition mediated by the complement alternative pathway and/or Factor D wherein the patient has previously (*e.g.* within 24 hours) been treated with a compound of formula (I).

The pharmaceutical compositions can be administered alone or in combination with other molecules known to have a beneficial effect on retinal attachment or damaged retinal tissue, including molecules capable of tissue repair and regeneration and/or inhibiting inflammation. Examples of useful, cofactors include anti-VEGF agents (such as an antibody or FAB against VEGF, e.g., Lucentis or Avastin), basic fibroblast growth factor (bFGF), ciliary neurotrophic factor (CNTF), axokine (a mutein of CNTF), leukemia inhibitory factor (LIF), neutrotrophin 3 (NT-3), neurotrophin-4 (NT-4), nerve growth factor (NGF), insulin-like growth factor II, prostaglandin E2, 30 kD survival factor, taurine, and vitamin A. Other useful cofactors include symptom-alleviating cofactors, including antiseptics, antibiotics, antiviral and antifungal agents and analgesics and anestheticsSuitable agents for combination treatment with the compounds of the invention include agents known in the art that are able to modulate the activities of complement components.

A combination therapy regimen may be additive, or it may produce synergistic results (*e.g.*, reductions in complement pathway activity more than expected for the combined use of the two agents). In some embodiments, the present invention provide a combination therapy for preventing and/or treating AMD or another complement related ocular disease as described above with a compound of the invention and an anti-angiogenic, such as anti-VEGF agent (including Lucentis and Avastin) or photodynamic therapy (such as verteporfin).

In some embodiments, the present invention provide a combination therapy for preventing and/or treating autoimmune disease as described above with a compound of the invention and a B-Cell or T-Cell modulating agent (for example cyclosporine or analogs thereof, rapamycin, RAD001 or analogs thereof, and the like). In particular, for multiple sclerosis therapy may include the combination of a compound of the invention and a second MS agent selected from fingolimod, cladribine, tysarbi, laquinimod, rebif, avonex and the like.

In one embodiment, the invention provides a method of modulating activity of the complement alternative pathway in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound according to the definition of formula (I). The invention further provides methods of modulating the activity of the

complement alternative pathway in a subject by modulating the activity of Factor D, wherein the method comprises administering to the subject a therapeutically effective amount of the compound according to the definition of Formula (I).

In one embodiment, the invention provides a compound according to the definition of formula (I), (Ia), (VII) or any subformulae thereof, for use as a medicament.

In one embodiment, the invention provides the use of a compound according to the definition of formula (I), (Ia), (VII) or any subformulae thereof, for the treatment of a disorder or disease in a subject mediated by complement activation. In particular, the invention provides the use of a compound according to the definition of formula (I), (Ia), (VII) or any subformulae thereof, for the treatment of a disorder or disease mediated by activation of the complement alternative pathway.

In one embodiment, the invention provides the use of a compound according to the definition of formula (I), (Ia), in the manufacture of a medicament for the treatment of a disorder or disease in a subject characterized by activation of the complement system. More particularly in the manufacture of a medicament for the treatment of a disease or disorder in a subject characterized by over activiation of the complement alternative pathway.

In one embodiment, the invention provides the use of a compound according to the definition of formula (I), (Ia), or subformulae thereof for the treatment of a disorder or disease in a subject characterized by activation of the complement system. More particularly, the invention provides uses of the compounds provided herein in the treatment of a disease or disorder characterized by over activiation of the complement alternative pathway or the C3 amplification loop of the alternative pathway. In certain embodiments, the use is in the treatment of a disease or disorder is selected from retinal diseases (such as age-related macular degeneration).

The present invention provides use of the compounds of the invention for treating a disease or disorder associated with increased complement activity by administering to a subject in need thereof an effective amount of the compounds of Formula (I) of the invention. In certain aspects, uses are provided for the treatment of diseases associated with increased activity of the C3 amplification loop of the complement pathway. In certain embodiments, uses of treating or preventing compelment mediated diseases are provided in which the complement activation is induced by antibody-antigen interactions, by a component of an autoimmune disease, or by ischemic damage.

In a specific embodiment, the present invention provides use of the compounds of the invention for treating or preventing age-related macular degeneration (AMD). In certain embodiments, patients who are currently asymptomatic but are at risk of developing a symptomatic macular degeneration related disorder are suitable for administration with a compound of the invention. The use in treating or preventing AMD include, but are not limited

to, uses in treating or preventing one or more symptoms or aspects of AMD selected from formation of ocular drusen, inflammation of the eye or eye tissue, loss of photoreceptor cells, loss of vision (including loss of visual acuity or visual field), neovascularization (including CNV), retinal detachment, photoreceptor degeneration, RPE degeneration, retinal degeneration, chorioretinal degeneration, cone degeneration, retinal dysfunction, retinal damage in response to light exposure, damage of the Bruch's membrane, and/ or loss of RPE function.

The compound of Formula (I) of the invention can be used, *inter alia*, to prevent the onset of AMD, to prevent the progression of early AMD to advanced forms of AMD including neovascular AMD or geographic atrophy, to slow and/or prevent progression of geographic atrophy, to treat or prevent macular edema from AMD or other conditions (such as diabetic retinopathy, uveitis, or post surgical or non-surgical trauma), to prevent or reduce the loss of vision from AMD, and to improve vision lost due to pre-existing early or advanced AMD. It can also be used in combination with anti-VEGF therapies for the treatment of neovascular AMD patients or for the prevention of neovascular AMD. The present invention further provides methods of treating a complement related disease or disorder by administering to a subject in need thereof an effective amount of the compound(s) of the invention, wherein said disease or disorder is selected from uveitis, adult macuar degeneration, diabetic retinopathy, retinitis pigmentosa, macular edema, Behcet's uveitis, multifocal choroiditis, Vogt-Koyangi-Harada syndrome, imtermediate uveitis, birdshot retino-chorioditis, sympathetic ophthalmia, ocular dicatricial pemphigoid, ocular pemphigus, nonartertic ischemic optic neuropathy, post-operative inflammation, and retinal vein occlusion.

In some embodiments, the present invention provides uses for treating a complement related disease or disorder. Examples of known complement related diseases or disorders include: neurological disorders, multiple sclerosis, stroke, Guillain Barre Syndrome, traumatic brain injury, Parkinson's disease, disorders of inappropriate or undesirable complement activation, hemodialysis complications, hyperacute allograft rejection, xenograft rejection, interleukin-2 induced toxicity during IL-2 therapy, inflammatory disorders, inflammation of autoimmune diseases, Crohn's disease, adult respiratory distress syndrome, thermal injury including burns or frostbite, myocarditis, post-ischemic reperfusion conditions, myocardial infarction, balloon angioplasty, post-pump syndrome in cardiopulmonary bypass or renal bypass, atherosclerosis, hemodialysis, renal ischemia, mesenteric artery reperfusion after aortic reconstruction, infectious disease or sepsis, immune complex disorders and autoimmune diseases, rheumatoid arthritis, systemic lupus erythematosus (SLE), SLE nephritis, proliferative nephritis, liver fibrosis, hemolytic anemia, myasthenia gravis, tissue regeneration and neural regeneration. In addition, other known complement related disease are lung disease and disorders such as dyspnea, hemoptysis, ARDS, asthma, chronic

obstructive pulmonary disease (COPD), emphysema, pulmonary embolisms and infarcts, pneumonia, fibrogenic dust diseases, inert dusts and minerals (*e.g.*, silicon, coal dust, beryllium, and asbestos), pulmonary fibrosis, organic dust diseases, chemical injury (due to irritant gases and chemicals, *e.g.*, chlorine, phosgene, sulfur dioxide, hydrogen sulfide, nitrogen dioxide, ammonia, and hydrochloric acid), smoke injury, thermal injury (*e.g.*, burn, freeze), asthma, allergy, bronchoconstriction, hypersensitivity pneumonitis, parasitic diseases, Goodpasture's Syndrome, pulmonary vasculitis, Pauci-immune vasculitis, immune complex-associated inflammation, uveitis (including Behcet's disease and other sub-types of uveitis), antiphospholipid syndrome.

In a specific embodiment, the present invention provides use of the compounds of the invention for treating a complement related disease or disorder, wherein said disease or disorder is asthma, arthritis (*e.g.*, rheumatoid arthritis), autoimmune heart disease, multiple sclerosis, inflammatory bowel disease, ischemia-reperfusion injuries, Barraquer-Simons Syndrome, hemodialysis, systemic lupus, lupus erythematosus, psoriasis, multiple sclerosis, transplantation, diseases of the central nervous system such as Alzheimer's disease and other neurodegenerative conditions, atypicaly hemolytic uremic syndrome (aHUS), glomerulonephritis (including membrane proliferative glomerulonephritis), blistering cutaneous diseases (including bullous pemphigoid, pemphigus, and epidermolysis bullosa), ocular cicatrical pemphigoid or MPGN II.

In a specific embodiment, the present invention provides use of the compounds of the invention for treating glomerulonephritis. Symptoms of glomerulonephritis include, but not limited to, proteinuria; reduced glomerular filtration rate (GFR); serum electrolyte changes including azotemia (uremia, excessive blood urea nitrogen--BUN) and salt retention, leading to water retention resulting in hypertension and edema; hematuria and abnormal urinary sediments including red cell casts; hypoalbuminemia; hyperlipidemia; and lipiduria. In a specific embodiment, the present invention provides methods of treating paroxysmal nocturnal hemoglobinuria (PNH) by administering to a subject in need thereof an effective amount of a composition comprising an compound of the present invention with or without concomitent administration of a complement C5 inhibitor or C5 convertase inhibitor such as Soliris.

In a specific embodiment, the present invention provides use of the compounds of the invention for reducing the dysfunction of the immune and/or hemostatic systems associated with extracorporeal circulation. The compounds of the present invention can be used in any procedure which involves circulating the patient's blood from a blood vessel of the patient, through a conduit, and back to a blood vessel of the patient, the conduit having a luminal surface comprising a material capable of causing at least one of complement activation, platelet activation, leukocyte activation, or platelet-leukocyte adhesion. Such procedures include, but are not limited to, all forms of ECC, as well as procedures involving the

introduction of an artificial or foreign organ, tissue, or vessel into the blood circuit of a patient. More particularly, such procedures include, but are not limited to, transplantation procedures including kidney, liver, lung or heart transplant procedures and islet cell transplant procedures.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees centrigrade (°C). If not mentioned otherwise, all evaporations are performed under reduced pressure, typically between about 15 mm Hg and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, *e.g.*, microanalysis and spectroscopic characteristics, *e.g.*, MS, IR, NMR. Abbreviations used are those conventional in the art.

All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesis the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21). Further, the compounds of the present invention can be produced by organic synthesis methods known to one of ordinary skill in the art as shown in the following examples.

Inter Alia the following *in vitro* tests may be used

Human complement factor D assay: Method 1

Recombinant human factor D (expressed in *E. coli* and purified using standard methods) at 10 nM concentration is incubated with test compound at various concentrations for 1 hour at room temperature in 0.1 M Hepes buffer, pH 7.5, containing 1 mM $MgCl_2$, 1 M NaCl and 0.05 % CHAPS. A synthetic substrate Z-Lys-thiobenzyl and 2,4-dinitrobenzenesulfonyl-fluoresceine are added to final concentrations of 200 µM and 25 µM, respectively. The increase in fluorescence is recorded at excitation of 485 nm and emission at 535 nm in a microplate spectrofluorimeter. IC_{50} values are calculated from percentage of inhibition of complement factor D-activity as a function of test compound concentration.

Human complement factor D assay: Method 2

Recombinant human factor D (expressed in *E. coli* and purified using standard methods) at a 10 nM concentration is incubated with test compound at various concentrations for 1 hour at room temperature in 0.1 M PBS pH 7.4 containing 7.5 mM $MgCl_2$ and 0.075% (w/v) CHAPS. Cobra venom factor and human complement factor B substrate complex is added to a final concentration of 200 nM. After 1 hour incubation at room temperature, the enzyme reaction was stopped by addition of 0.1 M sodium carbonate buffer pH 9.0 containing 0.15 M NaCl and 40 mM EDTA. The product of the reaction, Ba, was quantified by means of an enzyme-linked-

immunosorbent assay. IC_{50} values are calculated from percentage of inhibition of factor D-activity as a function of test compound concentration.

The following Examples, while representing preferred embodiments of the invention, serve to illustrate the invention without limiting its scope.

Abbreviations:

abs.	Absolute
Ac	acetyl
EtOAc	ethyl acetate
AcOH	acetic acid
aq	aqueous
cc	concentrated
c-hexane	cyclohexane
CSA	Camphor sulfonic acid
DIPEA	N,N-diisopropylethylamine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-dicyclohexylcarbodiimide
DIBALH	diisobutylaluminium hydride
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Ether	diethylether
Et_3N	triethylamine
Et_2O	diethylether
EtOH	ethanol
Flow	flow rate
h	hour(s)
HMPA	hexamethylphosphoroamide
HOBt	1-hydroxybenzotriazole
HBTU	2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
HPLC	High Performance Liquid Chromatography
iPrOH	isopropanol
L	liter(s)
KHMDS	potassium hexamethyldisilazane
LC-MS	Liquid Chromatography/Mass Spectrometry

LDA	lithium diisopropylamine
Me	methyl
MeI	methyl iodide
MeOH	methanol
MesCl	Mesyl Chloride
min	minute(s)
mL	milliliter
MS	Mass Spectrometry
NBS	N-Bromo succinimide
NMM	4-methylmorpholine
NMR	Nuclear Magnetic Resonance
Pd/C	palladium on charcoal
Ph	phenyl
PyBOP	(benzotriazol-1-yloxy)-tripyrrolidinophosphonium-Hexafluorophosphate
SEM-Cl	2-(Trimethylsilyl)ethoxymethyl chloride
RT	room temperature
TBAF	tetra-butylammonium fluoride
TBDMS-Cl	tert-butyldimethylsilyl chloride
TBDMS	tert-butyldimethylsilyl
TBME	tert-Butylmethylether
TEA	triethylamine
TMEDA	tetramethylethylenediamine
TEMPO	2,2,6,6,-tetramethyl-1-piperidinyloxy free radical
TFA	trifluoroacetic acid
THF	tetrahydrofurane
T_3P	Propylphosphonic anhydride
RP	reverse phase
Prep	Preparative
TLC	Thin Layer Chromatography
t_r	retention time

Trademarks

Celite	= Celite® (The Celite Corporation) = filtering aid based on diatomaceous earth
NH_2 Isolute	(= Isolute® NH_2, Isolute® is registered for Argonaut Technologies, Inc.) = ion exchange with amino groups based on

	silica gel
Nucleosil	= Nucleosil®, trademark of Machery & Nagel, Düren, FRG for HPLC materials
PTFE membrane	= Chromafil O-45/15MS Polytetrafluoroethylene Machereynagel)
PL Thiol Cartridge	= Stratosphere® SPE, PL-Thiol MP SPE+, 500mg per 6 mL tube, 1.5 mmol (nominal)

Temperatures are measured in degrees Celsius. Unless otherwise indicated, the reactions take place at RT.

Phase separator: Biotage - Isolute Phase separator (Part Nr: 120-1908-F for 70 mL and Part Nr: 120-1909-J for 150 mL)

TLC conditions: R_f values for TLC are measured on 5 x 10 cm TLC plates, silica gel F_{254}, Merck, Darmstadt, Germany.

HPLC conditions:

HPLC were performed using an Agilent 1100 or 1200 series instrument. Mass spectra and LC/MS were determined using an Agilent 1100 series instrument.

a: Waters Symmetry C18, 3.5um, 2.1x50mm, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min

b: Agilent Eclipse XDB-C18; 1,8um; 4.6x50mm 20-100% CH_3CN/H_2O/6min, 100%CH_3CN/1.5min, CH_3CN and H_2O containing 0.1% of TFA, flow : 1 mL/min

c. Agilent Eclipse XDB-C18, 1.8um, 4.6x50mm, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min

d. Waters XBridge C18, 2.5um, 3x30mm, 10-95% CH_3CN/H_2O/1.7 min/flow: 1.4 mL/min, 95% CH_3CN/flow: 0.7 min/1.6 mL/min, CH_3CN containing 0.05% TFA, H_2O containing 0.05% TFA and 5% CH_3CN

e. Waters XBridge C18, 2.5um, 3x30mm, 1% CH_3CN/H_2O/0.5 min/flow: 1.4 mL/min, 1-95% CH_3CN/H_2O/1.7 min/flow: 1.4 mL/min, 95% CH_3CN/flow: 0.7 min/1.6 mL/min, CH_3CN containing 0.05% TFA, H_2O containing 0.05% TFA and 5% CH_3CN

f. Waters Sunfire C18, 2.5um, 3x30mm, 10-98% in 2.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.4 mL/min

g. Waters Sunfire C18, 2.5um, 3x30mm, 0-10% in 0.5 min, 10-98% in 2.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.4 mL/min

h. Waters Sunfire C18, 2.5um, 3x30mm, 10-98% in 4.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.4 mL/min

i. Waters Sunfire C18, 5um, 21x50mm, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 0.6 mL/min

j. Waters Atlantis; 2.1x30mm, 20-95% CH_3CN/H_2O/2.5 min, 95% CH_3CN/H_2O/0.05 min, 20-95-20% CH_3CN/H_2O/0.45 min CH_3CN and H_2O containing 0.1% of HCOOH, flow: 0.6 mL/min

k. Agilent Eclipse XDB-C18; 1,8um; 2.1x30mm 5-100% CH_3CN/H_2O/3 min, 100% CH_3CN/0.75 min, CH_3CN and H_2O containing 0.1% of TFA, flow : 0.6 mL/min

l. Agilent Eclipse XDB-C18; 1,8um; 2.1x30mm 20-100% CH_3CN/H_2O/3min, 100%CH_3CN/0.75 min, CH_3CN and H_2O containing 0.1% of TFA, flow : 0.6 mL/min

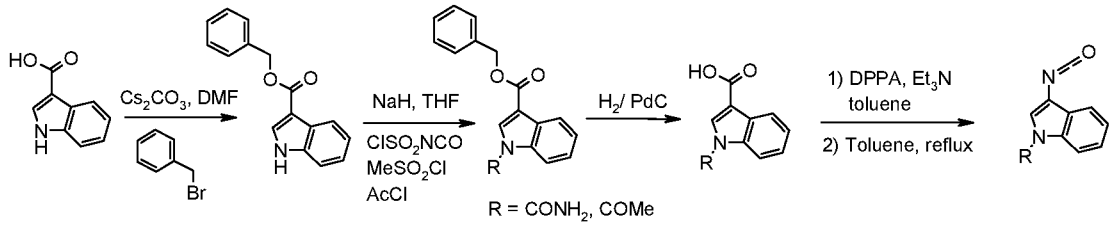
UPLC conditions:

m. UPLC/MS: Waters Acquity; UPLC column: Waters Acquility HSS T3; 1,8um; 2.1x50mm 10-95% CH_3CN/H_2O/1.5 min, H_2O containing 0.05% HCOOH and CH_3CN containing 0.04% HCOOH + 3.75 mM NH_4OAc, flow 1.2 mL/min

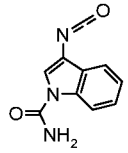
The asterisk (*) indicated in the name of a compound designate a racemic mixture.

Part A: Synthesis of substituted aromatic or heteroromatic building blocks:

Scheme A1: general protocol for the preparation of various isocyanate building blocks



3-isocyanato-indole-1-carboxylic acid amide



A. 1H-Indole-3-carboxylic acid benzyl ester

To a solution of 1H-indole-3-carboxylic acid (5 g, 31 mmol) in DMF (70 mL) under nitrogen atmosphere at 0°C was added cesium carbonate (11 g, 31 mmol) and benzyl bromide (4.05 mL, 34.1 mmol). The reaction mixture was stirred at RT for 48 h and poured into water. EtOAc was added and the layers were separated, the aqueous one being back extracted three times with EtOAc. The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated. The residue was taken up in Et_2O and the resulting precipitate was filtered-off to give the title compound. TLC, R_f (c-hexane/EtOAc 1:1) = 0.55; MS (LC-MS): 252.1 [M+H]+, 274.0 [M+Na]+, 525.1 [2M+Na]+, 250.1 [M-H]-; t_R (HPLC conditions a) 3.77 min.

B. 1-Carbamoyl-1H-indole-3-carboxylic acid benzyl ester

To a solution of 1H-indole-3-carboxylic acid benzyl ester (3.5 g, 13.9 mmol) in THF (70 mL) at 5°C, was added NaH (60 % in mineral oil, 557 mg, 13.9 mmol). The mixture was stirred at 5°C for 30 min before slow dropwise addition of chlorosulfonyl isocyanate (2.42 mL, 27.9 mmol) maintaining the temperature between 5°C and 10°C. The pale yellow solution was further stirred at RT for 3.5 h. Acetic acid (22.5 mL) was added (exothermic), and the resulting solution was stirred at RT for 1.5 h before addition of ice cubes and water (100 mL). The white thick suspension was stirred at RT for 30 min and the precipitate was filtered-off, taken up in MeOH and filtered-off again to afford the desired compound. 1H-NMR (400 MHz, DMSO): δ (ppm) 8.64 (s, 1H), 8.29 (d, 1H), 8.04 (d, 1H), 7.90 (m, 2H), 7.50 (d, 2H), 7.42 (t, 2H), 7.36-7.30 (m, 3H), 5.38 (s, 2H).

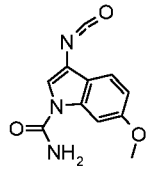
C. 1-carbamoyl-1H-indole-3-carboxylic acid

1-Carbamoyl-1H-indole-3-carboxylic acid benzyl ester (1.33 g, 4.52 mmol) was dissolved in a mixture of DMF/THF 1:1 (28 mL), Pd/C (10 %, 250 mg) was added and the solution was degassed 3 times replacing air by nitrogen and finally nitrogen by hydrogen. The reaction mixture was further stirred under hydrogen atmosphere overnight and the catalyst was removed through a pad of Celite and washed with THF. The solvents were concentrated under high vacuum to give a yellowish solid which was taken up in Et_2O and filtered-off to afford the title compound. 1H-NMR (400 MHz, DMSO): δ (ppm) 12.6 (m, 1H), 8.54 (bs, 1H), 8.28 (d, 1H), 8.05 (d, 1H), 7.85 (m, 2H), 7.34-7.27 (m, 2H).

D. 3-isocyanato-indole-1-carboxylic acid amide

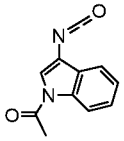
To a suspension of 1-carbamoyl-1H-indole-3-carboxylic acid (1.31 g, 6.42 mmol) in toluene (30 mL, *CH_2Cl_2 can also be used instead of toluene*) under nitrogen was added Et_3N (893 µl, 6.42 mmol). After 15 min DPPA (1.54 mL, 6.42 mmol) was added and the reaction mixture was further stirred at RT overnight. Toluene was concentrated, the residue was taken up in CH_2Cl_2 and the precipitate was filtered-off to give the acyl azide intermediate (565 mg). Toluene (20 mL) was added and the suspension refluxed for 1.5 h under nitrogen atmosphere until no more acyl azide could be detected by TLC. Toluene was concentrated under vacuum and the desired isocyanate was directly used in the next step without further purification. 1H-NMR (400 MHz, CDCl3): δ (ppm) 8.18 (d, 1H), 7.61 (d, 1H), 7.44 (t, 1H), 7.35 (t, 1H), 7.23 (s, 1H), 5.39 (bs, 2H).

3-Isocyanato-6-methoxy-indole-1-carboxylic acid amide



was prepared from 6-methoxy-indole-3-carboxylic acid using the protocol described for the preparation of 3-isocyanato-indole-1-carboxylic acid amide scheme A1.

1-(3-Isocyanato-indol-1-yl)-ethanone



A. 1-Acetyl-1H-indole-3-carboxylic acid benzyl ester

To a solution of 1H-indole-3-carboxylic acid benzyl ester (600 mg, 2.39 mmol) in THF (10 mL) at 0°C under nitrogen was added NaH (60 % in mineral oil, 191 mg, 4.78 mmol). The mixture was stirred for 20 min at 0°C, acetyl chloride (339 µl, 4.78 mmol) was added and the resulting suspension was stirred at RT for 48 h. The solvent was concentrated and the residue poured in water and extracted twice with CH_2Cl_2. The Combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 75:25) to give the desired product as a white solid. TLC, R_f (c-hexane/EtOAc 3:1) = 0.38; MS (LC-MS): 294.1 [M+H]+, 316.0 [M+Na]+; t_R (HPLC conditions a): 4.69 min.

B. 1-Acetyl-1H-indole-3-carboxylic acid

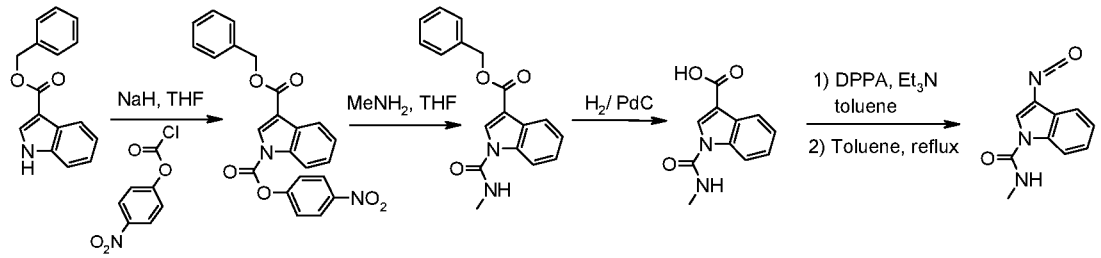
1-Acetyl-1H-indole-3-carboxylic acid benzyl ester (300 mg, 1.02 mmol) was dissolved in MeOH (10 mL), Pd/C 10 % (60 mg) was added and the solution was degassed 3 times replacing air by nitrogen and finally nitrogen by hydrogen. The reaction mixture was further stirred under hydrogen atmosphere 2 h and the catalyst was removed through a pad of Celite and washed with MeOH. The solvent was concentrated under vacuum to give a mixture of 1-acetyl-1H-indole-3-carboxylic acid and 1-acetyl-2,3-dihydro-1H-indole-3-carboxylic acid benzyl ester in a ~ 7:3 ratio as measured by NMR. The desired compound was not purified at this stage but was used directly in the next step. 1-Acetyl-1H-indole-3-carboxylic acid: TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.31; MS (LC-MS): 204.1 [M+H]+, 202.1 [M-H]-; t_R (HPLC conditions a): 3.14 min. 1-Acetyl-2,3-dihydro-1H-indole-3-carboxylic acid benzyl ester: MS (LC-MS): 206.1 [M+H]+, 228.1 [M+Na]+, 433.0 [2M+Na]+, 204.1 [M-H]-; t_R (HPLC conditions a): 1.93 min.

C. 1-(3-Isocyanato-indol-1-yl)-ethanone

To a suspension of of 1-acetyl-1H-indole-3-carboxylic acid (containing ca 30 % of 1-acetyl-2,3-dihydro-1H-indole-3-carboxylic acid benzyl ester, 194 mg) in toluene (5 mL) was added Et_3N (130 µl, 0.935 mmol) and the resulting solution was stirred at RT under nitrogen for 15 min. DDPA (225 µl, 0.935 mmol) was added and the reaction mixture was further stirred at RT overnight. Toluene was concentrated under vacuum and the residue was purified by flash

column chromatography on silica gel (c-hexane to c-hexane/EtOAc 1:1) to give the desired acyl azide intermediate as a white powder (96 mg; t_R HPLC conditions a: 3.86 min). Toluene (3 mL) was added and the mixture was refluxed for 1.5 h until completion of the reaction. Toluene was concentrated under vacuum to give the desired isocyanate. TLC, R_f (c-hexane/EtOAc 1:2) = 0.58; t_R (HPLC conditions a): 3.92 min. 1H-NMR (400 MHz, $CDCl_3$): δ (ppm): 8.44 (m, 1H), 7.56 (d, 1H), 7.44 (t, 1H), 7.36 (t, 1H), 7.23 (d, 1H), 2.60 (s, 3H).

Scheme A2: preparation of 3-Isocyanato-indole-1-carboxylic acid methylamide



A. Indole-1,3-dicarboxylic acid 3-benzyl ester 1-(4-nitro-phenyl) ester

To a solution of 1H-indole-3-carboxylic acid benzyl ester (100 mg, 0.398 mmol) in dry THF (2 mL) at 0°C under nitrogen was added NaH (60 % in mineral oil, 32 mg, 0.796 mmol). The resulting solution was stirred at 0°C for 10 min, and added dropwise to a stirred solution of 4-nitrophenyl chloroformate (160 mg, 0.796 mmol) in dry THF (2 mL) cooled at 0°C. The resulting solution was stirred at RT under nitrogen for 48 h. The mixture was poured into water and extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was successively purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 7:3) and by preparative HPLC (Waters SunFire C18-ODB, 5 µm, 19x50 mm, 20% CH_3CN/H_2O 2.5 min, 20-100% CH_3CN/H_2O in 10 min, CH_3CN/H_2O containing 0.1 % HCOOH flow: 20 mL/min) to give after extraction of the pure fractions the desired compound. TLC, R_f (c-hexane/EtOAc 1:1) = 0.8; MS (LC/MS): 439.0 [M+Na]+; t_R (HPLC conditions a): 4.58 min.

B. 1-Methylcarbamoyl-1H-indole-3-carboxylic acid benzyl ester

To a solution of indole-1,3-dicarboxylic acid 3-benzyl ester 1-(4-nitro-phenyl) ester (45 mg, 0.108 mmol) in dry THF (1 mL) was added methylamine (2 M in THF, 270 µl, 0.54 mmol) and the reaction was stirred at RT for 15 min. The mixture was concentrated and the residue was taken up in Et_2O and filtered to give the desired compound. TLC, R_f (c-hexane/EtOAc 1:1) = 0.52; MS (LC/MS): 309.1 [M+H]+, 331.1 [M+Na]+, 639.2 [2M+Na]+, 353.2 [M+HCOO]-; t_R (HPLC conditions a): 3.86 min.

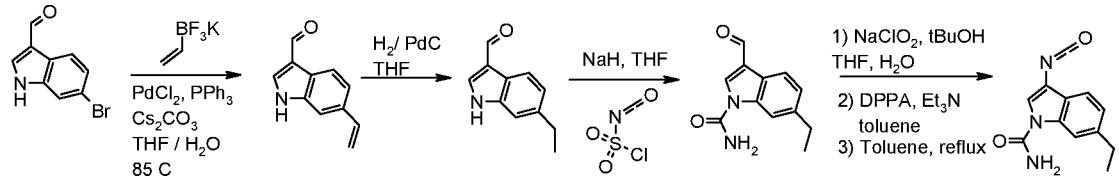
C. 1-Methylcarbamoyl-1H-indole-3-carboxylic acid

To 1-Methylcarbamoyl-1H-indole-3-carboxylic acid benzyl ester (115 mg, 0.373 mmol) dissolved in a mixture of MeOH/CH_2Cl_2 1-1 (4 mL), Pd/C 10 % (20 mg) was added and the solution was degassed 3 times replacing air by nitrogen and finally nitrogen by hydrogen. The reaction mixture was further stirred under hydrogen atmosphere for 1 h. The mixture was placed under a nitrogen atmosphere and the catalyst was removed through a pad of Celite and washed with MeOH. Solvents were concentrated under vacuum to give the desired compound. MS (LC/MS): 219.1 [M+H]+; t_R (HPLC conditions a): 2.54 min.

D. 3-Isocyanato-indole-1-carboxylic acid methylamide

A solution of 1-methylcarbamoyl-1H-indole-3-carboxylic acid (80 mg, 0.367 mmol) and Et_3N (51 µl, 0.367 mmol) in a mixture of toluene/THF 1/1 (4 mL) was stirred at RT under nitrogen for 30 min. DPPA (90 %, 88 µl, 0.367 mmol) was added and the reaction mixture was further stirred at RT under nitrogen overnight. Solvents were concentrated under vacuum and the residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 1-1) to give the acyl azide intermediate as white cristals (83 mg, t_R (HPLC conditions a): 3.40 min). The acyl azide intermediate was refluxed in toluene (2 mL) for 1 h to give after concentration of the solvent the desired isocyanate. The compound was used directly in the next step without further purification.

Scheme A3: preparation of 6-ethyl-3-isocyanato-indole-1-carboxylic acid amide



A. 6-Vinyl-1H-indole-3-carbaldehyde

6-bromoindole-3-carboxaldehyde (5 g, 22.3 mmol), potassium vinyltrifluoroborate (4.48 g, 33.5 mmol), $PdCl_2$ (396 mg, 2.23 mmol), PPh_3 (1.75 mg, 6.7 mmol) and Cs_2CO_3 (2.18 mg, 66.9 mmol) were combined in a 500 mL flask placed under a nitrogen atmosphere. THF (135 mL) and H_2O (15 mL) were added and the yellow solution was heated at 85°C for 2 days. The reaction was allowed to cool to RT, water was added and the mixture was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 1:1) to give the title compound. TLC, R_f (c-hexane/EtOAc 1:1) = 0.4; MS (LC/MS) : 172.0 [M+H]+ 170.1 [M-H]-; t_R (HPLC conditions a): 2.95 min.

B. 6-Ethyl-1H-indole-3-carbaldehyde

6-Vinyl-1H-indole-3-carbaldehyde (1.5 g, 8.76 mmol) was dissolved in THF (45 mL), Pd/C 10% (300 mg) was added and the solution was degassed 3 times replacing air by nitrogen and

finally nitrogen by hydrogen. The reaction mixture was further stirred under hydrogen atmosphere 4 h and the catalyst was removed through a pad of Celite and washed with THF. The solvent was concentrated under and the crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 1:1) to give the desired compound. TLC, R_f (c-hexane/EtOAc 1:1) = 0.40; MS (LC/MS): 174.1 [M+H]+, 196.1 [M+Na]+, 172.1 [M-H]-; t_R (HPLC conditions a): 3.05 min.

C. 6-Ethyl-3-formyl-indole-1-carboxylic acid amide

To a solution of NaH (60 % in mineral oil, 259 mg, 6.47 mmol) in THF (10 mL) cooled to 5°C under nitrogen a solution of 6-ethyl-1H-indole-3-carbaldehyde (1.12 g, 6.47 mmol) in THF (20 mL) was slowly added and the mixture was stired at 5°C for 30 min. While maintaining the internal temperature between 5°C and 10°C, chlorosulfonyl isocyanate (1.12 mL, 12.9 mmol) was added dropwise and the solution was further stirred at RT overnight. Acetic acid (15 mL) was added (slightly exothermic) and the solution was stirred at RT for 1.5 h. Ice cubes and water (25 mL) were added, and the solution was further stirred at RT for 30 min. Water was added and the mixture was extracted with EtOAc. The aqueous layer was back-extracted twice with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to EtOAc) to give the desired compound. LC/MS: 290.0 [M+H]+, 312.0 [M+Na]+; t_R (HPLC conditions a): 3.02 min.

D. 1-Carbamoyl-6-ethyl-1H-indole-3-carboxylic acid

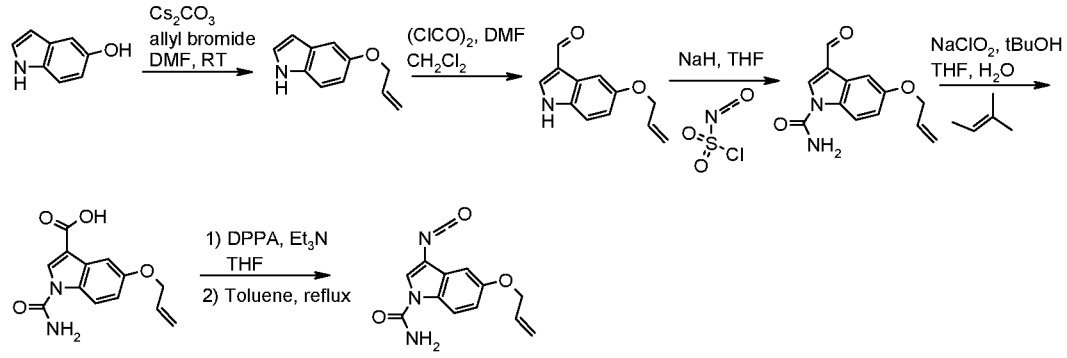
6-Ethyl-3-formyl-indole-1-carboxylic acid amide (720 mg, 3.33 mmol) was dissolved in a mixture of THF (60 mL) and t-butanol (18 mL). 2-methyl-2-butene (2 M solution in THF, 66.6 mL, 133 mmol) was added, followed by a water (16 mL) solution of $NaClO_2$ (80 %, 3.76 g, 33.3 mmol) and NaH_2PO_4 (3.20 g, 26.6 mmol). The resulting solution was stirred at RT for 4 h and THF was concentrated. EtOAc was added and the layers separated. The aqueous layer was acidified by addition of HCl 1N and extracted twice with EtOAc. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (eluent: c-hexane to EtOAc to CH_2Cl_2/MeOH 8:2) to give the desired compound. t_R (HPLC conditions a): 2.17 min. 1H-NMR (400 MHz, $CDCl_3$): δ (ppm): 12.9 (m, 1H), 8.81 (s, 1H), 8.66 (bs, 1H), 8.23 (d, 1H),), 8.09 (m, 2H), 7.70 (dd, 1H).

E. 6-Ethyl-3-isocyanato-indole-1-carboxylic acid amide

To a solution of 1-carbamoyl-6-ethyl-1H-indole-3-carboxylic acid (330 mg, 1.42 mmol) in toluene (8 mL) was added triethylamine (0.198 mL, 1.42 mmol) and the resulting suspension was stirred at RT under nitrogen for 15 min. DPPA (0.34 mL, 1.42 mmol) was added and the

reaction mixture was further stirred at RT for 3 h. TLC indicated completion of the reaction. The mixture was concentrated, CH_2Cl_2 was added and the suspension was filtered to give the acyl azide intermediate. Toluene (4 mL) was added and the reaction mixture was refluxed for 3 h. The crude compound was directly used in the next step.

Scheme A4: general protocol described for the preparation of 5-allyloxy-3-isocyanato-indole-1-carboxylic acid amide



A. 5-Allyloxy-1H-indole

To a suspension of 5-hydroxyindole (1.23 g, 9.24 mmol) and cesium carbonate (3.01 g, 9.24 mmol) in DMF (40 mL) under nitrogen atmosphere at 0°C was added allylbromide (879 µl, 10.16 mmol). The reaction mixture was stirred at RT for 2 h and poured into water and extracted with EtOAc (x3). The combined organic layers were washed twice with water, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 9:1) to give the desired compound. TLC, R_f (c-hexane/EtOAc 1:1) = 0.76; t_R (conditions a): 3.46 min.

B. 5-Allyloxy-1H-indole-3-carbaldehyde

To a solution of oxalyl chloride (1.22 mL, 14.1 mmol) in dry CH_2Cl_2 (20 mL) was added at 0°C under nitrogen a solution of dry DMF (1.3 mL) in dry CH_2Cl_2 (20 mL). The mixture was stirred at 0°C for 30 min and a solution of 5-allyloxy-1H-indole (1.25 g, 7.22 mmol) in CH_2Cl_2 (10 mL) was added. The resulting solution was allowed to reach RT and stirred for 4 h. The solvent was concentrated and the residue dissolved in THF (35 mL) and 20% aqueous ammonium acetate (48 mL) and heated at reflux for 30 min, cooled, treated with an aqueous saturated solution of $NaHCO_3$, and extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude solid was taken up in CH_2Cl_2 and filtered-off to give the desired compound. TLC, R_f (c-hexane/EtOAc 1:2) = 0.56; MS (LC/MS): 202.0 [M+H]+, 224.1 [M+Na]+, 200.1 [M-H]-, 159.1 [M-H-allyl]-; t_R (HPLC conditions a): 2.89 min.

C. 5-Allyloxy-3-formyl-indole-1-carboxylic acid amide

To a suspension of NaH (60 % in mineral oil, 352 mg, 8.79 mmol) in THF (12 mL) under nitrogen atmosphere at 5°C was added a solution of 5-allyloxy-1H-indole-3-carbaldehyde (1.18 g, 5.86 mmol) in THF (28 mL) and the resulting mixture was stirred at 5°C for 30 min before slow addition of chlorosulfonyl isocyanate (11.02 mL, 11.7 mmol) while maintaining the temperature between 5°C and 10°C. The solution was further stirred at RT for 4 h, acetic acid (11 mL) was added and the solution was stirred at RT for 1 h. Ice cubes and water (100 mL) were added and the mixture was stirred at RT for 30 min. The solution was extracted twice with EtOAc and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (100% c-hexane to 100% EtOAc) to give the title compound. TLC, R_f (c-hexane/EtOAc 1:2) = 0.36; MS (LC/MS): 245.1 [M+H]+, 267.0 [M+Na]+, 200.1 [M-$CONH_2$]-; t_R (HPLC conditions a): 2.95 min.

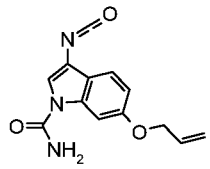
D. 5-Allyloxy-1-carbamoyl-1H-indole-3-carboxylic acid

5-Allyloxy-3-formyl-indole-1-carboxylic acid amide (530 mg, 2.17 mmol) was dissolved in a mixture of THF (38 mL) and t-butanol (12 mL). 2-methyl-2-butene 2 M solution in THF (40 mL, 80 mmol) was added, followed by a water (9.5 mL) solution of $NaClO_2$ (80 %, 2.45 g, 21.7 mmol) and NaH_2PO_4 (2.08 g, 17.4 mmol). The resulting solution was stirred at RT for 1 h, until consumption of the starting material. HCl 1N (3 mL) was added, and the organic solvents were concentrated. The remaining aqueous layer was filtered and the resulting precipitate was washed with water and Et_2O to give the desired compound. TLC, R_f (c-hexane/EtOAc 1:2) = 0.08; LC/MS: 261.1 [M+H]+, 259.0 [M-H]-, 216.1 [M-$CONH_2$]-, 519.1 [2M-H]-; t_R (HPLC conditions a): 2.8 min.

E. 5-Allyloxy-3-isocyanato-indole-1-carboxylic acid amide

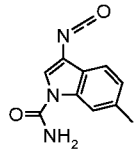
To a suspension of 5-allyloxy-1-carbamoyl-1H-indole-3-carboxylic acid (500 mg, 1.92 mmol) in THF (10 mL) was added Et_3N (267 µl, 1.92 mmol) and the resulting solution was stirred at RT under nitrogen for 15 min. DDPA (462 µl, 1.92 mmol) was added and the reaction was further stirred at RT under nitrogen for 1 h. TLC indicated consumption of the starting material. THF was concentrated and the residue was taken up in CH_2Cl_2 and filtered-off to give the crude acyl azide intermediate (TLC, R_f (c-hexane/EtOAc 1:2) = 0.65; t_R (HPLC conditions a): 3.50 min). The acyl azide intermediate was suspended in toluene (7 mL) and refluxed under nitrogen for 2 h until completion of the reaction. The crude isocyanate was used as was in the next step.

6-Allyloxy-3-isocyanato-indole-1-carboxylic acid amide



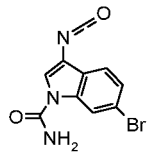
was prepared from 6-hydroxy-indole using the protocol described for the preparation of 5-allyloxy-3-isocyanato-indole-1-carboxylic acid amide in Scheme A4.

6-Methyl-3-isocyanato-indole-1-carboxylic acid amide



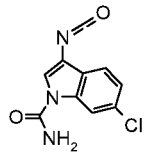
was prepared from 6-methyl-1H-indole-3-carbaldehyde using the protocol described for steps C, D and E in scheme A4 for the preparation of 5-allyloxy-3-isocyanato-indole-1-carboxylic acid amide.

6-Bromo-3-isocyanato-indole-1-carboxylic acid amide



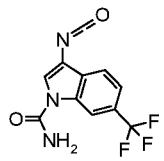
was prepared from 6-bromo-1H-indole-3-carbaldehyde using the protocol described for steps C, D and E in scheme A4 for the preparation of 5-allyloxy-3-isocyanato-indole-1-carboxylic acid amide.

6-Chloro-3-isocyanato-indole-1-carboxylic acid amide



was prepared from 6-chloroindole using the protocol described for steps B-E in scheme A4 for the preparation of 5-allyloxy-3-isocyanato-indole-1-carboxylic acid amide.

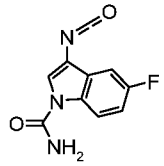
6-Trifluoromethyl-3-isocyanato-indole-1-carboxylic acid amide



was prepared from 6-trifluoromethylindole using the protocol described for steps B-E in scheme A4 for the preparation of 5-allyloxy-3-isocyanato-indole-1-carboxylic acid amide

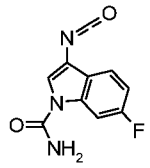
except that the acyl azide intermediate was prepared in 1,2 dimethoxyethane instead of toluene.

5-Fluoro-3-isocyanato-indole-1-carboxylic acid amide



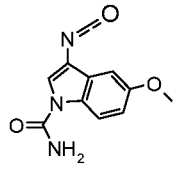
was prepared from 5-fluoro-1H-indole-3-carbaldehyde using the protocol described for steps C, D and E in scheme A4 for the preparation of 5-allyloxy-3-isocyanato-indole-1-carboxylic acid amide.

6-Fluoro-3-isocyanato-indole-1-carboxylic acid amide



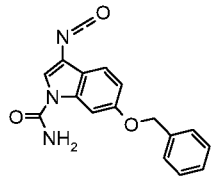
was prepared from 6-fluoro-1H-indole-3-carbaldehyde [2795-41-7] using the protocol described for steps C, D and E in scheme A4 for the preparation of 5-allyloxy-3-isocyanato-indole-1-carboxylic acid amide.

3-Isocyanato-5-methoxy-indole-1-carboxylic acid amide



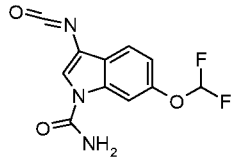
was prepared from 5-methoxy-1H-indole-3-carbaldehyde using the protocol described for steps C, D and E in scheme A4 for the preparation of 5-allyloxy-3-isocyanato-indole-1-carboxylic acid amide.

6-Benzyloxy-3-isocyanato-indole-1-carboxylic acid amide



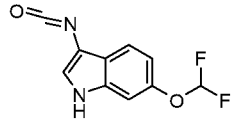
was prepared from 6-benzyloxyindole using the protocol described for steps B-E in scheme A4 for the preparation of 5-allyloxy-3-isocyanato-indole-1-carboxylic acid amide.

6-Difluoromethoxy-3-isocyanato-indole-1-carboxylic acid amide



was prepared from 6-difluoromethoxy-1H-indole [200207-21-2] using the protocol described for steps B-E in Scheme A4 for the preparation of 5-allyloxy-3-isocyanato-indole-1-carboxylic acid amide.

6-Difluoromethoxy-3-isocyanato-1H-indole

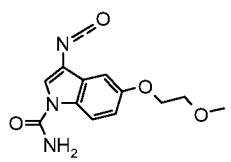


To a suspension of 1-carbamoyl-6-difluoromethoxy-1H-indole-3-carboxylic acid (180 mg, 0.66 mmol) in THF (6 mL) was added Et_3N (111 µl, 0.8 mmol) and the resulting solution was stirred at RT under nitrogen for 10 min. DDPA (220 µl, 0.8 mmol) was added and the reaction was further stirred at RT under nitrogen for 3 h. TLC indicated consumption of the starting material. The reaction mixture was concentrated and the crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 4:1 to 1:1) to give 6-difluoromethoxy-1H-indole-3-carbonyl azide (MS: 251 [M-H]-; t_R (HPLC conditions k): 3.57 min) and 1-carbamoyl-6-difluoromethoxy-1H-indole-3-carbonyl azide (MS: 251 [M-$CONH_2$]-; 268 [M-N_2]+; t_R (HPLC conditions k): 3.46 min). 6-Difluoromethoxy-1H-indole-3-carbonyl azide intermediate was suspended in toluene (6 mL) and refluxed under nitrogen for 3 h until completion of the reaction. The crude isocyanate was used as was in the next step.

1-Carbamoyl-6-difluoromethoxy-1H-indole-3-carboxylic acid

was prepared from 6-difluoromethoxy-1H-indole [200207-21-2] using the protocol described for steps B-D in Scheme A4 for the preparation of 5-allyloxy-3-isocyanato-indole-1-carboxylic acid amide.

3-Isocyanato-5-(2-methoxy-ethoxy)-indole-1-carboxylic acid amide

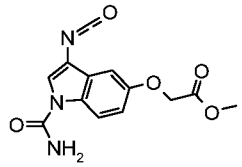


was prepared from 5-(2-methoxy-ethoxy)-1H-indole using the protocol described for steps B-E in scheme A4 for the preparation of 5-allyloxy-3-isocyanato-indole-1-carboxylic acid amide.

5-(2-Methoxy-ethoxy)-1H-indole

5-hydroxyindole (5 g, 15 mmol) was dissolved in acetone (75 mL), cesium carbonate (5.38 g, 16.5 mmol) and 2-bromoethyl methyl ether (1.55 mL, 16.5 mmol) were added and the reaction mixture was stirred at reflux under nitrogen overnight. Acetone was concentrated. The residue was dissolved in water and extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 7/3) to give the desired material. TLC, R_f (c-hexane/EtOAc 1:1) = 0.6; MS (LC-MS): 192.1 [M+H]+, 214.0 [M+Na]+, 405.1 [2M+Na]+; tR (HPLC conditions f): 1.56 min.

(1-Carbamoyl-3-isocyanato-1H-indol-5-yloxy)-acetic acid methyl ester

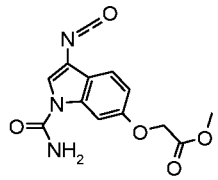


was prepared from (1H-indol-5-yloxy)-acetic acid methyl ester using the protocol described for steps B-E in scheme A4 for the preparation of 5-allyloxy-3-isocyanato-indole-1-carboxylic acid amide.

(1H-Indol-5-yloxy)-acetic acid methyl ester

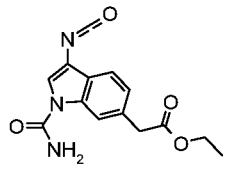
A solution of 5-hydroxyindole (5.07 g, 38.1 mmol) and cesium carbonate (12.4 g, 38.1 mmol) in acetone (150 mL) was cooled to 0°C and methyl bromoacetate (3.96 mL, 41.9 mmol) was added. The reaction mixture was then stirred at RT under nitrogen for 2 h. The reaction mixture was concentrated. The residue was diluted with water and extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The resulting solid was taken up in Et_2O and filtered-off to the desired material. TLC, R_f (c-hexane/EtOAc 1:1) = 0.55; MS (LC-MS): 206.1 [M+H]+, 433.0 [2M+Na]+; t_R (HPLC conditions f): 1.64 min.

(1-Carbamoyl-3-isocyanato-1H-indol-6-yloxy)-acetic acid methyl ester



was prepared from (1H-indol-6-yloxy)-acetic acid methyl ester using the protocol described for the preparation of (1-carbamoyl-3-isocyanato-1H-indol-5-yloxy)-acetic acid methyl ester.

(1-Carbamoyl-3-isocyanato-1H-indol-6-yl)-acetic acid ethyl ester



was prepared from (1H-indol-6-yl)-acetic acid ethyl ester using the protocol described for steps B-E in scheme A4 for the preparation of 5-allyloxy-3-isocyanato-indole-1-carboxylic acid amide.

(1H-Indol-6-yl)-acetic acid ethyl ester

To a solution of 6-ethoxycarbonylmethyl-indole-1-carboxylic acid methyl ester (965 mg, 3.25 mmol) in EtOH (10 mL) was added dimethylamine (~5.6 M in EtOH, 24.4 mL, 48.8 mmol) and the solution was stirred at RT overnight. EtOH was concentrated and the crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 85:15) to give the desired material. MS (UPLC): 204.2 [M+H]+, 221.2 [M+NH4]+, 248.2 [M+HCOO]-; t_R (HPLC conditions f): 1.87 min.

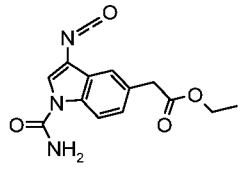
6-Ethoxycarbonylmethyl-indole-1-carboxylic acid methyl ester

A mixture of 6-bromo-indole-1-carboxylic acid methyl ester (1.12 g, 4.43 mmol), ethyl acetoacetate (1.23 mL, 9.74 mmol), palladium acetate (20 mg, 0.089 mmol), 2-di-tert-butylphosphino-2′-methylbiphenyl (55 mg, 0.177 mmol) and K_3PO_4 (2.58 g, 12.2 mmol) in toluene (6 mL) was heated at 100°C under nitrogen overnight. The reaction was poured into water and extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 93:7) to give the desired material. TLC, R_f (c-hexane/EtOAc 4:1) = 0.3; MS (UPLC): 262.2 [M+H]+, 279.2 [M+NH_4]+, 284.2 [M+Na]+, 523.3 [M+Na]+, 545.3 [2M+Na]+; t_R (HPLC conditions f): 2.11 min.

6-Bromo-indole-1-carboxylic acid methyl ester

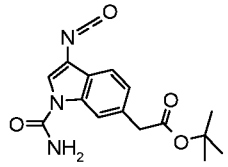
To a solution of 6-bromoindole (1.46 g, 7.44 mmol) in DMF (35 mL) under nitrogen atmosphere, was added NaH (60 % in mineral oil, 327 mg, 8.19 mmol), followed by methyl chloroformate (652 µL, 8.19 mmol) and the resulting solution was sitrred at RT overnight. The mixture was poured into water and extracted twice with EtOAc. The combined organic layers were washed again with water, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 88:12) to give the desired material. TLC, R_f (EtOAc) = 0.75; MS (UPLC): 254.2/255.2 [M+H]+; t_R (HPLC conditions f): 2.32 min.

(1-Carbamoyl-3-isocyanato-1H-indol-5-yl)-acetic acid ethyl ester



was prepared from 5-bromoindole as described for the synthesis of (1-carbamoyl-3-isocyanato-1H-indol-6-yl)-acetic acid ethyl ester.

(1-Carbamoyl-3-isocyanato-1H-indol-6-yl)-acetic acid tert-butyl ester

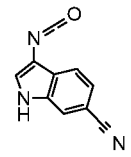


was prepared from (1H-indol-6-yl)-acetic acid tert-butyl ester using the protocol described for steps B-E in scheme A4 for the preparation of 5-allyloxy-3-isocyanato-indole-1-carboxylic acid amide.

(1H-Indol-6-yl)-acetic acid tert-butyl ester

To a solution of 6-bromoindole (2 g, 10.2 mmol) in THF (20 mL) under nitrogen atmosphere was added KH (30 % in mineral oil de-greased with pentane, 1.5 g, 11.22 mmol) and the mixture was stirred at RT for 30 min before addition of $[P(t\text{-}Bu)_3PdBr]_2$ (40 mg, 0.051 mmol) diluted in THF (20 mL). The resulting mixture was added to a solution of 2-tert-butoxy-2-oxoethylzinc chloride (0.5 M in Et_2O, 22.4 mL, 11.2 mmol) stirred under nitrogen atmosphere and the mixture was further stirred at RT for 24 h. The reaction mixture was diluted with EtOAc, and washed with a saturated aqueous solution of $NaHCO_3$, then with water. The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 94:6 to c-hexane/EtOAc 8:2) to give the desired material. TLC, R_f (c-hexane/EtOAc 4:1) = 0.3; MS (UPLC): 232.2 [M+H]+, 176.1 [MH-tBu]+, 249.2 $[M+NH_4]$+, 463.4 [2M+H]+, 273.3 [M+HCOO]-.

3-Isocyanato-1H-indole-6-carbonitrile



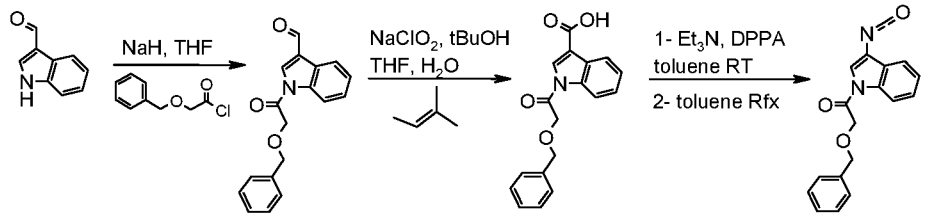
To a solution of 1-carbamoyl-6-cyano-1H-indole-3-carboxylic acid (210 mg, 0.916 mmol) in toluene (6 mL) was added Et_3N (128 µl, 0.916 mmol) and the resulting yellow suspension was stirred at RT under nitrogen 15 min before addition of DDPA (220 µl, 0.916 mmol). The

reaction mixture was further stirred at RT overnight. The crude reaction mixture was concentrated and purified by flash column chromatography (c-hexane to c-hexane/EtOAc 1:1) to give 6-cyano-1H-indole-3-carbonyl azide (TLC, R_f (EtOAc) = 1); t_R (HPLC conditions a): 3.29 min; 1H-NMR (400 MHz, DMSO): δ (ppm): 12.7 (bs, 1H), 8.45 (s, 1H), 8.20 (d, 1H), 8.04 (bs, 1H), 7.62 (dd, 1H). Toluene (4 mL) was added and the reaction mixture was refluxed for 3 h to generate the corresponding isocynate, which was used without purification in the next step.

1-Carbamoyl-6-cyano-1H-indole-3-carboxylic acid

was prepared from 6-cyano-indole using the protocol described for steps B-E in scheme A4 for the preparation of 5-allyloxy-3-isocyanato-indole-1-carboxylic acid amide.

Scheme A5: preparation of 2-benzyloxy-1-(3-isocyanato-indol-1-yl)-ethanone



A. 1-(2-Benzyloxy-acetyl)-1H-indole-3-carbaldehyde

To a solution of indole-3-carboxaldehyde (2 g, 13.8 mmol) in THF (70 mL) at 5°C, was added NaH (60 % in mineral oil, 551 mg, 13.8 mmol) under nitrogen atmosphere. The mixture was stirred at 5°C for 30 min before dropwise addition of benzyloxyacetyl chloride (2.6 mL, 16.53 mmol) over 20 min maintaining the internal temperature between 5°C and 10°C. The resulting dark solution was further stirred at RT for 1 h. As the reaction was not completed benzyloxyacetyl chloride (1 mL, 6.44 mmol, 0.5 eq) and NaH (60 % in mineral oil, 551 mg, 13.8 mmol) were added and the mixture was further stirred at RT for 3 days. The reaction mixture was concentrated, and the residue taken up in CH_2Cl_2 and washed with water. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 4-1) corresponding to the desired compound. TLC, R_f (c-hexane/EtOAc 1:1) = 0.61; MS (LC/MS): 294.1 [M+H]+, 316.1 [M+Na]+; t_R (HPLC conditions a): 3.87 min.

B. 1-(2-Benzyloxy-acetyl)-1H-indole-3-carboxylic acid

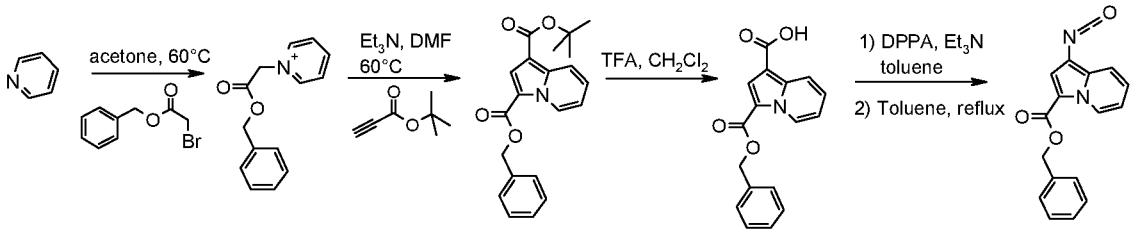
To a solution of 1-(2-benzyloxy-acetyl)-1H-indole-3-carbaldehyde (1.53 g, 5.22 mmol) in a mixture of THF (80 mL) and t-butanol (24 mL). A 2 M 2-methyl-2-butene solution in THF (104 mL, 209 mmol) was added, followed by a water (20 mL) solution of $NaClO_2$ (80 %, 5.9 g, 52.2 mmol) and NaH_2PO_4 (5 g, 41.7 mmol). The resulting yellow solution was stirred at RT for 2 h. The solvents were concentrated and the aqueous layer was filtered and the resulting

precipitate was washed with Et_2O to give the desired compound. LC/MS: 310.1 [M-H]-, 332.0 [M+Na]+, 308.0 [M-H]-, 617.0 [2M-H]-; t_R (HPLC conditions a): 3.62 min.

C. 2-Benzyloxy-1-(3-isocyanato-indol-1-yl)-ethanone

A solution of 1-(2-benzyloxy-acetyl)-1H-indole-3-carboxylic acid (200 mg, 0.647 mmol) and Et_3N (90 µl, 0.647 mmol) in toluene (3 mL) was stirred at RT under nitrogen for 15 min. DDPA (90 %, 155 µl, 0.647 mmol) was added and the reaction mixture was further stirred at RT for 3 h. Toluene was concentrated to give the acyl azide intermediate (TLC-R_f (c-hexane/EtOAc 1:1) = 0.73; t_R (HPLC conditions a) = 4.26 min). The crude azide was refluxed in toluene (3 mL) for 1 h and toluene was concentrated to give the desired isocyanate which was used in the next step without further purification.

Scheme A6: preparation of 1-isocyanato-indolizine-3-carboxylic acid benzyl ester



A. 1-Benzyloxycarbonylmethyl-pyridinium bromide

To a solution of benzyl bromoacetate (10 g, 43.7 mmol) in acetone (200 mL) was added a solution of pyridine (3.51 mL, 43.7 mmol) in acetone (20 mL) and the resulting mixture was stirred at 60°C under nitrogen over the week-end. Then allowed to cool to RT and concentrated to give the desired material. MS (LC/MS): 228.1 [MH]+.

B. Indolizine-1,3-dicarboxylic acid 3-benzyl ester 1-tert-butyl ester

To a suspension of 1-benzyloxycarbonylmethyl-pyridinium bromide (1.50 g, 9.74 mmol) and *tert*-butyl propiolate (1.34 mL, 9.74 mmol) in DMF (80 mL) was added a solution of triethylamine (4.1 mL, 29.2 mmol) in DMF (10 mL). The mixture was vigourously stirred 4 h at 60°C under air atmosphere. The solution was allowed to cool to RT, poured into water and extracted with EtOAc (2x). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 8:2) to give the desired material. TLC, R_f (c-hexane/EtOAc 8:2) = 0.6; MS (LC/MS): 725.3 [2M+Na]+; t_R (HPLC conditions a): 4.84 min.

C. Indolizine-1,3-dicarboxylic acid 3-benzyl ester

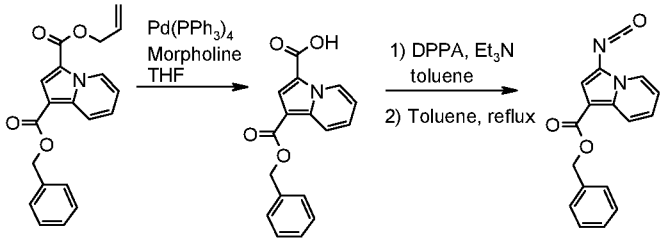
A solution of indolizine-1,3-dicarboxylic acid 3-benzyl ester 1-tert-butyl ester (400 mg, 1.14 mmol) and TFA (872 µl, 11.4 mmol) in CH_2Cl_2 (10 mL) was stirred at RT overnight. The

reaction mixture was concentrated and the crude solid was taken-up in a mixture of MeOH and CH_2Cl_2, the precipitate was filtered-off and washed with a minimum of MeOH to give the desired compound as a white powder. The filtrate was concentrated and purified by flash column chromatography on silica gel (CH_2Cl_2 to CH_2Cl_2/MeOH 95:5) to give again the desired compound. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.6; MS (LC/MS): 296.0 [M+H]+ 294.1 [M-H]-; t_R (HPLC conditions a): 3.64 min.

D. 1-Isocyanato-indolizine-3-carboxylic acid benzyl ester

was prepared from indolizine-1,3-dicarboxylic acid 3-benzyl ester using the protocol described in step E scheme A4 for the preparation of 5-allyloxy-3-isocyanato-indole-1-carboxylic acid amide.

Scheme A7: preparation of 3-isocyanato-indolizine-1-carboxylic acid benzyl ester



Indolizine-1,3-dicarboxylic acid 3-allyl ester 1-benzyl ester

The title compound was prepared using the protocol described in steps A and B for the preparation of 1-isocyanato-indolizine-3-carboxylic acid benzyl ester scheme A6 using bromo-acetic acid allyl ester in step A and propionic acid benzyl ester in step B. TLC, R_f (c-hexane/EtOAc 1:1)= 0.8; MS (LC/MS): 336.1 [M+H]+, 358.1 [M+Na]+, 693.2 [2M+Na]+; t_R (HPLC conditions a): 4.55 min.

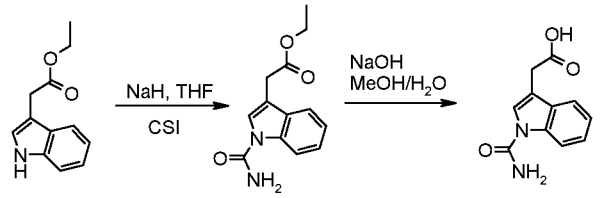
A. Indolizine-1,3-dicarboxylic acid 1-benzyl ester

To a solution of indolizine-1,3-dicarboxylic acid 3-allyl ester 1-benzyl ester (300 mg, 0.895 mmol) in THF (6 mL) were added $Pd(PPh_3)_4$ (34.5 mg, 0.09 mmol) and morpholine (260 mg, 8.95 mmol). The reaction mixture was stirred at RT under nitrogen atmosphere for 30 min. The reaction mixture was diluted in EtOAC, extracted twice with HCl 1N and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated to give the desired compound which was used without further purification in the next step TLC, R_f (CH_2Cl_2/MeOH 9:1)= 0.4: MS (LC/MS): 294.0 [M-H]-; t_R (HPLC conditions a): 3.62 min.

B. 3-Isocyanato-indolizine-1-carboxylic acid benzyl ester

The title compound was prepared from indolizine-1,3-dicarboxylic acid 1-benzyl ester using the protocol described in step E scheme A4 for the preparation of 5-allyloxy-3-isocyanato-indole-1-carboxylic acid amide.

Scheme A8: preparation of (1-carbamoyl-1H-indol-3-yl)-acetic acid



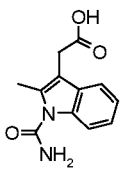
A. (1-Carbamoyl-1H-indol-3-yl)-acetic acid ethyl ester

To a solution of (1H-indol-3-yl)-acetic acid ethyl ester (2.5 g, 12.30 mmol) in THF (58 mL) at 0°C was added sodium hydride (60% in mineral oil, 0.354 g, 14.8 mmol) portionwise under argon. The dark brown solution was stirred at 0°C for 45 min before dropwise addition of chlorosulfonylisocyanate (2.14 mL, 24.6 mmol). The reaction mixture was allowed to warm to RT overnight under stirring. Acetic acid (3 mL) was then added to the mixture which was stirred at RT for 20 min. Ice was added to mixture which was stirred for 60 min then diluted with water and extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried (Phase separator) and concentrated in vacuo. The residual oil was purified via flash column chromatography on silica gel (EtOAc/cyclohexane 1:3 to 2:3) to give the desired material. TLC, R_f (EtOAc/cyclohexane 1:1) = 0.35; MS: 247 [M+H]+, 493 [2M+H]+; t_R (HPLC conditions b) 3.51 min.

B. (1-Carbamoyl-1H-indol-3-yl)-acetic acid

To a suspension of (1-carbamoyl-1H-indol-3-yl)-acetic acid ethyl ester in methanol (61 mL) and water (6.1 mL) was added an 1N aqueous solution of NaOH (12.2 mL, 12.2 mmol) and the resulting yellow solution was stirred at RT for 4 h. The reaction mixture was concentrated under reduced pressure and the residue was suspended in HCl 1N. The aqueous mixture was extracted with EtOAC (3x), the combined organic extracts were dried (phase separator) and concentrated in vacuo. The crude product was used directly in the next step without any further purification. MS: 219 [M+H]+, 437 [2M+H]+; t_R (HPLC conditions b) 2.16 min.

(1-Carbamoyl-2-methyl-1H-indol-3-yl)-acetic acid

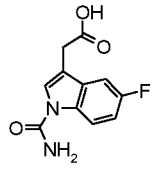


was prepared in a similar manner as described in Scheme A8 Step B for (1-carbamoyl-1H-indol-3-yl)-acetic acid starting from (1-carbamoyl-2-methyl-1H-indol-3-yl)-acetic acid ethyl ester. The crude product (brownish solid) obtained after extractive work-up was used directly in the next step without purification. MS: 233 [M+H]+; t_R (HPLC conditions b) 3.26 min.

(1-Carbamoyl-2-methyl-1H-indol-3-yl)-acetic acid ethyl ester

The title compound was prepared in a similar manner as described in Scheme A8 Step A starting from (2-methyl-1H-indol-3-yl)-acetic acid ethyl ester [21909-49-9] (1.20 g, 5.52 mmol), NaH (60 % in mineral oil, 331 mg, 8.28 mmol) and chlorosulfonylisocyanate (0.959 mL, 11.1 mmol). Purification by flash column chromatography on silica gel (EtOAc/c-hexane 1:4 to 1:1) afforded a yellowish solid. TLC, R_f (EtOAc/c-hexane 1:1) = 0.31; MS: 261 [M+H]+; t_R (HPLC conditions b) 3.54 min.

(1-Carbamoyl-5-fluoro-1H-indol-3-yl)-acetic acid

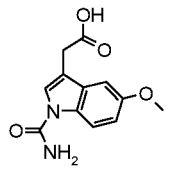


was prepared in a similar manner as described in Scheme A8 Step B for (1-carbamoyl-1H-indol-3-yl)-acetic acid starting from (1-carbamoyl-5-fluoro-1H-indol-3-yl)-acetic acid ethyl ester. The crude product (yellowish solid) obtained after extractive work-up was used directly in the next step without purification. MS: 236.9 [M+H]+; t_R (HPLC conditions b) 2.4 min.

(1-Carbamoyl-5-fluoro-1H-indol-3-yl)-acetic acid ethyl ester

The title compound was prepared in a similar manner as described in Scheme A8 Step A starting from (5-fluoro-1H-indol-3-yl)-acetic acid methyl ester [497258-29-4] (150 mg, 0.724 mmol), NaH (60 % in mineral oil, 37.4 mg, 0.869 mmol) and chlorosulfonylisocyanate (0.126 mL, 1.45 mmol). Purification by flash column chromatography on silica gel (EtOAc/c-hexane gradient 1:3 to 2:3) afforded the title compound. TLC, R_f (EtOAc/c-hexane 1:1) = 0.16; MS: 261 [M+H]+, 501 [2M+H]+; t_R (HPLC conditions b) 3.2 min.

(1-Carbamoyl-5-methoxy-1H-indol-3-yl)-acetic acid



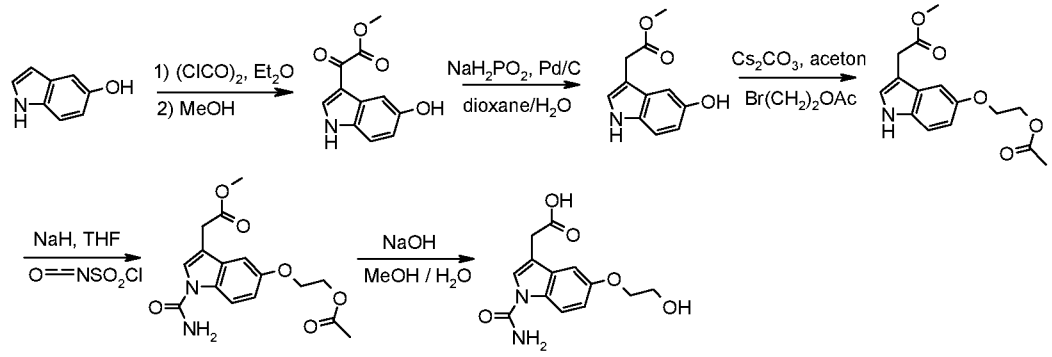
was prepared from 5-methoxy-3-indolylacetic acid methyl ester according to the protocol described scheme A8 for the preparation of (1-carbamoyl-1H-indol-3-yl)-acetic acid. Rf, TLC

(EtOAC) = 0.2; MS (LC/MS): 248.9 [M+H]+, 271.0 [M+Na]+, 247.1 [M-H]-, 495.1 [2M-H]-, 204.1 [M-$CONH_2$]-; t_R (HPLC conditions f): 1.54 min.

5-methoxy-3-indolylacetic acid methyl ester

To a suspension of 5-methoxy-3-indolylacetic acid (500 mg, 2.44 mmol) in CH_2Cl_2 (7 mL) were added DCC (553 mg, 2.68 mmol), DMAP (30 mg, 0.244 mmol) and methanol (99 µL, 2.44 mmol). The resulting white suspension was stirred at RT under nitrogen for 2.5 h. The mixture was filtered and the filtrate concentrated to give a brown oil which was purified by flash column chromatography on silica gel (c-hexane to c-hexane/ EtOAc 8-2) to afford the desired material as a brown oil. TLC, Rf (EtOAc) = 0.82; MS (LC-MS): 220.0 [M+H]+, 242.1 [M+Na]+, 461.0 [2M+Na]+, 218.1 [M-H]-; t_R (HPLC conditions f) 3.2 min.

Scheme A9: [1-carbamoyl-5-(2-hydroxy-ethoxy)-1H-indol-3-yl]-acetic acid



A. (5-Hydroxy-1H-indol-3-yl)-oxo-acetic acid methyl ester

To a solution of oxalyl chloride (3.18 mL, 37.6 mmol) in dry ether (50 mL) was added 5-hydroxyindole (2.5 g, 18.8 mmol) in small portions over 15 min at - 5°C under nitrogen, and the resulting mixture was stirred at RT for 30 min. The suspension was filtered and the residue was washed with Et_2O. Dry MeOH (60 mL) was carefully added, and the resulting mixture was stirred at RT for 1 h. The suspension was filtered and successively washed with MeOH and Et_2O to afford the desired material. TLC, R_f (EtOAc) = 0.75; MS (LC-MS): 220.0 [M+H]+, 242.1 [M+Na]+, 461.0 [2M+Na]+, 218.1 [M-H]-; t_R (HPLC conditions f): 1.02 min.

B. (5-Hydroxy-1H-indol-3-yl)-acetic acid methyl ester

To a suspension of (5-hydroxy-1H-indol-3-yl)-oxo-acetic acid methyl ester (1 g, 4.56 mmol) in dioxane (14 mL) was added Pd/C 10% (400 mg) and a solution of $NaH_2PO_2.H_2O$ (4.84 g, 45.6 mmol) in water (2.35 mL). The reaction mixture was stirred and heated to reflux for 1.5 h. After completion the reaction mixture was cooled to RT, and the catalyst removed by filtration through a pad of Celite and washed with MeOH. Solvents were concentrated, and the residue was dissolved in CH_2Cl_2 and washed with water. The organic layer was dried over Na_2SO_4, filtered and concentrated to give the desired material. TLC, R_f (EtOAc) = 0.85; MS (LC-MS):

206.1 [M+H]+. 1H-NMR (400 MHz, DMSO): δ (ppm): 10.64 (bs, 1H), 8.64 (s, 1H), 7.14 (m, 2H), 6.78 (d, 1H), 6.60 (dd, 1H), 3.65 (s, 3H), 3.58 (s, 2H).

C. [5-(2-Acetoxy-ethoxy)-1H-indol-3-yl]-acetic acid methyl ester

To a solution of (5-hydroxy-1H-indol-3-yl)-acetic acid methyl ester (670 mg, 3.26 mmol) in acetone (15 mL) was added cesium carbonate (1.17 g, 3.59 mmol) and 2-bromoethyl acetate (395 µL, 3.59 mmol). The suspension was refluxed overnight under nitrogen. Acetone was concentrated and the residue was dissolved in water and extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 6:4) to give the desired material. TLC, R_f (c-hexane/EtOAc 1:1) = 0.45; MS (LC-MS): 292.1 [M+H]+, 314.0 [M+Na]+, 290.0 [M-H]-; t_R (HPLC conditions f): 1.70 min.

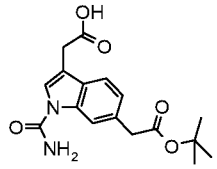
D. 5-(2-Acetoxy-ethoxy)-1-carbamoyl-1H-indol-3-yl]-acetic acid methyl ester

A suspension of NaH (60 % in mineral oil, 43 mg, 1.06 mmol) in THF (2.5 mL) under nitrogen atmosphere was cooled to 5°C and a solution of [5-(2-acetoxy-ethoxy)-1H-indol-3-yl]-acetic acid methyl ester (249 mg, 0.71 mmol) in THF (2.5 mL) was added. The mixture was stirred 30 min before slow addition of chlorosulfonyl isocyanate (123 µL, 1.42 mmol) at 5°C. The resulting solution was then stirred overnight allowing the temperature to slowly reach RT. Acetic acid (1.3 mL) was added, and the solution was stirred at RT for 1h, before addition of ice and water (16 mL). The mixture was further stirred at RT for 30 min and was extracted twice with EtOAc. The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (100% c-hexane to 100% EtOAc) to afford the desired material. TLC, R_f (EtOAc) = 0.7; MS (LC-MS): 335.0 [M+H]+, 357.1 [M+Na]+, 333.1 [M-H]-, 290.0 [M-$CONH_2$]-, 379.0 [M+HCOO]-; t_R (HPLC conditions f): 1.63 min.

E. [1-Carbamoyl-5-(2-hydroxy-ethoxy)-1H-indol-3-yl]-acetic acid

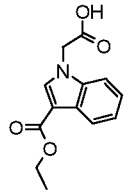
5-(2-Acetoxy-ethoxy)-1-carbamoyl-1H-indol-3-yl]-acetic acid methyl ester (54 mg, 0.153 mmol) was dissolved in MeOH (1.3 mL) and H2O (130 µL). NaOH 1N (307 µL, 0.307 mmol) was added and the mixture was stirred at RT for 1h. The reaction mixture was concentrated, the crude poured into HCl 1N and extracted twice with CH_2Cl_2. A precipitate formed in the aqueous layer and was filtered-off to give the desired material. TLC, R_f (EtOAc) = 0.15; MS (LC/MS): 279.1 [M+H]+, 301.0 [M+Na]+, 277.0 [M-H]-, 233.9 [M-$CONH_2$]-; 1H-NMR (400 MHz, DMSO): δ (ppm): 12.4 (bs, 1H), 8.13 (d, 1H), 7.73 (s, 1H), 7.43 (bs, 2H), 7.05 (d, 1H), 6.89 (dd, 1H), 4.0 (t, 2H), 3.74 (t, 2H), 3.64 (d, 2H).

(6-tert-Butoxycarbonylmethyl-1-carbamoyl-1H-indol-3-yl)-acetic acid



was prepared from (1H-indol-6-yl)-acetic acid tert-butyl ester (described for the preparation of (1-carbamoyl-3-isocyanato-1H-indol-6-yl)-acetic acid tert-butyl ester) according to the protocol described scheme A9 steps A, B, D, E for the preparation of [1-carbamoyl-5-(2-hydroxy-ethoxy)-1H-indol-3-yl]-acetic acid. MS (LC/MS): 350.2/352.2 [M+NH4]+, 687.2/689.2 [2M+Na]+, 277.0/279.0 [MH-tBu]+, 288.0/290.0 [M-$CONH_2$]-, 376.9/378.8 [M+HCOO]-, 662.8/664.7 [2M-H]-; t_R (HPLC conditions f): 1.79 min.

1-Carboxymethyl-1H-indole-3-carboxylic acid ethyl ester

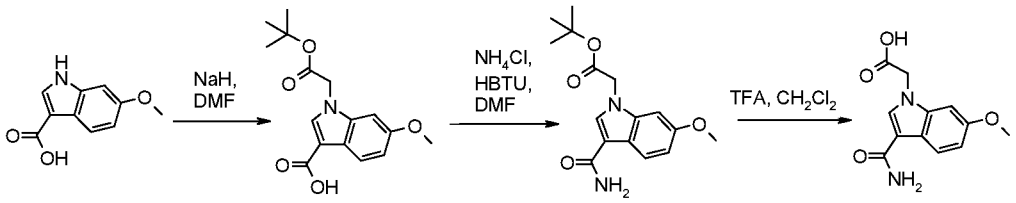


1-tert-Butoxycarbonylmethyl-1H-indole-3-carboxylic acid ethyl ester (700 mg, 2.31 mmol) was dissolved in CH_2Cl_2 (12 mL), TFA (2.65 mL, 34.6 mmol) was added and the solution was stirred at RT over week end. CH_2Cl_2 and water were added, the layers were separated and the aqueous one re-extracted with CH_2Cl_2 (2x). The combined organic layers were dried with Na_2SO_4, filtered and concentrated to give the desired compound. TLC, R_f (EtOAc) = 0.62; MS (LC/MS): 248.1 [M+H]+, 246.0 [M-H]- ; t_R (HPLC conditions a): 3.03 min.

1-tert-Butoxycarbonylmethyl-1H-indole-3-carboxylic acid ethyl ester

To a suspension of 1H-indole-3-carboxylic acid ethyl ester (800 mg, 4.23 mmol) and potassium carbonate (1.34 g, 9.72 mmol) in CH_3CN (21 mL) under nitrogen was added *tert*-butyl bromoacetate (875 µL, 5.92 mmol) and the reaction mixture was heated at reflux overnight. The reaction mixture was allowed to cool to RT, EtOAc and water were added and the layers were separated, the aqueous one being re-extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography (c-hexane to c-hexane/EtOAc 1:1) to afford the desired compound. TLC, R_f (EtOAc) = 0.77; MS (LC/MS) : 304.1 [M+H]+, 302.0 [M-H]-; t_R (HPLC conditions a): 4.01 min.

Scheme A10: preparation of (3-carbamoyl-6-methoxy-indol-1-yl)-acetic acid



A. 1-tert-Butoxycarbonylmethyl-6-methoxy-1H-indole-3-carboxylic acid

To an ice-cooled suspension of 6-methoxy-1H-indole-3-carboxylic acid (1 g, 5.23 mmol) in DMF (35 mL) was added NaH (60% suspension in oil; 0.523 g, 13.1 mmol) in one portion, and the mixture was stirred at 0°C for 30 min. Tert-butyl-2-bromoacetate (0.85 mL, 5.75 mmol) was then added dropwise, and stirring was continues at RT overnight. The reaction mixture was neutralized by addition of saturated NH_4Cl, and the solution was then adjusted to pH=2-3 by addition of 0.1N HCl. The aqueous layer was repeatedly extracted with CH_2Cl_2, the combined organics were washed with brine, dried (phase separator) and concentrated in vacuo. The residue was dissolved in a small volume of methanol, followed by addition of water until a solid precipitated. The precipiate was filtered off, washed with water and dried in vacuo to afford the title compound as a white solid. MS (LC/MS): 306 [M+H]+, 328 [M+Na]+; t_R (HPLC conditions c): 4.67 min.

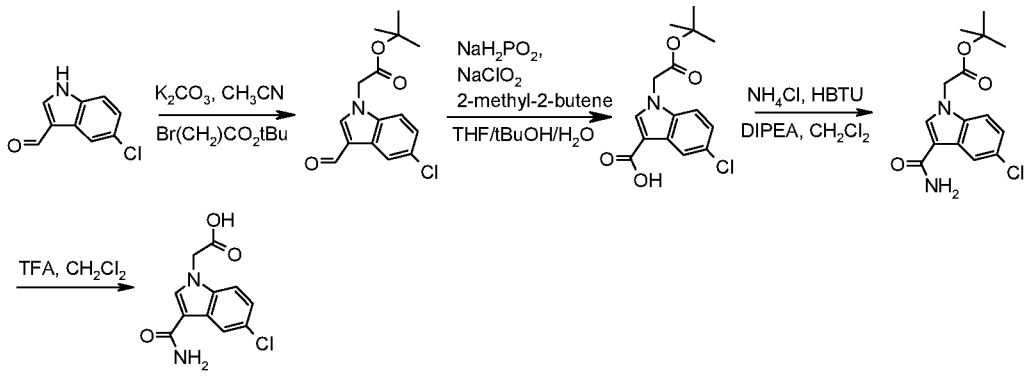
B. (3-Carbamoyl-6-methoxy-indol-1-yl)-acetic acid tert-butyl ester

To a mixture of 1-tert-butoxycarbonylmethyl-6-methoxy-1H-indole-3-carboxylic acid (500 mg, 1.28 mmol) in DMF (6 mL) were added successively NH_4Cl (137 mg, 2.55 mmol), HBTU (1.21 g, 3.19 mmol) and DIPEA (0.90 mL, 5.11 mmol), and stirring was continued at RT for 16 h. Additional aliquots of NH_4Cl (2 equiv) and DIPEA (4 equiv) were added to the reaction mixture. After stirring for 16 h, water was added and the aqueous layer was extracted repeatedly with EtOAc. The combined organics were washed with saturated aqueous $NaHCO_3$ solution and brine, dried (phase separator) and concentrated in vacuo. Purification by preparative HPLC (Macherey Nagel, VP250/40, C18 nucleosil 100-10, eluent: 20-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 mL/min) and lyophilization of the purified fractions afforded the title compound as a beige solid. MS: 305 [M+H]+, 609 [2M+H]+; t_R (HPLC conditions c): 4.26 min.

C. (3-Carbamoyl-6-methoxy-indol-1-yl)-acetic acid

To a solution of (3-carbamoyl-6-methoxy-indol-1-yl)-acetic acid tert-butyl ester (300 mg, 0.99 mmol) in CH_2Cl_2 (9 mL) was added TFA (4.5 mL) at RT, and stirring was continued for 2 h. Methanol was then added to the reaction mixture, and volatiles were removed in vacuo. The residue was taken up in methanol and concentrated under reduced pressure to afford the title compound as a grey solid: MS: 249 [M+H]+, 497 [2M+H]+; t_R (HPLC conditions c): 2.86 min. The material thus obtained was used in the next reaction step without further purification.

Scheme A11: preparation of (3-carbamoyl-5-chloro-indol-1-yl)-acetic acid



A. (5-Chloro-3-formyl-indol-1-yl)-acetic acid tert-butyl ester

To a suspension of 5-chloro-1H-indole-3-carbaldehyde [827-01-0] (500 mg, 2.78 mmol) and K_2CO_3 (885 mg, 6.40 mmol) in (14 mL) was added tert-butyl 2-bromoacetate (0.576 mL, 3.90 mmol) dropwise at RT. The resulting mixture was then heated to reflux for 18 h. After cooling to RT, the mixture was diluted with EtOAc and water. The organic layer was separated, subsequently washed with water (1x) and brine (1x), dried (Phase separator) and concentrated in vacuo to give the crude title compound. MS (LC/MS): 294 [M+H]+; t_R (HPLC conditions b): 5.45 min. The product was used in the next reaction step without further purification.

B. 1-tert-Butoxycarbonylmethyl-5-chloro-1H-indole-3-carboxylic acid

To a solution of (5-chloro-3-formyl-indol-1-yl)-acetic acid tert-butyl ester (902 mg, 2.92 mmol) in THF (12 mL) and tert-butanol (4.80 mL) were added successively 2-methyl-2-butene (9.27 mL, 88.0 mmol), a solution of $NaClO_2$ (2.64 g, 29.2 mmol) and sodium dihydrogen phosphate (2.80 g, 23.3 mmol) in water (4.80 mL), followed by stirring at RT for 18 h. The reaction mixture was acidified with 0.1N HCl (pH 2 to 3) and extracted with EtOAc (3x). The combined organics were dried (Phase separator) and concentrated in vacuo. The residue was triturated with diethyl ether, the solid was filtered off, washed with diethyl ether and dried in vacuo to afford the title compound as a white solid. MS (LC/MS): 310 [M+H]+; t_R (HPLC conditions b): 5.16 min.

C. (3-Carbamoyl-5-chloro-indol-1-yl)-acetic acid tert-butyl ester

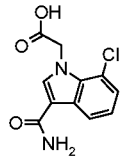
To a mixture of 1-tert-butoxycarbonylmethyl-5-chloro-1H-indole-3-carboxylic acid (400 mg, 1.29 mmol) in CH_2Cl_2 (6 mL) were added successively NH_4Cl (138 mg, 2.58 mmol), HBTU (1.22 g, 3.23 mmol) and DIPEA (0.902 mL, 5.17 mmol). Stirring was continued at RT for 16 h. Additional aliquots of NH_4Cl (2 equiv) and DIPEA (4 equiv) were added to the reaction mixture. After stirring for 4 h, the reaction mixture was diluted with CH_2Cl_2 and the solution was washed with water (2x), 0.1N aqeous HCl (2x), saturated aqueous $NaHCO_3$ (2x) and brine, dried (Phase separator) and concentrated in vacuo. The residue was purified by flash column

chromatography on silica gel (EtOAc/c-hexane gradient 2:1 to 1:0) to give the title compound as a white solid. TLC R_f (EtOAc/c-hexane 2:1) = 0.20; MS (LC/MS): 309 [M+H]+, 617 [2M+H]+; t_R (HPLC conditions b): 4.75 min.

D. (3-Carbamoyl-5-chloro-indol-1-yl)-acetic acid

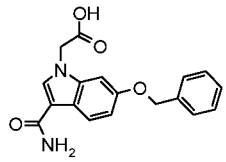
To a solution of (3-carbamoyl-5-chloro-indol-1-yl)-acetic acid tert-butyl ester (455 mg, 0.973 mmol) in CH_2Cl_2 (6.0 mL) was added TFA (3.0 mL) at RT and stirring was continued for 2 h. Methanol was then added to the reaction mixture and volatiles were removed in vacuo. The residue was taken up in methanol and concentrated again under reduced pressure. The residue was dissolved in 1N aqueous NaOH and washed with CH_2Cl_2 (3x). The water phase was acidified to pH 2 by adding 6N aqueous HCl to form a white suspension. The precipitate was filtered off, washed with water and dried in vacuo to afford the crude title compound as a white solid. MS (LC/MS): 253 [M+H]+, 505 [2M+H]+; t_R (HPLC conditions b): 3.99 min. The product was used in the next reaction step without further purification.

(3-Carbamoyl-7-chloro-indol-1-yl)-acetic acid



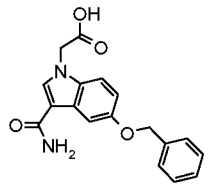
was prepared from 7-chloro-1H-indole-3-carbaldehyde [1008-07-7] using similar protocols as described in Scheme A11 for the preparation of (3-carbamoyl-5-chloro-indol-1-yl)-acetic acid. White solid. MS (LC/MS): 253 [M+H]+, 505 [2M+H]+; t_R (HPLC conditions b): 3.32 min.

(6-Benzyloxy-3-carbamoyl-indol-1-yl)-acetic acid



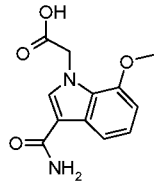
was prepared from 6-benzyloxy-1H-indole-3-carbaldehyde [92855-64-6] using similar protocols as described in Scheme A11 for the preparation of (3-carbamoyl-5-chloro-indol-1-yl)-acetic acid. White solid. MS (LC/MS): 325 [M+H]+, 649 [2M+H]+; t_R (HPLC conditions b): 4.06 min.

(5-Benzyloxy-3-carbamoyl-indol-1-yl)-acetic acid



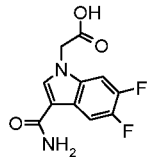
was prepared from 5-benzyloxy-1H-indole-3-carbaldehyde [6953-22-6] using similar protocols as described in Scheme A11 for the preparation of (3-carbamoyl-5-chloro-indol-1-yl)-acetic acid. White solid. MS (LC/MS): 325 [M+H]+, 649 [2M+H]+; t_R (HPLC conditions b): 4.04 min.

(3-Carbamoyl-7-methoxy-indol-1-yl)-acetic acid



was prepared from 7-methoxy-1H-indole-3-carbaldehyde [109021-59-2] in a similar manner as described in Scheme A11 for the preparation of (3-carbamoyl-5-chloro-indol-1-yl)-acetic acid. White solid. MS (LC/MS): 249 [M+H]+, 497 [2M+H]+; t_R (HPLC conditions c): 3.05 min.

(3-carbamoyl-5,6-difluoro-indol-1-yl)-acetic acid

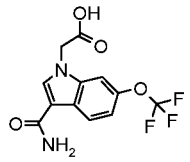


was prepared from 5,6-difluoro-1H-indole-3-carbaldehyde in a similar manner as described in Scheme A11 for the preparation of (3-carbamoyl-5-chloro-indol-1-yl)-acetic acid. The title compound was obtained as a white solid: MS (LC/MS): 255.0 [M+H]+, 509.0 [2M+H]+; t_R (HPLC conditions k): 2.58 min.

5,6-Difluoro-1H-indole-3-carbaldehyde

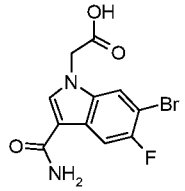
To an ice-cooled solution of oxalyl chloride (1.21 mL, 13.8 mmol) in CH_2Cl_2 (40 mL) was added a solution of DMF (2.02 mL) in CH_2Cl_2 (40.0 mL). The reaction was stirred for 30 min, then 5,6-difluoro-1H-indole [169674-01-5] (2.00 g, 13.1 mmol) was added in one portion. The reaction mixture was allowed to warm to RT overnight. Volatiles were evaporated, and the residue was taken up in THF (20 mL) and 20% aqueous ammonium acetate solution (20 mL). The resulting mixture was heated to reflux for 30 min. After cooling, the mixture was treated with saturated aqueous $NaHCO_3$ solution and extracted three times with EtOAc. The combined organic layers were dried (phase separator) and evaporated in vacuo to afford the title compound as a beige solid: MS (LC/MS): 182.0 [M+H]+; t_R (HPLC conditions c): 3.94 min. The material thus obtained was used in the next step without further purification.

(3-Carbamoyl-6-trifluoromethoxy-indol-1-yl)-acetic acid



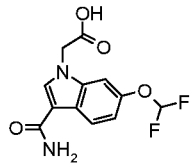
was prepared from 6-trifluoromethoxy-1H-indole [467451-91-8] in a similar manner as described for the preparation of (3-carbamoyl-5,6-difluoro-indol-1-yl)-acetic acid. White solid. MS (LC/MS): 303.0 [M+H]+, 605.0 [2M+H]+; t_R (HPLC conditions k): 2.75 min.

(6-Bromo-3-carbamoyl-5-fluoro-indol-1-yl)-acetic acid



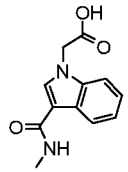
was prepared from 6-bromo-5-fluoro-1H-indole [259860-08-7] in a similar manner as described for the preparation of (3-carbamoyl-5,6-difluoro-indol-1-yl)-acetic acid. White solid. MS (LC/MS): 315.0 [M+H]+, 631.0 [2M+H]+; t_R (HPLC conditions k): 2.79 min.

(3-Carbamoyl-6-difluoromethoxy-indol-1-yl)-acetic acid



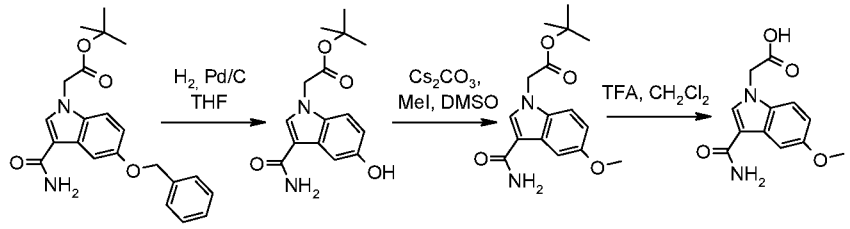
was prepared from 6-difluoromethoxy-1H-indole [200207-21-2] in a similar manner as described for the preparation of (3-carbamoyl-5,6-difluoro-indol-1-yl)-acetic acid. White solid. MS (LC/MS): 285 [M+H]+, 569 [2M+H]+; t_R (HPLC conditions k): 2.64 min.

(3-Methylcarbamoyl-indol-1-yl)-acetic acid



was prepared from 1H-indole-3-carbaldehyde using similar protocols as described in Scheme A11 for the preparation of (3-carbamoyl-5-chloro-indol-1-yl)-acetic acid (using methylamine hydrochloride in step C). MS (LC/MS): 233 [M+H]+; 465 [M+H]+; 231 [M-H]-; 463 [M+H]-; t_R (HPLC conditions b): 1.8 min.

Scheme A12 : Preparation of (3-Carbamoyl-5-methoxy-indol-1-yl)-acetic acid



A. (5-Benzyloxy-3-carbamoyl-indol-1-yl)-acetic acid tert-butyl ester

The title compound was prepared from 5-benzyloxy-1H-indole-3-carbaldehyde [6953-22-6] in a similar manner as described in Scheme A11 for steps A to C.

B. (3-Carbamoyl-5-hydroxy-indol-1-yl)-acetic acid tert-butyl ester

(5-Benzyloxy-3-carbamoyl-indol-1-yl)-acetic acid tert-butyl ester (250 mg, 0.657 mmol) was suspended in THF (13 mL). Air was removed from the flask and replaced with nitrogen three times. Pd/C 10 % (25 mg) was added to the solution which was again degassed, placed under a hydrogen atmosphere and stirred at RT overnight. The catalyst was removed through a 0.45 microns filter and concentrated in vacuo. The crude material was purified by preparative HPLC (SunFire C18-ODB, 5 µm, 30x100 mm, eluent: 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 mL/min) to give after lyophilization of the purified fractions the desired compound as a white solid. MS: 291 [M+H]+, 313 [M+Na]+, 581 [2M+H]+, 603 [2M+Na]+; t_R (HPLC conditions c): 3.75 min.

C. (3-Carbamoyl-5-methoxy-indol-1-yl)-acetic acid tert-butyl ester

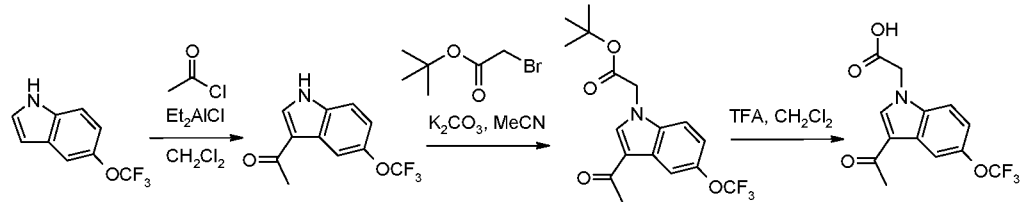
To a solution of (3-carbamoyl-5-hydroxy-indol-1-yl)-acetic acid tert-butyl ester (50 mg, 0.172 mmol) in DMSO (1.7 mL) was added Cs_2CO_3 (336 mg, 1.03 mmol). The mixture was stirred at RT for 5 min, followed by addition of methyl iodide (0.048 mL, 0.774 mmol), and stirring was continued at RT for 3 days. The reaction mixture was partitioned between water and CH_2Cl_2, the layers were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organics were washed twice with brine, dried (phase separator) and concentrated in vacuo to afford the title compound as a yellow solid: MS (LC/MS): 305 [M+H]+, 327 [M+Na]+, 609 [2M+H]+; t_R (HPLC conditions c): 4.31 min. The material thus obtained was used in the next reaction step without further purification.

D. (3-Carbamoyl-5-methoxy-indol-1-yl)-acetic acid

To a solution of (3-carbamoyl-5-methoxy-indol-1-yl)-acetic acid tert-butyl ester (45.0 mg, 0.118 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (1.0 mL) at RT, and stirring was continued for 3 h. Methanol was then added to the reaction mixture and volatiles were removed in vacuo. The residue was taken up in methanol and concentrated again under reduced pressure to afford

the title compound as a beige solid: MS (LC/MS): 249 [M+H]+, 277 [M+Na]+; t_R (HPLC conditions c): 2.93 min. The material thus obtained was used in the next reaction step without further purification.

Scheme A13 : Preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid



A. 1-(5-Trifluoromethoxy-1H-indol-3-yl)-ethanone

To a solution of 5-(trifluoromethoxy)-1H-indole [262593-63-5] (1.00 g, 4.97 mmol) in CH_2Cl_2 (20 mL), cooled to 0°C, was added dropwise diethylaluminum chloride (1M solution in hexane; 7.46 mL, 7.46 mmol), and stirring was continued for 30 min. A solution of acetyl chloride (0.532 mL, 7.46 mmol) in CH_2Cl_2 (20 mL) was subsequently added, and the reaction mixture was stirred at 0°C for 1 h. A 5% aqueous citric acid solution (100 mL) was then added at 0°C, and the mixture was stirred for 15 min at RT. The mixture (two phases) was filtered, and the precipitate was dried at 50°C in vacuo for 1 h to afford the title compound. Beige solid. MS : 244.0 [M+H]+; t_R (HPLC conditions c): 4.60 min. The material thus obtained was used directly in the next step without further purification

B. (3-Acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid tert-butyl ester

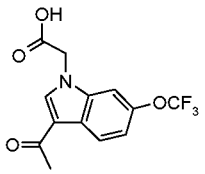
To a solution of 1-(5-trifluoromethoxy-1H-indol-3-yl)-ethanone (0.50 g, 2.06 mmol) in CH_3CN (10 mL) was added K_2CO_3 (0.313 g, 2.26 mmol) and tert-butyl 2-bromoacetate (0.334 mL, 2.26 mmol). The reaction mixture was stirred at 90°C overnight. The reaction mixture was filtered, and the filtrate was diluted with CH_2Cl_2. The organics were washed with 1M aqueous HCl solution (5 mL) and saturated aqueous $NaHCO_3$ solution (5 mL). The organic layer was dried (phase separator) and evaporated in vacuo to afford the title compound as a yellowish oil: MS: 358.0 [M+H]+; t_R (HPLC conditions c): 5.66 min. The material thus obtained was used directly in the next step without further purification.

C. (3-Acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid

To a solution of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid tert-butyl ester (680 mg, 1.90 mmol) in CH_2Cl_2 (10 mL) was added TFA (1.47 mL, 19.0 mmol), and stirring was continued at RT overnight. The reaction mixture was then diluted with CH_2Cl_2 and MeOH, and volatiles were evaporated under reduced pressure. The residue was taken up in MeOH and then evaporated again. The crude material was taken up in 1M aqueous NaOH solution (5

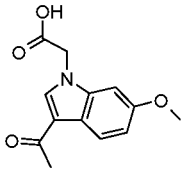
mL), and the water layer was washed with CH_2Cl_2 and subsequently acidified to pH=1 by addition of a 6M HCl solution. The precipitate was filtered and dried at 50°C in vacuo for 1 h to afford the title compound as a off-white solid: MS: 302.0 [M+H]+; t_R (HPLC conditions c): 4.40 min. The material thus obtained was used directly in the next step without further purification.

(3-Acetyl-6-trifluoromethoxy-indol-1-yl)-acetic acid



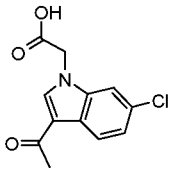
was prepared from 6-trifluoromethoxy-1H-indole [467451-91-8] in a similar manner as described in Scheme A13 for the preparation of (3-ccetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid. MS: 302.0 [M+H]+; t_R (HPLC conditions c): 4.39 min.

(3-Acetyl-6-methoxy-indol-1-yl)-acetic acid



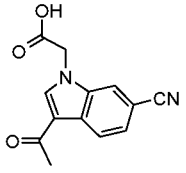
was prepared from 1-(6-methoxy-1H-indol-3-yl)-ethanone [99532-52-2] in a similar manner as described in step B and C of Scheme A13 for the preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid. Brown solid. MS: 248 [M+H]+, 517 [2M+Na]+; t_R (HPLC conditions k): 2.30 min.

(3-Acetyl-6-chloro-indol-1-yl)-acetic acid



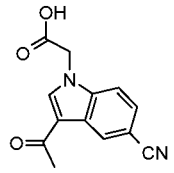
was prepared from 6-chloro-1H-indole in a similar manner as described in Scheme A13 for the preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid. Brown solid. MS: 252 [M+H]+, 274 [M+Na]+; t_R (HPLC conditions k): 2.89 min.

(3-Acetyl-6-cyano-indol-1-yl)-acetic acid



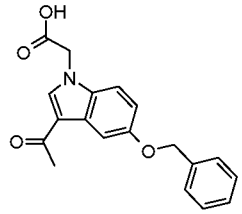
was prepared from 1H-indole-6-carbonitrile in a similar manner as described in Scheme A13 for the preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid. MS: 243 [M+H]+; t_R (HPLC conditions k): 2.72 min.

(3-Acetyl-5-cyano-indol-1-yl)-acetic acid



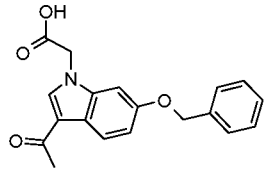
was prepared from 1H-indole-5-carbonitrile in a similar manner as described in Scheme A13 for the preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid. MS (LC/MS): 241.2 [M-H]-; 243.2 [M+H]+; t_R (HPLC conditions a): 2.62 min.

(3-Acetyl-5-benzyloxy-indol-1-yl)-acetic acid



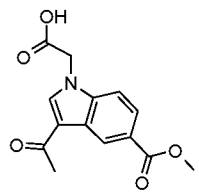
was prepared from 5-benzyloxy-1H-indole in a similar manner as described in Scheme A13 for the preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid. MS: 324 [M+H]+, 346 [M+Na]+; t_R (HPLC conditions k): 3.34 min.

(3-Acetyl-6-benzyloxy-indol-1-yl)-acetic acid



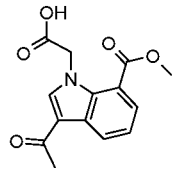
was prepared from 6-benzyloxy-1H-indole in a similar manner as described in Scheme A13 for the preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid. MS: 324 [M+H]+, 647 [2M+1]+; t_R (HPLC conditions k): 3.38 min.

3-Acetyl-1-carboxymethyl-1H-indole-5-carboxylic acid methyl ester



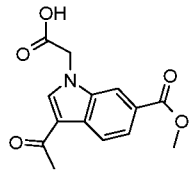
was prepared from 1H-indole-5-carboxylic acid methyl ester in a similar manner as described in Scheme A13 for the preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid. MS: 276 [M+H]+; t_R (HPLC conditions k): 2.84 min.

3-Acetyl-1-carboxymethyl-1H-indole-7-carboxylic acid methyl ester



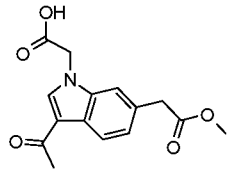
was prepared from 1H-indole-7-carboxylic acid methyl ester in a similar manner as described in Scheme A13 for the preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid. MS: 276 [M+H]+; t_R (HPLC conditions k): 2.89 min.

3-Acetyl-1-carboxymethyl-1H-indole-6-carboxylic acid methyl ester



was prepared from 3-acetyl-1H-indole-6-carboxylic acid methyl ester [106896-61-1] in a similar manner as described in step B and C of Scheme A13 for the preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid. Colored solid. MS: 276 [M+H]+; t_R (HPLC conditions k): 2.80 min.

(3-Acetyl-6-methoxycarbonylmethyl-indol-1-yl)-acetic acid



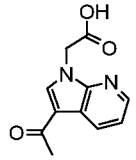
was prepared from (3-acetyl-1H-indol-6-yl)-acetic acid methyl ester in a similar manner as described in Scheme A13 for the preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid. Brown solid. MS: 290 [M+H]+; t_R (HPLC conditions k): 2.83 min.

(3-Acetyl-1H-indol-6-yl)-acetic acid methyl ester

To a stirred solution of (3-acetyl-1H-indol-6-yl)-acetic acid [39689-58-2] (500 mg, 2.85 mmol) in MeOH (14 mL), cooled to at 0°C, was added (trimethylsilyl)diazomethane (2M solution in Et_2O; 6.00 mL, 12.0 mmol). After stirring at RT for 30 min, the reaction mixture was concentrated in vacuo to afford the title compound as a yellow wax. MS: 190 [M+H]+; t_R (HPLC

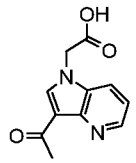
conditions k): 3.20 min. The material thus obtained was used directly in the next step without further purification.

(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetic acid



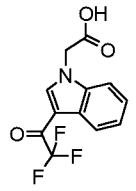
was prepared in a similar manner as described in step B and C of Scheme A13 for the preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid from 1-(1H-pyrrolo[2,3-b]pyridin-3-yl)-ethanone [83393-46-8]. MS (UPLC/MS): 219.2 [M+H]+, 217.2 [M-H]-, 263.3 [M+HCOO]-, 435.3 [2M-H]-; t_R (HPLC conditions f): 1.16 min. 1H-NMR (400 MHz, DMSO): δ (ppm): 8.55 (bs, 1H), 8.49 (dd, 1H), 8.36 (dd, 1H), 7.31 (dd, 1H), 5.12 (s, 2H), 2.48 (s,3H).

(3-Acetyl-pyrrolo[3,2-b]pyridin-1-yl)-acetic acid



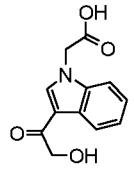
was prepared in a similar manner as described in step B and C of Scheme A13 for the preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid from 1-(1H-pyrrolo[3,2-b]pyridin-3-yl)-ethanone (prepared according to *J. Org. Chem.* **2002**, *67*, 6226). MS (UPLC/MS): 219.2 [M+H]+, 217.3 [M-H]-, 435.3 [2M-H]-; t_R (HPLC conditions f): 1.16 min. 1H-NMR (400 MHz, DMSO): δ (ppm): 8.79 (bs, 1H), 8.64 (m, 2H), 7.64 (m, 1H), 5.33 (s, 2H), 2.67 (s,3H).

[3-(2,2,2-Trifluoro-acetyl)-indol-1-yl]-acetic acid



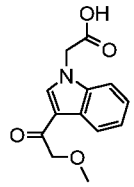
was prepared from 2,2,2-trifluoro-1-(1H-indol-3-yl)-ethanone in a similar manner as described in Scheme A13 (step B and C) for the preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid. White solid. MS: 272.0 [M+H]+; t_R (HPLC conditions c): 4.59 min.

[3-(2-Hydroxy-acetyl)-indol-1-yl]-acetic acid



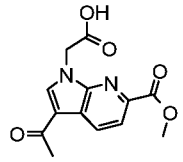
was prepared from 2-hydroxy-1-(1H-indol-3-yl)-ethanone [2400-51-3] in a similar manner as described in Scheme A13 (step B and C) for the preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid. Colored solid. MS: 234.0 [M+H]+, 489.0 [2M+Na]+; t_R (HPLC conditions c): 3.11 min.

[3-(2-Methoxy-acetyl)-indol-1-yl]-acetic acid



was prepared from 1H-indole in a similar manner as described in Scheme A13 (in step A, 2-methoxyacetyl chloride was used instead of acetyl chloride) for the preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid. Brown solid. MS: 248.0 [M+H]+; t_R (HPLC conditions c): 3.42 min.

3-Acetyl-1-carboxymethyl-1H-pyrrolo[2,3-b]pyridine-6-carboxylic acid methyl ester



was prepared from methyl 3-acetyl-1H-pyrrolo[2,3-b]pyridine-6-carboxylate using a similar protocol as described in Scheme A13, Steps C and D: MS (LC/MS): 277 [M+H]+; t_R (HPLC conditions k): 2.68 min.

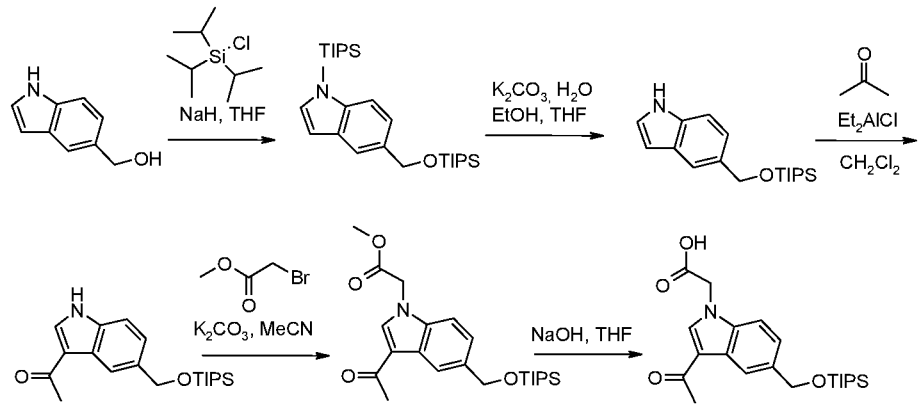
Methyl 3-acetyl-1H-pyrrolo[2,3-b]pyridine-6-carboxylate

was prepared from methyl 1H-pyrrolo[2,3-b]pyridine-6-carboxylate using a similar protocol as described in Scheme A17, Step A: MS (LC/MS): 219 [M+H]+; t_R (HPLC conditions k): 2.58 min.

Methyl 1H-pyrrolo[2,3-b]pyridine-6-carboxylate

To a stirred solution of 1H-pyrrolo[2,3-b]pyridine-6-carboxylic acid [898746-35-5] (500 mg, 3.08 mmol) in MeOH was added a 2M solution of trimethylsilyldiazomethane in Et_2O at 0°C, and the reaction mixture was stirred at RT for 30 min. The reaction mixture was concentrated in vacuo to give the title compound. MS (LC/MS): 177 [M+H]+, 375 [2M+H]+; t_R (HPLC conditions k): 2.71

Scheme A14: preparation of (3-acetyl-5-triisopropylsilanyloxymethyl-indol-1-yl)-acetic acid



A. 1-Triisopropylsilanyl-5-triisopropylsilanyloxymethyl-1H-indole

To a solution of (1H-indol-5-yl)-methanol (1.00 g, 6.79 mmol) in THF (60 mL), cooled to 0°C, was added sodium hydride (60% in mineral oil; 1.36 g, 34.0 mmol) portionwise. After stirring for 5 min, triisopropylsilyl chloride (2.88 mL, 13.6 mmol) was added, and the resulting solution was stirred at RT for 2 h. The reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution at 0°C. The aqueous layer was repeatedly extracted with EtOAc, and the combined organics were washed with H_2O (1x) and brine (1x), dried (phase separator) and concentrated in vacuo. Purification by flash column chromatography on silica gel (eluent gradient: c-hexane to c-hexane/EtOAc 9:1) afforded the title compound as a white solid. TLC, R_f (c-hexane/EtOAc 9:1) = 0.72. 1H-NMR (400 MHz, DMSO-d_6): δ ppm 7.61 (s, 1H), 7.49 (d, 1H), 7.32 (d, 1H), 6.93 (d, 1H), 6.57 (d, 1H), 4.92 (s, 2H), 1.60 - 1.85 (m, 3H), 1.01 - 1.12 (m, 39H).

B. 5-Triisopropylsilanyloxymethyl-1H-indole

To a suspension of 1-triisopropylsilanyl-5-triisopropylsilanyloxymethyl-1H-indole (2.80 g, 6.09 mmol) in EtOH (30 mL) / THF (10 mL) / water (10 mL) was added K_2CO_3 (4.21 g, 30.4 mmol), and the reaction mixture was heated at 85°C for 16 h. The reaction was quenched with 1N HCl at 0°C. The aqueous layer was extracted with CH_2Cl_2 (2x) and the combined organic layers were washed with brine, dried (phase separator) and concentrated under reduced pressure. The oily residue was purified by flash column chromatography on silica gel (eluent gradient: c-hexane to c-hexane/EtOAc 9:1) to afford the title compound as a yellow oil. TLC, R_f (c-hexane/EtOAc 9:1) = 0.29. t_R (HPLC conditions k): 5.02 min. MS (LC/MS): 304 [M+H]+.

C. 1-(5-Triisopropylsilanyloxymethyl-1H-indol-3-yl)-ethanone

The title compound was prepared from 5-triisopropylsilanyloxymethyl-1H-indole in a similar manner as described in step A of Scheme A13 for the preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid. Brown solid. MS: 346 [M+H]+; t_R (HPLC conditions c): 6.86 min.

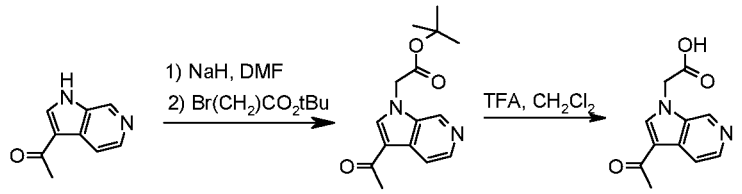
D. (3-Acetyl-5-triisopropylsilanyloxymethyl-indol-1-yl)-acetic acid methyl ester

The title compound was prepared from 1-(5-triisopropylsilanyloxymethyl-1H-indol-3-yl)-ethanone in a similar manner as described in step B of Scheme A13 for the preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid. MS: 418 [M+H]+; t_R (HPLC conditions k): 4.75 min.

E. (3-Acetyl-5-triisopropylsilanyloxymethyl-indol-1-yl)-acetic acid

To a solution of (3-acetyl-5-triisopropylsilanyloxymethyl-indol-1-yl)-acetic acid methyl ester (109 mg, 0.138 mmol) in THF (5 mL) and water (0.5 mL) was added 1N NaOH (0.69 mL, 0.69 mmol), and stirring was continued at RT for 16 h. The reaction mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAC (2x), the combined organics were dried (phase separator) and concentrated in vacuo to afford the title compound as a yellow wax. MS (LC/MS): 404 [M+H]+; t_R (HPLC conditions k): 4.35 min.

Scheme A15: Preparation of (3-acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetic acid trifluoroacetate



A. (3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetic acid tert-butyl ester

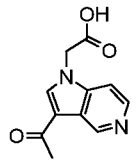
To a suspension of NaH (60 % in mineral oil, 90 mg, 2.25 mmol) in DMF (4.2 mL) cooled at 0°C was added a solution of 1-(1H-pyrrolo[2,3-c]pyridin-3-yl)-ethanone (prepared according to *J. Org. Chem.* **2002**, *67*, 6226) (300 mg, 1.87 mmol) in DMF (4.2 mL) and the resulting suspension was stirred at 0°C under nitrogen atmosphere for 30 min before slow addition of tert-butyl bromoacetate (277 µL, 1.87 mmol). The reaction mixture was allowed to reach RT and further stirred at RT for 1.5 h. After completion of the reaction, the mixture was purified first by catch-release on SiliaPrep Tosic Acid-(2x10 g) (Varian) (eluent: MeOH (50 mL) by 2 M ammonia in MeOH (50 mL)) to give a mixture of regioisomers: (3-acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetic acid tert-butyl ester and (3-acetyl-pyrrolo[2,3-c]pyridin-6-yl)-acetic acid tert-butyl ester followed by flash column chromatography on silica gel (CH_2Cl_2 to CH_2Cl_2/MeOH 85-15)

to give (3-acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetic acid tert-butyl ester as a yellow powder. TLC, R_f (CH_2Cl_2/ MeOH 9-1) = 0.50; MS (UPLC/MS): 275.3 [M+H]+, 319.2 [M+HCOO]-; t_R (HPLC conditions f): 1.28 min; 1H-NMR (400 MHz, DMSO-d_6): δ (ppm): 8.88 (s, 1H), 8.50 (s, 1H), 8.33 (d, 1H), 8.06 (d, 1H), 5.27 (s, 2H), 2.48 (s,3H), 1.45 (s, 9H).

B. (3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetic acid trifluoroacetate

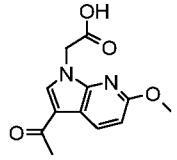
A solution of (3-acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetic acid tert-butyl ester (230 mg, 0.8 mmol) and TFA (0.915 mL, 11.95 mmol) in CH_2Cl_2 (3.1 mL) was stirred at RT overnight. The reaction mixture was concentrated and the residue was dried under high vacuum. The resulting solid was taken-up in Et_2O and filtered to give the desired compound (TFA salt) as beige powder which was used in the next step without purification. MS (UPLC/MS): 219.2 [M+H]+, 217.2 [M-H]-; 1H-NMR (400 MHz, DMSO): δ (ppm): 9.50 (s, 1H), 9.03 (s, 1H), 8.54 (d, 1H), 8.51 (d, 1H), 5.40 (s, 2H), 2.57 (s,3H).

(3-Acetyl-pyrrolo[3,2-c]pyridin-1-yl)-acetic acid trifluoroacetate



was prepared using similar procedures as described for the synthesis of (3-acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetic acid in Scheme A15 from 1-(1H-pyrrolo[3,2-c]pyridin-3-yl)-ethanone (prepared according to *J. Org. Chem.* **2002**, *67*, 6226). MS (UPLC/MS): 219.1 [M+H]+, 217.2 [M-H]-, 435.3 [2M-H]-; 1H-NMR (400 MHz, DMSO): δ (ppm): 9.54 (s, 1H), 8.89 (s, 1H), 8.66 (d, 1H), 8.30 (d, 1H), 5.38 (s, 2H), 2.58 (s, 3H).

(3-Acetyl-6-methoxy-pyrrolo[2,3-b]pyridin-1-yl)-acetic acid

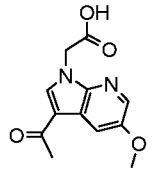


was prepared using similar procedures as described for the synthesis of (3-acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetic acid in Scheme A15 from 1-(6-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-ethanone. MS (UPLC/MS): 249.2 [M+H]+, 497.3 [2M+H]+, 519.3 [2M+Na]+, 247.1 [M-H]-, 293.2 [M+HCOO]-, 495.3 [2M+HCOO]-; t_R (HPLC conditions f): 1.55 min. 1H-NMR (400 MHz, DMSO): δ (ppm): 12.3 (bs, 1H), 8.33 (d, 1H), 8.21 (s, 1H), 6.70 (d, 1H), 3.89 (s, 3H), 3.32 (s, 2H), 2.43 (s,3H).

1-(6-methoxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-ethanone

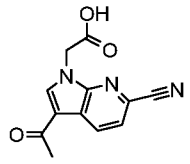
To a suspension of $AlCl_3$ (1.37 g, 10.3 mmol) in CH_2Cl_2 (40 mL) was added 6-methoxy-7-azaindole (315 mg, 2.07 mmol) and the mixture was stirred at RT for 30 min under nitrogen. Acetyl chloride (736 µL, 10.3 mmol) was added dropwise and the resulting mixture stirred at RT overnight. MeOH (8 mL) was added cautiously to quench the reaction and the solvents were removed under vacuum. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2 to CH_2Cl_2/MeOH 93-7) and by preparative HPLC (Waters Sunfire C18-ODB, 5 µm, 30x100 mm, 5% to 100% CH_3CN in H_2O in 25 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 mL/min) to give after neutralization (aqueous saturated $NaHCO_3$) and extraction (CH_2Cl_2) of the purified fractions the desired compound TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.55; MS (UPLC/MS): 191.2 [M+H]+, 189.1 [M-H]-, 379.2 [2M-H]-; t_R (HPLC conditions f): 1.45 min. 1H-NMR (400 MHz, DMSO): δ (ppm): 8.35 (d, 1H), 8.29 (s, 1H), 6.75 (d, 1H), 5.04 (s, 2H), 3.89 (s, 3H), 2.44 (s, 3H).

(3-Acetyl-5-methoxy-pyrrolo[2,3-b]pyridin-1-yl)-acetic acid trifluoroacetate



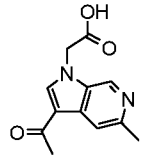
was prepared using similar procedures as described for the synthesis of (3-acetyl-6-methoxy-pyrrolo[2,3-b]pyridin-1-yl)-acetic acid in Scheme A15 from 1H-pyrrolo[2,3-b]pyridine-6-carbonitrile. TLC, R_f (CH_2Cl_2/MeOH 4:1) = 0.50; MS (UPLC/MS): 191.2 [M+H]+, 189.1 [M-H]-; t_R (HPLC conditions f): 1.23 min.

(3-Acetyl-6-cyano-pyrrolo[2,3-b]pyridin-1-yl)-acetic acid



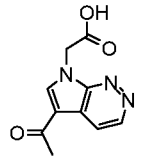
was prepared using similar procedures as described for the synthesis of (3-acetyl-6-methoxy-pyrrolo[2,3-b]pyridin-1-yl)-acetic acid in Scheme A15 from 1H-pyrrolo[2,3-b]pyridine-6-carbonitrile. MS (UPLC/MS): 244.1 [M+H]+, 242.1 [M-H]-; t_R (HPLC conditions f): 1.42 min.

(3-Acetyl-5-methyl-pyrrolo[2,3-c]pyridin-1-yl)-acetic acid trifluoroacetate



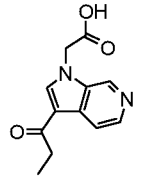
was prepared using similar procedures as described for the synthesis of (3-acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetic acid in Scheme A15 from 1-(5-methyl-1H-pyrrolo[2,3-c]pyridi n-3-yl)-ethanone (prepared according to *J. Org. Chem.* **2002**, *67*, 6226). MS (UPLC/MS): 233.2 [M+H]+, 231.2 [M-H]-.

(5-Acetyl-pyrrolo[2,3-c]pyridazin-7-yl)-acetic acid



was prepared using similar procedures as described for the synthesis of (3-acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetic acid in Scheme A15 from 1-(7H-pyrrolo[2,3-c]pyridazin-5-yl) -ethanone (prepared according to *J. Org. Chem.* **2002**, *67*, 6226). MS (UPLC/MS): 220.1 [M+H]+, 178.0 [MH-CH_3CO]+, 218.1 [M-H]-, 437.2 [2M-H]-.

(3-Propionyl-pyrrolo[2,3-c]pyridin-1-yl)-acetic acid trifluoroacetate

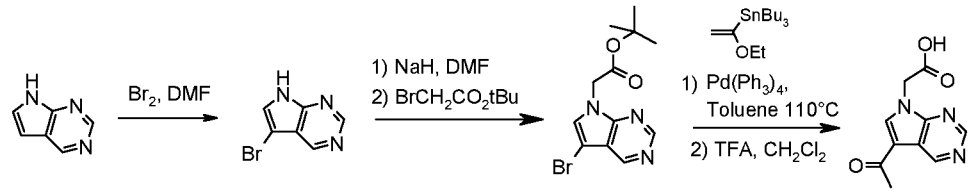


was prepared using similar procedures as described for the synthesis of (3-acetyl-6-methoxy-pyrrolo[2,3-b]pyridin-1-yl)-acetic acid in Scheme A15 from 1-(1H-pyrrolo[2,3-c]pyridin-3-yl)-propan-1-one. 1H-NMR (400 MHz, DMSO-d_6): δ (ppm): 9.56 (s, 1H), 9.09 (s, 1H), 8.58 (m, 2H), 5.42 (s, 2H), 3.0 (q, 2H), 1.15 (t, 3H).

1-(1H-Pyrrolo[2,3-c]pyridin-3-yl)-propan-1-one

6-Azaindole (500 mg, 4.23 mmol) was added to a suspension of $AlCl_3$ (2.82 g, 21.16 mmol) in CH_2Cl_2 (100 mL) under argon atmosphere. The mixture was stirred at RT for 30 min and propionyl chloride (1.84 mL, 21.16 mmol) was added dropwise. The reaction mixture was stirred for 2.5 h and quenched by cautious addition of MeOH (20 mL). The solvents were removed under reduced pressure and the crude residue was purified by flash column chromatography on silica gel (CH_2Cl_2 to CH_2Cl_2/ MeOH 87:13). TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.35; MS (UPLC/MS): 175.2 [M+H]+, 173.1 [M-H]-, 347.3 [2M-H]-, 219.1 [M+HCOO]-; t_R (HPLC conditions f): 0.42 min.

Scheme A16: Preparation of (5-Acetyl-pyrrolo[2,3-d]pyrimidin-7-yl)-acetic acid trifluoroacetate



A. 5-Bromo-7H-pyrrolo[2,3-d]pyrimidine

A solution of bromine (0.086 mL, 1.68 mmol) in DMF (5.5 mL) was added to a solution of 7H-pyrrolo[2,3-d]pyrimidine (200 mg, 1.68 mmol) in DMF (5.5 mL). The reaction mixture was stirred at RT for 4 h and poured into a mixture of ice and water containing $Na_2S_2O_3$. A saturated aqueous solution of $NaHCO_3$ was added (until basic pH), the layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. The material thus obtained was used without further purification in the next step. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.45; MS (UPLC/MS): 198.1/200.1 [M+H]+, 196.1/198.1 [M-H]-.

B. (5-Bromo-pyrrolo[2,3-d]pyrimidin-7-yl)-acetic acid tert-butyl ester

To suspension of NaH (60 % in mineral oil, 34 mg, 0.85 mmol) in DMF (1.5 mL) at 0°C under nitrogen atmosphere was added a solution of 5-bromo-7H-pyrrolo[2,3-d]pyrimidine (140 mg, 0.71 mmol) in DMF (1.5 mL). The reaction mixture was stirred at 0°C for 30 min and tert-butyl bromoacetate (104 µL, 0.71 mmol) was slowly added. The mixture was further stirred at RT for 30 min, then poured into water and extracted with EtOAc (x3). The combined organic extracts were washed with water, dried (Na_2SO_4), filtered and concentrated. MS (UPLC/MS): 312.3/314.2 [M+H]+.

C. (5-Acetyl-pyrrolo[2,3-d]pyrimidin-7-yl)-acetic acid tert-butyl ester

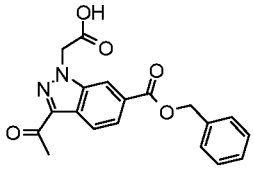
A solution of (5-bromo-pyrrolo[2,3-d]pyrimidin-7-yl)-acetic acid tert-butyl ester (220 mg, 0.71 mmol), tri-butyl(1-ethoxyvinyl)tin (285 µL, 0.85 mmol) and tetrakis(triphenylphosphine) palladium (16.28 mg, 14.1 µmol) in toluene (7 mL) was heated at 110°C for 72 h under argon atmosphere. The mixture was allowed to cool to RT, poured into water and extracted with EtOAc (x2). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (CH_2Cl_2 to CH_2Cl_2/ MeOH 94:6). TLC, Rf (CH_2Cl_2/ MeOH 9:1) = 0.54; MS (UPLC/MS): 276.3 [M+H]+, 320.4 [M+HCOO]-; t_R (HPLC conditions f): 1.40 min.

D. (5-Acetyl-pyrrolo[2,3-d]pyrimidin-7-yl)-acetic acid

A solution of (5-acetyl-pyrrolo[2,3-d]pyrimidin-7-yl)-acetic acid tert-butyl ester (146 mg, 0.53 mmol) and TFA (0.814 mL, 10.62 mmol) in CH_2Cl_2 (2.5 mL) was stirred at RT for 24 h. Solvents were removed under reduced pressure and the material thus obtained was used

without further purification in the next step. 1H-NMR (400 MHz, DMSO): δ (ppm): 9.45 (s, 1H), 9.0 (s, 1H), 8.68 (s, 1H), 7.66-7.56 (m, 2H), 5.16 (s, 2H), 2.53 (s, 3H).

3-Acetyl-1-carboxymethyl-1H-indazole-6-carboxylic acid benzyl ester



was prepared using similar protocols as described in Scheme A16 Step C and D from 3-bromo-1-tert-butoxycarbonylmethyl-1H-indazole-6-carboxylic acid benzyl ester. MS (UPLC/MS): 553.4 [M+H]+, 351.4 [M-H]-, 703.6 [2M-H]-; t_R (HPLC conditions f): 2.10 min.

3-Bromo-1-tert-butoxycarbonylmethyl-1H-indazole-6-carboxylic acid benzyl ester

was prepared using similar protocol as described in Scheme A20 Step C from 3-bromo-1H-indazole-6-carboxylic acid benzyl ester. MS (UPLC/MS): 445.4/447.3 [M+H]+; t_R (UPLC conditions m): 1.45 min.

3-Bromo-1H-indazole-6-carboxylic acid benzyl ester

A solution of 3-bromo-indazole-1,6-dicarboxylic acid 6-benzyl ester 1-tert-butyl ester (2.05 g, 4.75 mmol) and TFA (3.66 mL, 47.5 mmol) in CH_2Cl_2 (30 mL) was stirred at RT for 16 h. A saturated aqueous solution of $NaHCO_3$ was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated and the material thus obtained was used without further purification in the next step. MS (UPLC/MS): 331.2/333.2 [M+H]+, 329.3/331.2 [M-H]-; t_R (UPLC conditions m): 1.18 min.

3-Bromo-indazole-1,6-dicarboxylic acid 6-benzyl ester 1-tert-butyl ester

A solution containing 3-bromo-indazole-1,6-dicarboxylic acid 1-tert-butyl ester (1.80 g, 5.28 mmol), benzylbromide (0.753 mL, 6.33 mmol), Cs_2CO_3 (1.89 g, 5.80 mmol) and sodium iodide (0.095 g, 0.633 mmol) in DMF (30 mL) was stirred 16 h at RT. The mixture was diluted with water and extracted with EtOAc (x3). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/c-hexane 1:4). MS (UPLC/MS): 431.2/433.2 [M+H]+; t_R (UPLC conditions f): 2.77 min.

3-Bromo-indazole-1,6-dicarboxylic acid 1-tert-butyl ester

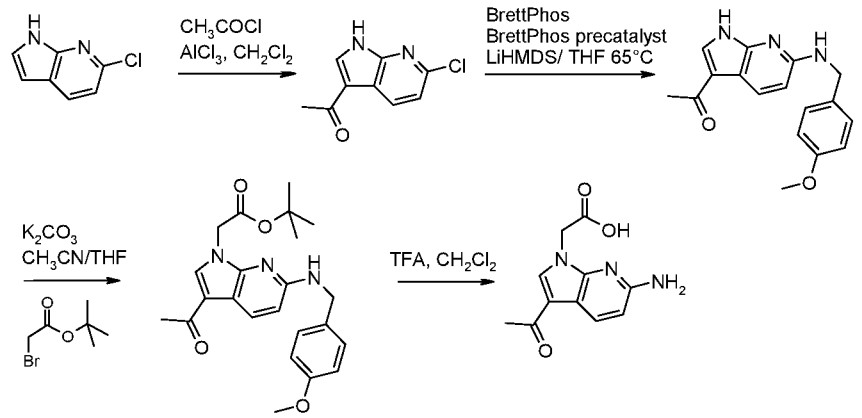
A solution containing 3-bromo-1H-indazole-6-carboxylic acid (1.40 g, 5.81 mmol), triethylamine (0.89 ml, 6.39 mmol), DMAP (0.071 g, 0.58 mmol) and $(Boc)_2O$ (1.90 g, 8.71 mmol) in CH_2Cl_2

(60 mL) was stirred 16 h at 25°C. Volatils were removed under reduced pressure, water and Et_2O were added. The aqueous layer was acidified by addition of $KHSO_4$ (10% in water) and extracted with EtOAc (x3). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The material thus obtained was used without further purification in the next step. MS (UPLC/MS): 441.2/443.2 [M+H]+.

3-Bromo-1H-indazole-6-carboxylic acid

Bromine (0.385 mL, 7.48 mmol) was added dropwise to a solution of 1H-indazole-6-carboxylic acid (1 g, 5.98 mmol) in acetic acid (30 mL) and the reaction mixture was stirred for 16 h at 25°C in the dark. The reaction was quenched by addition of a saturated aqueous solution of Na_2SO_3 (12 mL) and brine (25 mL) and extracted with EtOAc (x3). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. The material thus obtained was used without further purification in the next step. MS (UPLC/MS): 239.1/241.1 [M-H]-, 481.3/483.3 [2M-H]-; t_R (UPLC conditions f): 1.59 min.

Scheme A17: (3-Acetyl-6-amino-pyrrolo[2,3-b]pyridin-1-yl)-acetic acid



A. 1-(6-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-ethanone

6-Chloro-7-azaindole (1 g, 6.55 mmol) was added to a suspension of $AlCl_3$ (4.37 g, 32.8 mmol) in CH_2Cl_2 (150 mL) under nitrogen atmosphere. The mixture was stirred at RT for 30 min, and acetyl chloride (2.34 mL, 32.8 mmol) was added dropwise. The resulting mixture was further stirred at RT for 2 h. After completion, MeOH (40 mL) was added cautiously and volatils were removed under reduced pressure. The residue was diluted in CH_2Cl_2 and neutralized by addition of a saturated aqueous solution of $NaHCO_3$. The layers were separated and the organic extratcs were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified twice by flash column chromatography on silica gel (CH_2Cl_2 to CH_2Cl_2/ MeOH 95-5). TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.5; MS (UPLC/MS): 195.1/197.1 [M+H]+, 193.1/195.1 [M-H]-; t_R (HPLC conditions f): 1.54 min.

B. 1-[6-(4-Methoxy-benzylamino)-1H-pyrrolo[2,3-b]pyridin-3-yl]-ethanone

The reaction was performed according to the protocol described in *Org. Lett.*, **2010**, *12*(20), 4438-4441. A vial containing 1-(6-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-ethanone (100 mg, 0.49 mmol), BrettPhos (2.62 mg, 4.88 µmol) and BrettPhos precatalyst (3.9 mg, 4.88 µmol) and a magnetic stir bar was sealed with a teflon screw-cap, evacuated and backfilled with argon. A ballon of argon was placed on top of the vial, to allow a pressure balance and LiHMDS (1 M in THF, 1172 µL, 1.17 mmol) was added, followed by 4-methoxybenzylamine (76 µL, 0.59 mmol). The reaction mixture was stirred and heated at 65°C for 22 h, then allowed to cool to RT, quenched by the addition of 1 M HCl (1 mL) diluted with EtOAc and poured into a saturated aqueous solution of $NaHCO_3$. After extracting twice with EtOAc, the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude was purified by flash column chromatography on silica gel (c-hexane to EtOAc). TLC, R_f (EtOAc) = 0.75; MS (UPLC/MS): 296.2 [M+H]+, 591.3 [2M+H]+, 613.2 [2M+Na]+; t_R (HPLC conditions f): 1.5 min.

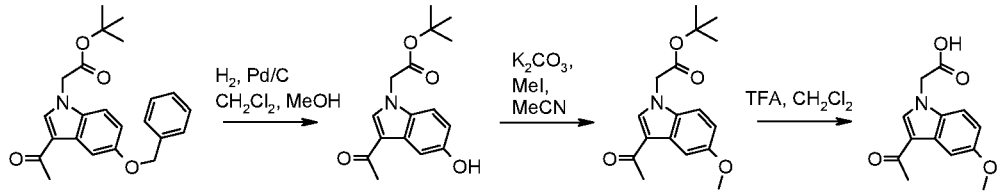
C. [3-Acetyl-6-(4-methoxy-benzylamino)-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid tert-butyl ester

Tert-butyl bromoacetate (27 µL, 0.18 mmol) was added to a suspension of 1-[6-(4-methoxy-benzylamino)-1H-pyrrolo[2,3-b]pyridin-3-yl]-ethanone (0.17 mmol) and potassium carbonate (27.5 mg, 0.20 mmol) in CH_3CN (0.33 mL) and THF (0.33 mL). The reaction mixture was stirred at RT for 7 h. Potassium carbonate (27.5 mg, 0.20 mmol) and tert-butyl bromoacetate (27 µL, 0.18 mmol) were added again and stirring was continued overnight, this operation was repeated the next day. The suspension was filtered, the filtrate concentrated under reduced pressure and the crude residue was purified by flash column chromatography on silica gel (CH_2Cl_2 to CH_2Cl_2/MeOH 98:2). TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.9; MS (UPLC/MS): 410.2 [M+H]+, 819.4 [2M+H]+, 841.3 [2M+Na]+, 454.1 [M+HCOO]-; t_R (HPLC conditions f): 2.30 min.

D. (3-Acetyl-6-amino-pyrrolo[2,3-b]pyridin-1-yl)-acetic acid trifluoroacetate

A solution of [3-acetyl-6-(4-methoxy-benzylamino)-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid tert-butyl ester (51 mg, 0.125 mmol) and TFA (191 µL, 2.49 mmol) in CH_2Cl_2 (0.6 mL) was stirred at RT for 24 h. Volatils were removed under reduced pressure and the brown solid thus obtained was used without further purification in the next step. MS (UPLC/MS): 234.1 [M+H]+, 232.1 [M-H]-. 1H-NMR (400 MHz, DMSO): δ (ppm): 8.08 (d, 1H), 8.02 (s, 1H), 6.83 (m, 2H), 6.44 (d, 1H), 4.90 (s, 2H), 2.38 (s, 3H).

Scheme A18: Preparation of (3-acetyl-5-methoxy-indol-1-yl)-acetic acid



A. (3-Acetyl-5-hydroxy-indol-1-yl)-acetic acid tert-butyl ester

To a solution of (3-acetyl-5-benzyloxy-indol-1-yl)-acetic acid tert-butyl ester (MS: 380.0 [M+H]+; t_R (HPLC conditions c): 5.72 min; prepared from 5-benzyloxy-1H-indole [1215-59-4] in a similar manner as described in Scheme A13 (step A and B)) (3.3 g, 8.70 mmol) in CH_2Cl_2/MeOH (80 mL) was added Pd/C (0.093 g, 0.870 mmol). The reaction mixture was stirred at RT for 5 h under H_2 atmosphere. The reaction mixture was filtered over a pad of Celite and washed with CH_2Cl_2 and MeOH. Volatiles were evaporated, and the crude mixture was purified by flash chromatography on silica gel (gradient c-hexane/EtOAc 2:1 to 100% EtOAc). TLC, R_f (c-hexane/EtOAc 1:1) = 0.35; MS: 312.0 [M+Na]+; t_R (HPLC conditions c): 4.27 min.

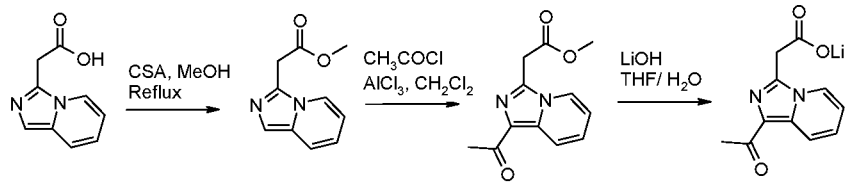
B. (3-Acetyl-5-methoxy-indol-1-yl)-acetic acid tert-butyl ester

To a solution of (3-acetyl-5-hydroxy-indol-1-yl)-acetic acid tert-butyl ester (500 mg, 1.73 mmol) in CH_3CN (15 mL) was added K_2CO_3 (358 mg, 2.59 mmol) and iodomethane (0.162 mL, 2.59 mmol). The reaction mixture was stirred at 50°C overnight. Additional K_2CO_3 (716 mg, 5.18 mmol) and iodomethane (0.324 mL, 5.18 mmol) were added and heating was continued for an additional 2 days. Volatiles were evaporated, the reaction mixture was taken up in water and extracted twice with AcOEt. The combined organic phases were dried (Phase separator) and evaporated to give the title compound. MS (LC/MS): 304.0 [M+H]+, 629.0 [2M+Na]+; t_R (HPLC conditions c): 4.92 min.

C. (3-Acetyl-5-methoxy-indol-1-yl)-acetic acid

To (3-acetyl-5-methoxy-indol-1-yl)-acetic acid tert-butyl ester (520 mg, 1.71 mmol) in CH_2Cl_2 (15 mL) was added TFA (1.32 mL, 17.1 mmol). The reaction mixture was stirred at RT overnight. Volatiles were evaporated, then the crude material was taken up in 5 mL of 1M aqueous NaOH solution and washed with CH_2Cl_2 which was discarded. The water phase was acidified to pH=1 by adding a 6M aqueous HCl solution, and then was extracted twice with AcOEt. The combined organic phases were dried (Phase separator) and evaporated to give the title compound. MS (LC/MS): 248.1 [M+H]+, 246.1[M-H]-; t_R (HPLC conditions c): 3.47 min.

Scheme A19 : Preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid



A. Imidazo[1,5-a]pyridin-3-yl-acetic acid methyl ester

A suspension of imidazo[1,5-a]pyridin-3-ylacetic acid (Ellanovalabs, 2 g, 11.35 mmol) and camphorsulfonic acid (2.9 g, 12.49 mmol) in MeOH (120 mL) was refluxed for 4 h. Then allowed to cool to RT and concentrated under reduced pressure. The crude residue was diluted in CH_2Cl_2 and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$. The organics were dried (Na_2SO_4), filtered and concentrated. The material thus obtained was used in the next step without further purification: TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.55; MS (UPLC/MS): 191.1 [M+H]+; t_R (HPLC conditions f): 0.4 min.

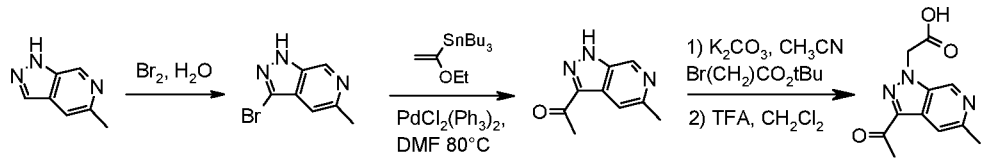
B. (1-Acetyl-imidazo[1,5-a]pyridin-3-yl)-acetic acid methyl ester

A solution of imidazo[1,5-a]pyridin-3-yl-acetic acid methyl ester (1.38 g, 7.26 mmol) in CH_2Cl_2 (50 mL) was added to a suspension of $AlCl_3$ (2.9 g, 21.77 mmol) in CH_2Cl_2 (115 mL) and the mixture was stirred at RT for 30 min under nitrogen atmosphere. Acetyl chloride (1.55 mL, 21.77 mmol) was subsequently added dropwise and the mixture was further stirred overnight. $AlCl_3$ (1.94 g, 14.51 mmol) and 15 min later acetyl chloride (1.04 mL, 14.51 mmol) were added and stirring was continued overnight to complete the reaction. The reaction mixture was cooled with at 0°C and carefully quenched by cautious addition of MeOH (35 mL). Solvents were evaporated under reduced pressure and the crude residue was purified by flash column chromatography on silica gel (eluent: CH_2Cl_2 to CH_2Cl_2/MeOH 94:6). TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.60; MS (UPLC/MS): 233.1 [M+H]+, 255.1 [M+Na]+, 487.1 [2M+Na]+; t_R (HPLC conditions f): 1.27 min.

C. Lithium (1-acetyl-imidazo[1,5-a]pyridin-3-yl)-acetate

To a solution of (1-acetyl-imidazo[1,5-a]pyridin-3-yl)-acetic acid methyl ester (1.12 g, 4.82 mmol) in THF (15 mL) and water (7.5 mL) was added $LiOH.H_2O$ (202 mg, 4.82 mmol). The reaction was stirred at RT for 5.5 h until completion of the reaction. The mixture was concentrated under reduced pressure and the material thus obtained was used in the next step without further purification: MS (UPLC/MS): 219.2 [M+H]+, 241.2 [M+Na]+, 217.2 [M-H]-; t_R (HPLC conditions f): 1.03 min.

Scheme A20: Preparation of (3-Acetyl-5-methyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid trifluoroacetate



A. 3-Bromo-5-methyl-1H-pyrazolo[3,4-c]pyridine

5-Methyl-1H-pyrazolo[3,4-c]pyridine (2 g, 15.02 mmol) and bromine (0.774 mL, 15.02 mmol) in water (71.5 mL) were stirred at RT for 1 h. The reaction mixture was neutralized with NaOH (20% in water), the precipitate was filtered, washed with water and dried under high vacuum. Yellow powder, MS (UPLC/MS): 212/214 [M+H]+, 210/212 [M-H]-; t_R (HPLC conditions f): 0.74 min.

B. 1-(5-Methyl-1H-pyrazolo[3,4-c]pyridin-3-yl)-ethanone

A solution of 3-bromo-5-methyl-1H-pyrazolo[3,4-c]pyridine (2.13 g, 10.04 mmol), tri-butyl(1-ethoxyvinyl)tin (6.78 mL, 20.09 mmol) and $PdCl_2(PPh_3)_2$ (0.705 mg, 1 mmol) in DMF (12.6 mL) was heated at 80°C overnight under argon atmosphere. Then concentrated under reduced pressure and diluted with EtOAc. HCl (2N) was added, the layers were separated and the aqueous layer was basified by addition of $NaHCO_3$ (1N in water) and extracted with EtOAc (3x). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The yellow oil thus obtained was used without further purification in the next step. TLC, Rf (c-hexane/ EtOAC 1:1) = 0.05; MS (UPLC/MS): 176 [M+H]+, 174 [M-H]-.

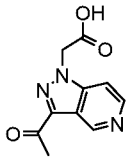
C. (3-Acetyl-5-methyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid tert-butyl ester

To a solution of 1-(5-methyl-1H-pyrazolo[3,4-c]pyridin-3-yl)-ethanone (1 g, 5.71 mmol) in CH_3CN (30 mL) were added potassium carbonate (1.81 g, 13.13 mmol) and tert-butyl bromoacetate (0.927 mL, 6.28 mmol). The reaction mixture was stirred at reflux for 1 h, then poured into water and extracted with EtOAc (x3). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 1:0 to 3:2). TLC, Rf (c-hexane/ EtOAC 1:1) = 0.25; MS (UPLC/MS): 290 [M+H]+; t_R (HPLC conditions f): 1.50 min.

D. (3-Acetyl-5-methyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid

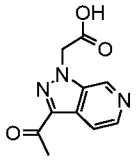
A solution of (3-acetyl-5-methyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid tert-butyl ester (126 mg, 0.37 mmol) and TFA (0.171 mL, 2.22 mmol) in CH_2Cl_2 (5 mL) was stirred at RT for 24 h. Solvents were removed under reduced pressure, Et_2O was added and the precipitate was filtered, washed with Et_2O and dried under high vacuum. The material thus obtained was used without further purification in the next step. MS (UPLC/MS): 234 [M+H]+, 232 [M-H]-, 465 [2M-H]-; t_R (HPLC conditions f): 0.53 min.

(3-Acetyl-pyrazolo[4,3-c]pyridin-1-yl)-acetic acid trifluoroacetate



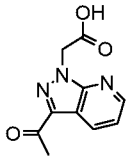
was prepared using similar procedures as described for the synthesis of (3-acetyl-5-methyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid in Scheme A20 from 1-(1H-pyrazolo[4,3-c]pyridin-3-yl)-ethanone (Sphinx Scientific laboratory LLC, catalog number: PPY-CS0001). 1H-NMR (400 MHz, DMSO): δ (ppm): 9.57 (s, 1H), 8.52 (m, 1H), 8.08 (m, 1H), 5.56 (s, 2H), 2.69 (s, 3H).

(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid trifluoroacetate



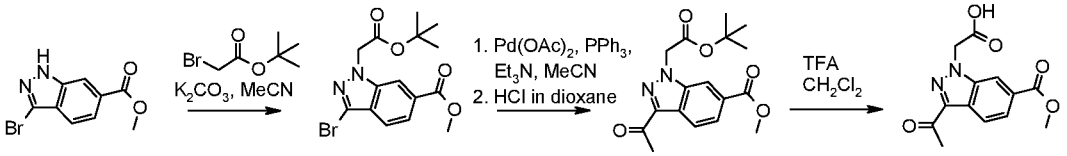
was prepared using similar procedures as described for the synthesis of (3-acetyl-5-methyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid in Scheme A20 from 1-(1H-pyrazolo[3,4-c]pyridin-3-yl)-ethanone (Sphinx Scientific laboratory LLC, catalog number: PPY-1-CS01). MS (UPLC/MS): 220 [M+H]+; t_R (HPLC conditions l): 0.69 min.

(3-Acetyl-pyrazolo[3,4-b]pyridin-1-yl)-acetic acid trifluoroacetate



was prepared using similar procedures as described for the synthesis of (3-acetyl-5-methyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid in Scheme A20 from 1-(1H-pyrazolo[3,4-b]pyridin-3-yl)-ethanone (Sphinx Scientific laboratory LLC, [889451-31-4], PYP-3-0043). MS (UPLC/MS): 220 [M+H]+, 218.2 [M-H]-; t_R (HPLC conditions k): 2.51 min.

Scheme A21: Preparation of 2-(3-acetyl-6-(methoxycarbonyl)-1H-indazol-1-yl)acetic acid



A. Methyl 3-bromo-1-(2-tert-butoxy-2-oxoethyl)-1H-indazole-6-carboxylate

The title compound was prepared from methyl 3-bromo-1H-indazole-6-carboxylate [192945-56-5] in a similar manner as described in step B of Scheme A13 for the preparation of (3-

acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid. MS: 392 [M+Na]+, 313 [M-tBu]+; t_R (HPLC conditions k): 4.08 min.

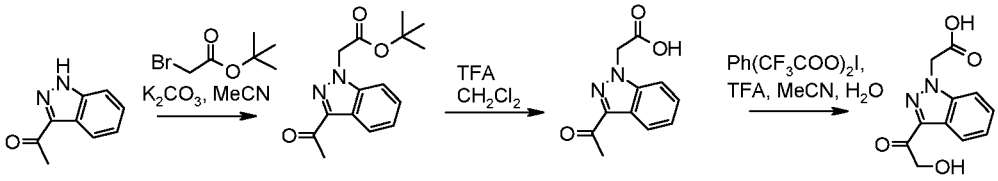
B. Methyl 3-acetyl-1-(2-tert-butoxy-2-oxoethyl)-1H-indazole-6-carboxylate

A solution of methyl 3-bromo-1-(2-tert-butoxy-2-oxoethyl)-1H-indazole-6-carboxylate (1.00 g, 2.71 mmol), n-butyl vinylether (1.75 mL, 13.5 mmol), palladium acetate (61 mg, 0.27 mmol), triphenylphosphine (142 mg, 0.54 mmol) and triethylamine (0.45 mL, 3.25 mmol) in dry CH_3CN (10 mL) was heated at 100°C under microwave irradiation for 7 h. Then, the mixture was further heated at 120°C for 5 h under microwave irradiation . The solvent was evaporated, and the residue was then treated with 4N HCl/dioxane with stirring at RT for 16 h. Volatiles were evaporated and the residue was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, flow: 40 mL/min, eluent: 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) to give after lyophilization of the pure fractions the title compound. MS (LC-MS): 333 [M+H]+, 355 [M+Na]; t_R (HPLC conditions k): 3.83 min.

C. 2-(3-Acetyl-6-(methoxycarbonyl)-1H-indazol-1-yl)acetic acid

The title compound was prepared from methyl 3-acetyl-1-(2-tert-butoxy-2-oxoethyl)-1H-indazole-6-carboxylate in a similar manner as described in step C of Scheme A13 for the preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid. MS: 277 [M+H]+; t_R (HPLC conditions k): 2.95 min.

Scheme A22: Preparation of 2-(3-(2-yydroxyacetyl)-1H-indazol-1-yl)acetic acid



A. Tert-butyl 2-(3-acetyl-1H-indazol-1-yl)acetate

The title compound was prepared from 1-(1H-indazol-3-yl)ethanone [4498-72-0] in a similar manner as described in step B of Scheme A13 for the preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid. MS: 275 [M+H]+; t_R (HPLC conditions k): 3.78 min.

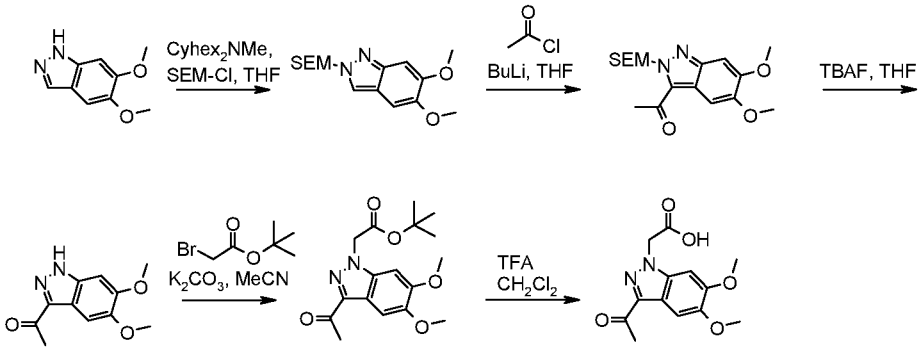
B. 2-(3-Acetyl-1H-indazol-1-yl)acetic acid

The title compound was prepared from tert-butyl 2-(3-acetyl-1H-indazol-1-yl)acetate in a similar manner as described in step C of Scheme A13 for the preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid. MS: 219 [M+H]+; t_R (HPLC conditions k): 2.78 min.

C. 2-(3-(2-Hydroxyacetyl)-1H-indazol-1-yl)acetic acid

The title compound was prepared in a similar manner as described by N.Yoshikawa *et al.*, *J. Org. Chem.*, **2002**, 67, 2556-2565: A mixture of 2-(3-acetyl-1H-indazol-1-yl)acetic acid (100 mg, 0.46 mmol), TFA (0.71 mL, 0.92 mmol) and bis-(trifluoroacetoxy)-iodobenzene (394 mg, 0.92 mmol) in CH_3CN (4 mL) and water (0.6 mL) was heated to reflux (90°C) for 16 h. Solvents were evaporated and the crude product was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, flow: 40 mL/min, eluent: 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) to give after lyophilization of the purified fractions the title compound. MS (LC-MS): 233 [M+H]+; t_R (HPLC conditions k): 2.41 min.

Scheme A23: Preparation of 2-(3-acetyl-5,6-dimethoxy-1H-indazol-1-yl)acetic acid



A. 5,6-Dimethoxy-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-indazole

The title compound was prepared in a similar manner as described by G. Luo *et al.*, *J. Org. Chem.* **2006**, 71, 5392-5395: To a solution of 5,6-dimethoxyindazole [7746-30-7] (356 mg, 2.00 mmol) in THF (20 mL) was added dicyclohexylmethylamine (0.51 mL, 2.40 mmol) followed by SEM-Cl (0.43 mL, 2.40 mmol). The mixture was stirred at RT for 24 h, followed by dilution with EtOAc and quench with 1N aqueous NaOH solution. The layers were separated and the organic layer was washed with water and brine, then dried (Phase separator) and evaporated. The residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 4:1 to 1:1) to separate from the regioisomer 5,6-dimethoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole and to provide the title compound. TLC, R_f (c-hexane/EtOAc 1:1) = 0.37; MS (LC/MS): 309 [M+H; t_R (HPLC conditions k): 3.70 min.

B. 1-(5,6-Dimethoxy-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-indazol-3-yl)ethanone

The title compound was prepared in a similar manner as described by G. Luo *et al.*, *J. Org. Chem.* **2006**, 71, 5392-5395: To a solution of 5,6-dimethoxy-2-((2-(trimethylsilyl) ethoxy)methyl)-2H-indazole (200 mg, 0.65 mmol) in THF (5 mL) at –78°C was added dropwise a 2.5 M solution of n-BuLi in hexanes (0.29 mL, 0.71 mmol). The reaction mixture was stirred at –78°C for 20 min. Acetyl chloride (0.07 mL, 0.97 mmol) was then added dropwise, and the mixture was stirred at RT for 16 h. Saturated aqueous NH_4Cl solution was added to the reaction mixture, followed by stirring for 30 min. The aqueous phase was extracted twice with

EtOAc and the combined organics were washed with brine, dried (Phase separator) and evaporated to give the crude title compound which was used directly in the next step without further purification.

C. 1-(5,6-Dimethoxy-1H-indazol-3-yl)ethanone

The title compound was prepared in a similar manner as described by G. Luo *et al.*, *J. Org. Chem.* **2006**, 71, 5392-5395: To a solution of 1-(5,6-dimethoxy-2-((2-(trimethylsilyl) ethoxy)methyl)-2H-indazol-3-yl)ethanone (200 mg, 0.57 mmol) in THF (6 mL) was added a 1M solution in THF of TBAF (2.85 mL, 2.85 mmol), and the mixture was heated to reflux for 16 h. The reaction mixture was then diluted with EtOAc and successively washed with water and brine, then dried (Phase separator) and evaporated. The crude product was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, flow: 40 mL/min, eluent: 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) to give after lyophilization of the purified fractions the title compound. MS (LC-MS): 221 [M+H]+; t_R (HPLC conditions k): 2.61 min.

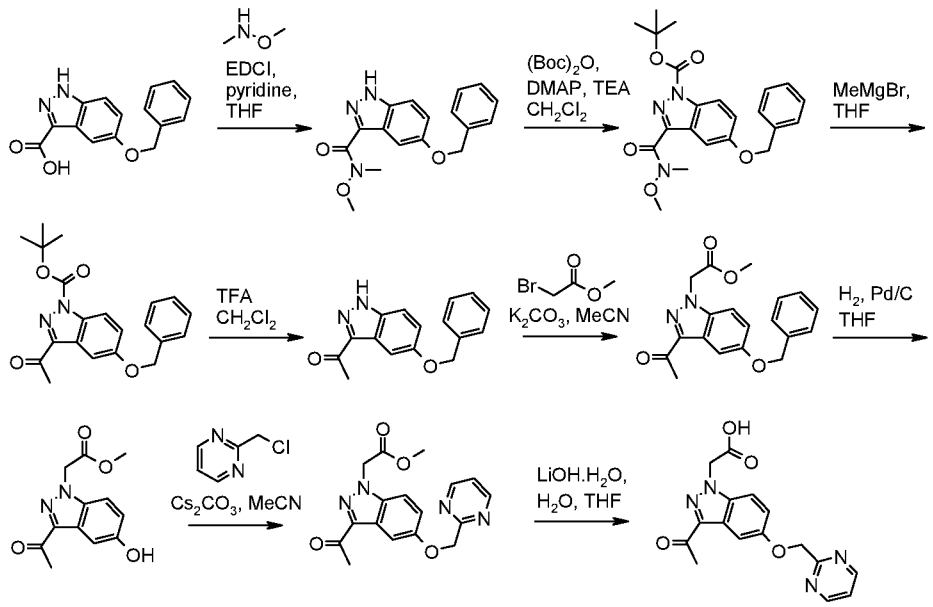
D. Tert-butyl 2-(3-acetyl-5,6-dimethoxy-1H-indazol-1-yl)acetate

The title compound was prepared from 1-(5,6-dimethoxy-1H-indazol-3-yl)ethanone in a similar manner as described in step B of Scheme A13 for the preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid. MS: 335 [M+H]+; t_R (HPLC conditions k): 3.58 min.

E. 2-(3-Acetyl-5,6-dimethoxy-1H-indazol-1-yl)acetic acid

The title compound was prepared from tert-butyl 2-(3-acetyl-5,6-dimethoxy-1H-indazol-1-yl)acetate in a similar manner as described in step C of Scheme A13 for the preparation of (3-acetyl-5-trifluoromethoxy-indol-1-yl)-acetic acid. MS: 279 [M+H]+; t_R (HPLC conditions k): 2.73 min.

Scheme A24: Preparation of 2-(3-acetyl-5-(pyrimidin-2-ylmethoxy)-1H-indazol-1-yl)acetic acid



A. 5-(Benzyloxy)-N-methoxy-N-methyl-1H-indazole-3-carboxamide

The title compound was prepared in a similar manner as described by F. Crestey *et al.*, *Tetrahedron* **2007**, 63, 419-428: To 5-(benzyloxy)-1H-indazole-3-carboxylic acid [177941-16-1] (3.50 g, 13.1 mmol) in THF (70 mL) was added N,O-dimethylhydroxylamine (1.40 g, 14.4 mmol). The mixture was cooled to 0°C before the addition of pyridine (2.30 mL, 28.7 mmol). The solution was stirred at 0°C for 1.5 h, and then at RT for 1 h. Pyridine (2.10 mL, 26.1 mmol) and EDCI (5.00 g, 26.1 mmol) were added and the mixture was stirred at RT overnight. Water was added to the reaction mixture followed by extraction (x3) with CH_2Cl_2. The combined organics were washed with saturated aqueous $NaHCO_3$ solution, then dried (Phase separator) and evaporated to give the title compound. MS (LC/MS): 312.0 [M+H]+, 334.0 [M+Na]+, 645.1 [2M+Na]+, 310.0 [M-H]-; t_R (HPLC conditions c): 4.44 min.

B. Tert-butyl 5-(benzyloxy)-3-(methoxy(methyl)carbamoyl)-1H-indazole-1-carboxylate

The title compound was prepared in a similar manner as described by F. Crestey *et al.*, *Tetrahedron* **2007**, 63, 419-428: To a solution of 5-(benzyloxy)-N-methoxy-N-methyl-1H-indazole-3-carboxamide (3.40 g, 10.9 mmol) in CH_2Cl_2 (70 mL) was added DMAP (0.13 g, 1.09 mmol), TEA (1.67 mL, 12.0 mmol) and Boc-anhydride (3.80 mL, 16.4 mmol) at 0°C. The reaction mixture was stirred at 0°C for 1 h and allowed to return to RT overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with 50 mL of 0.1 M aqueous HCl solution and water. The organic phase was dried (Phase separator) and evaporated to give the title compound. MS (LC/MS): 434.0 [M+Na]+, 845.0 [2M+Na]+; t_R (HPLC conditions c): 5.79 min.

C. Tert-butyl 3-acetyl-5-(benzyloxy)-1H-indazole-1-carboxylate and 1-(5-(benzyloxy)-1H-indazol-3-yl)ethanone

The title compound was prepared in a similar manner as described by F. Crestey *et al.*, *Tetrahedron* **2007**, 63, 419-428: To tert-butyl 5-(benzyloxy)-3-(methoxy(methyl)carbamoyl)-1H-indazole-1-carboxylate (4.70 g, 11.4 mmol) in THF (60 mL), cooled to -78°C, was added a 3 M solution of MeMgBr (22.9 mL, 68.5 mmol) in Et_2O. The reaction mixture was stirred at -78°C for 1 h. A saturated aqueous NH_4Cl solution was added to the reaction mixture and temperature was allowed to raise to RT. The mixture was extracted twice with CH_2Cl_2, the combined organics were dried (Phase separator) and evaporated to give the title mixture which was used without purification in the next step.

D. 1-(5-(Benzyloxy)-1H-indazol-3-yl)ethanone

To the mixture of tert-butyl 3-acetyl-5-(benzyloxy)-1H-indazole-1-carboxylate and 1-(5-(benzyloxy)-1H-indazol-3-yl)ethanone (3.80 g, 10.4 mmol) in CH_2Cl_2 (50 mL) was added TFA (7.99 mL, 104 mmol). The reaction mixture was stirred at RT overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with 100 mL of 2N aqueous NaOH solution. The basic phase was extracted twice with CH_2Cl_2, then the combined organic phases were dried (Phase separator) and evaporated to give the title compound. MS (LC/MS): 267.0 [M+H]+, 289.0 [M+Na]+, 265.1 [M-H]-; t_R (HPLC conditions c): 4.71 min.

E. Methyl 2-(3-acetyl-5-(benzyloxy)-1H-indazol-1-yl)acetate

To 1-(5-(benzyloxy)-1H-indazol-3-yl)ethanone (3.50 g, 13.1 mmol) in CH_3CN (100 mL) was added K_2CO_3 (4.54 g, 32.9 mmol) and methyl 2-bromoacetate (1.33 mL, 14.5 mmol). The reaction mixture was stirred at 90°C for 90 min. The reaction mixture was filtered and the solid was washed with CH_3CN. Volatiles were evaporated and then the crude mixture was purified by flash column chromatography on silica gel (gradient: c-hexane/EtOAc 1:1 to 1:3). TLC, R_f (c-hexane/EtOAc 1:3) = 0.64; MS (LC/MS): 339.0 [M+H]+, 361.0 [M+Na]+; t_R (HPLC conditions c): 5.09 min.

F. Methyl 2-(3-acetyl-5-hydroxy-1H-indazol-1-yl)acetate

To methyl 2-(3-acetyl-5-(benzyloxy)-1H-indazol-1-yl)acetate (3.70 g, 10.9 mmol) in THF (80 mL) was added Pd/C (10%, 400 mg). The reaction mixture was stirred at 50°C overnight under a H_2 atmosphere. The reaction mixture was filtered over a pad of Celite and washed with CH_2Cl_2, then volatiles were evaporated to give the title compound. MS (LC/MS): 248.9 [M+H]+, 271.0 [M+Na]+; t_R (HPLC conditions c): 3.36 min.

G. Methyl 2-(3-acetyl-5-(pyrimidin-2-ylmethoxy)-1H-indazol-1-yl)acetate

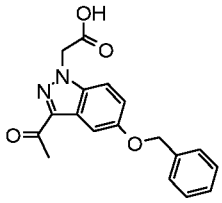
To methyl 2-(3-acetyl-5-hydroxy-1H-indazol-1-yl)acetate (1.80 g, 7.25 mmol) in CH_3CN (75 mL) was added 2-(chloromethyl)pyrimidine hydrochloride salt (1.32 g, 7.98 mmol) and Cs_2CO_3

(5.91 g, 18.13 mmol). The reaction mixture was stirred at 70°C for 2 h. The reaction mixture was filtered and washed with CH_3CN. Solvent was evaporated and the crude mixture was purified by flash column chromatography on silica gel (gradient: c-hexane/EtOAc 1:1 to 1:3). TLC, R_f (c-hexane/EtOAc 1:3) = 0.35; MS (LC/MS): 340.9 [M+H]+, 363.0 [M+Na]+; t_R (HPLC conditions c): 3.64 min.

H. 2-(3-Acetyl-5-(pyrimidin-2-ylmethoxy)-1H-indazol-1-yl)acetic acid

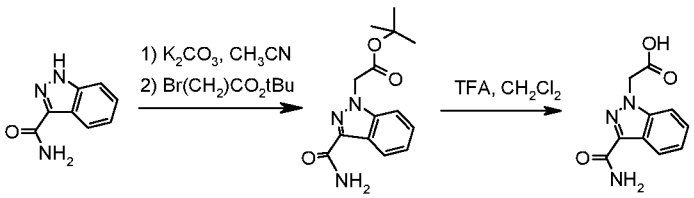
To methyl 2-(3-acetyl-5-(pyrimidin-2-ylmethoxy)-1H-indazol-1-yl)acetate (1.93 g, 5.67 mmol) in THF (15 mL) and water (15 mL) was added $LiOH.H_2O$ (0.25 g, 5.95 mmol). The reaction mixture was stirred at RT for 1.5 h. Volatiles were evaporated and the residue was freeze-dried overnight to give the title compound. MS (LC/MS): 327.0 [M+H]+, 325.1 [M+H]+; t_R (HPLC conditions c): 3.24 min.

(3-Acetyl-5-benzyloxy-indazol-1-yl)-acetic acid



To a solution of (3-acetyl-5-benzyloxy-indazol-1-yl)-acetic acid methyl ester (prepared as described in Scheme A24, 1.50 g, 4.43 mmol) in MeOH (40 mL) was added a 10% aqueous solution of NaOH (5.32 mL, 13.30 mmol) and the resulting mixture was stirred at RT for 16 h. The mixture was concentrated, diluted in water and acidified to pH = 2 with 6N HCl. The mixture was then extracted with EtOAc and the organic layer was dried (Na_2SO_4), filtered and concentrated. The product was used in the next step without further purification. MS (UPLC-MS): 325 [M+H]+; t_R (UPLC conditions m): 0.90 min.

Scheme A25: Preparation of (3-carbamoyl-indazol-1-yl)-acetic acid



A. Tert-butyl 2-(3-carbamoyl-1H-indazol-1-yl)acetate

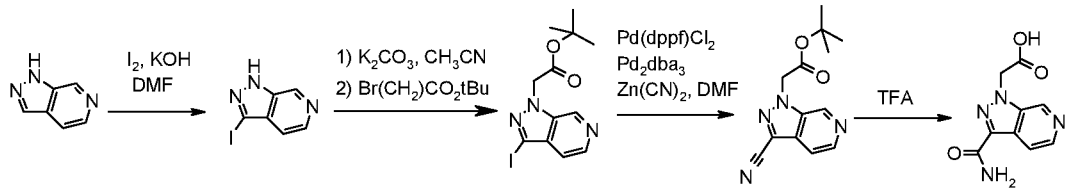
To a suspension of 1H-indazole-3-carboxamide [90004-04-9] (2.00 g, 12.4 mmol) and potassium carbonate (4.12 g, 29.8 mmol) in CH_3CN (60 mL) was added tert-butyl bromoacetate (2.20 mL, 14.9 mmol) dropwise at RT, and the resulting mixture was heated to reflux for 16 h. The mixture was then cooled to RT and filtered, the solid was washed with CH_3CN and the filtrate was concentrated under vacuum. The residual oil was used directly in

the next reaction step without further purification. MS (LC/MS): 276.0 [M+H]+; t_R (HPLC conditions k): 3.22 min.

B. (3-Carbamoyl-indazol-1-yl)-acetic acid

To a solution of tert-butyl 2-(3-carbamoyl-1H-indazol-1-yl)acetate (3.42 g, 12.4 mmol) in CH_2Cl_2 (20 mL) was added TFA (10 mL, 130 mmol) and the resulting mixture was stirred at RT for 16 h. The reaction mixture was concentrated in vacuo, the residual solid was suspended in methanol and concentrated again in vacuo to give the title compound. MS (LC/MS): 220 [M+H]+; t_R (HPLC conditions k): 1.79 min.

Scheme A26: Preparation of 2-(3-carbamoyl-1H-pyrazolo[3,4-c]pyridin-1-yl)acetic acid



A. 3-Iodo-1H-pyrazolo[3,4-c]pyridine

To a solution of 1H-pyrazolo[3,4-c]pyridine [271-47-6] (4.00 g, 33.6 mmol) in DMF (50 mL) were added iodine (12.8 g, 50.4 mmol) and potassium hydroxide (4.70 g, 84.0 mmol). The reaction mixture was stirred at RT for 16 h. The mixture was diluted with 10% sodium thiosulfate and water, then extracted (3x) with EtOAc. The combined organic extracts were washed with brine, then dried (Phase separator) and concentrated under vacuum. MS (LC/MS): 246.0 [M+H]+; t_R (HPLC conditions k): 0.48 min.

B. Tert-butyl 2-(3-iodo-1H-pyrazolo[3,4-c]pyridin-1-yl)acetate

To a suspension of 3-iodo-1H-pyrazolo[3,4-c]pyridine (6.24 g, 22.9 mmol) and potassium carbonate (7.29 g, 52.7 mmol) in acetonitrile (50 mL) was added tert-butyl bromoacetate (4.06 mL, 27.5 mmol) dropwise at RT and the resulting mixture was heated to reflux for 2 h. The mixture was cooled to RT and filtered, the solid was washed with CH_3CN and the filtrate was concentrated under vacuum. The residual oil was purified by flash column chromatography on silica gel (gradient EtOAc/c-hexane 1:4, then 1:2, then 1:1). MS (LC/MS): 360.0 [M+H]+; t_R (HPLC conditions k): 2.93 min.

C. Tert-butyl 2-(3-cyano-1H-pyrazolo[3,4-c]pyridin-1-yl)acetate

A mixture of tert-butyl 2-(3-iodo-1H-pyrazolo[3,4-c]pyridin-1-yl)acetate (3.76 g, 10.5 mmol), $Zn(CN)_2$ (1.35 g, 11.5 mmol), $Pd(dppf)Cl_2$ (855 mg, 1.05 mmol), $Pd_2(dba)_3$ (959 mg, 1.05 mmol), water (4 mL) and DMF (30 mL) was stirred at 100°C for 16 h under argon. The reaction mixture was diluted with EtOAc and then was successively washed with water, sat. aq.

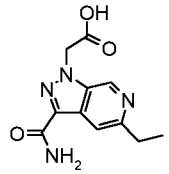
$NaHCO_3$ (2x) and brine, dried (Phase separator) and concentrated under vacuum. The residual oil was purified by flash column chromatography on silica gel (EtOAc/c-hexane 1:1 then 100% EtOAc). MS (LC/MS): 259.0 [M+H]+; t_R (HPLC conditions k): 3.10 min. Further elution of the column with CH_2Cl_2/MeOH 8:2 and subsequent purification by preparative HPLC (Macherey-Nagel Nucleosil 100-10 C18, 5 µm, 40x250 mm, flow: 40 mL/min, eluent: 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) afforded tert-butyl 2-(3-carbamoyl-1H-pyrazolo[3,4-c]pyridin-1-yl)acetate as a side-product. MS (LC/MS): 277.0 [M+H]+; t_R (HPLC conditions k): 2.39 min.

D. 2-(3-Carbamoyl-1H-pyrazolo[3,4-c]pyridin-1-yl)acetic acid

A solution of tert-butyl 2-(3-cyano-1H-pyrazolo[3,4-c]pyridin-1-yl)acetate (663 mg, 2.40 mmol) in TFA (6 mL) was subjected to microwave irradiation at 140°C for 90 min. The reaction mixture was concentrated in vacuo, the residual solid was suspended in MeOH and volatiles were removed again in vacuo. MS: 221.0 [M+H]+; t_R (HPLC conditions k): 0.23 min.

From tert-butyl 2-(3-carbamoyl-1H-pyrazolo[3,4-c]pyridin-1-yl)acetate:
To a solution of tert-butyl 2-(3-carbamoyl-1H-pyrazolo[3,4-c]pyridin-1-yl)acetate (663 mg, 2.40 mmol) in CH_2Cl_2 (20 mL) was added TFA (10 mL, 130 mmol), and the resulting mixture was stirred at RT for 6 h. The reaction mixture was concentrated in vacuo, the residual solid was suspended in methanol and volatiles were removed again in vacuo to give the title compound.

(3-Carbamoyl-5-ethyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid



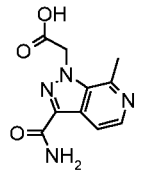
was prepared from 5-ethyl-1H-pyrazolo[3,4-c]pyridine by using the same procedures as for the preparation of 2-(3-carbamoyl-1H-pyrazolo[3,4-c]pyridin-1-yl)acetic acid (Scheme A26). MS (LC-MS): 249 [M+H]+, t_R (HPLC conditions k): 0.49 min.

5-Ethyl-1H-pyrazolo[3,4-c]pyridine

Triethylaluminum (21.7 mL, 40.4 mmol, 25 wt% solution in toluene) was added to a vigorously stirred solution of 5-bromo-1H-pyrazolo[3,4-c]pyridine [929617-35-6] (4.00 g, 20.2 mmol) and $Pd(PPh_3)_4$ (1.17 g, 1.01 mmol) in THF (100 mL) under argon. The reaction mixture was stirred at 65°C for 60 h. The mixture was cooled to RT and poured into sat. aq. NH_4Cl. The resulting suspension was filtered, the solid was washed with water and discarded. The filtrate and combined washings were extracted with EtOAc (3x). The combined organic extracts were washed with brine, then dried (Phase separator) and concentrated under reduced pressure.

The residual oil was purified by flash column chromatography on silica gel (EtOAc/c-hexane 50:50, then 75:25, then 100:0). TLC, R_f (c-hexane/EtOAc 1:3) = 0.22; MS (LC-MS): 148 [M+H]+, t_R (HPLC conditions k): 0.71 min.

(3-Carbamoyl-7-methyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid



was prepared using the same procedure as for the preparation of 2-(3-carbamoyl-1H-pyrazolo[3,4-c]pyridin-1-yl)acetic acid starting from 7-methyl-1H-pyrazolo[3,4-c]pyridine (Scheme A26). MS (LC-MS): 235 [M+H]+, t_R (HPLC conditions k): 0.6 min.

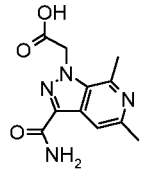
7-Methyl-1H-pyrazolo[3,4-c]pyridine

Trimethylaluminum (23.9 mL, 47.8 mmol, 2M sol. in toluene) was added to a vigorously stirred solution of 7-chloro-1H-pyrazolo[3,4-c]pyridine (3.67 g, 23.9 mmol) and $Pd(PPh_3)_4$ (1.38 g, 1.19 mmol) in THF (109 mL) under argon. The reaction mixture was stirred at 65°C for 16 h. The mixture was cooled to RT and poured into sat. aq. NH_4Cl. The resulting suspension was filtered, the solid washed with water and discarded. The filtrate and the combined washings were extracted with EtOAc (3x). The combined organic extracts were washed with brine then dried (Phase separator) and concentrated under reduced pressure to give 7-methyl-1H-pyrazolo[3,4-c]pyridine as a solid. MS (LC-MS): 134 [M+H]+, t_R (HPLC conditions k): 0.25 min.

7-Chloro-1H-pyrazolo[3,4-c]pyridine

A solution of 2-chloro-4-methylpyridin-3-amine [133627-45-9] (3.0 g, 21.0 mmol) in acetic acid (300 mL) was treated with a solution of sodium nitrite (1.45 g, 21.0 mmol) in water (2.5 mL). The reaction mixture was stirred at rt for 15 min then allowed to stand at ambient temperature for 24 h. An additional solution of sodium nitrite (500 mg, 7.25 mmol) in water (1 mL) was added to the mixture which was allowed to stand at rt for 3 h. Acetic acid was evaporated under reduced pressure and the residual aqueous solution was partitioned between EtOAc and sat. aq. $NaHCO_3$. The insoluble solid was filtered off (dried under vacuum; batch 1) and the organic filtrate was washed with water and brine, then dried (Phase separator) and concentrated under vacuum (batch 2). The two batches were combined to give 7-chloro-1H-pyrazolo[3,4-c]pyridine as a solid. MS (LC-MS): 153 [M+H]+, t_R (HPLC conditions k): 0.9 min.

(3-Carbamoyl-5,7-dimethyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid



was prepared from 5,7-dimethyl-1H-pyrazolo[3,4-c]pyridine by using the same procedures as described for the preparation of 2-(3-carbamoyl-1H-pyrazolo[3,4-c]pyridin-1-yl)acetic acid (Scheme A26). MS (LC-MS): 249 [M+H]+, t_R (HPLC conditions c): 0.9 min.

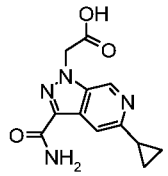
5,7-Dimethyl-1H-pyrazolo[3,4-c]pyridine

To a vigorously stirred solution of 7-bromo-5-methyl-1H-pyrazolo[3,4-c]pyridine (3.65 g, 14.6 mmol) and $Pd(PPh_3)_4$ (845 mg, 0.73 mmol) in THF (65 mL) was added trimethylaluminum (14.6 mL, 29.3 mmol; 2 M sol. in toluene) under argon. The reaction mixture was stirred at 65°C for 60 h, and then was cooled to RT and poured into a sat. aq. NH_4Cl solution. The resulting suspension was filtered, the solid was washed with water and discarded. The filtrate and the combined washings were extracted with EtOAc (3x). The combined organics were washed with brine, then dried (Phase separator) and concentrated under reduced pressure to give 5,7-dimethyl-1H-pyrazolo[3,4-c]pyridine as a solid. MS (LC-MS): 148 [M+H]+, t_R (HPLC conditions k): 0.50 min.

7-Bromo-5-methyl-1H-pyrazolo[3,4-c]pyridine

A solution of 2-bromo-4,6-dimethylpyridin-3-amine [104829-98-3] (4.00 g, 19.9 mmol) in acetic acid (300 mL) was treated with a solution of sodium nitrite (1.37 g, 19.9 mmol) in water (2.5 mL). The reaction mixture was stirred at RT for 15 min and was then allowed to stand at ambient temperature for 24 h. An additional solution of sodium nitrite (500 mg, 7.25 mmol) in water (1 mL) was added to the mixture which was allowed to stand at RT for 16 h. Acetic acid was evaporated under reduced pressure and the residual aqueous solution was partitioned between EtOAc and sat. aq. $NaHCO_3$. The precipitate was filtered off, washed and discarded. The combined filtrates were washed with water and brine, then dried (Phase separator) and concentrated under vacuum to give 7-bromo-5-methyl-1H-pyrazolo[3,4-c]pyridine as a solid. MS (LC-MS): 212 [M+H]+, t_R (HPLC conditions k): 2.49 min.

(3-Carbamoyl-5-cyclopropyl-1H-pyrazolo[3,4-c]pyridin-1-yl)acetic acid



was prepared by using the same procedure as described for the preparation of 2-(3-carbamoyl-1H-pyrazolo[3,4-c]pyridin-1-yl)acetic acid and by starting from 5-cyclopropyl-1H-

pyrazolo[3,4-c]pyridine (Scheme A26). MS (LC-MS): 261 [M+H]+, t_R (HPLC conditions c): 1.84 min.

5-Cyclopropyl-1H-pyrazolo[3,4-c]pyridine

A solution of 6-cyclopropyl-4-methylpyridin-3-amine (130 mg, 0.88 mmol) in AcOH (10 mL) was treated with a solution of sodium nitrite (61 mg, 0.88 mmol) in water (0.5 mL). The reaction mixture was stirred at RT for 15 min and then was allowed to stand at RT for 24 h. AcOH was evaporated under reduced pressure and the residual aqueous solution was partitioned between EtOAc and sat. aq. $NaHCO_3$. The organic solution was washed with water and brine, then dried (Phase separator) and concentrated under. MS (LC-MS): 160 [M+H]+, t_R (HPLC conditions c): 2.07 min.

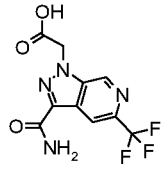
6-Cyclopropyl-4-methylpyridin-3-amine

To a solution of 2-cyclopropyl-4-methyl-5-nitropyridine (201 mg, 0.96 mmol) in MeOH (5 mL) were added 3N aqueous HCl (9.6 mL, 28.8 mmol) and Zn powder (376 mg, 5.75 mmol). The mixture was stirred 18 h at RT. The solution was neutralized with a sat. aq. $NaHCO_3$ solution and extracted with CH_2Cl_2 (3x). The combined organics were dried (Phase Separator) and concentrated under reduced pressure. MS (LC-MS): 149 [M+H]+, t_R (HPLC conditions c): 2.22 min.

2-Cyclopropyl-4-methyl-5-nitropyridine

Potassium cyclopropyltrifluoroborate (857 mg, 5.79 mmol), 2-chloro-4-methyl-5-nitropyridine (500 mg, 2.90 mmol), $Pd(OAc)_2$ (26 mg, 0.12 mmol), Cs_2CO_3 (2.83 g, 8.69 mmol), and n-butyl-di-adamantylphosphine (62 mg, 0.17 mmol) were charged into a capped vial. The vial was purged with argon and then sealed with a septum cap. Toluene/H_2O 10:1 (11 mL) was added by syringe and the mixture was heated at 100°C for 16 h. More potassium cyclopropyltrifluoroborate (857 mg, 5.79 mmol) was added to the mixture which was further heated at 100°C for 72 h. The mixture was diluted with CH_2Cl_2 and filtered through a pad of Celite. The filtrate was dried (Phase separator) and concentrated under reduced pressure. The residue was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, flow: 40 mL/min, eluent: 5-100% CH_3CN/H_2O/30 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA). MS (LC-MS): 179 [M+H]+, t_R (HPLC conditions c): 4.26 min.

(3-Carbamoyl-5-(trifluoromethyl)-1H-pyrazolo[3,4-c]pyridin-1-yl)acetic acid

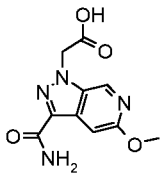


was prepared by using the same procedure as described for the preparation of 2-(3-carbamoyl-1H-pyrazolo[3,4-c]pyridin-1-yl)acetic acid and by starting from 5-trifluoromethyl-1H-pyrazolo[3,4-c]pyridine (Scheme A26). MS (LC-MS): 289 [M+H]+, t_R (HPLC conditions c): 2.93 min.

5-Trifluoromethyl-1H-pyrazolo[3,4-c]pyridine

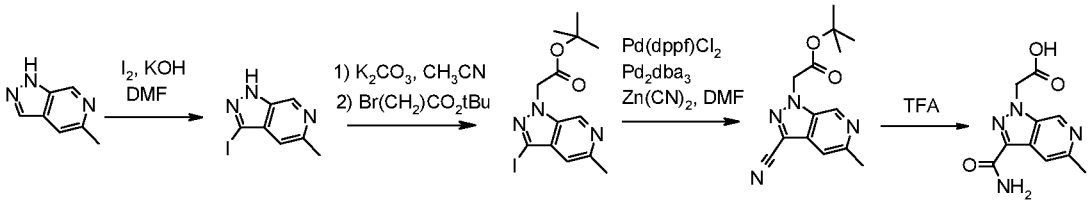
A solution of 4-methyl-6-(trifluoromethyl)pyridin-3-amine [944317-54-8] (1.00 g, 5.68 mmol) in acetic acid (75 mL) was treated with a solution of sodium nitrite (392 mg, 5.68 mmol) in water (1 mL). The reaction mixture was stirred at RT for 15 min and then was allowed to stand at ambient temperature for 48 h. Acetic acid was evaporated under reduced pressure and the residual aqueous solution was partitioned between EtOAc and sat. aq. $NaHCO_3$. The organic solution was washed with water and brine, then dried (Phase separator) and concentrated under vacuum. MS (LC-MS): 188 [M+H]+, t_R (HPLC conditions k): 2.49 min.

(3-Carbamoyl-5-methoxy-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid



was prepared from 5-methoxy-1H-pyrazolo[3,4-c]pyridine [76006-07-0] by using the same procedures as described for the preparation of 2-(3-carbamoyl-1H-pyrazolo[3,4-c]pyridin-1-yl)acetic acid (Scheme A26). MS (LC-MS): 251 [M+H]+, t_R (HPLC conditions k): 0.62 min.

Scheme A27: Preparation of (3-carbamoyl-5-methyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid



A. 3-Iodo-5-methyl-1H-pyrazolo[3,4-c]pyridine

To a solution of 5-methyl-1H-pyrazolo[3,4-c]pyridine [76006-06-9] (1.00 g, 7.51 mmol) in DMF (15 mL) were added iodine (2.86 g, 11.3 mmol) and potassium hydroxide (1.05 g, 18.8 mmol). The reaction mixture was stirred at RT for 60 h. The mixture was diluted with 10% sodium thiosulfate and water, the resulting suspension was filtered. The solid was washed with water and then dried under vacuum. MS (LC/MS): 260.0 [M+H]+; t_R (HPLC conditions k): 0.28 min.

B. Tert-butyl 2-(3-iodo-5-methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)acetate

To a suspension of 3-iodo-5-methyl-1H-pyrazolo[3,4-c]pyridine (1.00 g, 3.86 mmol), and potassium carbonate (1.28 g, 9.26 mmol) in acetonitrile (40 mL) was added tert-butyl bromoacetate (0.685 mL, 4.63 mmol) dropwise at RT and the resulting mixture was heated to reflux for 16 h. The mixture was cooled to RT and filtered, the solid was washed with acetonitrile and the filtrate was concentrated under vacuum. The residual oil was used directly in the next step without further purification. MS (LC/MS): 374.0 [M+H]+; t_R (HPLC conditions k): 2.96 min.

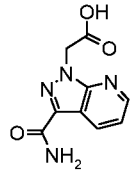
C. Tert-butyl 2-(3-cyano-5-methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)acetate

A mixture of tert-butyl 2-(3-iodo-5-methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)acetate (1.00 g, 2.55 mmol), $Zn(CN)_2$ (329 mg, 2.55 mmol), $Pd(dppf)Cl_2$ (208 mg, 0.25 mmol), $Pd_2(dba)_3$ (233 mg, 0.25 mmol), water (2.7 mL) and DMF (20 mL) was subjected to microwave irradiation at 120°C for 30 min under argon. The reaction mixture was filtered through a pad of Celite and the filtrate was diluted with water and EtOAc. The phases were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, then dried (Phase separator) and concentrated under vacuum. The residual oil was purified by flash chromatography on silica gel (EtOAc/c-hexane 1:2 then 1:1). MS (LC/MS): 273.0 [M+H]+; t_R (HPLC conditions k): 3.04 min.

D. (3-Carbamoyl-5-methyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid

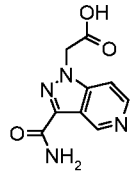
A solution of tert-butyl 2-(3-cyano-5-methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)acetate (250 mg, 0.92 mmol) in TFA (4 mL) was subjected to microwave irradiation at 140°C for 90 min. The reaction mixture was concentrated in vacuo, the residual solid was suspended in methanol and concentrated again in vacuo. MS: 235.0 [M+H]+; t_R (HPLC conditions k): 0.24 min.

(3-Carbamoyl-pyrazolo[3,4-b]pyridin-1-yl)-acetic acid



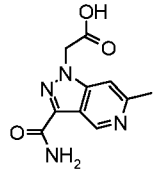
was prepared from 1H-pyrazolo[3,4-b]pyridine [271-73-8] by using the same procedures as described for the preparation of (3-carbamoyl-5-methyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid (Scheme A27). MS (LC-MS): 221 [M+H]+, t_R (HPLC conditions k): 0.87 min.

(3-Carbamoyl-pyrazolo[4,3-c]pyridin-1-yl)-acetic acid



was prepared from 1H-pyrazolo[4,3-c]pyridine [271-52-3] by using the same procedures as for the preparation of (3-carbamoyl-5-methyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid (Scheme A27). MS (LC-MS): 221 [M+H]+, t_R (HPLC conditions k): 0.19 min.

(3-Carbamoyl-6-methyl-pyrazolo[4,3-c]pyridin-1-yl)-acetic acid

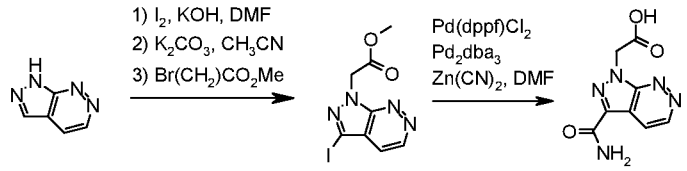


was prepared from 6-methyl-1H-pyrazolo[4,3-c]pyridine by using the same procedures as for the preparation of (3-carbamoyl-5-methyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid (Scheme A27). MS (LC-MS): 235 [M+H]+, t_R (HPLC conditions k): 0.29 min.

6-Methyl-1H-pyrazolo[4,3-c]pyridine

A solution of 4-chloro-6-methyl-1H-pyrazolo[4,3-c]pyridine [1159828-70-2] (750 mg, 4.48 mmol) in a mixture of ethanol (25 mL) and THF (10 mL) was hydrogenated over 10% Pd/C (75 mg, 0.07 mmol) at RT for 24 h. The reaction mixture was filtered, the catalyst was washed with ethanol and the filtrate was concentrated under vacuum. MS (LC-MS): 134 [M+H]+, t_R (HPLC conditions k): 0.23 min.

Scheme A28: Preparation of 2-(3-carbamoyl-1H-pyrazolo[3,4-c]pyridazin-1-yl)acetic acid



A. Methyl 2-(3-iodo-1H-pyrazolo[3,4-c]pyridazin-1-yl)acetate

To a solution of 1H-pyrazolo[3,4-c]pyridazine [271-75-0] (450 mg, 3.75 mmol) in DMF (10 mL) was added iodine (951 mg, 3.75 mmol) and KOH (525 mg, 9.37 mmol). The mixture was stirred at RT for 16 h until completion of the reaction. Methyl 2-bromoacetate (0.380 mL, 4.12 mmol) was then added to the reaction mixture and stirring was continued at RT for 2 h. The mixture was diluted with EtOAc and washed with water (10 mL), the organic phase was dried (Na_2SO_4) and evaporated under vacuum. The crude mixture was purified by flash column chromatography on silica gel (c-Hex/EtOAc 66 :33) to afford the title compound as a brown

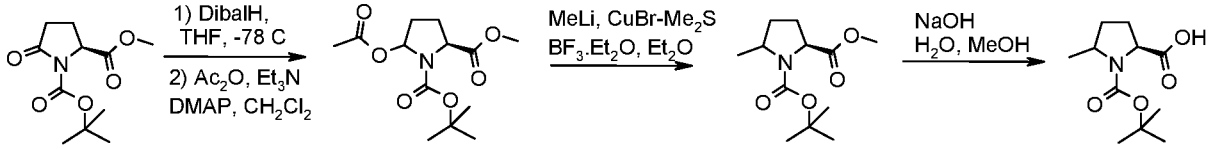
solid. TLC, R_f (c-Hex/EtOAc 1:1) = 0.40; MS (LC/MS): 318.9 [M+H]+; t_R (HPLC conditions c): 3.35 min.

B. 2-(3-Carbamoyl-1H-pyrazolo[3,4-c]pyridazin-1-yl)acetic acid

To a solution of methyl 2-(3-iodo-1H-pyrazolo[3,4-c]pyridazin-1-yl)acetate (675 mg, 2.12 mmol) in DMF (7.5 mL) and water (1.5 mL) was added $Zn(CN)_2$ (274 mg, 2.33 mmol), Pd_2dba_3 (194 mg, 0.21 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ adduct (173 mg, 0.21 mmol). The reaction mixture was stirred at 100°C for 16 h. The resulting suspension was filtered and the filtrate was evaporated under vacuum. The residue was suspended in CH_3CN/MeOH 1:1, the solid was filtered off and the filtrate was purified by preparative HPLC (Macherey Nagel, VP250/40, C18 Nucleosil 100-10, flow: 40 mL/min, eluent: 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) to give the title compound after lyophilisation. MS (LC/MS): 222.1 [M+H]+; t_R (HPLC conditions c): 1.34 min.

Part B: Synthesis of various 5-membered heterocycles :

Scheme B1: Preparation of (2S,5R) and (2S,5S)-5-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester in a (7:1) ratio following a similar procedure as described in *J. Org. Chem.* **2003**, *60*, 7219.



A. (S)-5-Acetoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester

To a solution of (S)-5-oxo-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (prepared according to *J. Org. Chem.* **2003**, *60*, 7219) (1.9 g, 7.8 mmol) in THF (25 mL), cooled to -78°C, was slowly added DibalH (1 M in toluene; 11.0 mL, 11.0 mmol) under an argon atmosphere, followed by stirring of the solution at -78°C for 1 h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (30 mL). The mixture was allowed to warm up to RT, and a 10% aqueous Na_2CO_3 solution (20 mL) and CH_2Cl_2 (70 mL) were subsequently added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2x50 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (25 mL), acetic anhydride (2.21 mL, 23.4 mmol), NEt_3 (3.26 mL, 23.4 mmol) and 4-dimethylaminopyridine (0.2 g, 1.6 mmol) were subsequently added and the reaction mixture was stirred at RT overnight. The organics were washed with a saturated aqueous $NaHCO_3$ solution (10 mL) and 1M aqueous HCl, dried (Phase separator) and concentrated in vacuo. The residue was purified by flash column chromatography on silica

gel (c-hexane/EtOAc gradient 3:1 to 1:1) to give the title compound. TLC, R_f (c-hexane/EtOAc 1:1) = 0.5; MS: 310.0 [M+Na]+, 597.3 [2M+Na]+.

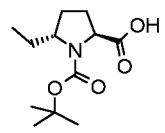
B. (2S,5R)- and (2S,5S)-5-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester

To a suspension of copper bromide-dimethylsulfide complex (1.09 g, 5.32 mmol) in Et_2O (30 mL), cooled to -40°C, was added methyl lithium (1.6M in Et_2O; 3.32 mL, 5.32 mmol) dropwise under an argon atmosphere. The solution was stirred for 45 min, then cooled to -78°C, and boron trifluoride etherate was added dropwise (0.67 mL, 5.32 mmol). After 15 min, a solution of (S)-5-acetoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (0.51 g, 1.77 mmol) in Et_2O (5 mL) was added dropwise. The reaction mixture was stirred for 15 min and was, after warming up to RT over 1 h, quenched by addition of a 1:1 (v/v) mixture of an aqueous saturated NH_4Cl solution and a 25% aqueous NH_4OH solution (10 mL). After stirring for 30 min, the two layers were separated and the aqueous phase was extracted with Et_2O (2x50 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 8:2) to give the title compound as a (trans:cis) mixture of diastereoisomers in a 7:1 ratio. TLC, R_f (c-hexane/EtOAc 3:1) = 0.42; MS: 266.0 [M+Na]+, 509.2 [2M+Na]+.

C. (2S,5R)- and (2S,5S)-5-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester

To a solution of (2S,5R)- and (2S,5S)-5-methyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (0.33 g, 1.35 mmol; trans:cis ratio 7:1) in MeOH (2 mL) was added 1N NaOH (2 mL) and the reaction mixture was stirred at RT overnight. An additional aliquot of 1N NaOH (2 mL) was added and the mixture was heated at 50°C for 5 h. Volatiles were removed under reduced pressure, and the aqueous phase was acidified to pH 1 by addition of 6N HCl, followed by extraction with CH_2Cl_2 (2x25 mL). The combined organics were dried (Phase separator) and concentrated to afford the title compound a (trans:cis) mixture of diastereoisomers in a 7:1 ratio. TLC, R_f (CH_2Cl_2/MeOH (10% AcOH) 9:1) = 0.41; MS (LC/MS): 227.9 [M-H]-.

(2S,5S)-5-Ethyl-pyrrolidine-1,2-diarboxylic acid 1-tert-butyl ester



A. (2S,5R)-5-Ethyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester

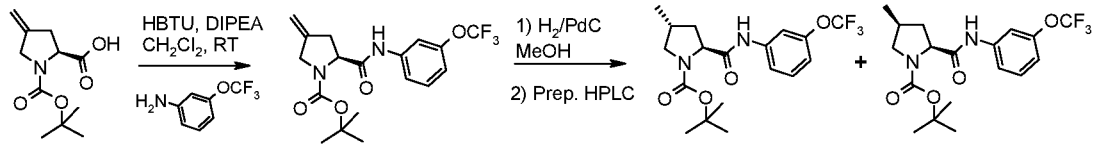
To a stirred suspension of copper bromide-dimethylsulfide complex (2.15 g, 10.4 mmol) in dry Et_2O (40 mL), cooled to -40°C, was added dropwise ethyl magnesium chloride (2M in Et_2O;

5.22 mL, 10.4 mmol; Aldrich 300330) under an argon atmosphere. After stirring for 45 min, the mixture was cooled to -78°C, followed by dropwise addition of boron trifluoride etherate (1.32 mL, 10.4 mmol) and stirring for 15 min. Then, a solution of (S)-5-acetoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (1.00 g, 3.48 mmol, prepared as described in Scheme B1) in dry Et_2O (10 mL) was added dropwise to result in a black suspension. The reaction mixture was stirred for 15 min and subsequently was allowed to warm up to RT over a period of 1 h. The reaction was quenched by addition of a (1:1)-mixture of a saturated aqueous NH_4Cl solution and a concentrated aqueous NH_3 solution (10 mL), followed by stirring for 30 min. The organic layer was separated, and the aqueous phase was extracted with Et_2O (2x50 mL). The combined organics were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/c-hexane 2:8) to afford the title compound (contained less than 10% of the minor (2S,5S)-diastereoisomer according to 1H-NMR). TLC R_f (EtOAc/c-hexane 1:3) = 0.48.

B. (2S,5S)-5-Ethyl-pyrrolidine-1,2-diarboxylic acid 1-tert-butyl ester

To a solution of (2S,5R)-5-ethyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (containing <10 % of the minor (2S,5R)-diastereomer) (340 mg, 1.32 mmol) in MeOH (15 mL) was added a 2N aqueous NaOH solution (1.32 mL, 2.64 mmol), followed by stirring the reaction mixture at 50°C overnight. An additional aliquot of NaOH (2 equiv) was added and stirring was continued at 50°C for 6 h. Volatiles were removed under reduced pressure and the residue was taken up in water. The aqueous layer was acidified (pH 1) by adding 6N aqueous HCl, followed by extraction with CH_2Cl_2 (2x20 mL). The combined organics were dried (Phase separator) and evaporated in vacuo to afford the title compound (contained less than 10% of the minor (2S,5S)-diastereoisomer). TLC, R_f (CH_2Cl_2/MeOH (2% AcOH): 9:1) = 0.40.

Scheme B2: preparation of (2S,4R) and (2S,4S)-2-(3-Trifluoromethoxy-phenylcarbamoyl)-4-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester



A. (S)-2-(3-Trifluoromethoxy-phenylcarbamoyl)-4-methylene-pyrrolidine-1-carboxylic acid tert-butyl ester

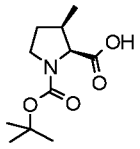
To a suspension of N-Boc-4-methylene-L-proline (1 g, 4.4 mmol) in CH_2Cl_2 (40 mL) was added 3-(trifluoromethoxy)aniline (0.71 mL, 5.28 mmol), HBTU (1.14 g, 6.6 mmol) and diisopropylethylamine (1.51 mL, 8.8 mmol). The reaction mixture was stirred at RT for 2 days. The mixture was successively washed with 30 mL of a saturated aqueous $NaHCO_3$ solution and an HCl 1M solution. The organic layers were dried (phase separator) and concentrated

under vacuum. The crude residue was purified by flash column chromatography on silica gel (eluent: c-hexane/EtOAc: 65/35) to give the title compound. TLC, R_f (c-hexane/EtOAc: 1:1) = 0.55; MS (LC/MS): 287.0 [M-Boc]+, 385.0 [M-H]-.

B. (2S,4R) and (2S,4S)-2-(3-Trifluoromethoxy-phenylcarbamoyl)-4-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (S)-2-(3-trifluoromethoxy-phenylcarbamoyl)-4-methylene-pyrrolidine-1-carboxylic acid tert-butyl ester (0.5 g, 1.29 mmol) in EtOAc (15 mL) was added Pd/C (10 %) and the reaction mixture was placed under hydrogen atmosphere overnight. The reaction mixture was filtered on a pad of Celite, the catalyst residue was washed with EtOAc and the solvent was concentrated. The crude material was purified by preparative HPLC (waters SunFire C18-ODB, 5 µm, 30x100 mm, eluent: 20-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 mL/min, loading 150 mg per run) to give after lyophilization of the purified fractions the desired compounds: (2S,4S)-2-(3-trifluoromethoxy-phenylcarbamoyl)-4-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester: t_R (HPLC conditions b): 5.34 min; LC/MS: 387.0 [M-H]-; (2S,4R)-2-(3-trifluoromethoxy-phenylcarbamoyl)-4-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester: t_R (HPLC conditions b): 5.53 min ; MS (LC/MS): 387.0 [M-H]-.

(2S,3R)-3-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester



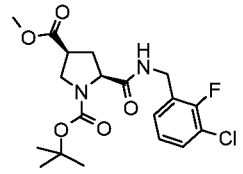
A. (2S,3R)-3-Methyl-1-((S)-1-phenyl-ethyl)-pyrrolidine-2-carboxylic acid benzyl ester was prepared following the procedure described in *Tet. Lett.* **1997**, *38* (1), 89-92 starting from [but-3-enyl-((S)-1-phenyl-ethyl)-amino]-acetic acid benzyl ester.

B. (2S,3R)-3-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester

(2S,3R)-3-Methyl-1-((S)-1-phenyl-ethyl)-pyrrolidine-2-carboxylic acid benzyl ester (245 mg, 0.758 mmol) and Boc_2O (165 mg, 0.758 mmol) were dissolved in MeOH (3.5 mL). Air was removed from the flask and replaced with nitrogen three times. Pd/C 10 % (76 mg) was added and the solution was again degassed and placed under a hydrogen atmosphere. The mixture was stirred at RT for 1.5 h, filtered through a pad of Celite and the solvent was concentrated in vacuo. The residue was dissolved in EtOAc and an aqueous saturated solution of $NaHCO_3$ was added. The layers were separated and the aqueous one acidified with HCl 1 N (pH = 1) and extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give the desired compound which was used without further purification in

the next step. 1H-NMR (400 MHz, DMSO): δ (ppm): 12.5 (bs, 1H), 4.02 (d, 1H), 3.47 (q, 1H), 3.19 (m, 1H), 2.4 (m, 1H), 1.92 (m, 1H), 1.54 (m, 1H), 1.40 and 1.35 (2s, 9H), 0.96 (d, 3H).

(3S,5S)-5-(3-Chloro-2-fluoro-benzylcarbamoyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester



A. (2S,4S)-4-Cyano-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester

A solution of N-boc-cis-4-cyano-L-proline methyl ester (800 mg, 3.15 mmol) in MeOH (27 mL) was cooled to 0°C and $LiOH.H_2O$ (792 mg, 18.9 mmol) was added. The colorless solution was allowed to reach RT and stirred for 4 h. $LiOH.H_2O$ (792 mg, 18.9 mmol) was added and the reaction further stirred at for 1 hour to complete the reaction. MeOH was concentrated and the residue diluted in CH_2Cl_2 and treated with aqueous 1M HCl adjusting the pH to 1. The layers were separated and the aqueous one re-extracted with CH_2Cl_2 (x2). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to give the desired compound which was used in the next step without further purification. MS (LC/MS) : 263.0 [M+Na]+, 503.2 [2M+Na]+, 239.1 [M-H]-.

B. (2S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-cyano-pyrrolidine-1-carboxylic acid tert-butyl ester

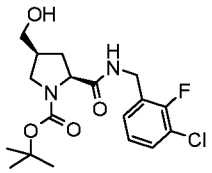
To a mixture of (2S,4S)-4-cyano-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (700 mg, 2.91 mmol), 3-chloro-2-fluorobenzylamine (558 mg, 3.50 mmol), HBTU (1.66 g, 4.37 mmol) in DMF (15 mL) was added DIPEA (1.5 mL, 8.74 mmol) and the resultion mixture was stirred at RT under nitrogen for 48 h. The mixture was poured in water and extracted with EtOAc (2x). The combined organic extracts were washed with water (1x), dried (Na_2SO_4), filtered and concentrated. The crude material was purified by flash column chromatography (c-hexane to c-hexane/EtOAc 1:1) to give the desired compound. TLC, R_f (c-hexane/EtOAc 1:1) = 0.40; MS: 404.0 [M+Na]+, 380.0 [M-H]-, t_R (HPLC conditions a): 3.45 min.

C. (3S,5S)-5-(3-Chloro-2-fluoro-benzylcarbamoyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester

Chlorotrimethylsilane (5.66 mL, 44.8 mmol) was added dropwise to dry MeOH (7.6 mL) at 0°C followed by a solution of (2S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-cyano-pyrrolidine-1-carboxylic acid tert-butyl ester (900 mg, 2.36 mmol) in dry CH_2Cl_2 (6.7 mL) and the resulting mixture was stirred at RT for 5 h. The mixture was cooled to 0°C, quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (x3). To the organic extracts was

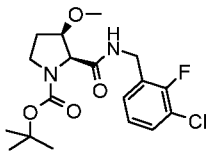
added di-tert-butyl dicarbonate (514 mg, 2.36 mmol) at RT and the resulting solution was stirred overnight. The reaction mixture was concentrated in vacuo and the crude material purified by flash column chromatography (c-hexane to c-hexane/EtOAc 1:1) to give the expected compound. t_R (HPLC conditions a): 3.50 min.

(2S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester



To a solution (3S,5S)-5-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester (550 mg, 1.33 mmol) in THF (6 mL) was added lithium borohydride (2 M in THF,1.46 mL, 2.92 mmol) at RT and the mixture was further stirred for 2 h under N_2 atmosphere. After completion brine and CH_2Cl_2 were added, the layers were separated and the aqueous one re-extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The crude was purified by flash column chromatography on silica gel (eluent: EtOAc) to give the desired material. MS (LC/MS) : 409.1 [M+Na]+, 287.0 [MH-Boc]+, 385.1 [M-H]-; t_R (HPLC conditions f): 1.82 min.

(2S,3R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester



A. (2S,3R)-3-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester

To a solution of (2S,3R)-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester [186132-96-7] (500 mg, 2.16 mmol; Chem-Impex International, Inc.) in acetone (10 mL) were added successively Ag_2O (1.65 g, 7.14 mmol) and MeI (0.473 mL, 7.57 mmol), followed by stirring at RT overnight. The reaction mixture was filtered, the filtrate was evaporated and the residue was taken up again in acetone (10 mL). To this solution was added Ag_2O (1.65 g, 7.14 mmol) and MeI (0.473 mL, 7.57 mmol) and the reaction mixture was stirred for 60 h. Solids were then removed by filtration, the filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (EtOAC/c-hexane gradient 1:2 to 1:1) to afford the title compound as a colorless oil. MS (LC/MS): 282 [M+Na]+; 160 [M-BOC]+; t_R (HPLC conditions b): 3.37 min.

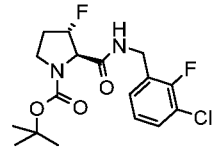
B. (2S,3R)-3-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester

To a solution of (2S,3R)-3-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (150 mg, 0.578 mmol) in THF (4 mL) and water (2.0 mL) was added LiOH (69.3 mg, 2.89 mmol) and the reaction mixture was stirred at RT for 40 h. Another aliquot of LiOH was added (69.3 mg, 2.89 mmol). Stirring was continued at RT for 60 h and subsequently at 50°C for 16 h to complete the reaction. Water was added and volatiles were removed under reduced pressure. The aqueous phase was adjusted to pH 2 to 3 by addition of 1N aqueous HCl, followed by extraction with EtOAC (3x). The combined organics were dried (Phase separator) and concentrated in vacuo to give the title compound as a white solid. MS (LC/MS): 262 [M+Na]+, 190 [MH-tBu]+, 146 [MH-Boc]+, t_R (HPLC conditions b): 3.51 min.

C. (2S,3R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester

The mixture of (2S,3R)-3-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (60.0 mg, 0.245 mmol), (3-chloro-2-fluorophenyl)methanamine (0.034 mL, 0.269 mmol), HBTU (139 mg, 0.367 mmol) and DIPEA (0.085 mL, 0.489 mmol) in CH_2Cl_2 (5 mL) was stirred for 20 h at RT. The rection mixture was then diluted with CH_2Cl_2, and the organics were washed subsequently with 0.1N aqueous HCl (3x), aqueous $NaHCO_3$ solution (2x) and brine. The organic layers were dried (Phase separator), concentrated in vacuo and the residue was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm; flow: 40 mL/min; eluent: 5-100% CH_3CN/H_2O for 20 min, 100% CH_3CN for 2 min, CH_3CN and H_2O containing 0.1% TFA) to afford the title compound as a white solid. MS (LC/MS): 387 [M+H]+, 331 [MH-tBu]+, 287 [MH-Boc]+; t_R (HPLC conditions b): 4.26 min.

(2R,3S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester



A. (2S,3R)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

To a solution of (2S,3R)-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester [186132-96-7] (500 mg, 2.162 mmol; Chem-Impex International, Inc.) in MeOH (9.0 mL), cooled to 0°C, was added with stirring a solution of Cs_2CO_3 (704 mg, 2.162 mmol) in water (6.0 mL). The mixture was concentrated by rotary evaporation and the residue was suspended in DMF (17.0 mL). The suspension was cooled to 0°C, followed by additon of benzylbromide (0.514 mL, 4.32 mmol) and stirring overnight at RT. The reaction mixture was filtered, the filtrate was concentrated under reduced pressure and the residue was dissolved in EtOAc. The organics

were washed with aqueous $NaHCO_3$ (2x) and water (2x), dried (Phase separator) and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/c-hexane 2:3) to give the title compound as an oil. MS (LC/MS): 322 [M+H]+, 665 [2M+Na]+; t_R (HPLC conditions b): 4.12 min.

B. (2R,3S)-3-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

The title compound was prepared in a similar manner as described by J. A. Hodges *et al.*, *J. Amer. Chem. Soc.* **2005**, *127*, 15923-15932: To a solution of (2S,3R)-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (490 mg, 1.53 mmol) in CH_2Cl_2 (30 mL), cooled to -78°C, was added dropwise DAST (1.01 mL, 7.62 mmol). The reaction mixture was stirred at -78°C for 5 h, and then was allowed to warm to RT and stirred overnight. After cooling to 0°C, the reaction was quenched with MeOH, followed by addition of aqueous $NaHCO_3$ solution. Volatiles were removed under reduced pressure and the residue was taken up in EtOAc. The organics were washed with aqueous $NaHCO_3$ (3x), water and brine, dried (Phase separator) and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/c-hexane 1:9) to give the title compound (89% purity by HPLC/215 nm). MS (LC/MS): 346 [M+Na]+, 268 [MH-tBu]+, 224 [MH-Boc]+; t_R (HPLC conditions b): 5.31 min.

C. (2R,3S)-3-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester

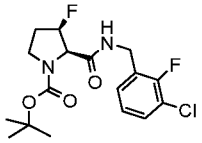
A solution of (2R,3S)-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (252 mg, 0.778 mmol; 72% purity by HPLC/215 nm) in MeOH (20 mL) was hydrogenated at RT (1 atm) over Pd/C 10% (35 mg, 10% w/w) for 24 h. The reaction mixture was filtered through a 0.45 microns filter and concentrated under reduced pressure to give the crude title compound (70% purity by HPLC/215 nm) as a white solid. This material was used in the next reaction step without further purification. MS (LC/MS): 232 [M-H]+; t_R (HPLC conditions b): 2.78 min.

D. (2R,3S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-3-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (2R,3S)-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (120 mg, 0.514 mmol) in CH_2Cl_2 (5 mL) were added successively 3-chloro-2-fluorobenzylamine (0.065 mL, 0.514 mmol), HBTU (293 mg, 0.772 mmol) and DIPEA (0.18 mL, 1.03 mmol), and stirring was continued at RT for 20 h. The reaction mixture was then diluted with CH_2Cl_2, and the organics were washed with 0.1N aqeous HCl (2x), aqueous $NaHCO_3$ (2x) and brine (1x), dried (Phase separator) and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/c-hexane gradient 1:4 to 1:3) to afford the title compound

as a white foam. TLC R_f (EtOAc/c-hexane 1:1) = 0.62; MS (LC/MS): 397 [M+Na]+, 319 [MH-tBu]+, 275 [MH-Boc]+; t_R (HPLC conditions b): 4.72 min.

(2R,3R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-3-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester



A. (2S,3R)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

To a solution of (2S,3S)-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester [187039-57-2] (500 mg, 2.16 mmol) in MeOH (9.0 mL), cooled to 0°C, was added with stirring a solution of Cs_2CO_3 (704 mg, 2.162 mmol) in water (6.0 mL). The mixture was concentrated by rotary evaporation and the residue was suspended in DMF (17.0 mL). The suspension was cooled to 0°C, followed by additon of benzylbromide (0.514 mL, 4.32 mmol) and stirring overnight at RT. The reaction mixture was filtered, the filtrate was concentrated under reduced pressure and the residue was dissolved in EtOAc. The organics were washed with aqueous $NaHCO_3$ (2x) and water (2x), dried (Phase separator) and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/c-hexane 2:3) to give the title compound as a white solid. MS (LC/MS): 665 [2M+Na]+, 266 [MH-tBu]+, 222 [MH-Boc]+; t_R (HPLC conditions b): 4.18 min.

B. (2R,3R)-3-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

The title compound was prepared in a similar manner as described by L. Demange *et al.*, *Tetrahedron Letters* **2001**, *42*, 651-653: To a solution of (2S,3R)-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (360 mg, 1.12 mmol) in CH_2Cl_2 (30 mL), cooled to -78°C, was added dropwise DAST (0.740 mL, 5.60 mmol). The reaction mixture was stirred at -78°C for 5 h, and then was allowed to warm to RT and stirred overnight. After cooling to 0°C, the reaction was quenched with MeOH, followed by addition of aqueous $NaHCO_3$ solution. Volatiles were removed under reduced pressure and the residue was taken up in EtOAc. The organics were washed with aqueous $NaHCO_3$ (3x), water and brine, dried (Phase separator) and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/c-hexane 1:9) to give the title compound (99% purity by HPLC/215 nm). TLC R_f (EtOAc/c-hexane 1:4) = 0.2; MS (LC/MS): 346 [M+Na]+, 268 [MH-tBu]+, 224 [MH-Boc]+; t_R (HPLC conditions b): 5.01 min.

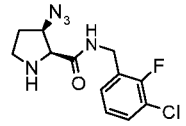
C. (2R,3R)-3-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester

A solution of (2R,3R)-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (70.0 mg, 0.216 mmol) in MeOH (10 mL) was hydrogenated at RT (1 atm) over Pd/C 10% (35 mg, 50% w/w) for 48 h. The reaction mixture was filtered through a 0.45 microns filter and concentrated under reduced pressure to give the crude title compound (>95% purity by 1H-NMR) as a white solid. MS (LC/MS): 232 [M-H]+; t_R (HPLC conditions b): 2.26 min. This material was used in the next reaction step without further purification.

D. (2R,3R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-3-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (2R,3R)-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (45.0 mg, 0.193 mmol) in CH_2Cl_2 (5 mL) were added successively 3-chloro-2-fluorobenzylamine (0.024 mL, 0.193 mmol), HBTU (110 mg, 0.289 mmol) and DIPEA (0.067 mL, 0.386 mmol), and stirring was continued at RT for 20 h. The rection mixture was then diluted with CH_2Cl_2, and the organics were washed with 0.1N aqueous HCl (2x), aqueous $NaHCO_3$ (2x) and brine (1x), dried (Phase separator) and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc/c-hexane gradient 1:4 to 1:3) to afford the title compound. TLC R_f (EtOAc/c-hexane 1:1) = 0.31; MS (LC/MS): 397 [M+Na]+, 319 [MH-tBu]+, 275 [MH-Boc]+; t_R (HPLC conditions b): 4.37 min.

Procedure 1 for the preparation of (2S,3R)-3-Azido-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide trifluoroacetate



A. (2S,3R)-3-Azido-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester

To a solution of (2S,3R)-3-azido-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester [361367-97-7] (210 mg, 0.777 mmol; Sunshine Ltd) in THF (6 mL) was added a solution of LiOH (55.8 mg, 2.33 mmol) in water (3 mL), followed by stirring at RT for 20 h. The reaction mixture was concentrated under reduced pressure and the residual aqueous phase was washed with EtOAc (3x). The water phase was adjusted to pH 2 to 3 by adding 1N aqueous HCl, followed by extraction with EtOAc (3x). The combined organics were dried (Phase separator) and concentrated in vacuo to give the crude title compound as a colorless oil. The crude product was used in the next reaction step without further purification. MS (LC/MS): 279 [M+Na]+, 200 [MH-tBu]+, 157 [MH-Boc]+; t_R (HPLC conditions b): 2.77 min.

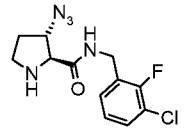
B. (2S,3R)-3-Azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrrolidine-1-carboxylic acid tert-butylester

To (2S,3R)-3-azido-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (170 mg, 0.663 mmol) in CH_2Cl_2 (12 mL) were added successively 3-chloro-2-fluorobenzylamine (0.092 mL, 0.730 mmol), HBTU (377 mg, 0.995 mmol) DIPEA (0.232 mL, 1.33 mmol) and stirring was continued at RT for 20 h. The reaction mixture was diluted with CH_2Cl_2 and the organics were washed with 1N aqueous HCl (2x), aqueous 1N NaOH 1N (2x) and brine, dried (Phase separator) and concentrated in vacuo. The crude product was purified in two steps: first by preparative HPLC (Macherey-Nagel Nucleosil 100-10 C18, 5 µm, 40x250 mm; flow: 20 mL/min; eluent: 20-100% CH_3CN/H_2O for 20 min, 100% CH_3CN for 2 min, CH_3CN and H_2O containing 0.1% TFA) and subsequently by flash column chromatography on silica (EtOAc/c-hexane gradient 1:3 to 1:1) to afford the title compound as a colorless wax. TLC R_f (EtOAc/c-hexane 1:1) = 0.41; MS (LC/MS): 420 [M+Na]+, 342 [MH-tBu]+, 298 [MH-Boc]+; t_R (HPLC conditions b): 4.66 min.

C. (2S,3R)-3-Azido-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide trifluoroacetate

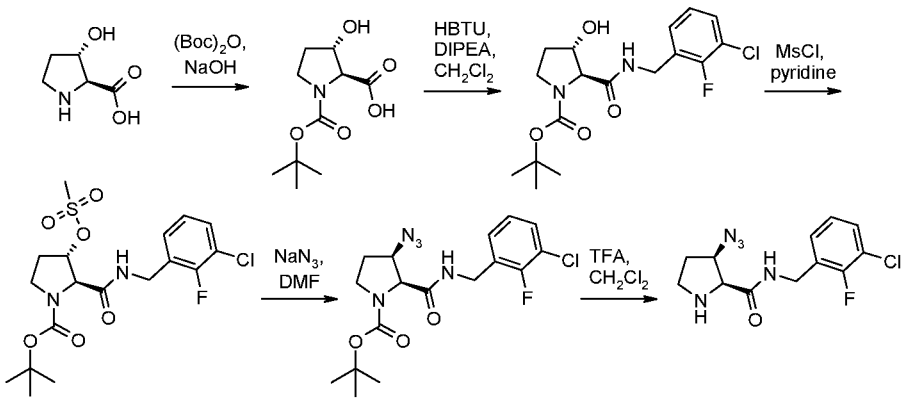
To a solution of (2S,3R)-3-azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrrolidine-1-carboxylic acid tert-butylester (87 mg, 0.22 mmol) in CH_2Cl_2 (6 mL) was added TFA at RT, and stirring was continued overnight at RT. Methanol was added to the reaction mixture and volatiles were removed under reduced pressure. The residue was taken up in MeOH and concentrated in vacuo to afford the crude title compound as a colorless wax. The product was used in the next reaction step without further purification. MS (LC/MS): 298 [M+H]+; t_R (HPLC conditions b): 2.71 min.

(2S,3S)-3-Azido-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide trifluoroacetate



was prepared in a similar manner as described in procedure 1 for (2S,3R)-3-azido-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide trifluoroacetate from (2S,3S)-3-azido-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester [361367-99-9]. MS (LC/MS): 298 [M+H]+; t_R (HPLC conditions b): 2.68 min.

Alternative procedure 2 for the preparation of (2S,3R)-3-Azido-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide trifluoroacetate



A. (2S,3S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (2S,3S)-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (800 mg, 3.46 mmol; prepared according to *J. Amer. Chem. Soc.* **2005**, *127*, 15923-15932) in CH_2Cl_2 (35 mL) were added successively 3-chloro-2-fluorobenzylamine (0.435 mL, 3.46 mmol), HBTU (1.97 g, 5.19 mmol), DIPEA (1.21 mL, 6.92 mmol). After stirring at RT for 18 h, the reaction mixture was diluted with CH_2Cl_2 and the organics were washed with water (2x), 0.1N aqueous HCl (2x), aqueous $NaHCO_3$ solution (2x) and brine, dried (phase separator) and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (EtOAc/c-hexane 1:2 to 4:1 then EtOAc) to afford the title compound as a colorless wax. TLC R_f (EtOAc/c-hexane 1:1) = 0.32; MS (LC/MS): 373 [M+H]+, 395 [M+Na]+, 767[2M+Na]+; t_R (HPLC conditions C): 4.42 min.

B. (2S,3S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-3-methanesulfonyloxy-pyrrolidine-1-carboxylic acid tert-butyl ester

To an ice-cooled solution of (2S,3S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (0.98 g, 2.64 mmol) in dry pyridine (13 mL) was added methanesulfonyl chloride (0.31 mL, 3.96 mmol). The reaction was stirred at 0°C for 2 h and then at RT for 72 h. The volatiles were evaporated in vacuo and the residue was partitioned between water and EtOAc. The aqueous layer was repeatedly extracted with EtOAc, the combined organics were washed with 0.1 N HCl and brine, dried (phase separator) and concentrated in vacuo to afford the title compound. Brown oil. MS (LC-MS): 451 [M+H]+, 395 [MH-tBu]+, 351 [MH-Boc]+; t_R (HPLC conditions c): 5.08 min. The material thus obtained was used without any purification.

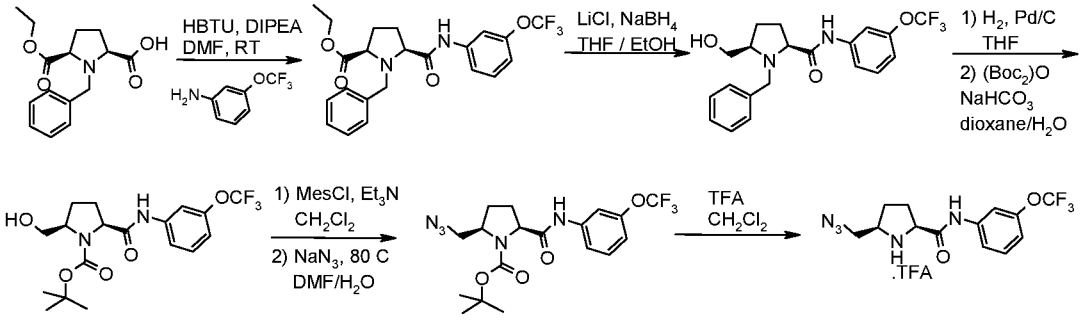
C. (2S,3R)-3-Azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

A mixture of (2S,3S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-methanesulfonyloxy-pyrrolidine-1-carboxylic acid tert-butyl ester (1.60 g, 2.35 mmol) and NaN_3 (0.370 g, 5.67 mmol) in dry DMF (12 mL) was stirred at 110°C for 60 h. The mixture was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc (3x), the combined organics were washed with brine, dried (phase separator) and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (EtOAc/c-hexane 1:4 to 1:2) to afford the title compound as a colorless foam. MS (LC-MS): 398 [M+H]+, 342 [MH-tBu]+, 298 [MH-Boc]+; t_R (HPLC conditions c): 5.15 min.

D. (2S,3R)-3-Azido-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide trifluoroacetate

To a solution of (2S,3R)-3-azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (560 mg, 1.41 mmol) in CH_2Cl_2 (8 mL) was added TFA (4 mL), and the solution was stirred at RT for 2 h. Methanol was added then added, and volatiles were removed under reduced pressure. The residue was taken up in methanol and concentrated in vacuo to afford the crude title compound as a yellow resin. MS (LC/MS): 298.0 [M+H]+; t_R (HPLC conditions c): 3.59 min. The product was used directly in the next step without further purification.

Scheme B3: preparation of -(2S,5R)-5-Azidomethyl-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide



(2R,5S)-1-Benzyl-pyrrolidine-2,5-dicarboxylic acid monoethyl ester

The title compound was prepared according to the procedure described in *Gazzetta Chimica Italiana*, **1996**, *126*, 543-554 from (2R,5S)-1-benzyl-pyrrolidine-2,5-dicarboxylic acid diethyl ester prepared from benzylamine and diethyl *meso*-dibromoadipate according to the procedure described in *J. Med. Chem.* **2006**, *49*, 11, 3068-3076.

A. (2R,5S)-1-Benzyl-5-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid ethyl ester

To a suspension of (2R,5S)-1-benzyl-pyrrolidine-2,5-dicarboxylic acid monoethyl ester (2 g, 7.21 mmol) in DMF (25 mL) was added 3-(trifluoromethoxy)aniline (1.53 mL, 8.65 mmol),

HBTU (4.19 g, 10.8 mmol) and diisopropylethylamine (3.78 mL, 21.6 mmol). The reaction mixture was stirred at RT overnight. EtOAc and 1N HCl were added, the layers were separated and the aqueous one was back-extracted with EtOAc (x3). The combined organic extracts were washed with an aqueous solution containing 5% of $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc gradient 100:0 to 80:20) to give the title compound. MS (LC/MS): 437.2 [M+H]+; t_R (HPLC conditions b) 5.50 min.

B. (2S,5R)-1-Benzyl-5-hydroxymethyl-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide

To a solution of (2R,5S)-1-benzyl-5-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid ethyl ester (2.5 g, 5.73 mmol) in a mixture of THF (40 mL) and EtOH (20 mL) was added LiCl (486 mg, 11.5 mmol) followed by $NaBH_4$ (451 mg, 11.5 mmol) and the mixture was stirred at RT overnight. The crude reaction mixture was concentrated, EtOAc and 1N HCl were added, the layers were separated and the aqueous one back-extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was used without further purification in the next step. MS (LC/MS): 395 [M+H]+; t_R (HPLC conditions b): 3.66 min.

C. (2S,5R)-5-Hydroxymethyl-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide

To a solution of (2S,5R)-1-benzyl-5-hydroxymethyl-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide (500 mg, 1.27 mmol) in THF (5 mL) containing 5 drops of MeOH was added Pd/C (10%, 27 mg). The solution was degassed 3 times replacing air by nitrogen and finally nitrogen by hydrogen. The reaction mixture was further stirred under hydrogen atmosphere overnight. The catalyst was removed through a pad of Celite and washed with THF. Solvents were concentrated and the resulting material was used without purification in the next step. MS (LC/MS): 305 [M+H]+; t_R (HPLC conditions b): 2.89 min.

D. (2S,5R)-5-Hydroxymethyl-2-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

A mixture of (2S,5R)-5-hydroxymethyl-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide (422 mg, 1.27 mmol), $(Boc)_2O$ (420 mg, 1.91 mmol) and $NaHCO_3$ (161 mg, 1.91 mmol) in water/dioxane (2.5/2.5 mL) was stirred for 48 h. CH_2Cl_2 and HCl 0.1 N were added, the layers were separated and the aqueous one re-extracted with CH2Cl2. The crude organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc gradient

100:0 to 1:1) to give the desired compound. MS (LC-MS): 403 [M-H]-; t_R (HPLC conditions b) 4.76 min.

E. (2R,5S)-2-Methanesulfonyloxymethyl-5-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (2S,5R)-5-hydroxymethyl-2-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (390 mg, 0.97 mmol) in CH_2Cl_2 (3.5 mL) was added at 0°C under nitrogen atmosphere Et_3N (296 µl, 2.12 mmol) and mesylchloride (167 µl, 2.12 mmol) and the mixture was further stirred at RT for 3 h. CH_2Cl_2 and HCl 0.1 N were added, the layers were separated and the aqueous one re-extracted with CH_2Cl_2. The crude organic extracts were washed with brine dried over Na_2SO_4, filtered and concentrated. The crude material was used without purification in the next step. MS (LC-MS): 383 [MH-Boc]+; t_R (HPLC conditions b) 5.1 min.

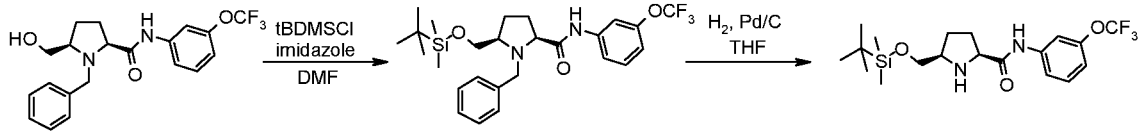
F. (2R,5S)-2-Azidomethyl-5-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (2R,5S)-2-methanesulfonyloxymethyl-5-(3-trifluoromethoxy-phenylcarba moyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (465 mg, 0.97 mmol) in DMF (3 mL) was added a solution of sodium azide (313 mg, 4.82 mmol) in water (0.5 mL) and the mixture was stirred at 80°C under nitrogen atmosphere overnight. EtOAc and a saturated aqueous solution of $NaHCO_3$ were added, the layers were separated and the aqueous one back-extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc gradient 100:0 to 1:1) to give the desired compound. MS (LC-MS): 330 [MH-Boc]+; t_R (HPLC conditions b) 5.75 min.

G. (2S,5R)-5-Azidomethyl-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide

(2R,5S)-2-Azidomethyl-5-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (100 mg, 0.233 mmol) was dissolved in CH_2Cl_2 (0.2 mL), TFA (0.18 mL, 2.33 mmol) was added and the solution was stirred at RT 3 h. The solution was concentrated under high vacuum to give the desired TFA salt. MS (LC/MS): 328 [M-H]-; t_R (HPLC conditions b): 3.45 min.

(2S,5R)-5-(tert-Butyl-dimethyl-silanyloxymethyl)-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide



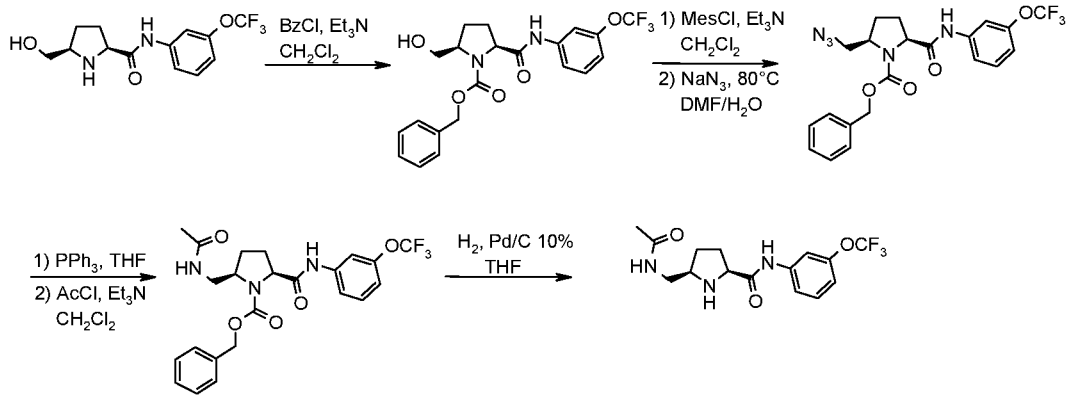
A. (2S,5R)-1-Benzyl-5-(tert-butyl-dimethyl-silanyloxymethyl)-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide

A mixture containing (2S,5R)-1-benzyl-5-hydroxymethyl-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide (300 mg, 0.76 mmol)(prepared as described in Scheme B3), TBDMSCl (129 mg, 0.84 mmol) and imidazole (57 mg, 0.84 mmol) in DMF (3 mL) was stirred at RT overnight. The mixture was concentrated and the residue taken-up in CH_2Cl_2, 1 N aqueous HCl was added, the layers were separated and the aqueous one back-extracted with CH_2Cl_2. The organic extracts were washed whith brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc gradient 100:0 to 1:1) to give the title compound. MS (LC/MS): 509.2 [M+H]+; t_R (HPLC conditions b): 5.99 min.

B. (2S,5R)-5-(tert-Butyl-dimethyl-silanyloxymethyl)-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide

To a solution of (2S,5R)-1-benzyl-5-(tert-butyl-dimethyl-silanyloxymethyl)-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide (97 mg, 0.19 mmol) in THF (1 mL) was added Pd/C (10%, 20 mg). The solution was degassed 3 times replacing air by nitrogen and finally nitrogen by hydrogen. The reaction mixture was further stirred under hydrogen atmosphere overnight. The catalyst was removed through a pad of Celite and washed with THF. Solvent was concentrated and the crude residue was purified by preparative HPLC (Waters SunFire C18-ODB 5 μm, 19x50, 5-100% CH_3CN/H_2O in 17 min, 100% CH_3CN for 3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 20 mL/min) to give the desired compound. MS (LC/MS): 419 [M+H]+; t_R (HPLC conditions b): 5.28 min.

<u>Scheme B4: preparation of (2S,5R)-5-(acetylamino-methyl)-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide</u>



A. (2R,5S)-2-Hydroxymethyl-5-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

To a solution of (2S,5R)-5-hydroxymethyl-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide (797 mg, 2.62 mmol)(prepared as described in Scheme B3) in CH_2Cl_2 (10 mL) was added under nitrogen atmosphere Et_3N (440 µl, 3.14 mmol) and benzylchloroformate (406 µl, 2.88 mmol) and the mixture was further stirred at RT overnight. CH_2Cl_2 and HCl 0.1 N were added, the layers were separated and the aqueous one re-extracted with CH_2Cl_2. The crude organic extracts were washed with brine dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash column chromatography on silica gel (c-hexane/EtOAc gradient 100:0 to 1:1) to give the title compound. MS (LC-MS): 439 [M+H]+; t_R (HPLC conditions b) 4.88 min.

B. (2R,5S)-2-Methanesulfonyloxymethyl-5-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

To a solution of (2R,5S)-2-hydroxymethyl-5-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (500 mg, 1.14 mmol) in CH_2Cl_2 (5 mL) was added at 0°C under nitrogen atmosphere Et_3N (350 µl, 2.5 mmol) and mesylchloride (197 µl, 2.5 mmol) and the mixture was further stirred at RT for 3 h. CH_2Cl_2 and HCl 0.1 N were added, the layers were separated and the aqueous one re-extracted with CH_2Cl_2. The crude organic extracts were washed with brine dried over Na_2SO_4, filtered and concentrated. The crude material was used without further purification in the next step. MS (LC-MS): 517 [MH-Boc]+; t_R (HPLC conditions b) 5.15 min.

C. (2R,5S)-2-Azidomethyl-5-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

To a solution of (2R,5S)-2-methanesulfonyloxymethyl-5-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (589 mg, 1.14 mmol) in DMF (4.5 mL) was added a solution of sodium azide (371 mg, 5.7 mmol) in water (0.5 mL) and the mixture was stirred at 80°C under nitrogen atmosphere overnight. EtOAc and a water were added, the layers were separated and the aqueous one back-extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc gradient 100:0 to 6:5) to give the desired compound. MS (LC-MS): 464 [MH-Boc]+; t_R (HPLC conditions b) 5.73 min.

D. (2R,5S)-2-Aminomethyl-5-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

A mixture of (2R,5S)-2-azidomethyl-5-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (460 mg, 0.99 mmol) and triphenylphosphine (312 mg, 1.19 mmol) in THF (4 mL) was stirred at RT overnight. After completion of the reaction, THF was removed and the crude reaction mixture was purified by preparative HPLC (Waters SunFire C18-ODB 5 μm, 19x50, 5-100% CH_3CN/H_2O in 17 min, 100% CH_3CN for 3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 20 mL/min) to give the title compound. MS: 438 [M+H]+; t_R (HPLC conditions b): 3.8 min.

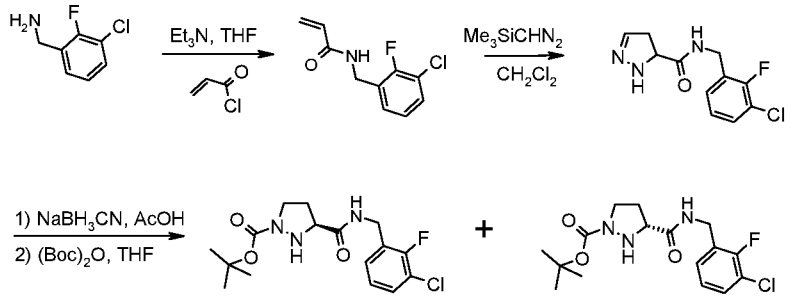
E. (2R,5S)-2-(Acetylamino-methyl)-5-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

To a solution of (2R,5S)-2-aminomethyl-5-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (200 mg), and Et_3N (77 μL, 0.55 mmol) in CH_2Cl_2 (3 mL) was added under nitrogen atmosphere at 0°C acetyl chloride (39 μL, 0.55 mmol) and the mixture was stirred at 0°C for 1 h. CH_2Cl_2 and 1 N aqueous HCl were added, the layers were separated and the aqueous one back-extracted with CH_2Cl_2. The combined organic extracts were washed whith brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc gradient 100:0 to 0:100) to give the title compound. MS (LC/MS): 480.1 [M+H]+; t_R (HPLC conditions b): 4.69 min.

F. (2S,5R)-5-(Acetylamino-methyl)-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide

To a solution of (2R,5S)-2-(acetylamino-methyl)-5-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester (48 mg, 0.1 mmol) in THF (0.3 mL) was added Pd/C (10%, 2.1 mg). The solution was degassed 3 times replacing air by nitrogen and finally nitrogen by hydrogen. The reaction mixture was further stirred under hydrogen atmosphere for 5 h. The catalyst was removed through a pad of Celite and washed with THF. Solvents were concentrated and the resulting residue was used without further purification in the next step. MS (LC/MS): 346 [M+H]+; t_R (HPLC conditions b): 2.94 min.

Scheme B5: preparation of 3,4-dihydro-2H-pyrazole-3-carboxylic acid 3-chloro-2-fluoro-benzylamide



A. N-(3-Chloro-2-fluoro-benzyl)-acrylamide

To a solution of 2-fluoro-3-chlorobenzylamine (1 g, 6.27 mmol) and TEA (1.05 mL, 7.52 mmol) in THF (20.9 mL) was added acryloyl chloride (0.61 mL, 7.52 mmol) dropwise and the reaction mixture was stirred at 23°C for 2 h. The reaction mixture was diluted in EtOAc, HCl 1N was added and the layers separated. The aqueous layer was extracted again with EtOAc and the combined organic layers were dried, filtered and concentrated to dryness. The crude residue was purified by flash column chromatography on silica gel (xyclohexane/EtOAc gardient 100:0 to 1:1) to give the desired material. TLC, R_f (c-hexane/EtOAc 5:5) = 0.41; MS (LC/MS): 214.0 [M+H]+; t_R (HPLC conditions b) : 3.35 min.

B. (S)-3,4-Dihydro-2H-pyrazole-3-carboxylic acid 3-chloro-2-fluoro-benzylamide

To a solution of N-(3-chloro-2-fluoro-benzyl)-acrylamide (1.25 g, 5.85 mmol) in 1/1 mixture of toluene (58.5 mL)/hexane (58.5 mL) was added trimethylsilyldiazomethane (5.85 mL, 11.7 mmol, 2M in hexane). The reaction was stirred at 23°C for 20 h until completion. Solvents were removed in vacuo then CH_2Cl_2 (58.5 mL) was added followed by TFA (0.49 mL, 6.44 mmol) and the reaction mixture was further stirred at 23°C for 1 h. The reaction mixture was quenched with $NaHCO_3$ 5% aqueous solution and extracted with CH_2Cl_2. The combined organic layers were dried, filtered and evaporated to dryness. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc gradient 100:0 to 0:100) followed by preparative HPLC (Waters SunFire C18ODB, 5 µm, 30x100, eluent: 20% CH_3CN/80% H_2O to 100% CH_3CN in 20 min, CH_3CN and H_2O containing 0.1% of TFA, flow 40 mL/min) to give the desired material after lyophilization of the purified fractions. TLC, R_f (EtOAc) = 0.23; MS (LC-MS): 256.0 [M+H]+; t_R (HPLC conditions b) : 2.53 min.

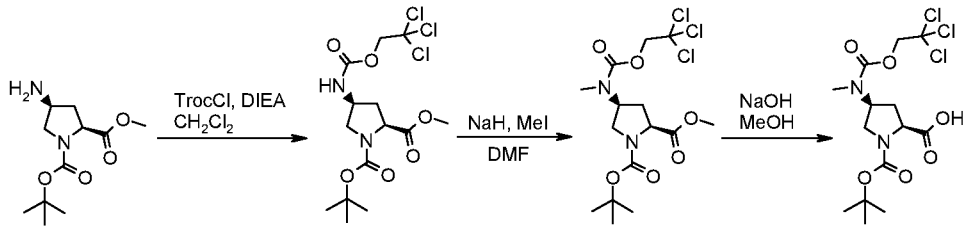
C. (S)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-pyrazolidine-1-carboxylic acid tert-butyl ester and (R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-pyrazolidine-1-carboxylic acid tert-butyl ester

To a solution of pyrazolidine-3-carboxylic acid 3-chloro-2-fluoro-benzylamide (600 mg, 2.35 mmol) in acetic acid glacial (10.4 mL) was added $NaCNBH_3$ (369 mg, 5.87 mmol) and the reaction mixture was stirred at 23°C for 2 h. The reaction mixture was diluted with EtOAc and

quenched with a saturated aqueous K_2CO_3 solution. The layers were separated and the aqueous one extracted again with EtOAc. The combined organic layers were dried, filtered and evaporated to dryness to give the desired material which was used in the next step without purification. The residue was dissolved in THF (9.4 mL), Boc_2O (0.817 mL, 3.52 mmol), TEA (0.654 mL, 4.69 mmol) and DMAP (28.7 mg, 0.235 mmol) were added and the reaction mixture was stirred at 23°C for 2 h. The crude was concentrated and purified by flash column chromatography on silica gel (c-hexane/EtOAc gradient 100:0 to 0:100) to give the desired racemic material. TLC, R_f (EtOAc) = 0.4; MS (LC/MS): 380 [M+Na]+, 258 [MH-Boc]+; t_R (HPLC conditions b): 4.22 min.

The racemic mixture was purified by chiral preparative HPLC (Chiralpak AD 00SC-JF004, 5 x 50 cm, heptane/isopropanol 90/10, flow 35 mL/min, detection 210 nM) to give peak 1 (t_R: 61.43 min) and peak 2 (t_R: 99.77 min). Peak 1: ($R^{\S}$)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrazolidine-1-carboxylic acid tert-butyl ester, MS : 258.0 [MH+-boc], 379.9 [MNa+]; t_R (HPLC, Chiralpak AD, 250mmx4.6mm, heptane/isopropanol 91/10, flow 1 mL/min, detection 220 nM): 14.1 min. Peak 2: ($S^{\S}$)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrazolidine-1-carboxylic acid tert-butyl ester, MS : 258.0 [MH+-boc] [MH+], 379.9 [MNa+]; t_R (HPLC, Chiralpak AD, 250mmx4.6mm, heptane/isopropanol 91/10, flow 1 mL/min, detection 220 nM): 22.37 min. The absolute stereochemistry has been assigned tentatively based on the test results for the final compounds **Example 432** and **Example 433** in the biological assay.

Scheme B6: preparation of ((2S,4S)-4-[Methyl-(2,2,2-trichloro-ethoxycarbonyl)-amino]-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester



A. (2S,4S)-4-(2,2,2-Trichloro-ethoxycarbonylamino)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester

To a solution of (2S,4S)-1-tert-butyl 2-methyl 4-aminopyrrolidine-1,2-dicarboxylate (4.6 g, 10.7 mmol) in CH_2Cl_2 (100 mL) were added 2,2,2-trichloroethyl carbonochloridate (1.73 mL, 12.88 mmol) and DIPEA (2.81 mL, 16.1 mmol). The reaction mixture was stirred at RT for 2 h then was poured into water. The desired compound was extracted with EtOAc (2 x 100 mL), the organic phases were joined, washed with 1N HCl then brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 1:1). MS (UPLC): 421 [M+H]+, 419 [M-H]-; t_R (HPLC conditions f): 1.11 min.

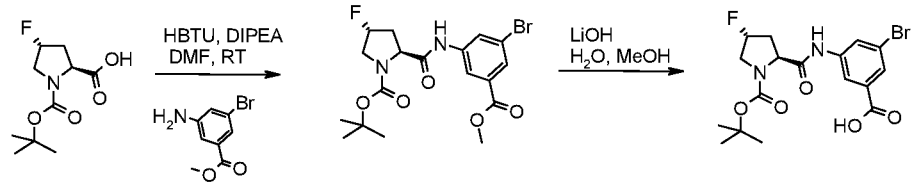
B. (2S,4S)-4-[Methyl-(2,2,2-trichloro-ethoxycarbonyl)-amino]-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester

To a solution of (2S,4S)-4-(2,2,2-trichloro-ethoxycarbonylamino)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (420 mg, 1 mmol) and methyl iodide (0.18 mL, 3 mmol) in DMF (10 mL) cooled at 0°C under argon was added sodium hydride (44 mg, 1.1 mmol). The reaction mixture was stirred at RT for 2 h then was poured into water. The desired compound was extracted with EtOAc (2 x 25 mL), the organic phases were joined, washed with 1N HCl then brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 1:1). MS (UPLC): 436 [M+H]+, 434 [M-H]-; t_R (HPLC conditions f): 2.35 min.

C. (2S,4S)-4-[Methyl-(2,2,2-trichloro-ethoxycarbonyl)-amino]-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester

To a solution of ((2S,4S)-4-[methyl-(2,2,2-trichloro-ethoxycarbonyl)-amino]-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (360 mg, 0.83 mmol) in MeOH (20 mL) was added aq. 1N NaOH (1.66 mL, 1.66 mmol). The reaction was stirred at RT for 16 h then was concentrated. The residue was acidified with aq 2N HCl to pH 3, extracted with EtOAc (2 x 25 mL). The organic phases were joined, dried over Na_2SO_4, filtered and concentrated. The crude residue was used without further purification in the next step. MS (UPLC): 421 [M+H]+, 419 [M-H]- ; t_R (HPLC conditions f): 1.00 min.

Scheme B7: preparation of (2S,4R)-2-(3-Bromo-5-carboxy-phenylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester



A. (2S,4R)-2-(3-Bromo-5-methoxycarbonyl-phenylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

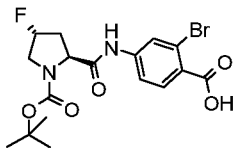
To a mixture of N-Boc-trans-4-fluoro-L-proline (500 mg, 2.14 mmol), methyl 3-amino-5-bromobenzoate (592 mg, 2.57 mmol) and HBTU (1.22 g, 3.22 mmol) in DMF (6 mL) was added DIPEA (734 µl, 4.29 mmol) and the resulting solution was stirred at RT under nitrogen overnight. The mixture was poured into water and extracted three times with EtOAc. The combined organic layers were washed twice with water, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane 100% to c-hexane/EtOAc 70:30) to give the desired material. TLC, R_f (c-hexane/EtOAc

1:2) = 0.8; MS (LC/MS): 467.0/469.0 [M+Na]+, 345.1/347.0 [MH-Boc]+, 443.1/445.1 [M-H]-; tR (HPLC conditions a): 3.77 min.

B. (2S,4R)-2-(3-Bromo-5-carboxy-phenylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (2S,4R)-2-(3-bromo-5-methoxycarbonyl-phenylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (480 mg, 1.08 mmol) in MeOH (10 mL), cooled to 0°C was added $LiOH.H_2O$ (271 mg, 6.47 mmol) and the resulting solution was allowed to reach RT and stirred for 5 h. MeOH was concentrated and the residue was diluted in CH_2Cl_2, HCl 1 M was added (pH = 1) and the layers were separated. The aqueous layer was back extracted twice with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4, filtered and concentrated to give the desired material which was used without further purification in the next step. MS (LC-MS): 453.0/455.0 [M+Na]+, 375.1/377.1 [MH-tBu]+, 331.1/333.1 [MH-Boc]+, 429.0/431.0 [M-H]-; t_R (HPLC conditions a): 3.27 min.

(2S,4R)-2-(3-Bromo-4-carboxy-phenylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester



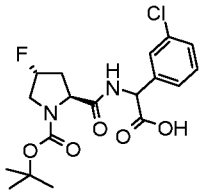
A. (2S,4R)-2-(3-Bromo-4-methoxycarbonyl-phenylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

A mixture of (2S,4R)-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (355 mg, 1.52 mmol), and 4-amino-2-bromo-benzoic acid methyl ester (prepared as described in Part C) (350 mg, 1.52 mmol), HBTU (865 mg, 2.282 mmol) and DIPEA (0.531 mL, 3.04 mmol) in CH_2Cl_2 (15 mL) was stirred at RT for 60 h. Additional aliquots of (2S,4R)-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (180 mg), HBTU (580 mg) and DIPEA (0.265 mL) were added to the mixture, and stirring was continued at RT for 20 h and subsequently at 40°C for 24 h. The reaction mixture was diluted with CH_2Cl_2 and the organic layer was washed with water, 1N aqueous HCl (3x), aqueous $NaHCO_3$ solution (2x) and brine, dried (Phase separator) and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc/c-hexane gradient 1:3 to 1:2) to afford the title compound as a white foam. TLC R_f (EtOAc/c-hexane 1:2) = 0.24; MS (LC/MS): 468 [M+Na]+, 388/390 [MH-tBu]+, 345/347 [MH-Boc]+; t_R (HPLC conditions b): 4.36 min.

B. (2S,4R)-2-(3-Bromo-4-carboxy-phenylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (2S,4R)-2-(3-bromo-4-methoxycarbonyl-phenylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (400 mg, 0.898 mmol) in MeOH (9 mL) was added a 2N aqueous NaOH solution (1.78 mL, 3.59 mmol). The reaction mixture was stirred at RT for 20 h and then evaporated under reduced pressure. The residue was taken up in water and the aqueous phase was acidified (pH 2 to 3) by adding 0.1N aqueous HCl. The resulting suspension was extracted with EtOAc (4x) and the combined organics were concentrated under reduced pressure to afford the crude title compound as a pale yellow solid. This product was used in the next reaction step without further purification. MS (LC/MS): 454 [M+Na]+, 374 [MH-tBu]+, 330 [MH-Boc]+; t_R (HPLC conditions b): 3.41 min.

(2S,4R)-2-{[carboxy-(3-chloro-phenyl)-methyl]-carbamoyl}-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester



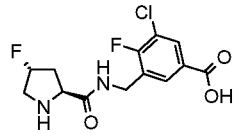
(2S,4R)-2-{[(3-Chloro-phenyl)-methoxycarbonyl-methyl]-carbamoyl}-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

To a mixture of N-Boc-trans-4-fluoro-L-proline (200 mg, 0.86 mmol), amino-(3-chloro-phenyl)-acetic acid methyl ester (233 mg, 0.94 mmol) and HBTU (488 mg, 1.29 mmol) in DMF (2.5 mL) was added DIPEA (294 µl, 1.72 mmol) and the mixture was stirred at RT under nitrogen overnight. Then poured into water and extracted twice with EtOAc. The combined organic layers were washed again with water, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (CH_2Cl_2 to CH_2Cl_2/MeOH 9:1) to give the desired material. TLC, R_f (CH_2Cl_2/MeOH 4:1) = 0.3; MS (LC/MS) : 437.0 [M+Na]+, 315.1 [MH-Boc]+, 413.0 [M-H]-; t_R (HPLC conditions a): 3.59 min.

(2S,4R)-2-{[carboxy-(3-chloro-phenyl)-methyl]-carbamoyl}-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (2S,4R)-2-{[(3-chloro-phenyl)-methoxycarbonyl-methyl]-carbamoyl}-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (diastereomeric mixture, 365 mg, 0.88 mmol) in MeOH (8 mL) was added $LiOH.H_2O$ (222 mg, 5.28 mmol) at 0°C. The solution was slowly allowed to reach RT and stirred for 1 h. MeOH was concentrated and the residue was diluted in CH_2Cl_2 and acidified by addition of HCl 1N. The layers were separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, fitered and concentrated to give the desired material. TLC, R_f (EtOAc) = 0.1; MS (LC-MS): 301.0/303.0 [MH-Boc]+; t_R (HPLC conditions a): 3.20 min.

3-Chloro-4-fluoro-5-{[((2S,4R)-4-fluoro-pyrrolidine-2-carbonyl)-amino]-methyl}-benzoic acid



(2S,4R)-2-(3-Chloro-2-fluoro-5-methoxycarbonyl-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

To a mixture of N-boc-trans-4-fluoro-L-proline (143 mg, 0.61 mmol), 3-aminomethyl-5-chloro-4-fluoro-benzoic acid methyl ester (prepared as described in Part C, 275 mg, 0.61 mmol) and HATU (0.35 g, 0.92 mmol) in DMF (4 mL) was added DIPEA (430 µl, 2.45 mmol) and the resulting solution was stirred overnight at ambient temperature. The reaction mixture was splitted in two batches and the crude product was purified without aqueous workup by RP-preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 ml/min) to give the title compound. MS (LC-MS): 333.0 [M-100]+; t_R (HPLC conditions c): 5.05 min.

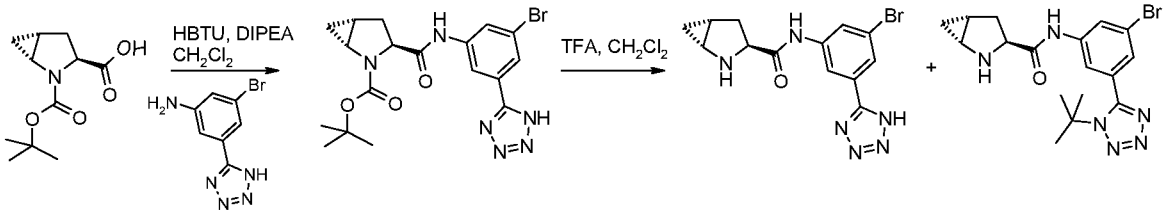
(2S,4R)-2-(5-Carboxy-3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

To a mixture of (2S,4R)-2-(3-chloro-2-fluoro-5-methoxycarbonyl-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (140 mg, 0.3 mmol) in THF/MeOH/H_2O 2:1:1 (4 mL) was added LiOH (7 mg, 0.3 mmol). The reaction mixture was stirred for 4 h at ambient temperature and the solvent was removed in vacuo to give the title compound which was used without further purification. MS (LC/MS): 319.0 [M-100]+. t_R (HPLC conditions c): 4.40 min.

3-Chloro-4-fluoro-5-{[((2S,4R)-4-fluoro-pyrrolidine-2-carbonyl)-amino]-methyl}-benzoic acid

To a mixture of (2S,4R)-2-(5-carboxy-3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (146 mg, 0.3 mmol) in CH_2Cl_2 (4 mL) was added TFA (1 mL). The reaction mixture was stirred for 1 h at ambient temperature and the solvent was removed in vacuo to give the title compound which was used without further purification. t_R (HPLC conditions c): 3.11 min.

Scheme B8: preparation of (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [3-bromo-5-(1H-tetrazol-5-yl)-phenyl]-amide and (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [3-bromo-5-(1-tert-butyl-1H-tetrazol-5-yl)-phenyl]-amide



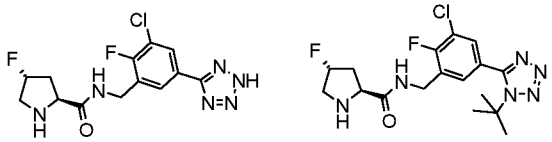
A. (1R,3S,5R)-3-[3-Bromo-5-(1H-tetrazol-5-yl)-phenylcarbamoyl]-2-aza-bicyclo[3.1.0] hexane-2-carboxylic acid tert-butyl ester

To a solution of (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester (250 mg, 1.1 mmol) in CH_2Cl_2 (6 mL) was added 3-bromo-5-(1H-tetrazol-5-yl)-phenylamine dihydrochloride (prepared as described in Part C, 365 mg, 1.32 mmol), HBTU (626 mg, 1.65 mmol) and DIPEA (0.576 ml, 3.3 mmol). The reaction mixture was stirred at RT overnight. The reaction mixture was diluted with CH_2Cl_2 and successively washed with 1M aqueous HCl solution (30 mL) and a saturated aqueous $NaHCO_3$ solution. The organic phase was dried (phase separator) and evaporated under vacuum. The crude mixture was purified by preparative HPLC (C18 Nucleosil 100-10, flow: 40 ml/min, eluent: 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA). After combination of the purified fractions, CH_3CN was removed under vacuum and lyophilization gave the desired compound. MS (LC/MS): 447.1 [M-H]-; t_R (HPLC conditions k): 4.62 min.

B. (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-3-carboxylic acid [3-bromo-5-(1H-tetrazol-5-yl)-phenyl]-amide and (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-3-carboxylic acid [3-bromo-5-(1-tert-butyl-1H-tetrazol-5-yl)-phenyl]-amide

To a solution of (1R,3S,5R)-3-[3-bromo-5-(1H-tetrazol-5-yl)-phenylcarbamoyl]-2-aza-bicyclo[3.1.0] hexane-2-carboxylic acid tert-butyl ester (200 mg, 0.445 mmol) in CH_2Cl_2 (2 mL) was added TFA (0.686 ml, 8.9 mmol). The reaction mixture was stirred at RT for 4 h. After completion the reaction mixture was diluted with CH_2Cl_2 and MeOH and the volatiles were removed under vacuum. MeOH was added and the reaction mixture concentrated again under vacuum. This operation was repeated twice to afford a mixture in a 2/3 ratio of (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [3-bromo-5-(1H-tetrazol-5-yl)-phenyl]-amide: MS (LC/MS): 349.2 [M+H]+; t_R (HPLC conditions k): 3.06 min and (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [3-bromo-5-(1-tert-butyl-1H-tetrazol-5-yl)-phenyl]-amide: MS (LC/MS): 405.3 [M+H]+; t_R (HPLC conditions k): 4.46 min.

(2S,4R)-4-Fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-5-(2H-tetrazol-5-yl)-benzylamide and (2S,4R)-4-Fluoro-pyrrolidine-2-carboxylic acid 5-(1-tert-butyl-1H-tetrazol-5-yl)-3-chloro-2-fluoro-benzylamide

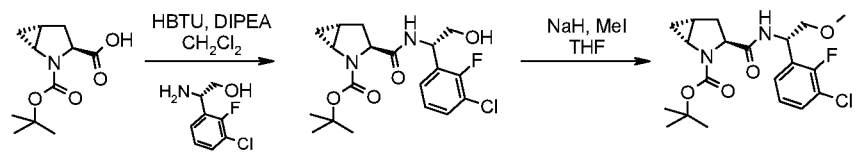


To a solution of a 1:2 mixture of (2S,4R)-2-[5-(1-tert-butyl-1H-tetrazol-5-yl)-3-chloro-2-fluoro-benzylcarbamoyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester and (2S,4R)-2-[3-chloro-2-fluoro-5-(2H-tetrazol-5-yl)-benzylcarbamoyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (86 mg, 0.19 mmol) in CH_2Cl_2 (3 mL) was added TFA (1 mL) and the reaction mixture was stirred for 2 h at ambient temperature. The solvent was removed in vacuo to give the title compounds which were used without separation in the next step. (2S,4R)-4-Fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-5-(2H-tetrazol-5-yl)-benzylamide: MS (LC-MS): 343.0 [M]+; t_R (HPLC conditions c): 2.47 min and (2S,4R)-4-fluoro-pyrrolidine-2-carboxylic acid 5-(1-tert-butyl-1H-tetrazol-5-yl)-3-chloro-2-fluoro-benzylamide : MS (LC-MS): 399.0 [M]+; t_R (HPLC conditions c): 3.16 min.

(2S,4R)-2-[3-Chloro-2-fluoro-5-(2H-tetrazol-5-yl)-benzylcarbamoyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester and (2S,4R)-2-[5-(1-tert-Butyl-1H-tetrazol-5-yl)-3-chloro-2-fluoro-benzylcarbamoyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

To a mixture of N-boc-trans-4-fluoro-L-proline (107 mg, 0.46 mmol) and HATU (260 mg, 0.69 mmol) in DMF (2 mL) was added a 1:2 mixture of 5-(1-tert-butyl-1H-tetrazol-5-yl)-3-chloro-2-fluoro-benzylamine and 3-chloro-2-fluoro-5-(2H-tetrazol-5-yl)-benzylamine (preparation described in Part C, 220 mg, 0.46 mmol) and DIPEA (319 µl, 1.8 mmol) and the resulting solution was stirred overnight at ambient temperature. The reaction mixture was purified without aqueous workup by RP-preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 ml/min) to give the title compounds (2S,4R)-2-[3-chloro-2-fluoro-5-(2H-tetrazol-5-yl)-benzylcarbamoyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester: MS (LC-MS): 343.0 [M-100]+; t_R (HPLC conditions c): 3.27 min and (2S,4R)-2-[5-(1-tert-butyl-1H-tetrazol-5-yl)-3-chloro-2-fluoro-benzylcarbamoyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester: MS (LC-MS): 499.0 [M]+; t_R (HPLC conditions c): 4.02 min.

Scheme B9: preparation of (1R,3S,5R)-3-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-methoxy-ethylcarbamoyl]-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester



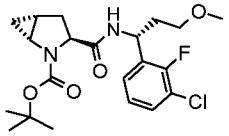
A. (1R,3S,5R)-3-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-hydroxy-ethylcarbamoyl]-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester

To a mixture of (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester (750 mg, 3.30 mmol), (2S)-2-amino-2-(3-chloro-2-fluorophenyl)ethan-1-ol (746 mg, 3.30 mmol) and HBTU (1.75 g, 4.62 mmol) in CH_2Cl_2 (30 mL) was added under nitrogen DIPEA (2.31 mL, 13.20 mmol). The reaction mixture was stirred at RT overnight. CH_2Cl_2 and water were added, the layers were separated and the aquoues one back-extracted with CH_2Cl_2 (x3). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude material was purified by flash column chromatography on silca gel (c-hexane/EtOAc 1:1 to EtOAc) to give the desired compound as a colorless oil. MS (UPLC/MS): 399.3/401.3 [M+H]+, 443.4/445.3 [M+HCOO]-; t_R (HPLC conditions a): 3.28 min.

B. (1R,3S,5R)-3-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-methoxy-ethylcarbamoyl]-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester

To a suspension of NaH (60 % in mineral oil, 25.7 mg, 0.64 mmol) in THF (3 mL) cooled at 0°C under Argon was added (1R,3S,5R)-3-[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethylcarbamoyl]-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester (270 mg, 0.64 mmol). The reaction mixture was stirred at 0°C for 30 min and iodomethane (0.06 mL, 0.97 mmol) was added. After 1 h the reaction mixture was poured into saturated $NaHCO_3$ aqueous solution. CH_2Cl_2 was added, the layers were separated and the aqueous one back-extracted with CH_2Cl_2 (x3). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude material was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 20:80) the desired compound as a colorless oil. TLC, R_f (EtOAc) = 0.65; MS (UPLC/MS): 413.4/415.4 [M+H]+, 457.4/459.4 [M+HCOO]-; t_R (HPLC conditions a): 3.67 min.

(1R,3S,5R)-3-[(R)-1-(3-Chloro-2-fluoro-phenyl)-3-methoxy-propylcarbamoyl]-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester

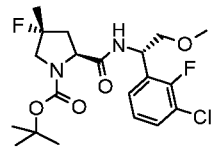


was prepared according to Scheme B9 (Step B) from (1R,3S,5R)-3-[(R)-1-(3-chloro-2-fluoro-phenyl)-3-hydroxy-propylcarbamoyl]-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester. TLC, R_f (EtOAc) = 0.82; MS (UPLC/MS): 427.4/429.4 [M+H]+, 471.4 [M+HCOO]-; t_R (HPLC conditions a): 3.71 min.

(1R,3S,5R)-3-[(R)-1-(3-Chloro-2-fluoro-phenyl)-3-hydroxy-propylcarbamoyl]-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester

was prepared according to Scheme B9 (Step A) using (3R)-3-amino-3-(3-chloro-2-fluorophenyl)propan-1-ol. TLC, R_f (EtOAc) = 0.55; MS (UPLC/MS): 413.4/415.4 [M+H]+, 457.5 [M+HCOO]-; t_R (HPLC conditions a): 3,33 min.

(2S,4R)-2-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-methoxy-ethylcarbamoyl]-4-fluoro-4-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester

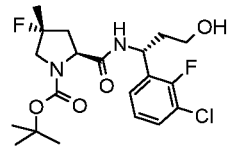


was prepared according to Scheme B9 (Step B) from (2S,4R)-2-[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethylcarbamoyl]-4-fluoro-4-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester. TLC, R_f (EtOAc) = 0.90; MS (UPLC-MS): 433.4/435.4 [M+H]+, 477.4 [M+HCOO]-; t_R (HPLC conditions a): 3.73 min.

(2S,4R)-2-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-hydroxy-ethylcarbamoyl]-4-fluoro-4-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester

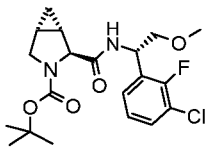
was prepared according to Scheme B9 (Step A) from (2S,4R)-4-fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (prepared as described Scheme B18). TLC, R_f (EtOAc) = 0.8; MS (UPLC-MS): 419.3 [M+H]+, 463.2 [M+HCOO]-; t_R (HPLC conditions A): 3.35 min.

(2S,4R)-2-[(R)-1-(3-Chloro-2-fluoro-phenyl)-3-hydroxy-propylcarbamoyl]-4-fluoro-4-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester



was prepared according to Scheme B9 (Step A) from (2S,4R)-4-fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (prepared as described Scheme B18) and (R)-3-amino-3-(3-chloro-2-fluoro-phenyl)-propan-1-ol. TLC, R_f (EtOAc) = 0.55; MS (UPLC/MS): 433.3 [M+H]+, 477.3 [M+HCOO]-; t_R (HPLC conditions a): 3.26 min.

(1S,2S,5R)-2-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-methoxy-ethylcarbamoyl]-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester

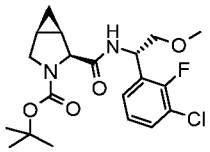


was prepared according to Scheme B9 (Step B) from (1S,2S,5R)-2-[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethylcarbamoyl]-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester. TLC, R_f (EtOAc): 0.65; MS (UPLC/MS): 413.4/415,4 [M+H]+, 457.4/459,4 [M+HCOO]-; t_R (HPLC conditions a): 3.67 min.

(1S,2S,5R)-2-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-hydroxy-ethylcarbamoyl]-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester

was prepared according to Scheme B9 (Step A) from (1S,2S,5R)-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-tert-butyl ester (Enamine, EN-400-12629). TLC, R_f (EtOAc) = 0.65; MS (UPLC/MS): 399.3/401,3 [M+H]+, 443.4/445,4 [M+HCOO]-; t_R (HPLC conditions a): 3.28 min.

(1R,2S,5S)-2-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-methoxy-ethylcarbamoyl]-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester



was prepared according to Scheme B9 (Step B) from (1R,2S,5S)-2-[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethylcarbamoyl]-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester. TLC, R_f (EtOAc): 0.45; MS (UPLC/MS): 413.3/415.3 [M+H]+, 457.3 [M+HCOO]-; t_R (HPLC conditions a): 3.64 min.

(1R,2S,5S)-2-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-hydroxy-ethylcarbamoyl]-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester

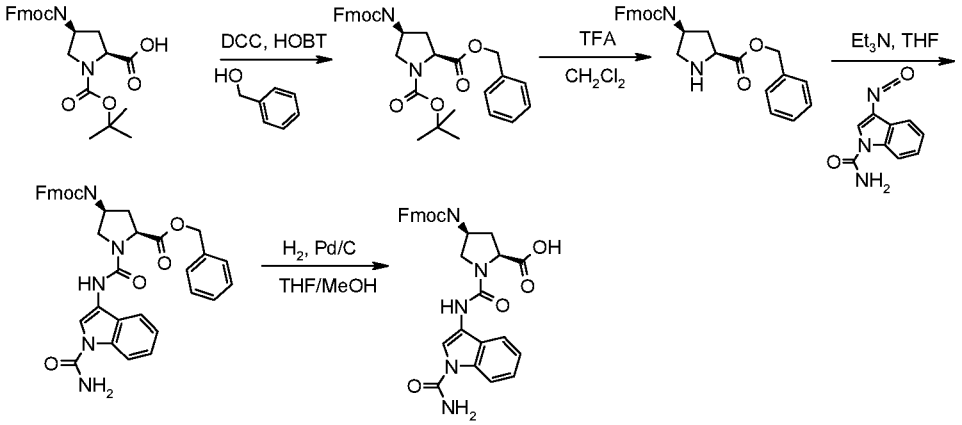
was prepared according to Scheme B9 (Step A) from racemic (1R*,2S*,5S*)-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-tert-butyl ester. Diastereoisomers were separated by chiral HPLC (Chiralpak ADOOCM-EL001, 5x50cm, mobile phase: n-heptane/ IPA 75/25, Flow: 50ml/min, detection: 220 nm) to give (1S,2R,5R)-2-[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethylcarbamoyl]-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester: t_R (HPLC, Chiralpak (20µm) 046x25cm, n-Heptan/IPA 80:20, flow: 1ml/min): 7.25 min; TLC, R_f (EtOAc) = 0.58; MS (UPLC/MS): 399.4 [M+H]+, 443.3 [M+HCOO]- and (1R,2S,5S)-2-[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethylcarbamoyl]-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester: t_R (HPLC, Chiralpak (20µm) 046x25cm, n-Heptan/IPA 80:20, flow: 1ml/min): 8.37min; TLC, R_f (EtOAc) = 0.58; MS (UPLC/MS): 399.3 [M+H]+, 443.3 [M+HCOO]-.

The absolute stereochemistry of the diastereoisomers was assigned based on the test results for the final compound **Example 212** in the biological assay.

(1R*,2S*,5S*)-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-tert-butyl ester

To a solution of racemic (1R*,2S*,5S*)-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid (10 g, 79 mmol)(ABCR [22255-16-19]) in a mixture of THF (84 mL) and water (42 mL) was added a solution of NaOH (4.18 g, 105 mmol) in water (42 mL, 10% w/v) and a solution of Boc_2O (27.4 mL, 118 mmol) in THF (84 mL) and water (42 mL). The resulting biphasic mixture was stirred at RT overnight. The mixture was concentrated under vacuum and the resulting aqueous layer was extracted EtOAc (x5), then acidified to pH 2-3 by addition of HCl 1N, satured with NaCl and extracted with $CHCl_3$/EtOH 2:1 (x3). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give the desired material which was used without further purification in the next step. MS (UPLC/MS): 226.2 [M-H]-; 1H-NMR (400 MHz, DMSO): δ (ppm) 12,4 (m, 1H), 4,19 (m, 1H), 3,46 (m, 1H), 3,38 (m, 1H), 1,88 (m, 1H), 1,64 (m, 1H), 1.35 (1, 9H), 0,65 (m, 1H), 0,54 (m, 1H).

Scheme B10: preparation of (2S,4S)-4-(9H-fluoren-9-ylmethoxycarbonylamino)-1-(R-carbamoyl) pyrrolidine-2-carboxylic acid



A. (2S,4S)-4-(9H-fluoren-9-ylmethoxycarbonylamino)-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

To a suspension of (2S,4S)-Fmoc-4-amino-1-boc-pyrrolidine-2-carboxylic acid (7.7 g, 17.1 mmol) in CH_2Cl_2 (50 mL) were added DCC (4.2 g, 20.5 mmol), DMAP (0.2 g, 1.7 mmol) and benzyl alcohol (1.7 mL, 17.08 mmol). The resulting white suspension was stirred at RT overnight under nitrogen. TLC indicated completion of the reaction. The mixture was filtered, and the filtrate was concentrated to give the crude residue which was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 4:1) to afford the title compound. TLC, R_f (c-hexane/EtOAc 3:1) = 0.25; MS (LC/MS): 565.3 [M+Na]+, 443.2 [MH-Boc]+; t_R (HPLC conditions a): 4.5 min; 1H-NMR (400 MHz, DMSO): δ (ppm) 7.91 (d, 2H,), 7.70 (d, 2H),

7.53 (d, 1H), 7.45-7.32 (m, 9H), 5.23-5.06 (m, 2H), 4.35-4.22 (m, 4H), 4.05 (q, 1H), 3.72-3.65 (m, 1H), 3.11-3.06 (m, 1H), 1.86-1.81 (m, 1H), 1.41 (s, 4H), 1.28 (s, 5H).

B. (2S,4S)-4-(9H-fluoren-9-ylmethoxycarbonylamino)-pyrrolidine-2-carboxylic acid benzyl ester

To a solution of (2S,4S)-4-(9H-fluoren-9-ylmethoxycarbonylamino)-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (7.3 g, 13.49 mmol) in CH_2Cl_2 (45 mL) was added TFA (5.1 mL, 67.5 mmol). The solution was stirred at RT overnight. The solvent was concentrated and the residue co-evaporated three times with CH_2Cl_2 to remove the excess of TFA. The crude residue was taken-up in diethylether and the resulting precipitate filtered-off to give the title compound as a white powder. MS (LC/MS): 443.2 [MH]+; t_R (HPLC conditions a): 3.3 min; 1H-NMR (400 MHz, DMSO): δ (ppm) 9.84 (s, 1H), 9.14 (s, 1H), 7.90 (d, 2H), 7.68 (d, 2H), 7.62 (d, 1H), 7.45-7.33 (m, 9H), 5.28-5.21 (m, 2H), 4.59-4.54 (m, 1H), 4.41 (d, 2H), 4.26-4.16 (m, 2H), 3.46-3.41 (m, 1H), 3.16-3.11 (m, 1H), 2.64-2.58 (m, 1H).

C. (2S,4S)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-(9H-fluoren-9-ylmethoxy carbonylamino)-pyrrolidine-2-carboxylic acid benzyl ester

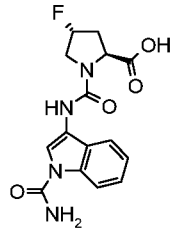
To a solution of (2S,4S)-4-(9H-fluoren-9-ylmethoxycarbonylamino)-pyrrolidine-2-carboxylic acid benzyl ester (3.03 g, 5.45 mmol) and Et_3N (1.1 mL, 8.2 mmol) in dry THF (60 mL) was added a solution of 3-isocyanato-indole-1-carboxylic acid amide (1.1 g, 5.4 mmol, prepared as described in Scheme A1) in dry THF (60 mL). The resulting solution was stirred at RT under nitrogen for 20 min. The mixture was poured into water and extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under high vacuum (the temperature of the water bath of the rotary evaporator was kept to RT) to give the title compound. R_f (c-hexane/EtOAc 1:3) = 0.39 ; MS (LCMS): 644.2 [M+H]+, 666.2 [M+Na]+; t_R (HPLC conditions a): 4.0 min.

D. (2S,4S)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-(9H-fluoren-9-ylmethoxy carbonylamino)-1-(R-carbamoyl)pyrrolidine-2-carboxylic acid

(2S,4S)-4-(9H-Fluoren-9-ylmethoxycarbonylamino)-1-(R-carbamoyl)pyrrolidine-2-carboxylic acid benzyl ester (2.83 g, 4.4 mmol) was dissolved in a mixture of MeOH/THF (1:1) (60 mL). Air was removed from the flask and replaced with nitrogen three times. Then Pd/C 10 % (425 mg) was added to the solution which was once again degassed and refilled with nitrogen three times. The mixture was placed under a hydrogen atmosphere, and stirred at RT for 2 h. The catalyst was removed through a pad of Celite and washed with THF. The filtrate was concentrated, the residue was taken up in diethylether and the resulting precipitate filtered-off

to give the title compound. MS (LC/MS): 554.2 [M+H]+, 552.1 [M-H]-; t_R (HPLC conditions a): 3.5 min.

(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carboxylic acid



A. (2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

To a suspension of N-Boc-trans-4-fluoro-L-proline (4.5 g, 19.29 mmol) in CH_2Cl_2 (68 mL) were added DCC (4.78 g, 23.15 mmol), DMAP (0.236 g, 1.93 mmol) and benzyl alcohol (2 mL, 19.29 mmol). The resulting white suspension was stirred at RT for 48 h and filtered. The filtrate was concentrated to give a colorless oil which was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 4-1) to give the desired compound. TLC, R_f (c-hexane/EtOAc 3:1) = 0.3; MS: 346.0 [M+Na]+; t_R (HPLC conditions a): 3.85 min.

B. (2S,4R)-4-Fluoro-pyrrolidine-2-carboxylic acid benzyl ester

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (3.16 g, 9.76 mmol) was dissolved in CH_2Cl_2 (50 mL), TFA (7.47 mL, 98 mmol) was added and the solution was stirred at RT 16 h. The solution was concentrated under high vacuum to give the desired TFA salt as a brown oil which was used without further purification in the next step. MS (LC/MS): 224.1 [M+H]+.

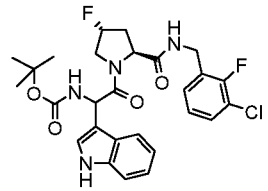
C. (2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carboxylic acid benzyl ester

To a solution of (2S,4R)-4-fluoro-pyrrolidine-2-carboxylic acid benzyl ester TFA salt (4.45 g, 13.2 mmol), 3-isocyanato-indole-1-carboxylic acid amide (2.65 g, 13.2 mmol) (prepared as described in Scheme A1) and THF (66 mL) was added triethylamine (5.51 mL, 39.6 mmol). The resulting solution was stirred at RT under nitrogen for 1 h until completion of the reaction. The mixture was poured in water and extracted with EtOAc. The organic layer was washed with an aqueous saturated solution of $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash column chromatography on silica gel (c-hexane/EtOAc 9:1 to pure EtOAc) to give the desired compound. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.40; MS: 425.2 [M+H]+; t_R (HPLC conditions a): 3.6 min.

D. (2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carboxylic acid

To a solution of (2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carboxylic acid benzyl ester (2.5 g, 5.89 mmol) in THF (40 mL) was added Pd/C 10% (500 mg). Air was removed from the flask under high vacuum and replaced with nitrogen, this operation was repeated three times and finally nitrogen was removed and replaced with hydrogen. The mixture was stirred under a hydrogen atmosphere for 16 h. Hydrogen was removed under vacuum and replaced with nitrogen and the catalyst was removed by filtration over a pad of Celite and washed with THF. Solvents were concentrated to give the title product. MS (LC/MS): 335.0 [M+H]+, 691.2 [2M+Na]+, 333.1 [M-H]-; t_R (HPLC conditions a): 2.22 min.

{1-(1-Acetyl-1H-indol-3-yl)-2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-carbamic acid tert-butyl ester

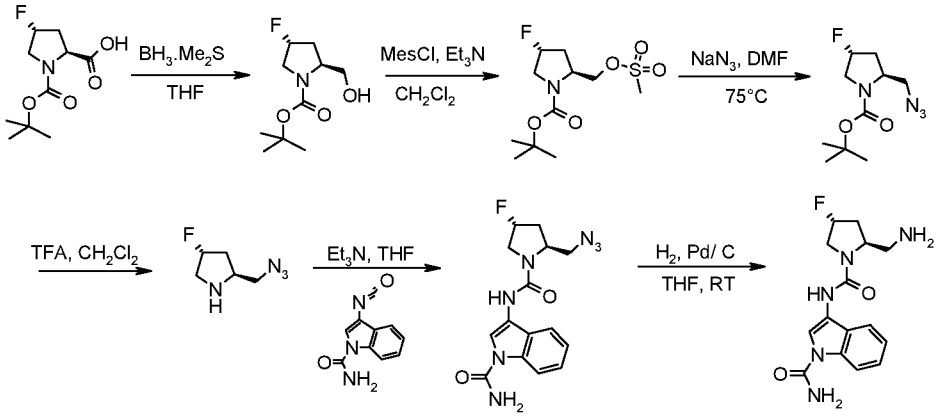


To a solution of (2S,4R)-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide. TFA salt (600 mg, 1.54 mmol), N-Boc-2-(indole-3-yl)-DL-glycine (538 mg, 1.85 mmol) and HBTU (878 mg, 2.32 mmol) in DMF (5.14 mL) was added DIPEA (809 µL, 4.63 mmol) and the reaction mixture was stirred at 23°C for 24h. The mixture was diluted with EtOAc and successively washed with HCl 1N and aqueous $NaHCO_3$ 5%. The organic layer was dried (Na_2SO_4), filtered and condentrated. The crude residue was purified by flash column chromatography on silica gel (Cyclohexane/EtOAc gradient 100:0 to 1:1) to give two fractions P1 and P2 containing each one diastereosiomer. P1: TLC, R_f (c-hexane/EtOAc 1:1) = 0.25; MS (LC/MS): 545.2 [M-H]-; t_R (HPLC conditions b): 4.89 min. P2: TLC, R_f (c-hexane/EtOAc 1:1) = 0.15; MS (LC/MS): 545.2 [M-H]-; t_R (HPLC conditions b) : 4.96 min.

(2S,4R)-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide

The title compound was prepared as a TFA salt according to Scheme D5 (steps A and B) from 3-chloro-2-fluoro-benzylamine and (2S,4R)-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester. MS (LC-MS): 274.9 [M+H]+; t_R (HPLC conditions b) : 2.23 min.

Scheme B11: preparation of 3-[((2S,4R)-2-Aminomethyl-4-fluoro-pyrrolidine-1-carbonyl)-amino]-indole-1-carboxylic acid amide



A. (2S,4R)-4-Fluoro-2-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (2S,4R)-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (3 g, 12.9 mmol) in dry THF (130 mL) under nitrogen at - 10°C was added dropwise over 45 min a solution of borane dimethyl sulfide complex (2N in THF, 14.1 mL, 28.3 mmol) and the resulting solution was allowed to warm to RT, and stirred overnight under nitrogen. The reaction was quenched by careful addition of methanol (30 mL). The mixture was co-evaporated with methanol (2x140 mL), then CH_2Cl_2 and a saturated aqueous solution of $NaHCO_3$ were added. The layers were separated and the aqueous one extracted with CH_2Cl_2 (x2), dried over Na_2SO_4, filtered and concentrated to give the desired material. TLC, R_f (EtOAc) = 0.70; 1H-NMR (400 MHz, DMSO): δ (ppm) 5.23 (d, 1H), 4.78 (bs, 1H), 3.85 (m, 1H), 3.71 (m, 1H), 3.55 (m, 1H), 3.48 (m, 1H), 3.7-3.3 (m, 1H), 2.17 (m, 2H), 1.42 (s, 9H).

B. (2S,4R)-4-Fluoro-2-methanesulfonyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

(2S,4R)-4-Fluoro-2-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (2.87 g, 13.1 mmol) was dissolved in 45 mL of CH_2Cl_2. The mixture was cooled down to 0°C, and methanesulfonyl chloride (2.55 mL, 32.8 mmol) and triethylamine (4.56 mL, 32.8 mmol) were added. The mixture was allowed to warm to RT and stirred for 1.5 h. The mixture was quenched with a saturated aqueous solution of $NaHCO_3$, extracted twice with CH_2Cl_2, dried over Na_2SO_4 and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAC 3:7) to afford the desired material. TLC, R_f (c-hexane/EtOAc 1:1) = 0.4; MS: 320.0 [M+Na]+, 198.1 [MH-Boc]+, 617.2 [2M+Na]+.

C. (2S,4R)-2-Azidomethyl-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

A mixture of (2S,4R)-4-fluoro-2-methanesulfonyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (3.3 g, 11.1 mmol) and NaN_3 (721 mg, 11.1 mmol) in DMF (50 mL) was stirred at 75°C under nitrogen overnight. The mixture was diluted with water and extracted with EtOAc (x3). The combined organic extracts were washed with water (x3), dried over Na_2SO_4, and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-

hexane/EtOAc 100/0 to 0/100) to give the desired material. 1H-NMR (400 MHz, DMSO): δ (ppm) 5.25 (d, 1H), 4.03 (m, 1H), 3.92-3.70 (m, 2H), 3.5-3.25 (m, 2H), 2.27 (m, 1H), 2.2-1.8 (m, 1H), 1.43 (s, 9H).

D. (2S,4R)-2-Azidomethyl-4-fluoro-pyrrolidine

To a solution of (2S,4R)-2-azidomethyl-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (600 mg, 2.45 mmol) in CH_2Cl_2 (2.5 mL) was added TFA (1.88 mL, 24.6 mmol) and the solution was stirred at RT for 2 h. CH_2Cl_2 was concentrated and the crude was dried under high vacuum to give the desired material which was used without further purification in the next step.

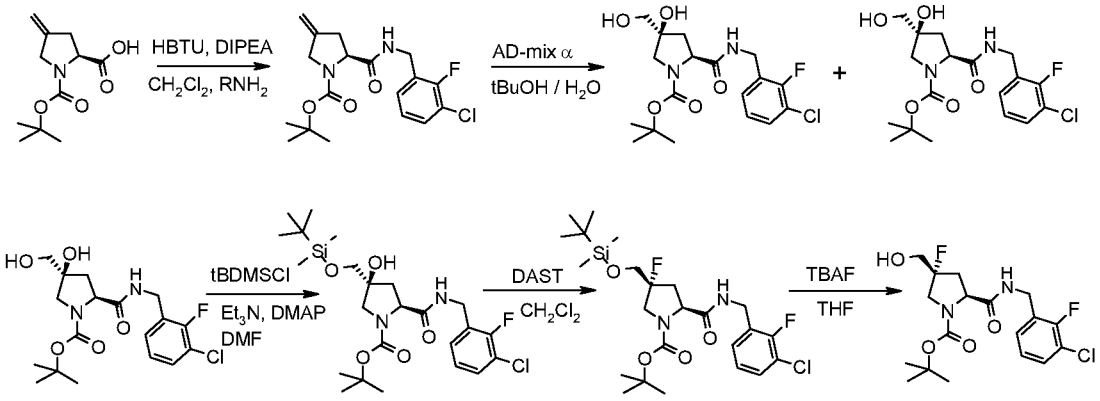
E. 3-[((2S,4R)-2-Azidomethyl-4-fluoro-pyrrolidine-1-carbonyl)-amino]-indole-1-carboxylic acid amide

To a solution of (2S,4R)-2-azidomethyl-4-fluoro-pyrrolidine (2.46 mmol) and Et_3N (1.7 mL, 12.3 mmol) in THF (8 mL) was added a solution of 3-isocyanato-indole-1-carboxylic acid amide (543 mg, 2.70 mmol) in THF (4 mL) and the resulting solution was stirred at RT under nitrogen for 20 min. The mixture was poured into water and extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 1:4 to 100 % EtOAc) to give the desired material. TLC, R_f (EtOAc) = 0.7; MS (LC-MS): 346.1 [M+H]+, 368.0 [M+Na]+, 344.0 [M-H]-; t_R (HPLC conditions f): 1.61 min.

F. 3-[((2S,4R)-2-Aminomethyl-4-fluoro-pyrrolidine-1-carbonyl)-amino]-indole-1-carboxylic acid amide

3-[((2S,4R)-2-Azidomethyl-4-fluoro-pyrrolidine-1-carbonyl)-amino]-indole-1-carboxylic acid amide (500 mg, 2.84 mmol) was suspended in THF (5 mL). Air was removed from the flask and replaced with nitrogen three times. Pd/C 10 % (100 mg) was added to the solution which was again degassed, placed under a hydrogen atmosphere, and stirred at RT for 1.5 h. The catalyst was removed through a pad of Celite and washed with THF and MeOH to give the desired material which was used in the next step without further purification. MS (LC-MS): 320.2 [M+H]+, 639.2 [2M+H]+, 661.3 [2M+Na]+, 318.1 [M-H]-; t_R (HPLC conditions f): 0 + 1.02 + 1.61 min.

Scheme B12: preparation of (2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester



A. (S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-methylene-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of N-Boc-4-methylene-L-proline (5.3 g, 22.6 mmol) in CH_2Cl_2 (25 mL) was added a solution of 3-chloro-2-fluorobenzylamine (3.61 g, 22.6 mmol) in CH_2Cl_2 (25 mL) followed by HBTU (10.3 g, 27.1 mmol) and DIPEA (5.81 mL, 33.9 mmol) and the resulting solution was stirred at RT under nitrogen for 2 h. The mixture was poured into HCl 1N and extracted twice with CH_2Cl_2. The combined organic layers were neutralized with an aqueous saturated solution of $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 85:15 to c-hexane/EtOAc 50:50) to give the desired material. TLC, R_f (EtOAc) = 0.75; MS (LC-MS): 391.0/393.1 [M+Na]+, 313.0/315.0 [MH-tBu]+, 413.0/415.0 [M+HCOO]-; t_R (HPLC conditions f): 2.12 min.

B. (2S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester and (2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

A flask was charged with t-butanol (13 mL), water (13 mL), and AD-mix-α (3.8 g). The mixture was stirred at RT until both phases were clear, and then cooled to 0°C. (S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-methylene-pyrrolidine-1-carboxylic acid tert-butyl ester (1 g, 2.71 mmol) was added at once, and the heterogeneous slurry was stirred vigorously from 0°C to RT overnight. The reaction was quenched at 0°C by addition of sodium sulfite (4 g) and then warmed to RT and stirred for 45 min. The reaction mixture was extracted with CH_2Cl_2 (x 3). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give a mixture of diastereosiomers in a 2:1 ratio. The crude mixture was purified by flash column chromatography on silica gel (c-hexane/EtOAc 1-1 to 100% EtOAc, and then from CH_2Cl_2 to CH_2Cl_2/MeOH 8:2) to give (2S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (major isomer): TLC, R_f (EtOAc) = 0.3; MS (LC-MS): 403.1/405.1 [M+H]+, 425.0/427.1 [M+Na]+, 827.2/829.2 [2M+Na]+, 347.0/349.0 [MH-tBu]+, 401.0/403.0 [M-H]-, 447.1/449.0 [M+HCOO]-; t_R (HPLC conditions f):

1.71 min and (2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (minor isomer): TLC, R_f (EtOAc) = 0.2; MS (LC-MS): 425.0/427.1 [M+Na]+, 827.2/829.2 [2M+Na]+, 347.0/349.0 [MH-tBu]+, 447.1/449.0 [M+HCOO]-; t_R (HPLC conditions f): 1.66 min.

C. (2S,4S)-4-(tert-Butyl-dimethyl-silanyloxymethyl)-2-(3-chloro-2-fluoro-benzyl carbamoyl)-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (2S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (200 mg, 0.5 mmol) in DMF (2 mL) was added tert-butyldimetylsilyl chloride (75 mg, 0.5 mmol), triethylamine (69 µL, 0.5 mmol) and DMAP (6 mg, 0.05 mmol). The mixture was stirred at RT under nitrogen overnight. Tert-butyldimetylsilyl chloride (75 mg, 0.5 mmol), and triethylamine (69 µL, 0.5 mmol) were again added and the mixture further stirred at RT for 2.5 h. The mixture was poured into an aqueous saturated $NaHCO_3$ solution, and extracted with EtOAc (x 3). The combined organic layers were washed with water, dried (Na_2SO_4), filtered and concentrated. The crude mixture was purified by flash column chromatography on silica gel (eluent: EtOAc) to afford the desired material. TLC, R_f (c-hexane/EtOAc 1:1) = 0.50; MS (LC-MS): 518.2/520.2 [M+H]+, 540.2/542.2 [M+Na]+, 462.0/464.0 [MH-tBu]+, 516.0/518.2 [M-H]-; t_R (HPLC conditions f): 2.72 min.

D. (2S,4R)-4-(tert-Butyl-dimethyl-silanyloxymethyl)-2-(3-chloro-2-fluoro-benzyl carbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

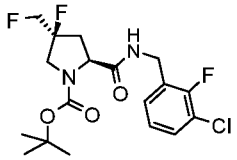
To a solution of (2S,4S)-4-(tert-butyl-dimethyl-silanyloxymethyl)-2-(3-chloro-2-fluoro-benzyl carbamoyl)-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (200 mg, 0.35 mmol) in CH_2Cl_2 (10 mL) under N_2 atmosphere at -78°C was added DAST (92 µL, 0.7 mmol). The reaction mixture was then allowed to reach RT and further stirred for 1.5 h then poured into an aqueous saturated solution of $NaHCO_3$ and extracted twice with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give the desired material which was used without further purification in the next step. TLC, R_f (c-hexane/EtOAc 1:1) = 0.75; MS (LC/MS): 541.2/543.1 [M+Na]+, 463.1/465.1 [MH-tBu]+, 419.0/421.1 [MH-Boc]+; t_R (HPLC conditions f): 2.81 min.

E. (2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

A solution of (2S,4S)-4-(tert-butyl-dimethyl-silanyloxymethyl)-2-(3-chloro-2-fluoro-benzyl carbamoyl)-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (180 mg, 0.34 mmol) in THF (1.5 mL) and TBAF (680 µL, 0.680 mmol, 1M solution in THF) was stirred at RT under nitrogen for 30 min. After completion of the reaction, the mixture was poured in water and extracted

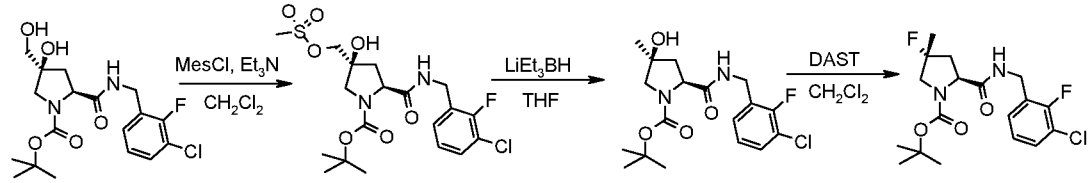
twice with EtOAc. The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash column chromatography on silica gel (c-hexane/EtOAc gradient 1:1 to EtOAc) to give the desired material. TLC, R_f (EtOAc) = 0.45; MS (LC-MS): 427.0 [M+Na]+, 349.0 [MH-tBu]+, 305.0 [MH-Boc]+, 403.1/405.1 [M-H]-, 449.2/451.1 [M+HCOO]-; t_R (HPLC conditions f): 1.91 min.

(2S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-fluoromethyl-pyrrolidine-1-carboxylic acid tert-butyl ester



To a solution of (2S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (80 mg, 0.19 mmol)(prepared using the same protocol as described in Scheme B12 for (2S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester) in CH_2Cl_2 (5 mL) at -78°C under nitrogen was added DAST (50 µL, 0.375 mmol) and the solution was allowed to reach RT and stirred for 2 h. The reaction mixture was poured into an aqueous saturated solution of $NaHCO_3$ and extracted twice with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc gardient 2:1 to 1:3) to give the desired material. TLC, R_f (EtOAc) = 0.72; MS (LC-MS): 429.1/431.0 [M+Na]+, 351.0/353.0 [MH-tBu]-, 451.1/453.1 [M+HCOO]-; t_R (HPLC conditions f): 2.14 min.

Scheme B13: preparation of (2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester



A. (2S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-4-methanesulfonyloxy methyl-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (2S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (3.53 g, 8.76 mmol)(prepared as described Scheme B12) and Et_3N (1.46 mL, 10.5 mmol) in CH_2Cl_2 (90 mL) at 0°C under nitrogen, was added methanesulfonyl chloride (819 µL, 10.52 mmol) dropwise. The resulting solution was stirred at 0°C for 1.5 h and quenched with a saturated aqueous solution of $NaHCO_3$, extracted twice with CH_2Cl_2, dried (Na_2SO_4), filtered and concentrated. The crude material was purified

by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 4:6) to give the desired material. TLC, R_f (EtOAc) = 0.7, MS (UPLC/MS): 481.3/483.3 [M+H]+, 381.2/383.2 [MH-Boc]+, 425.2/427.2 [MH-tBu]+, 479.3/481.3 [M-H]-, 525.3/527.3 [M+HCOO]-; t_R (HPLC conditions f): 2.04 min.

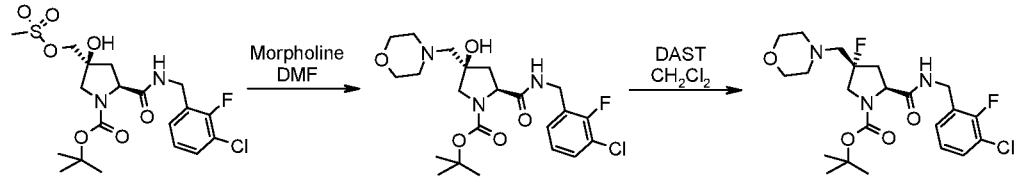
B. (2S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-4-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester

(2S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-4-methanesulfonyloxy methyl-pyrrolidine-1-carboxylic acid tert-butyl ester (1 g, 2.08 mmol) was dissolved in THF (21 mL) under nitrogen atmosphere before addition of lithium triethylborohydride (1 M in THF, 20.8 mL, 20.8 mmol). The solution was stirred at RT for 15 min, then poured into cold water and extracted with EtOAc (x 2). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude material was purified by flash column chromatography on slica gel (c-hexane/EtOAc 1:1) to give the desired material. TLC, R_f (EtOAc) = 0.7; MS (UPLC/MS): 387.3/389.3 [M+H]+, 409.3/411.3 [M+Na]+, 331.2/333.2 [MH-tBu]+, 287.2/289.2 [MH-Boc]+, 795.5/797.6 [2M+Na]+, 385.3/387.2 [M-H]-, 431.3/433.3 [M+HCOO]-.

C. (2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (2S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-4-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester (865 mg, 2.1 mmol) in CH_2Cl_2 (60 mL) under nitrogen at -78°C was added DAST (550 µL, 4.16 mmol) and the solution was slowly allowed to reach RT and stirred for 1 h. The reaction mixture was poured into cold aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (x 2). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give the desired material which was used in the next step without further purification. TLC, R_f (EtOAc) = 0.75; MS (UPLC/MS): 389.3/391.3 [M+H]+, 411.3/413.2 [M+Na]+, 333.2/335. [MH-tBu]+, 289.2/291.2 [MH-Boc]+, 387.2/389.4 [M-H]-, 433./435.2 [M+HCOO]-; t_R (HPLC conditions f): 2.2 min.

<u>Scheme B14: preparation of (2S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-morpholin-4-ylmethylpyrrolidine-1-carboxylic acid tert-butyl ester</u>



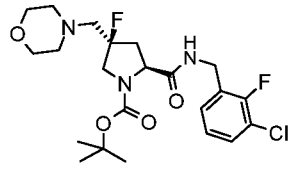
A. (2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-4-morpholin-4-ylmethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (2S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-4-methanesulfonyloxy methyl-pyrrolidine-1-carboxylic acid tert-butyl ester (200 mg, 0.416 mmol)(prepared as described Scheme B13) in DMF (10 mL) was added morpholine (181 mL, 2.079 mmol) and the solution was stirred for 16 h at 80°C. The reaction mixture was diluted with EtOAc, washed with a saturated aqueous solution of $NaHCO_3$ (3 times). The organic layers were dried (Na_2SO_4), filtered and concentrated. The crude material was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH 8:2) to give the desired material. MS (LC/MS): 472.1/474.1 [M+H]+, 470.0/472.1 [M-H]-; t_R (HPLC conditions f): 1.58 min; 19F NMR (100 MHz, DMSO-d_6) δ (ppm): -120.

B. (2S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-morpholin-4-ylmethyl pyrrolidine-1-carboxylic acid tert-butyl ester

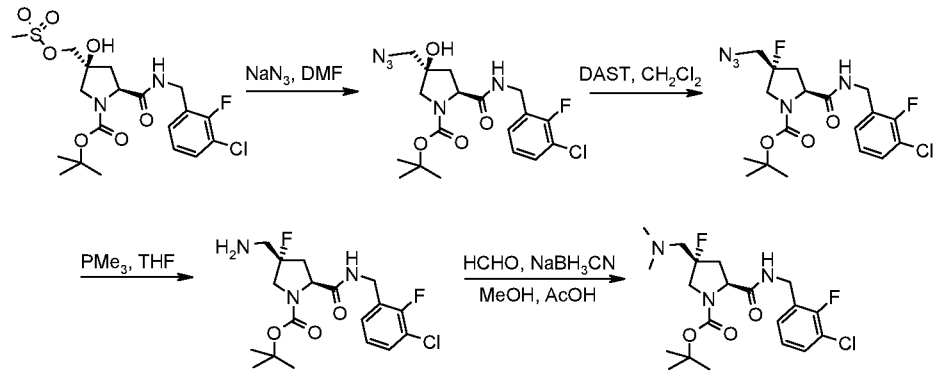
To a solution of (2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-4-morpholin-4-ylmethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (85 mg, 0.18 mmol) in CH_2Cl_2 (10 mL) under N_2 atmosphere at - 78°C was added DAST (47 µL, 0.359 mmol). The reaction mixture was then allowed to reach RT and further stirred for 1.5 h then poured into an aqueous saturated solution of $NaHCO_3$ and extracted twice with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude material was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH 8:2) to give the desired material. MS (LC/MS): 474.1/476.2 [M+H]+, 472.1 [M-H]-; t_R (HPLC conditions f): 1.59 min.

(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-morpholin-4-ylmethyl-pyrrolidine-1-carboxylic acid tert-butyl ester



was obtained using the same protocols as described in Scheme B14 for the preparation of (2S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-morpholin-4-ylmethylpyrrolidine-1-carboxylic acid tert-butyl ester starting from starting from (2S,4R)-2-(3-chloro-2-fluoro-benzyl carbamoyl)-4-hydroxy-4-methanesulfonyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared from (2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester as described scheme B13). MS (LC/MS): 474.1/476.2 [M+H]+, 472.1 [M-H]-; t_R (HPLC conditions f): 1.62 min.

Scheme B15: (2S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-dimethylaminomethyl-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester



A. (2S,4S)-4-azidomethyl-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (2S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-4-methanesulfonyloxy methyl-pyrrolidine-1-carboxylic acid tert-butyl ester (580 mg, 1.21 mmol) (prepared as described Scheme B13) in DMF (20 mL) was added sodium azide (392 mL, 6.03 mmol) and the solution was stirred for 16 h at 80°C. The reaction mixture was diluted with EtOAc, washed with a saturated aqueous solution of $NaHCO_3$ (3 times). The organic layers were dried (Na_2SO_4), filtered and concentrated. The crude material was purified by flash column chromatography on silica gel (c-hexane/EtOAc 1:1) to give the desired material. MS (LC/MS): 430.1/432.1 [M+H]+, 374.1 [MH-tBu]+, 332 [MH-Boc]+; t_R (HPLC conditions f): 2.22 min.

B. (2S,4R)-4-azidomethyl-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (2S,4S)-4-azidomethyl-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (430 mg, 1.0 mmol) in CH_2Cl_2 (25 mL) under N_2 atmosphere at -78°C was added DAST (266 µL, 2.01 mmol). The reaction mixture was allowed to warm up to RT and further stirred for 1.5 h. The reaction mixture was poured into an aqueous saturated solution of $NaHCO_3$ and extracted twice with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude material was purified by flash column chromatography on silica gel (c-hexane/EtOAc 1:1) to give the desired material. MS (LC/MS): 474.1/476.2 [M+H]+, 472.1 [M-H]-; t_R (HPLC conditions f): 2.23 min, 19F NMR (100 MHz, DMSO-d_6) δ (ppm): -120, -150.

C. (2S,4S)-4-aminomethyl-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

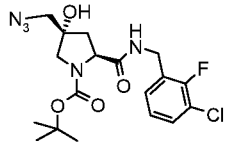
To a solution of (2S,4R)-4-azidomethyl-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (380 mg, 0.884 mmol) in THF (25 mL) under N_2 atmosphere at RT was added 1M PMe_3 in THF (1,06 mL, 1.06 mmol). The reaction mixture was stirred for 16 h then quenched with water and extracted twice with EtOAc. The combined

organic layers were dried (Na_2SO_4), filtered and concentrated. The crude material was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH 8:2) to give the desired material. MS (LC/MS): 404/406 [M+H]+, 402 [M-H]-; t_R (HPLC conditions f): 1.57 min, 19F NMR (100 MHz, DMSO-d_6) δ (ppm): -120, -154.

D. (2S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-dimethylaminomethyl-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

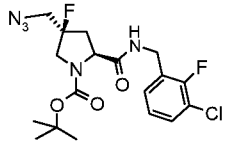
To a solution of (2S,4S)-4-aminomethyl-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (245 mg, 0.607 mmol) in MeOH (2 mL) were added formaldehyde (836 µL, 6.07 mmol), sodium cyanoborohydride (126 mg, 2.0 mmol) and acetic acid (69.5 µL, 1.21 mmol). The reaction mixture was stirred for 16 h at RT then concentrated. The crude material was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH 8:2) to give the desired material. MS (LC/MS): 432.1/434.1 [M+H]+, 430.1 [M-H]-; t_R (HPLC conditions f): 1.62 min, 19F NMR (100 MHz, DMSO-d_6) δ (ppm): -121, -149.

(2S,4R)-4-Azidomethyl-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester



was obtained using the same protocols as described in Scheme B15 step A for the preparation of (2S,4R)-4-azidomethyl-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester starting from (2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-4-methanesulfonyloxy methyl-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared from (2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester as described scheme B13). MS (UPLC/MS): 450/452 [M+Na]+, 472/474 [M+HCOO]-; t_R (HPLC conditions f): 2.08 min.

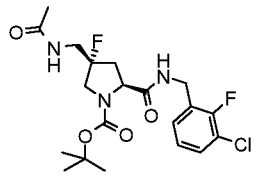
(2S,4S)-4-Azidomethyl-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester



was obtained using the same protocols as described in Scheme B15 step A and B for the preparation of (2S,4R)-4-azidomethyl-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester starting from (2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-4-methanesulfonyloxy methyl-pyrrolidine-1-carboxylic acid tert-

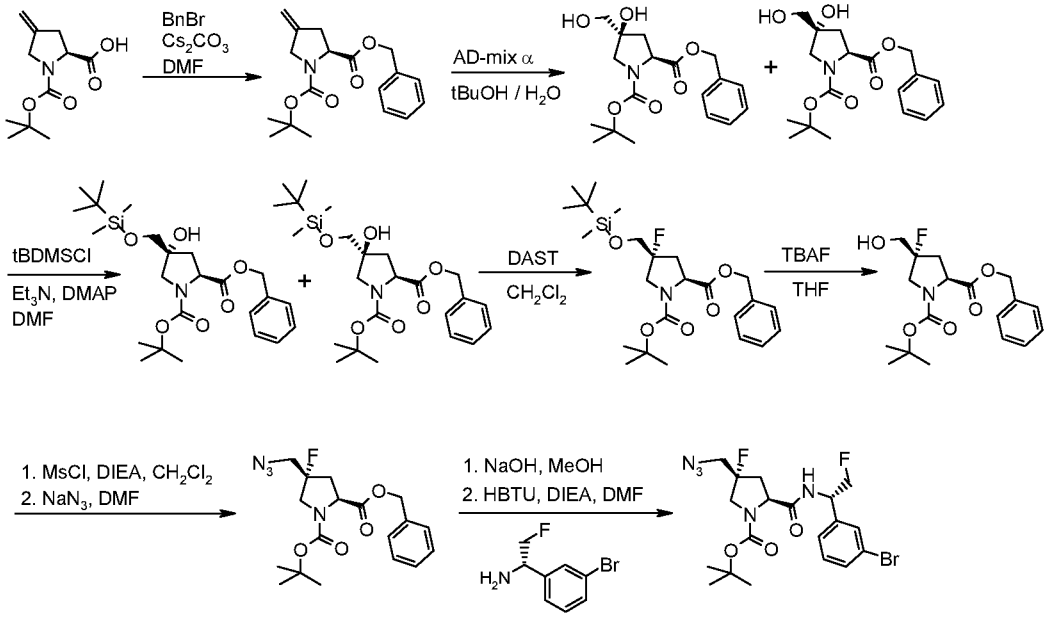
butyl ester (prepared from (2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester as described scheme B13). MS (LC/MS): 474.1/476.2 [M+H]+, 472.1 [M-H]-; t_R (HPLC conditions f): 2.180 min, 19F NMR (100 MHz, DMSO-d_6) δ (ppm): -120 , -150.

(2S,4S)-4-(Acetylamino-methyl)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester



To a solution of (2S,4S)-4-aminomethyl-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (179 mg, 0.51 mmol) in MeOH (5 ml) was added acetic anhydride (0.52 mL, 5.1 mmol). The reaction mixture was stirred at RT for 16 hours then quenched with 6N NaOH. After extraction with CH_2Cl_2 (3 x 30 mL), the organic phases were joined and dried on Na2SO4, filtered and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 1:1).]. MS (UPLC/MS): 395 [M+H]+; t_R (HPLC conditions f): 2.02 min.

Scheme B16: preparation of (2S,4R)-4-Azidomethyl-2-[(S)-1-(3-bromo-phenyl)-2-fluoro-ethylcarbamoyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester



A. (S)-4-Methylene-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

To (S)-1-(tert-butoxycarbonyl)-4-methylenepyrrolidine-2-carboxylic acid (4 g, 17.60 mmol) dissolved in DMF (100 mL) at 0°C were added benzyl bromide (2.51 mL, 21.12 mmol) and cesium carbonate (6.31 g, 19.36 mmol). The solution was stirred 16 h at RT then was

concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 1:1). MS (UPLC/MS): 218 [MH-tBu]+, t_R (HPLC conditions f): 2.44 min.

B. (2S,4S)-4-Hydroxy-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester and (2S,4S)-4-Hydroxy-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

A solution of AD-mix-alpha (30 g, 21.43 mmol) in tBuOH (120 mL) and Water (120 mL) was stirred until both phases were clear and then cooled to 0°C. (S)-4-Methylene-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (6.48 g, 20.42 mmol) was added and the reaction mixture was stirred at RT for 16 h. The reaction mixture was quenched at 0°C by addition of sodium sulfite (14.5 g) and then allowed to reach RT and stirred for 1 h. After extraction with CH_2Cl_2 (3 x 100 mL), the organic phases were joined, dried with Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 1:1) gave the desired compounds as an unseparable mixture. MS (UPLC/MS): 352 [M+H]+, t_R (HPLC conditions f): 1.50 min.

C. (2S,4R)-4-(tert-Butyl-dimethyl-silanyloxymethyl)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester and (2S,4S)-4-(tert-Butyl-dimethyl-silanyloxymethyl)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

To a solution of (2S,4S)-4-hydroxy-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester and (2S,4S)-4-hydroxy-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (5.46 g, 15.54 mmol) in DMF (80 mL) were added tert-butyl dimethylchlorosilane (2.45 g, 16.32 mmol), triethylamine (2.16 mL, 15.54 mmol) and DMAP (0.19 g, 1.55 mmol). The solution was stirred for 16 h at RT then was washed with sat $NaHCO_3$ (2 x 100 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 9:1) gave (2S,4R)-4-(tert-butyl-dimethyl-silanyloxymethyl)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester: MS (UPLC/MS): 466 [M+H]+]+, 510 [M+HCOO]-; t_R (HPLC conditions f): 2.83 min and (2S,4S)-4-(tert-butyl-dimethyl-silanyloxymethyl)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester: MS (UPLC/MS): 466 [M+H]+ , 510 [M+HCOO]-; t_R (HPLC conditions f): 2.95 min.

D. (2S,4R)-4-(tert-Butyl-dimethyl-silanyloxymethyl)-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

To a solution of (2S,4S)-4-(tert-butyl-dimethyl-silanyloxymethyl)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (5.20 g, 11.17 mmol) in CH_2Cl_2 (100 mL) at -

78°C was added DAST (2.21 mL, 16.75 mmol). The solution was stirred for 16 hours at RT then was washed with sat $NaHCO_3$ (2 x 100 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 9:1). MS (UPLC/MS): 468 [M+H]+ , 512 [M+HCOO]-; t_R (HPLC conditions f): 3.00 min.

E. (2S,4R)-4-Fluoro-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

To a solution of (2S,4R)-4-(tert-butyl-dimethyl-silanyloxymethyl)-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (4.10 g, 8.77 mmol) in THF (80 mL) at RT was added 1M TBAF in THF (17.53 mL, 17.53 mmol). The reaction was stirred at RT for 30 min then poured into water and extracted with EtOAc. The organic layer was dried with Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 3:2). MS (UPLC/MS): 354 [M+H]+, 398 [M+HCOO]-; t_R (HPLC conditions f): 2.07 min.

F. (2S,4R)-4-Azidomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

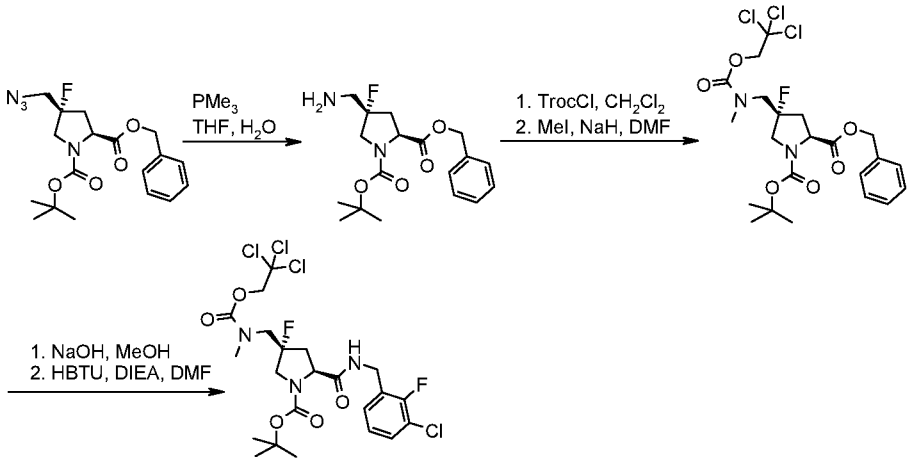
To a solution of (2S,4R)-4-fluoro-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (1.76 g, 4.98 mmol) in CH_2Cl_2 (30 mL) and few drops of NEt_3 was stirred at RT for 10 min then methanesulfonyl chloride (0.39 mL, 5.03 mmol) was added. The reaction was stirred at RT for 30 min then poured into water and extracted with EtOAc. The organic layer was dried with Na_2SO_4, filtered and concentrated. The residue (2.25 g, 4.21 mmol) was dissolved in DMF (50 mL) and sodium azide (1.69 g, 26.1 mmol) was added. The solution was stirred for 16 hours at 80°C then was cooled to RT, poured into water and extracted with EtOAc. The organic layer was dried with Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 1:1). MS (UPLC/MS): 379 [M+H]+; t_R (HPLC conditions f): 2.44 min.

G. (2S,4R)-4-Azidomethyl-2-[(S)-1-(3-bromo-phenyl)-2-fluoro-ethylcarbamoyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (2S,4R)-4-azidomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (500 mg, 1.32 mmol) in methanol (20 mL), 1M sodium hydroxide (2.64 mL, 2.64 mmol) was added. The solution was stirred for 2 hours at RT then was diluted with water, the methanol was removed under reduced pressure. The aqueous layer was washed with Et_2O (2 x 100 mL). The aqueous layer was acidified until pH 3 with 2N HCl and extracted with EtOAc (2 x 100 mL), dried with Na_2SO_4, filtered and concentrated. To the residue (100 mg,

0.34 mmol), (S)-1-(3-bromo-phenyl)-2-fluoro-ethylamine (described in Part C) (83 mg, 0.38 mmol) and HBTU (197 mg, 0.52 mmol) in DMF (5 mL) was added DIPEA (0.12 mL, 0.69 mmol). The reaction mixture was stirred for 16 h at RT then poured into water and extracted with EtOAc. The organic layer was dried with Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 1:1). MS (UPLC/MS): 488 [M+H]+, 532 [M+HCOO]-; t_R (HPLC conditions f): 2.32 min.

Scheme B17: preparation of (2S,4S)-4-Fluoro-4-{[methyl-(2,2,2-trichloro-ethoxycarbonyl)-amino]-methyl}-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester



A. (2S,4S)-4-Aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

A solution of (2S,4R)-4-azidomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (prepared as described in Scheme B16) (1 g, 2.64 mmol), trimethylphosphine in THF (3.17 mL, 3.17 mmol) and water (0.10 mL, 5.29 mmol) in THF (40 mL) was stirred for 16 h at RT. The reaction mixture was quenched with water, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (CH_2Cl_2/MeOH 9:1). MS (UPLC/MS): 353 [M+H]+, 411 [M+HCOO]-; t_R (HPLC conditions f): 1.62 min.

B. (2S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-{[methyl-(2,2,2-trichloro-ethoxycarbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester

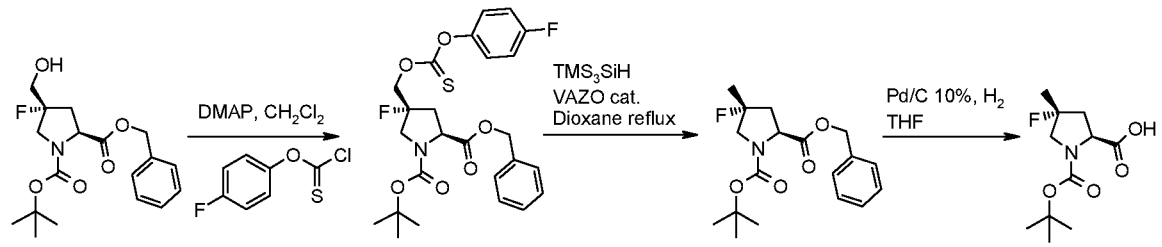
To a solution of (2S,4S)-4-aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (100 mg, 0.28 mmol) in CH_2Cl_2 (10 mL) was added Troc-Cl (0.05 mL, 0.34 mmol). The reaction mixture was stirred for 16 h at RT. The reaction mixture was quenched with water, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, concentrated and purified by flash column chromatography on silica gel (c-hexane/EtOAc 1:1). To a solution of (2S,4S)-4-Fluoro-4-[(2,2,2-trichloro-ethoxycarbonylamino)-methyl]-pyrrolidine-

1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (50 mg, 0.09 mmol) and methyl iodide (0.02 mL, 0.28 mmol) in DMF (5 mL) at 0°C was added sodium hydride (2.50 mg, 0.10 mmol) in portions. The reaction mixture was stirred 90 min at 0°C and 16 h at RT. The reaction mixture was quenched with water, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 1:1). MS (UPLC/MS): 541/543 [M+H]+, 586/587 [M+HCOO]- ; t_R (HPLC conditions f): 2.66 min.

C. (2S,4S)-4-Fluoro-4-{[methyl-(2,2,2-trichloro-ethoxycarbonyl)-amino]-methyl}-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

To a solution of (2S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-{[methyl-(2,2,2-trichloro-ethoxycarbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester (110 mg, 0.20 mmol) in methanol (5 mL), 1M sodium hydroxide 0.40 mL, 0.40 mmol) was added. The solution was stirred for 2 h at RT then was diluted with water, the methanol was removed under reduced pressure. The aqueous layer was washed with Et_2O (2 x 25 mL). The aqueous layer was acidified until pH 3 with 2N HCl and extracted with EtOAc (2 x 25 mL), dried with Na_2SO_4, filtered and concentrated. To the residue (80 mg, 0.17 mmol), (3-chloro-2-fluorophenyl)methanamine (33.9 mg, 0.21 mmol) and HBTU (101 mg, 0.26 mmol) dissolved in DMF (5 mL) was added DIPEA (0.06 mL, 0.35 mmol). The reaction mixture was stirred for 16 h at RT. The reaction mixture was quenched with water, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 1:1). MS (UPLC/MS): 592/594 [M+H]+, 636/638 [M+HCOO]-; t_R (HPLC conditions f): 2.49 min.

Scheme B18: preparation of (R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester



A. (2S,4R)-4-Fluoro-4-(4-fluoro-phenoxythiocarbonyloxymethyl)-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

To a solution of (2S,4R)-4-fluoro-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (synthesis described in Scheme B16) (300 mg, 0.85 mmol) in CH_2Cl_2 (10 mL) was added 4-fluorophenylthiono chloro formate (0.18 mL, 1.27 mmol) and DMAP (311

mg, 2.55 mmol). The reaction mixture was stirred at RT for 2 days then was diluted with CH_2Cl_2 (40 mL), washed with aq 0.5 HCl (50 mL), water (50 mL) and brine, dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 3:1) gave the desired compound. MS (UPLC/MS): 508 [M+H]+; t_R (HPLC conditions f): 2.73 min.

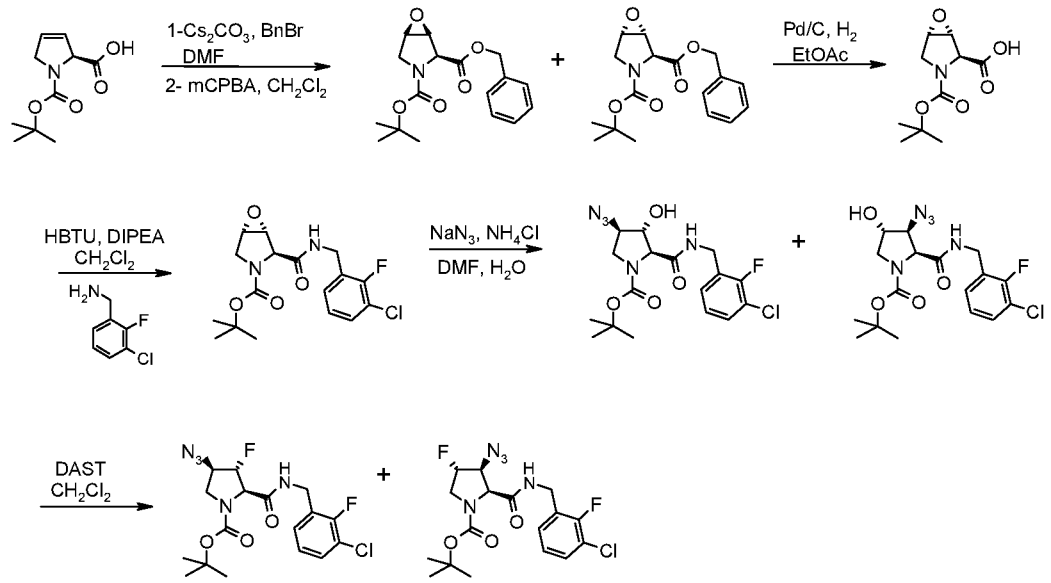
B. (2S,4R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

To a solution of (2S,4R)-4-fluoro-4-(4-fluoro-phenoxythiocarbonyloxymethyl)-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (290 mg, 0.57 mmol) in dioxane (5 mL) were added VAZO (69 mg, 0.28 mmol) and tris(trimethylsilyl) silane (0.24 mL, 0.77 mmol). The reaction mixture was refluxed for 30 min then was stirred for 16 h at RT and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 4:1). MS (UPLC/MS): 338 [M+H]+; t_R (HPLC conditions f): 2.38 min.

C. (2S,4R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester

A solution containing (2S,4R)-4-fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (700 mg, 2.075 mmol) and Pd/C 10% (221 mg, 2.075 mmol) in THF (6 mL) was placed under a nitrogen atmosphere and stirred for 5 h. The catalyst was removed through a pad of celite and washed with MeOH. Solvents were removed under vacuum to give the desired material as a colorless oil which was used without further purification in the next step. MS (UPLC/MS): 246,2 [M-H]-, 292,2 [M+HCOO-]-, 493,4 [2M-H]-.

Scheme B19: preparation of (2R,3R,4R)-4-Azido-3-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide and (2S,3S,4S)-3-azido-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide



A. (S)-2,5-Dihydro-pyrrole-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

To a solution of (S)-1-(tert-butoxycarbonyl)-2,5-dihydro-1H-pyrrole-2-carboxylic acid (10 g, 46.9 mmol) in DMF (249 mL) cooled at 0ºC were added cesium carbonate (16.8 g, 51.6 mmol) then benzyl bromide (6.69 mL, 56.3 mmol) and the mixture was allowed to warm up to RT overnight. The reaction mixture was quenched with water (500 mL) and extracted with ethyl acetate (3 x 200 mL). The organic layers were combined and washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 4:1) to give the desired material. TLC, R_f (c-hexane/EtOAc 4:1) = 0.25; MS (UPLC): 326 [M+Na]+, 204 [MH-Boc]+; t_R (HPLC conditions f): 2.35 min.

B. (1R,2S,5S)-6-Oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-benzyl ester 3-tert-butyl ester and (1S,2S,5R)-6-oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-benzyl ester 3-tert-butyl ester

To a solution of (S)-2,5-dihydro-pyrrole-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (6.14 g, 20.2 mmol) were added 3-chloroperbenzoic acid (6.99 g, 40.5 mmol) and 4,4' thiobis(6-tert-butyl-m cresol) (0.726 g, 2.02 mmol). The mixture was refluxed under nitrogen atmosphere overnight then an additional batch of 3-chloroperbenzoic acid (6.99 g, 40.5 mmol) and 4,4' thiobis(6-tert-butyl-m cresol) (0.726 g, 2.02 mmol) was added. Refluxing was continued for 24 h. The reaction mixture was diluted with CH_2Cl_2, washed with sodium metabisulphite aqueous (5%), saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated. The diastereomeric epoxides in a ratio of 65/35 (determined by NMR on the crude mixture) were separated by flash column chromatography (c-hexane to c-hexane/EtOAc 4:1) to give (1R,2S,5S)-6-oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-benzyl ester 3-tert-butyl ester: TLC, R_f (c-hexane/EtOAc 4:1) = 0.20; MS (LC/MS): 220 [MH-Boc]+, 342 [M+Na]+; t_R (HPLC conditions f): 2.14 min and (1S,2S,5R)-6-oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-benzyl ester 3-tert-butyl ester: TLC, R_f (c-hexane/EtOAc 4:1) = 0.15 ; MS (LC/MS): 220 [MH-Boc]+, 342 [M+Na]+; t_R (HPLC conditions f): 2.03 min .

C. (1R,2S,5S)-6-Oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-tert-butyl ester

A solution (1R,2S,5S)-6-oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-benzyl ester 3-tert-butyl ester (2.62 g, 8.21 mmol) in ethyl acetate (32 mL) was hydrogenated under H_2 with palladium hydroxide on carbon (1.15 g, 8.21 mmol) for 1 night. The reaction mixture was filtered over a glass fiber filter, quenched with Na_2CO_3 saturated aqueous solution and was extracted twice with EtOAc. The aqueous layer was acidified with HCl 1N to pH = 2 and extracted 4 times with ethyl acetate, washed with brine, dried over Na_2SO_4, filtered and

concentrated to give the desired material which was used in the next step without further purification. MS (UPLC): 230 [M+H]+, 228 [M-H]-.

D. (1R,2S,5S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-6-oxa-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester

To a mixture of (1R,2S,5S)-6-oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-tert-butyl ester (1.55 g, 6.79 mmol), (3-chloro-2-fluoro) benzylamine (1.63 g, 10.19 mmol) and HBTU (3.86 g, 10.2 mmol) in CH_2Cl_2 (17 mL) was added diisopropylethylamine (1.78 mL, 10.19 mmol). The resulting solution was stirred overnight at RT under nitrogen then poured into an aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (x3). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 1:1). TLC, R_f (EtOAc) = 0.65; MS (UPLC): 371 [M+H]+, 271 [MH-Boc]+; t_R (HPLC conditions f): 2.04 min.

E. (2S,3R,4R)-4-Azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester and (2S,3S,4S)-3-Azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester

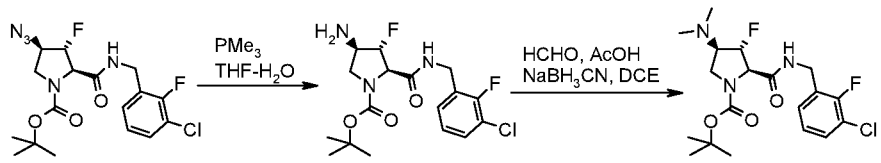
A solution of (1R,2S,5S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-6-oxa-3-aza-bicyclo [3.1.0]hexane-3-carboxylic acid tert-butyl ester (2.3 g, 5.95 mmol), sodium azide (2.32 g, 35.7 mmol) and NH_4Cl (0.637 g, 11.9 mmol) in DMF (23 mL) with H_2O (3.22 mL, 179 mmol) was heated at 100°C for 1 h. The reaction mixture was poured into ice, extracted with CH_2Cl_2, washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 1:1) to give a mixture of unseparable regioisomers (2S,3R,4R)-4-azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester and (2S,3S,4S)-3-azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester in a ratio 3:2 (absolute stereochemistry was assigned by NMR). TLC, R_f (c-hexane/EtOAc 1:1) = 0.3; MS (UPLC): 414 [M+H]+, 315 [MH-Boc]+, 412 [M-H]-; t_R (HPLC conditions f): 2.06 min.

F. (2R,3R,4R)-4-Azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester and (2S,3S,4S)-3-Azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (2S,3R,4R)-4-azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester and (2S,3S,4S)-3-azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (ratio 3/2, 1.14 g,

2.75 mmol) in CH_2Cl_2 (55 mL) was added DAST (1.456 mL, 11.02 mmol) at -78°C and the reaction mixture was stirred overnight at RT. The reaction mixture was carefully quenched with a saturated aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 9:1) to give a mixture of the two regioisomers, which were separated by preparative HPLC (Sunfire prep C18-ODB, 5 µm, 30X100 mm, 30% CH_3CN/H_2O 1.5 min, 30-100% CH_3CN/H_2O in 58.5 min, CH_3CN/H_2O containing 0.1 % TFA flow: 20 mL/min) to give after lyophilization of the purified fractions: (2R,3R,4R)-4-azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester; TLC, R_f (c-hexane/EtOAc 4:1) = 0.23; MS (LC/MS): 416 [M+H]+, 316 [MH-Boc]+; 414 [M-H]- , t_R (HPLC conditions h): 3.11 min and (2S,3S,4S)-3-azido-2-(3-chloro-2-fluoro-benzyl carbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester; R_f (c-hexane/EtOAc 4:1) = 0.13; MS (LC/MS): 416[M+H]+, 316 [MH-Boc]+; 414 [M-H]-; t_R (HPLC conditions h): 3.02 min.

Scheme B20: preparation of (2R,3S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-dimethylamino-3-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester



A. (2R,3S,4R)-4-Amino-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

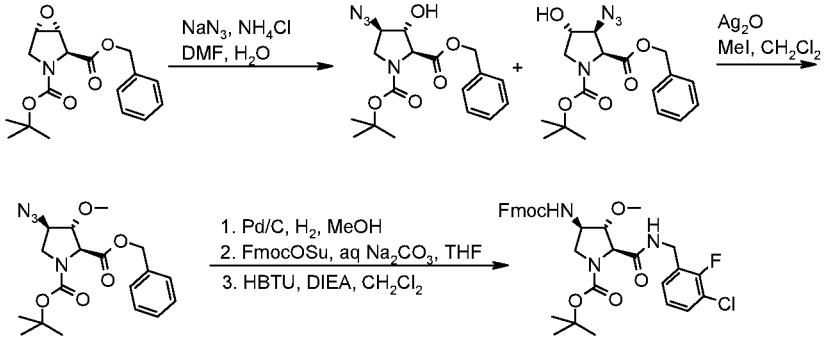
A solution of (2R,3R,4R)-4-azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (described in Scheme B19) (485 mg, 1.16 mmol), trimethylphosphine in THF (2.33 mL, 2.33 mmol) and water (0.04 mL, 2.33 mmol) in THF (20 mL) was stirred for 16 h at RT. The reaction mixture was quenched with water and extracted twice with EtOAc. The organic phase was washed with brine , dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (CH_2Cl_2/MeOH 95:5). MS (UPLC/MS): 390/392 [M+H]+, 434/436 [M+HCOO]-; t_R (HPLC conditions f): 1.64 min.

B. (2R,3S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-dimethylamino-3-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (2R,3S,4R)-4-amino-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (190 mg, 0.48 mmol) in MeOH (2 mL) was added formaldehyde (134 µl, 4.87 mmol). The reaction mixture was stirred 30 min at RT before addition of sodium cyanoborohydride (101 mg, 1.60 mmol) and acetic acid (56 µl, 0.97 mmol). After stirring for 30 min, the solution was concentrated. Purification by flash column

chromatography on silica gel (c-hexane/EtOAc 1:1) gave the desired compound. MS (UPLC/MS): 418/420 [M+H]+, 462/464 [M+HCOO]- ; t_R (HPLC conditions f): 1.61 min.

Scheme B21: preparation of [(3R,4S,5S)-1-tert-Butylcarbamoyl-5-(3-chloro-2-fluoro-benzylcarbamoyl)-4-methoxy-pyrrolidin-3-yl]-carbamic acid 9H-fluoren-9-ylmethyl ester



A. (2S,3R,4R)-4-Azido-2-benzylcarbamoyl-3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester and (2S,3S,4S)-3-azido-2-benzylcarbamoyl-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester

A solution of (1R,2S,5S)-6-oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-benzyl ester 3-tert-butyl ester (described in Scheme B19) (5.43 g, 11.90 mmol), sodium azide (4.64 g, 71.4 mmol) and NH_4Cl (1.27 g, 23.80 mmol) in DMF (74 mL) with H_2O (6.43 mL, 357 mmol) was heated at 100°C for 1 h. The reaction mixture was poured into ice, extracted with CH_2Cl_2 (3 x 250 mL), washed with water and brine, dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 1:1) gave the desired compounds as an unseparable mixture. MS (UPLC/MS): 307 [MH-tBu]+, 407 [M+HCOO]- ; t_R (HPLC conditions f): 1.04 min.

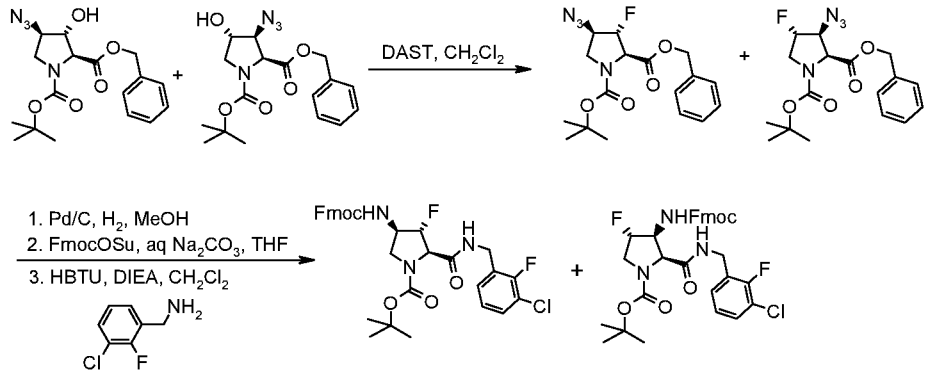
B. (2S,3R,4R)-4-Azido-3-methoxy-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

A solution of (2S,3R,4R)-4-azido-2-benzylcarbamoyl-3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester and (2S,3S,4S)-3-azido-2-benzylcarbamoyl-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (517 mg, 1.42 mmol) in CH_2Cl_2 (10 mL), silver oxide (1.32 g, 5.71 mmol) and methyl iodide (0.35 mL, 5.71 mmol) was heated in a sealed tube for 1 week at 40°C in the dark. The reaction mixture was filtered over celite pad and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 4:1) gave only (2S,3R,4R)-4-azido-3-methoxy-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester. MS (UPLC/MS): 321 [MH-tBu]+, 421 [M+HCOO]- ; t_R (HPLC conditions f): 2.40 min.

C. (2S,3S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-(9H-fluoren-9-ylmethoxy carbonylamino)-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester

A solution of (2S,3R,4R)-4-azido-3-methoxy-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (440 mg, 1.16 mmol) in methanol (3 mL) was hydrogenated with palladium on carbon 10% (124 mg, 1.16 mmol) overnight. The reaction mixture was filtered over a glass fiber filter, washed with methanol and evaporated in vacuo. The residue was dissolved in THF (2 mL) and a 10% aqueous Na_2CO_3 (3.09 mL, 1.11 mmol) solution was added. The reaction mixture was cooled at 0°C then FmocOSu dissolved in THF (7 mL) was added and stirred for 2 h at RT. The reaction mixture was concentrated in vacuo to leave a residue which was dissolved in EtOAc (10 mL) and treated with saturated aq. NH_4Cl solution. The mixture was extracted with EtOAc (3 x 20 mL) and the organic layers were collected, dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in DMF (3 mL) then 3-chloro-2-fluoro benzylamine (267 mg, 1.67 mmol) and HBTU (526 mg, 1.38 mmol), DIPEA (292 µl, 1.67 mmol) were added. The resulting orange solution was stirred overnight at RT. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 3:2) afforded the title compound. MS (UPLC/MS): 624/626 [M+H]+, 668/670 [M+HCOO]-; t_R (HPLC conditions f): 2.65 min.

Scheme B22: preparation of (2R,3S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-(9H-fluoren-9-ylmethoxycarbonylamino)-3-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester and (2S,3S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-(9H-fluoren-9-ylmethoxycarbonylamino)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester



A. (2R,3R,4R)-4-Azido-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester and (2S,3S,4S)-3-azido-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

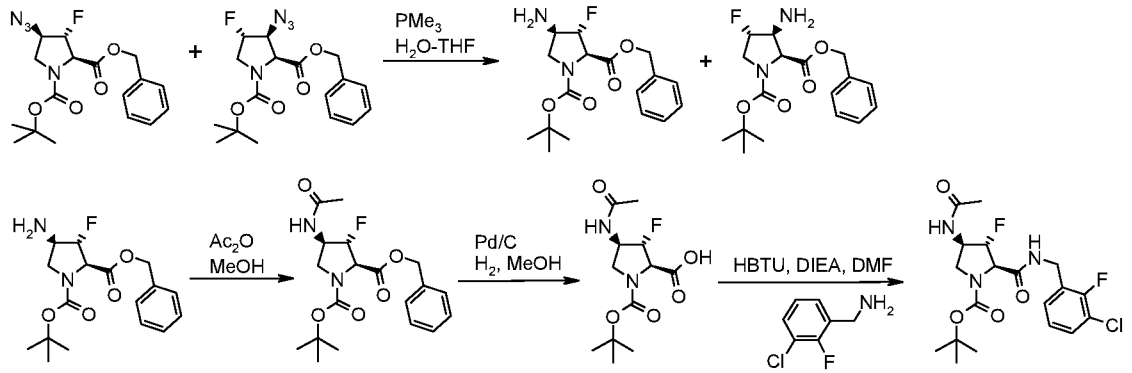
A solution of (2S,3R,4R)-4-azido-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester and (2S,3S,4S)-3-azido-4-hydroxy-pyrrol idine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (described in Scheme B21) (3.95 g, 10 mmol) in CH_2Cl_2 (100 mL) was cooled under Argon at -78°C then DAST (6.62 mL) was added. The reaction mixture was stirred for 16 h at RT, carefully quenched with sat. aq. $NaHCO_3$ (100 mL) and stirred for 30 min at 0°C, extracted twice with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated. Purification

by flash column chromatography on silica gel (c-hexane/EtOAc 1:1). MS (UPLC/MS): 365 [M+H]+; t_R (HPLC conditions f): 2.40 min.

B. (2R,3S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-(9H-fluoren-9-ylmethoxy carbonylamino)-3-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester and (2S,3S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-3-(9H-fluoren-9-ylmethoxycarbonylamino)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

A solution of (2R,3R,4R)-4-azido-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester and (2S,3S,4S)-3-azido-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (2.78 g, 7.63 mmol) in methanol (25 mL) was hydrogenated with palladium on carbon 10% (812 mg, 0.76 mmol) overnight. The reaction mixture was filtered over a glass fiber filter, washed with methanol and concentrated. 200 mg (0.084 mmol) of the residue was dissolved in THF (2 mL) and a 10% aqueous Na_2CO_3 (1 mL, 1 mmol) solution was added. The reaction mixture was cooled at 0°C then FmocOSu (284 mg, 0.084 mmol) dissolved in THF (7 mL) was added and stirred for 2 h at RT. The reaction mixture was concentrated in vacuo to give a residue which was dissolved in EtOAc (10 mL) and treated with saturated aq NH_4Cl solution. The mixture was extracted with EtOAc (3 x 20 mL) and the organic layers were collected, dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in DMF (3 mL) then 3-chloro-2 fluoro benzylamine (192 mg, 1.2 mmol) and HBTU (456 mg, 1.2 mmol), DIPEA (210 µl, 1.2 mmol) were added. The resulting solution was stirred overnight at RT. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 4:1). MS (UPLC/MS): 612/614 [M+H]+, 656/658 [M+HCOO]-; t_R (HPLC conditions f): 0.75/0.76 min.

<u>Scheme B23: preparation of (2R,3S,4R)-4-Acetylamino-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester and (2S,3S,4S)-3-acetylamino-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester</u>



A. (2S,3S,4S)-3-Amino-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester and (2R,3S,4R)-4-amino-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

A mixture of (2R,3R,4R)-4-azido-2-benzylcarbamoyl-3-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester and (2S,3S,4S)-3-azido-2-benzylcarbamoyl-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (3.52 g, 8.98 mmol) (described in Scheme B22), trimethylphosphine in THF (17.97 mL, 17.97 mmol) and water (0.32 mL, 17.97 mmol) in THF (100 mL) was stirred for 16 h at RT. The reaction mixture was quenched with water and extracted twice with EtOAc. The organic phases were joined, washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 1:1) gave (2S,3S,4S)-3-amino-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester: MS (UPLC/MS): 339 [M+H]+ ; t_R (HPLC conditions f): 1.59 min and (2R,3S,4R)-4-amino-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester: MS (UPLC/MS): 339 [M+H]+ ; t_R (HPLC conditions f): 1.62 min.

B. (2R,3S,4R)-4-Acetylamino-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester

To a solution of (2S,3S,4S)-3-amino-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (762 mg, 2.25 mmol) in methanol (20 mL) was added acetic anhydride (3.19 mL, 33.8 mmol) under argon. The reaction mixture was stirred for 16 h at RT. After concentration, the residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 3:1). MS (UPLC/MS): 381 [M+H]+, 281 [MH-Boc]- ; t_R (HPLC conditions f): 2.00 min.

C. (2R,3S,4R)-4-Acetylamino-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester

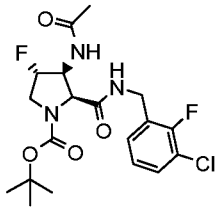
A solution of (2R,3S,4R)-4-acetylamino-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (315 mg, 0.82 mmol) in methanol (2 mL) was hydrogenated with palladium on carbon 10% (88 mg, 0.82 mmol) overnight. The reaction mixture was filtered over glass fiber and was concentrated. The residue was used as was for the next step.

D. (2R,3S,4R)-4-Acetylamino-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

To a mixture of (2R,3S,4R)-4-acetylamino-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (245 mg, 0.84 mmol), (3-chloro-2-fluoro) benzylamine (202 mg, 1.26 mmol) and HBTU (480 mg, 1.26 mmol) in DMF (7.5 mL) was added DIPEA (0.22 mL, 1.26 mmol). The resulting solution was stirred overnight at RT. The reaction mixture was poured into aq. sat. $NaHCO_3$ and was extracted with CH_2Cl_2 (3 X 20 mL). The organic phases were joined, washed with

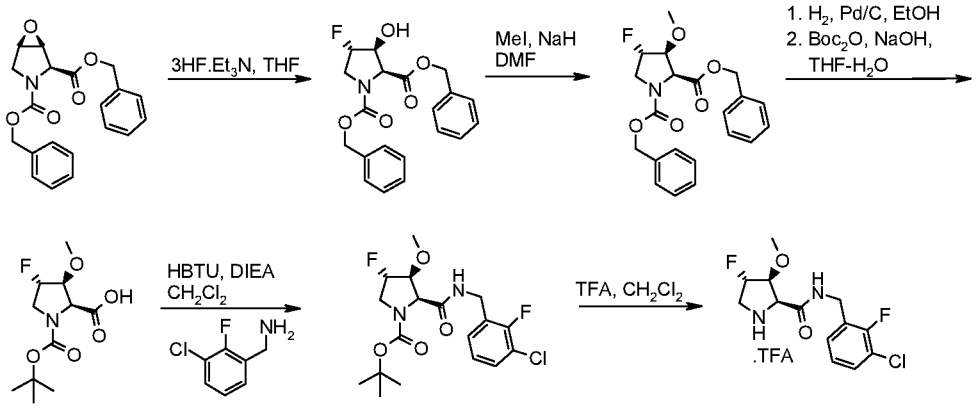
brine, dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 1:1). MS (UPLC/MS): 376 [MH-tBu]+, 476 [M+HCOO]-; t_R (HPLC conditions f): 1.93 min.

(2S,3S,4S)-3-Acetylamino-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester



The title compound was prepared in a similar manner as described above from (2R,3S,4R)-4-amino-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester. MS (UPLC/MS): 432 [M+H]+, 476 [M+HCOO]-; t_R (HPLC conditions f): 1.96 min.

Scheme B24: preparation of (2S,3S,4S)-4-Fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide trifluoroacetate



A. (2S,3S,4S)-4-fluoro-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid dibenzyl ester

To a solution of (1S,2S,5R)-6-oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid dibenzyl ester (prepared as described Scheme B19, 4 g, 11.3 mmol) in THF (3 mL) was added 3HF.Et_3N (18.5 mL, 113 mmol). The reaction mixture was microwaved at 130°C (6x40 min) then was poured into a saturated solution of Na_2CO_3 and stirred for 30 min. The mixture was extracted with EtOAc (2 x 100 mL), the organic phases were joined, washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 7:3) to give a mixture containing (2S,3S,4S)-4-fluoro-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid dibenzyl ester as the major isomer. MS (UPLC): 374 [M+H]+; t_R (HPLC conditions f): 2.13 min.

B. (2S,3S,4S)-4-Fluoro-3-methoxy-pyrrolidine-1,2-dicarboxylic acid dibenzyl

To a solution of (2S,3S,4S)-4-fluoro-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid dibenzyl ester (531 mg, 1.42 mmol) cooled with an ice-bath and under argon was added NaH (60 % in mineral oil, 62 mg, 1.52 mmol). The reaction mixture was stirred for 30 min then MeI (0.26 mL, 4.27 mmol) was added. The reaction mixture was stirred for 30 min then was quenched with water. After extraction with EtOAc (2 x 25 mL), the organic phases were joined, washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 7:3). MS (UPLC): 388 [M+H]+ ; t_R (HPLC conditions f): 2.36 min.

C. (2S,3S,4S)-4-Fluoro-3-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester

To a solution of (2S,3S,4S)-4-fluoro-3-methoxy-pyrrolidine-1,2-dicarboxylic acid dibenzyl ester (430 mg, 1.11 mmol) in MeOH (25 mL) was added Pd/C 10% (100 mg). The reaction was placed under hydrogen atmosphere and was stirred for 2 h then was filtered over glass-fiber, rinsed with MeOH (25 mL) and water (25 mL). After concentration, the residue was lyophilized overnight. The powder obtained was dissolved in THF/Water 1/1 (20 mL) then aq. 1N NaOH (0.755 mL) and Boc anhydride (412 mg , 2.22 mmol) were added and the reaction mixture was stirred at RT overnight. After concentration, the crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 1:1 + 0.5% AcOH). MS (UPLC): 264 [M+H]+; t_R (HPLC conditions f): 0.65 min.

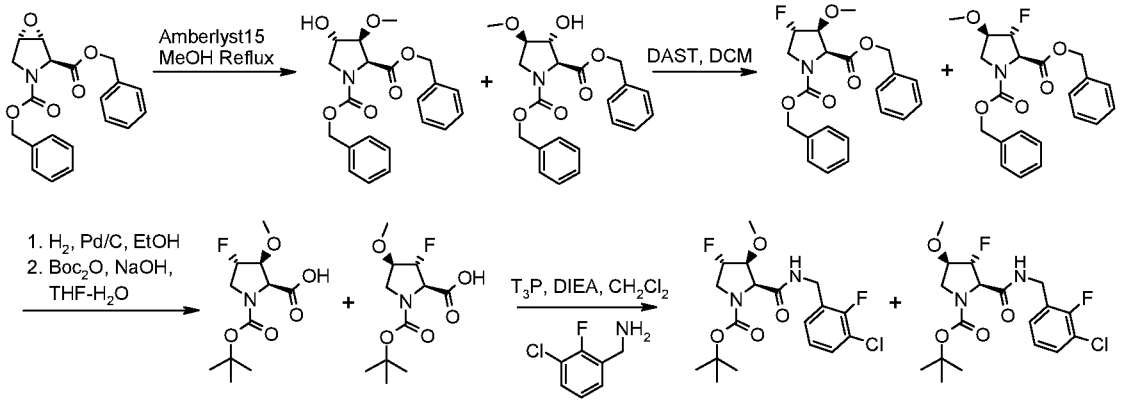
D. (2S,3S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (2S,3S,4S)-4-fluoro-3-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (500 mg, 1.90 mmol) in DMF (20 mL) were added 3-chloro-2-fluoro-benzylamine (330 mg, 2.1 mmol), HBTU (1.4 g, 3.8 mmol) and DIPEA (1.32 mL, 7.6 mmol). The reaction mixture was stirred at RT for 2 h then was poured into water (50 mL). After extraction with ETOAc (3 x 30 mL), the organic phases were joined, washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 1:1) to give (2S,3S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester: R_f, TLC (c-hexane/EtOAc 1:1) = 0.37; MS (UPLC): 405.1/407.2 [M+H]+, 349.1/351.1 [MH-tBu]+, 449.2/451.2 [M+HCOO]-; t_R (HPLC conditions f): 2.12 min. 1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.59 (m, 1H), 7.48 (m, 1H), 7.37 (m, 1H), 7.20 (m, 1H), 5.20 (br.d, 1H), 4.47 – 4.26 (m, 3H), 4.19 (ddd, 1H), 3.81-3.65 (m, 1H), 3.54 – 3.40 (m, 1H), 3.36 (s, 3H), 1.42 and 1.27 (2 s, 9H).

E. (2S,3S,4S)-4-Fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide trifluoroacetate

TFA (0.86 mL, 11.12 mmol) was added to a solution of (2S,3S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester (450 mg, 1.12 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred overnight then was concentrated. The residue was triturated with Et_2O (10 mL) to give a precipitate which was filtered off, washed with Et_2O (10 mL) then dried under high vacuum. The absolute stereochemistry was confirmed by X-ray. t_R (HPLC conditions f): 0.40 min; MS (UPLC): 349 [M+HCOO]-, 305 [M+H]+.

Scheme B25: Alternative for the preparation of (2S,3S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester



A. (2S,3S,4S)-4-Hydroxy-3-methoxy-pyrrolidine-1,2-dicarboxylic acid dibenzyl ester and (2S,3R,4R)-3-hydroxy-4-methoxy-pyrrolidine-1,2-dicarboxylic acid dibenzyl ester

To a solution of (1R,2S,5S)-6-Oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid dibenzyl ester (prepared as described Scheme B19, 30 g, 85 mmol) in MeOH (150 mL) was added Amberlyst 15 (30 g). The reaction mixture was heated overnight at 65°C, then allowed to cool to RT and filtered. Amberlyst 15 residue was washed with MeOH. The combined filtrates were combined and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane 100% to EtOAc 100%) to give a mixture of the 2 regioisomers as a yellow oil. R_f, TLC (c-hexane/EtOAc 1:1) = 0.5; MS (UPLC): 386.2 [M+H]+, 430.2 [M+HCOO]-; t_R (HPLC conditions a): 1.93 min.

B. (2S,3S,4S)-4-Fluoro-3-methoxy-pyrrolidine-1,2-dicarboxylic acid dibenzyl ester and (2R,3R,4R)-3-fluoro-4-methoxy-pyrrolidine-1,2-dicarboxylic acid dibenzyl ester

A solution of (2S,3S,4S)-4-hydroxy-3-methoxy-pyrrolidine-1,2-dicarboxylic acid dibenzyl ester and (2S,3R,4R)-3-hydroxy-4-methoxy-pyrrolidine-1,2-dicarboxylic acid dibenzyl ester (17.8 g, 46.2 mmol) in CH_2Cl_2 (250 mL) was cooled under Argon at -78°C then DAST (12.2 mL, 92 mmol) was added dropwise. The reaction mixture was allowed to reach RT and further stirred for 16 h. The reaction mixture was diluted with CH_2Cl_2 and carefully quenched with sat. aq. $NaHCO_3$. The layers were separated, the aqueous layer extracted twice with CH_2Cl_2, the

combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 100:0 to 0:100) gave a mixture of the 2 regioisomers as a yellow solid. MS (UPLC/MS): 388.3 [M+H]+, 405.3 [M+NH_4]+; t_R (HPLC conditions f): 2.34 min.

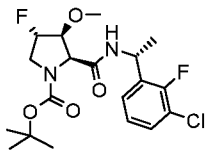
C. (2S,3S,4S)-4-Fluoro-3-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester and (2R,3R,4R)-3-Fluoro-4-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester

were obtained as a mixture using the protocol described in Scheme B24 step C. R_f, TLC (EtOAc) = 0.1.

D. (2S,3S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester and (2R,3R,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-3-fluoro-4-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester.

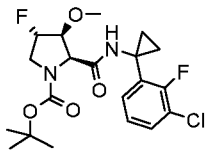
To a solution of (2S,3S,4S)-4-fluoro-3-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester and (2R,3R,4R)-3-fluoro-4-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (1.55 g, 5.89 mmol) in CH_2Cl_2 (50 mL) were added 3-chloro-2-fluoro-benzylamine (1,03 g, 6.48 mmol), propylphosphonic anhydride (50% in EtOAc, 5.20 mL, 8.83 mmol) and DIPEA (3.08 mL, 17.7 mmol). The reaction mixture was stirred at RT for 2 h and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 7:3) to give (2S,3S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester: R_f, TLC (c-hexane/EtOAc 1:1) = 0.35; MS (UPLC): 405.1/407.2 [M+H]+, 349.1/351.1 [MH-tBu]+, 449.2/451.2 [M+HCOO]-; t_R (HPLC conditions f): 2.12 min and (2R,3R,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-fluoro-4-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester: R_f, TLC (c-hexane/EtOAc 1:1) = 0.5; MS (UPLC): 405.1/407.2 [M+H]+, 349.0/351.1 [MH-tBu]+, 449.2/451.2 [M+HCOO]-; t_R (HPLC conditions f): 2.20 min.

(2S,3S,4S)-2-[(R)-1-(3-Chloro-2-fluoro-phenyl)-ethylcarbamoyl]-4-fluoro-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester



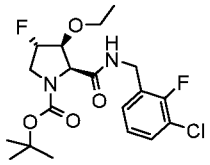
was prepared according to the same protocols described in Scheme B25 using (R)-1-(3-chloro-2-fluoro-phenyl)-ethylamine in Step D. Separation of two regioisomers was performed by flash column chromatography on silica gel (c-hexane/EtOAc 6:4) to give ((2S,3S,4S)-2-[(R)-1-(3-chloro-2-fluoro-phenyl)-ethylcarbamoyl]-4-fluoro-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester. MS (UPLC): 405/407 [M+H]+; t_R (HPLC conditions f): 2.14 min.

(2S,3S,4S)-2-[1-(3-Chloro-2-fluoro-phenyl)-cyclopropylcarbamoyl]-4-fluoro-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester



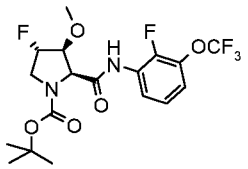
was prepared according to the same protocols described in Scheme B25 using 1-(3-chloro-2-fluoro-phenyl)-cyclopropylamine in Step D. 1-(3-chloro-2-fluoro-phenyl)-cyclopropylamine is prepared as described in Part C. Separation of two regioisomers was performed by flash column chromatography on silica gel (c-hexane/EtOAc 1:1) to give (2S,3S,4S)-2-[1-(3-chloro-2-fluoro-phenyl)-cyclopropylcarbamoyl]-4-fluoro-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester. MS (UPLC): 431/433 [M+H]+; t_R (HPLC conditions f): 2.21 min.

(2S,3S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-3-ethoxy-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester



was prepared according to the same protocols described in Scheme B25 using EtOH instead of MeOH in Step A. Separation of two regioisomers was performed by flash column chromatography on silica gel (c-hexane/EtOAc 6:4) to give(2S,3S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-ethoxy-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester. MS (UPLC): 419/421 [M+H]+; t_R (HPLC conditions f): 2.23 min.

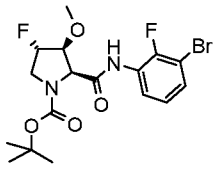
(2S,3S,4S)-4-Fluoro-2-(2-fluoro-3-trifluoromethoxy-phenylcarbamoyl)-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester



To a solution of (2S,3S,4S)-4-fluoro-3-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester and (2R,3R,4R)-3-fluoro-4-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (prepared as described in Scheme B25, 1.00 g, 3.80 mmol) in CH_2Cl_2 (10 mL) at 0°C under nitrogen atmosphere was added 1-chloro-N,N,2-trimethylprop-1-en-1-amine (609 mg, 4.56 mmol) and the mixture was stirred at this temperature for 1 h. 2-Fluoro-3-(trifluoromethoxy)aniline (0.815 mg, 4.18 mmol) was then added, followed by DIPEA (1.327 mL, 7.60 mmol) and the mixture was stirred at RT for 1 h. The crude residue was purified by

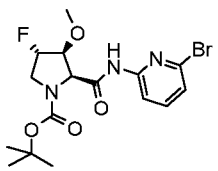
flash column chromatography on silica gel (c-hexane/EtOAc 1:0 to 1:1) to give (2S,3S,4S)-4-fluoro-2-(2-fluoro-3-trifluoromethoxy-phenylcarbamoyl)-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester. 1H NMR (400 MHz, DMSO-d_6) 2:1 mixture of rotamers δ (ppm): 10.15 (m, 1H), 7.87 (m, 1/3H), 7.77 (m, 2/3H), 7.31 (m, 2H), 5.29-5.11 (m, 1H), 4.76 (d, 1/3H), 4.70 (d, 2/3H), 4.29 (m, 1H), 3.80-3.53 (m, 2H), 3.39 (m, 3H), 1.39 (s, 3H), 1.31 (s, 6H). MS (UPLC-MS): 441 [M+H]+; t_R (HPLC conditions f): 2.14 min.

(2S,3S,4S)-2-(3-Bromo-2-fluoro-phenylcarbamoyl)-4-fluoro-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester



To a solution of (2S,3S,4S)-4-fluoro-3-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester and (2R,3R,4R)-3-fluoro-4-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (prepared as described in Scheme B25, 100 mg, 0.380 mmol) in CH_2Cl_2 (2.4 mL) at 0°C under nitrogen atmosphere was added 1-chloro-N,N,2-trimethylprop-1-en-1-amine (50.8 mg, 0.38 mmol) and the mixture was stirred at this temperature for 2 h. 3-Bromo-2-fluoroaniline (144 mg, 0.76 mmol) was then added, followed by DIPEA (0.265 mL, 1.52 mmol) and the mixture was stirred at RT for 1 h. The reaction mixture was concentrated and the crude residue was purified by preparative HPLC (Waters Sunfire C18-ODB, 5µm, 30x100mm, eluent: 0-0.5 min 5% CH_3CN in H_2O Flow: 5mL/min, 0.5-18.5 min 5 to 100% CH_3CN/H_2O Flow: 40mL/min, 18.5-20 min 100% CH_3CN, CH_3CN and H_2O both containing 0.1% TFA). The purified HPLC fractions were neutralized by addition of a saturated aqueous solution of Na_2CO_3, the layer were separated and the aqueous layer was extracted with CH_2Cl_2 (x2). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. White solid. R_f, TLC (c-hexane/EtOAc 1:1) = 0.75; MS (UPLC): 435.1/437.1 [M+H]+, 433.1/435.1 [M-H]-; t_R (HPLC conditions f): 2.06 min.

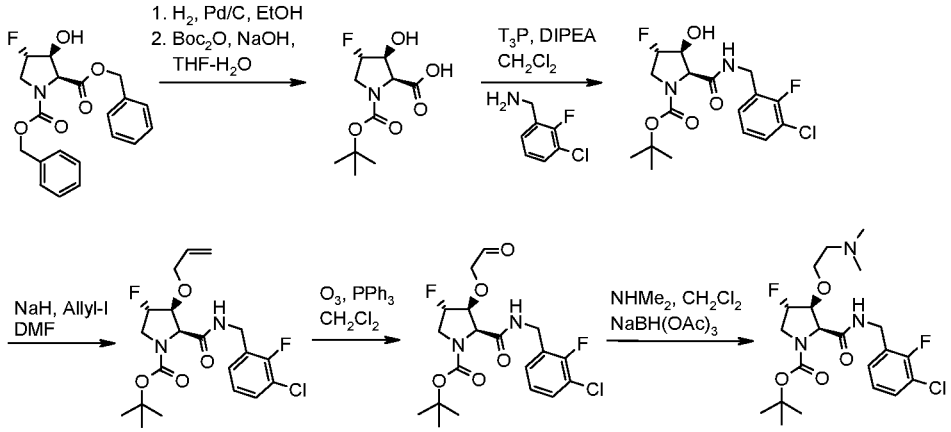
(2S,3S,4S)-2-(6-Bromo-pyridin-2-ylcarbamoyl)-4-fluoro-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester



was prepared according to the same protocols described for the synthesis of(2S,3S,4S)-2-(3-bromo-2-fluoro-phenylcarbamoyl)-4-fluoro-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl

ester. White solid. R_f, TLC (EtOAc) = 0.8; 418.1/420.1 [M+H]+, 416.2/418.1 [M-H]-; t_R (HPLC conditions f): 2.0 min.

Scheme B26: Preparation of (2S,3S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-(2-dimethylamino-ethoxy)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester



A. (2S,3S,4S)-4-fluoro-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester

To a solution of (2S,3S,4S)-4-fluoro-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid dibenzyl ester (390 mg, 1.04 mmol) in MeOH (10 mL) was added Pd/C 10% (39 mg). The reaction was placed under hydrogen atmosphere and stirred 2 h then was filtered over glass-fiber and rinsed with water. After concentration, the residue was dissolved in THF/Water 2/1 (30 mL), aqueous NaOH (1 N, 2.09 mL, 2.09 mmol) and Boc anhydride (456 mg , 2.09 mmol) were added and the reaction mixture was stirred 16 h at RT. THF was removed under reduced pressure and the aqueous layer was extracted with Et_2O (x2), acidified by addition of $KHSO_4$ (10% in water) and extracted with EtOAc (x2). The combined EtOAc extracts were dried (Na_2SO_4), filtered and concentrated. The material thus obtained was used in the next step without further purification.

B. (2S,3S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (2S,3S,4S)-4-fluoro-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (195 g, 0.782 mmol) in CH_2Cl_2 (10 mL) were added 3-chloro-2-fluoro-benzylamine (150 mg, 0.94 mmol), propylphosphonic anhydride (50% in EtOAc, 0.346 mL, 1.17 mmol) and DIPEA (0.41 mL, 2.35 mmol). The reaction mixture was stirred 1 h at RT, then quenched by addition of a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (x2). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 1:1). MS (UPLC): 391.3/393.1 [M+H]+, 435.4/437.4 [M+HCOO]-; t_R (HPLC conditions f): 1.95 min.

C. (2S,3S,4S)-3-allyloxy-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of NaH (60 % in mineral oil, 8.6 mg, 0.215 mmol) in DMF (5 mL) cooled with an ice-bath and under argon was added (2S,3S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (70 mg, 0.179 mmol). The reaction mixture was stirred for 20 min before addition of allyl iodide (0.025 mL, 0.269 mmol) at 0°C. The reaction mixture was stirred for 30 min then quenched by addition of water and extracted with EtOAc (x2). The organic extracts were combined, washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 3:2). MS (UPLC): 431.4/433.1 [M+H]+, 475.5/577.5 [M+HCOO]-; t_R (HPLC conditions f): 2.29 min.

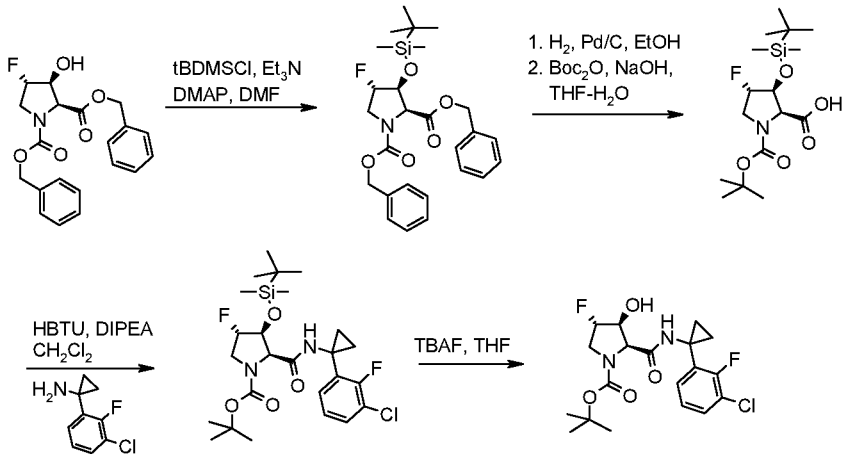
D. (2S,3S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-3-(2-oxo-ethoxy)-pyrrolidine -1-carboxylic acid tert-butyl ester

Ozone was bubbled through a solution of (2S,3S,4S)-3-allyloxy-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (59 mg, 0.137 mmol) in CH_2Cl_2 (20 mL) at -78°C. When the solution turned blue, ozone addition was stopped and nitrogen was passed through the solution until the blue color was discharged. Triphenylphosphine (35.9 mg, 0.137 mmol) was added to the ozonide solution at -78°C and the reaction mixture was allowed to slowly reach RT. The reaction mixture was concentrated and the material thus obtained used without further purification in the next step. MS (UPLC): 433.4/435.4 [M+H]+, 477.4/579.5 [M+HCOO]-.

E. (2S,3S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-3-(2-dimethylamino-ethoxy)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of the crude material obtained in the previous step and dimethylamine (2 N in MeOH, 173 µl, 0.347 mmol) in MeOH (3 mL) at 25°C were successively added AcOH (100 µL) and sodium triacetoxyborohydride (73.5 mg, 0.347 mmol). The reaction mixture was stirred 2 h and concentrated. The crude residue was purified by preparative HPLC ((Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 mL/min). MS (UPLC): 462.4/464.4 [M+H]+, 506.5/508.5 [M+HCOO]-; t_R (UPLC conditions m): 0.70 min.

Scheme B27: Preparation of (2S,3S,4S)-2-[1-(3-Chloro-2-fluoro-phenyl)-cyclopropylcarbamoyl]-4-fluoro-3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester



A. (2S,3S,4S)-3-(tert-Butyl-dimethyl-silanyloxy)-4-fluoro-pyrrolidine-1,2-dicarboxylic acid dibenzyl ester

To a solution of (2S,3S,4S)-4-fluoro-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid dibenzyl ester (1.90 g, 5.09 mmol) in DMF (40 mL) were added tert-butyldimethylchlorosilane (0.844 g, 5.60 mmol), triethylamine (0.709 ml, 5.09 mmol) and DMAP (0.062 g, 0.509 mmol). The reaction mixture was stirred 25°C for 1 week. Then quenched by addition of a saturated aqueous solution of $NaHCO_3$. The layers were separated and the organic extract was dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 9:1). MS (UPLC): 588.4 [M+H]+, 505.5 [M+NH_4]+, 510.4 [M+Na]+; t_R (HPLC conditions f): 2.90 min.

B. (2S,3S,4S)-3-(tert-Butyl-dimethyl-silanyloxy)-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester

was prepared from (2S,3S,4S)-3-(tert-butyl-dimethyl-silanyloxy)-4-fluoro-pyrrolidine-1,2-dicarboxylic acid dibenzyl ester according to the protocol described in Scheme B26 step A. t_R (UPLC conditions m): 1.21 min.

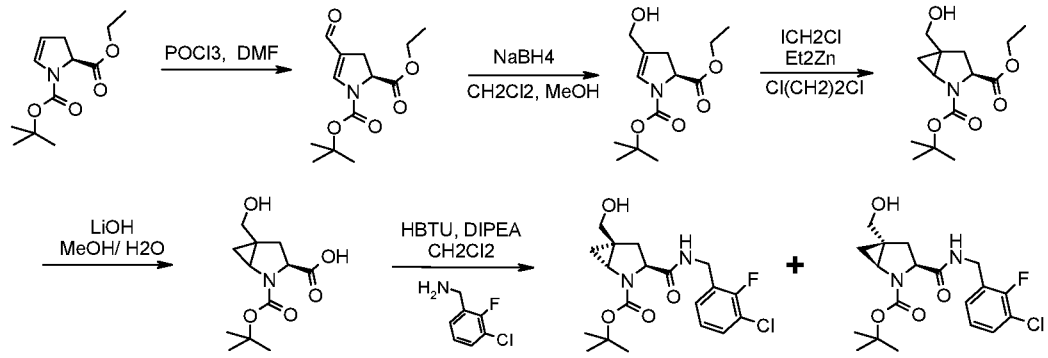
C. (2S,3S,4S)-3-(tert-Butyl-dimethyl-silanyloxy)-2-[1-(3-chloro-2-fluoro-phenyl)-cyclopropyl carbamoyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (2S,3S,4S)-3-(tert-butyl-dimethyl-silanyloxy)-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (300 mg, 0.825 mmol), 1-(3-chloro-2-fluoro-phenyl)-cyclopropylamine (prepared as described in Part C, 272 mg, 0.908 mmol) and HBTU (376 mg, 0.99 mmol) in DMF (10 mL) was added DIPEA (0.432 ml, 2.476 mmol) under nitrogen atmosphere. The reaction mixture was stirred 2 h at 25°C. Then quenched by addition of a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc (x2). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc1:1). MS (UPLC): 531.5/533.5 [M+H]+, 505.5 [M+NH_4]+, 510.4 [M+Na]+; t_R (UPLC conditions m): 1.55 min.

(2S,3S,4S)-2-[1-(3-Chloro-2-fluoro-phenyl)-cyclopropylcarbamoyl]-4-fluoro-3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester

TBAF (1N in THF, 0.547 ml, 0.547 mmol) was added to a solution of (2S,3S,4S)-3-(tert-butyl-dimethyl-silanyloxy)-2-[1-(3-chloro-2-fluoro-phenyl)-cyclopropyl carbamoyl]-4-fluoro-pyrroli dine-1-carboxylic acid tert-butyl ester (242 mg, 0.456 mmol) in THF (10 mL) and the reaction mixture was stirred 30 min at 25°C. Then poured into water, extracted with EtOAc (x2), dried (Na_2SO_4), filtered and concentrated. The material thus obtained was used without further purification in the next step. MS (UPLC): 417.5/419.5 [M+H]+, 461.5/463.5 [M+HCOO]-; t_R (HPLC conditions f): 2.04 min.

Scheme B28: preparation of (1R,3S,5S) and (1S,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-5-hydroxymethyl-2-aza-bicyclo [3.1.0]hexane-2-carboxylic acid tert-butyl ester



A. (S)-4-Formyl-2,3-dihydro-pyrrole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester

$POCl_3$ (7.59 mL, 83 mmol) was added in 25 min at 0°C under N_2 atmosphere to DMF (6.39 mL, 83 mmol) and the mixture was stirred at RT for 20 min. Dry CH_2Cl_2 (150 mL) was added at 0°C, followed by a solution of (S)-2,3-dihydro-pyrrole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (10 g, 41.4 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred 30 min at RT until completion. The mixture was slowly poured into an ice cold aqueous solution of NaOH 10 N (150 mL) and extracted with CH_2Cl_2 (x3). The combined organic extracts were washed with brine (x2), with water, dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 9:1) to give the desired material as a yellow oil. R_f, TLC (c-hexane/EtOAc 4:1) = 0.2; MS (UPLC-MS): 270 [M+H]+, 170 [M-Boc]-; t_R (HPLC conditions f): 1.93 min.

B. (S)-4-Hydroxymethyl-2,3-dihydro-pyrrole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester

A solution of (S)-4-formyl-2,3-dihydro-pyrrole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (3.32 g, 12.3 mmol) in CH_2Cl_2 (51.4 mL) was cooled at -78°C under nitrogen atmosphere,

solid $NaBH_4$ (1 g, 24.7 mmol) was added portionwise maintaining the temperature at -78°C. MeOH (25.7 mL) was added dropwise and the reaction mixture was allowed to reach 0°C and was stirred 1h30 at 0°C. The reaction was quenched with an aqueous saturated solution of NH_4Cl and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 1:1 to EtOAc) to give the desired material as a yellow oil. R_f, TLC (c-hexane/EtOAc 1:1) = 0.30; MS (UPLC-MS): 272.2 [M+H]+, 316 [M+HCOO]-; t_R (HPLC conditions f): 1.74 min.

C. (1R,3S,5S) and (1S,3S,5R)-5-Hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester 3-ethyl ester

To a solution of (S)-4-hydroxymethyl-2,3-dihydro-pyrrole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (1.12 g, 4.13 mmol) in CH_2Cl_2 (115 mL) under argon at -20°C were slowly added diethylzinc (1M in hexanes, 8.26 mL, 8.26 mmol) and diiodomethane (0.73 mL, 9.08 mmol) and the reaction mixture was further stirred at -10°C for 2 h. Diethylzinc (1M in hexanes, 8.26 mL, 8.26 mmol) and diiodomethane (0.73 mL, 9.08 mmol) were again added and the reaction mixture was further stirred at -10°C for 2 h to complete the reaction. A saturated aqueous solution of NH_4Cl was added slowly (exothermic) at -20°C followed by CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (x2). To the combined organic layers were added few crystals of Na_2S and water (ratio CH_2Cl_2/H_2O 20:1) and the biphasic mixture was stirred for 30 min. Water was added, the layers were separated, dried (Na_2SO_4), filtered and concentrated to give a mixture of diastereoisomers. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 1:1) to give a mixture of diastereoisomers (4:6 (1R,3S,5S)/(1S,3S,5R)). The absolute stereochemistry of the diastereoisomers was determined by NMR. R_f, TLC (c-hexane/EtOAc 1:1) = 0.25; MS (UPLC-MS): 186.1[MH-Boc]+, 230.2 [MH-tBu]+, 286.3 [MH+H]+, 308.2 [MH+Na]+, 330.3 [M+HCOO]-; t_R (HPLC conditions f): 1.75 min.

Alternatively (1R,3S,5S) and (1S,3S,5R)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester 3-ethyl ester were prepared according to the procedure below derived from *J. Amer. Chem. Soc.*, **1998**, 120, 46, 11943.

To a solution of dry DME (198 µL, 1.91 mmol) in dry CH_2Cl_2 (4 mL) under argon atmosphere and cooled at -10°C was added diethylzinc (1 M in hexanes, 2.05 mL, 2.05 mmol) followed by chloroiodomethane (330 µL, 4.1 mmol) over a 15-20 min period while maintaining the internal temperature at -10°C. The solution was stirred for an additional 10 min at -10°C and a solution of butylboronic acid N,N,N',N'-tetramethyl-D-tartaric acid diamide ester (346 µL, 1.36 mmol) in anhydrous CH_2Cl_2 (1 mL) was added over a 5 min period immediately followed by the addition of a solution of (S)-4-hydroxymethyl-2,3-dihydro-pyrrole-1,2-dicarboxylic acid 1-tert-butyl ester

2-ethyl ester (185 mg, 0.68 mmol) in dry CH_2Cl_2 (1 mL). The reaction mixture was stirred at -10°C. The reaction was quenched with 1 mL of a saturated aqueous NH_4Cl and 10 % $KHSO_4$ (3 mL), EtOAc was added, the layers were separated and the aqueous layer back-extracted with EtOAc (x2). To the combined organic layers was added a solution containing 6 mL of 2 N aqueous NaOH and 1 mL of 30 % aqueous H_2O_2 and the resulting biphasic solution was vigorously stirred for 5 min. The two layers were separated and the organic layer was successively washed with saturated aqueous Na_2SO_3, $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 6-4) to give a mixture of diastereoisomers (approximatively 70/30 (1R,3S,5S)/(1S,3S,5R)).

D. (1R,3S,5S) and (1S,3S,5R)-5-Hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester

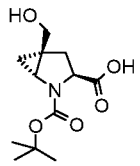
To a diastereoisomeric mixture of (1R,3S,5S) and (1S,3S,5R)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester 3-ethyl ester (ratio 4:6, 100 mg, 0.31 mmol) in THF (1.5 mL) and H_2O (0.15 mL) at 0°C was added NaOH (1 M in water, 0.63 mL, 0.63 mmol). The solution was stirred 1 h at RT and poured into 10 % $KHSO_4$ (until pH 1), EtOAc was added and the layers were separated (x3). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was used without further purification in the next step. MS (HPLC/MS): 256.2 [M-H]-, 258.3 [M+H]+, 280.3 [M+Na]+, 200.2 [MH-tBu]+, 515.54 [2M+H]+, 537.4 [2M+Na]+; t_R (HPLC conditions f): 1.28 min.

E. (1R,3S,5S) and (1S,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-5-hydroxymethyl-2-aza-bicyclo [3.1.0]hexane-2-carboxylic acid tert-butyl ester

To a diastreoisomeric mixture of (1R,3S,5S) and (1S,3S,5R)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester (312 mg, 1.21 mmol), 3-chloro-2-fluorobenzylamine (232 mg, 1.46 mmol), HBTU (690 mg, 1.82 mmol) in CH_2Cl_2 (6 mL) was added DIPEA (0.623 mL, 3.64 mmol). The resulting solution was stirred at RT under nitrogen overnight. DIPEA (0.21 mL, 1.21 mmol), HBTU (230 mg, 0.6 mmol) and 3-chloro-2-fluorobenzylamine (97 mg, 0.606 mmol) were added and the mixture was further stirred overnight at RT under N2. The mixture was poured into an aqueous solution of HCl 1N (pH-1) and extracted with CH_2Cl_2 (2x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 40:60) to give (1S,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-5-hydroxymethyl-2-aza-bicyclo [3.1.0]hexane-2-carboxylic acid tert-butyl ester: TLC, R_f (EtOAc) = 0.55 (stained with ninhydrine); MS (UPLC-MS): 399.2/401.2 [M+H]+, 299.2/301.2 [MH-Boc]+, 343.2/345.2 [MH-tBu]+, 443.2/445.3 [M+HCOO]-

; t_R (HPLC conditions f): 1.95 min, and (1R,3S,5S)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-5-hydroxymethyl-2-aza-bicyclo [3.1.0]hexane-2-carboxylic acid tert-butyl ester: TLC, R_f (EtOAc) = 0.45 (stained with ninhydrine); MS (UPLC-MS): 399.2/401.2 [M+H]+, 299.2/301.2 [MH-Boc]+, 343.2/345.2 [MH-tBu]+, 443.2/445.3 [M+HCOO]-; t_R (HPLC conditions f): 1.89 min.

(1R,3S,5S)-5-Hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester

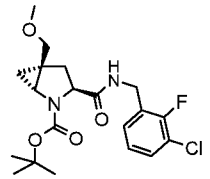


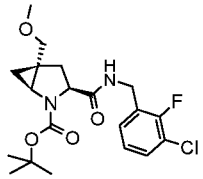
was obtained using the same protocols as described in Scheme B28 step D from (1R,3S,5S)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester 3-ethyl ester. 1H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.5 (m, 1H), 4.71 (m, 1H), 3.92 (m, 1H), 3.42 - 3.35 (m, 2H), 3.17 (m, 1H), 2.31 (m, 1H), 2.08 (m, 1H), 1.41 and 1.33 (2 s, 9H), 0.79 (m, 1H), 0.67 (m, 1H).

(1R,3S,5S)-5-Hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester 3-ethyl ester

The mixture of (1R,3S,5S) and (1S,3S,5R)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester 3-ethyl ester (360 g) was separated into its diastereoisomers by preparative chiral HPLC column: 8 SMB columns Chiralpak AD, 20 um, 250 x 30 mm; eluent: heptane–EtOH 80:20) to give (1R,3S,5S)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester 3-ethyl ester: t_R (Chiralpak AD-prep, 20 uM, 250 x 4.6 mm, n-heptane/EtOH 80/20, flow rate 1 mL/min, detection: UV at 210 nm): 6.94 min and (1S,3S,5R)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester 3-ethyl ester: t_R (Chiralpak AD-prep, 20 uM, 250 x 4.6 mm, n-heptane/EtOH 80/20, flow rate 1 mL/min, detection: UV at 210 nm): 4.20 min.

(1R,3S,5S) and (1S,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-5-methoxymethyl-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester





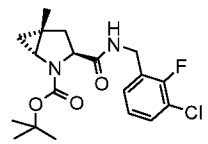
were obtained using the same protocols as described in Scheme B28 steps D and E for the preparation of (1R,3S,5S) and (1S,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-5-hydroxymethyl-2-aza-bicyclo [3.1.0]hexane-2-carboxylic acid tert-butyl ester starting from

(1R,3S,5S) and (1S,3S,5R)-5-methoxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester 3-ethyl ester. NaOH was replaced by $LiOH.H_2O$ in step D. The diastereoisomers were separated by flash column chromatography on silica gel (c-hexane/EtOAc 1:1 to EtOAc) to give (1S,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-5-methoxymethyl-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester as a colorless oil: TLC, R_f (c-hexane/EtOAc 1:1) = 0.50; MS (UPLC/MS): 413.3/415.2 [M+H]+, 457.3/459.3 [M+HCOO]-; t_R (HPLC conditions a): 3.74 min and (1R,3S,5S)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-5-methoxymethyl-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester as a colorless oil: TLC, R_f (c-hexane/EtOAc 1:1) = 0.30; MS (UPLC/MS): 413.2/415.3 [M+H]+, 457.3/459.3 [M+HCOO]-; t_R (HPLC conditions a): 3.57 min.

(1R,3S,5S) and (1S,3S,5R)-5-Methoxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester 3-ethyl ester

(1R,3S,5S) and (1S,3S,5R)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester 3-ethyl ester as mixture of diastereoisomers (35:65 (1R,3S,5S)/(1S,3S,5R)) (840 mg, 2.94 mmol) were slowly added at 0°C under Argon to a suspension of NaH (60 % in mineral oil, 141 mg, 3.53 mmol) in THF (9 mL). The reaction mixture was stirred at 0°C for 30 min and iodomethane (0.28 mL, 4.42 mmol) was added slowly at 0°C. The reaction mixture was further stirred at RT overnight. Saturated $NaHCO_3$ and CH_2Cl_2 were added, the layers were separated and the aqueous one back-extracted twice with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude material was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 2:8) to give the title compound as an unseparable mixture of diastereosisomers. TLC, R_f (c-hexane/EtOAc 1:1) = 0.70; MS (UPLC/MS): 300.3 [M+H]+, 599.5 [2M+H]+; t_R (HPLC conditions a): 3.45 min. The absolute stereochemistry of the diastereoisomers was tentatively assigned by NMR and based on the test results for the final compounds **Example 214** and **Example 184** in the biological assay.

(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-5-methyl-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester



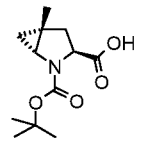
Lithium triethylborohydride (1N in THF, 2.06 mL, 2.06 mmol) was added at 0°C to a solution of (1R,3S,5S)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-5-methanesulfonyloxymethyl-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester (385 mg, 0.67 mmol) in THF (6.8 mL) under argon atmosphere. The solution was stirred 10 min at 0°C, then poured into cold water

and extracted with EtOAc (x2). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 75:25). TLC, R_f (c-hexane/EtOAc 1:1) = 0.55; MS (UPLC/MS): 383.3/385.3 [M+H]+, 427.5/429.4 [M+HCOO]-; t_R (HPLC conditions f): 2.24 min.

(1R,3S,5S)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-5-methanesulfonyloxymethyl-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester

To a solution of (1R,3S,5S)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester (290 mg, 0.72 mmol) and Et_3N (144 µL, 1.04 mmol) in CH_2Cl_2 (6.5 mL) at 0°C under nitrogen atmosphere was added methanesulfonyl chloride (81 µL, 1.04 mmol) and the mixture was stirred at RT for 1 h. Et_3N (48 µL, 0.35 mmol) and methanesulfonyl chloride (27 µL, 0.35 mmol) were again added and the mixture was further stirred for 0.5 h to complete the reaction. A saturated aqueous solution of $NaHCO_3$ was added, the layers were separated and the aqueous layer extracted with CH_2Cl_2 (x2), dried (Na_2SO_4), filtered and concentrated. The material thus obtained was used in the next step without further purification. TLC, R_f (EtOAc) = 0.65; MS (UPLC/MS): 477.3/479.3 [M+H]+, 521.3/523.3 [M+HCOO]-

(1R,3S,5R)-5-Methyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester



To a solution of (1R,3S,5R)-5-methyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester 3-ethyl ester (185 mg, 0.69 mmol) in MeOH (1.1 mL), THF (1.1 mL) and H_2O (1.1 mL) was added KOH (77 mg, 1.37 mmol). The solution was stirred 2.5 h at RT, HCl (0.1 N) was added (until pH 1), CH_2Cl_2 was added and the layers were separated (x2). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The material (yellow oil) thus obtained was used without further purification in the next step. 1H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.46 (m, 1H), 3.86 (m, 1H), 3.06 (m, 1H), 2.40 (dd, 1H), 1.86 (m, 1H), 1.37 (m, 9H), 1.18 (s, 3H) 0.65 (m, 2H).

(1R,3S,5R)-5-Methyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester 3-ethyl ester

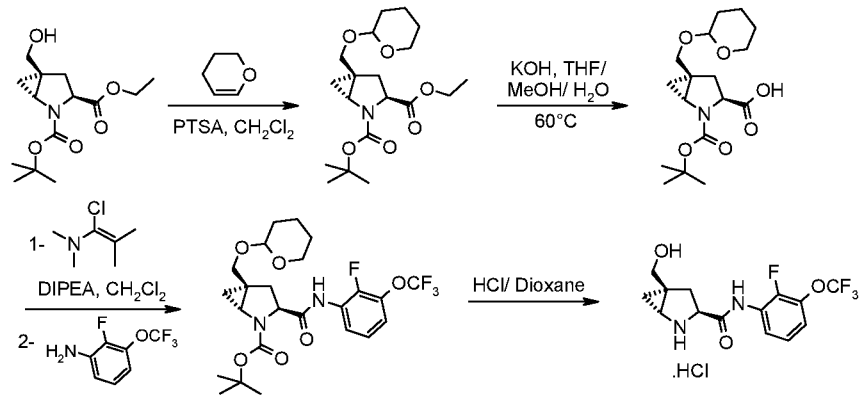
To a solution of (1R,3S,5S)-5-methanesulfonyloxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester (100 mg, 0.24 mmol) in DME (2.6 mL) were successively added NaI (355 mg, 2.37 mmol) and zinc powder (155 mg, 2.37 mmol). The reaction mixture was refluxed 30 min under argon atmosphere, cooled to RT and quenched by addition of a

saturated aqueous solution of NH_4Cl (1.6 mL). CH_2Cl_2 (1.6 mL) and few Na_2S crytals were added and the biphasic mixture was stirred at RT for 1 h. The layers were separated, the organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (eluent: c-hexane to c-hexane/ EtOAc). TLC, R_f (c-hexane/ EtOAc 2:1) = 0.60; MS (UPLC/MS): 270.3 [M+H]+, 214.2 [MH-tBu]+, 170.2 [MH-Boc]+; 1H NMR (400 MHz, DMSO-d_6) δ (ppm): 4.11 (m, 2H), 3.95 (m, 1H), 3.10 (m, 1H), 2.42 (m, 1H), 1.84 (m, 1H), 1.38 (m, 9H), 1.20 (t, 3H), 1.18 (s, 3H) 0.69 (dd, 1H), 0.64 (m, 1H).

(1R,3S,5S)-5-methanesulfonyloxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester

To a solution of (1R,3S,5S)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester 3-ethyl ester (500 mg, 1.75 mmol) and Et_3N (366 µL, 2.63 mmol) in CH_2Cl_2 (16 mL) was added methanesulfonyl chloride (205 µL, 2.63 mmol) at 0°C under nitrogen atmosphere. The reaction mixture was slowly allowed to reach RT and stirred 1 h. The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$, the layers were separated and the aqueous layer extracted twice with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The material thus obtained was used without further purification in the next step. Yellow oil, TLC, R_f (EtOAc) = 0.80.

Scheme B29: Preparation of (1R,3S,5S)-5-Hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (2-fluoro-3-trifluoromethoxy-phenyl)-amide hydrochloride



A. (1R,3S,5S)-5-(Tetrahydro-pyran-2-yloxymethyl)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester 3-ethyl ester

A mixture of (1R,3S,5S)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylicacid 2-tert-butyl ester 3-ethyl ester (500 mg, 1.75 mmol), 3,4-dihydro-2H-pyran (176 µL, 1.93 mmol) and $TsOH.H_2O$ (33 mg, 0.17 mmol) in CH_2Cl_2 (6 mL) was stirred 3 h at RT. Then poured into a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (x2). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by

flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 1:1). Colorless oil. TLC, R_f (EtOAc) = 0.85; MS (UPLC/MS): 370.4 [M+H]+, 387.4 [M+H_2O]+; t_R (HPLC conditions f): 2.28 min.

B. (1R,3S,5S)-5-(Tetrahydro-pyran-2-yloxymethyl)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester

To a solution of (1R,3S,5S)-5-(tetrahydro-pyran-2-yloxymethyl)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester 3-ethyl ester (510 mg, 1.38 mmol) in MeOH (2.3 mL), THF (2.3 mL) and water (2.3 mL) was added KOH (155 mg, 2.76 mmol). The reaction was stirred at 60°C for 45 min. Then allowed to cool to RT and diluted with EtOAc. The layers were separated, the aqueous layer was acidified by addition of HCl (0.1 N, until pH 1) and extracted with EtOAc (x2). The organics were dried (Na_2SO_4), filtered and concentrated. MS (UPLC/MS): 359.4 [M+NH_4]+, 340.4 [M-H]-, 386.4 [M+HCOO]-, 681.5 [2M-H]-; t_R (HPLC conditions f): 1.84 min.

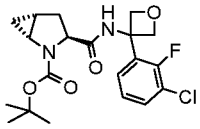
C. (1R,3S,5S)-3-(2-Fluoro-3-trifluoromethoxy-phenylcarbamoyl)-5-(tetrahydro-pyran-2-yloxymethyl)-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester

To a solution of (1R,3S,5S)-5-(tetrahydro-pyran-2-yloxymethyl)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester (100 mg, 0.29 mmol) in dry CH_2Cl_2 (1 mL) under argon at 0°C was added 1-chloro-N,N,2-trimethylpropenylamine (58 µL, 0.44 mmol) and the reaction mixture was stirred at 0°C for 1.5 h. 2-Fluoro-3-(trifluoromethoxy)aniline (86 mg, 0.44 mmol) was added, followed by DIPEA (100 µL, 0.59 mmol) and the mixture was stirred at RT overnight. Then poured into water and extracted with CH_2Cl_2 (x2), the organics were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (eluent: c-hexane to c-hexane/EtOAc 85:15). TLC, R_f (c-hexane/EtOAc 2:1) = 0.45; MS (UPLC/MS): 519.3 [M+H]+, 536.3 [M+NH_4]+, 517.4 [M-H]-, 563.3 [M-HCOO]-; t_R (HPLC conditions f): 2.51 min.

D. (1R,3S,5S)-5-Hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (2-fluoro-3-trifluoromethoxy-phenyl)-amide hydrochloride

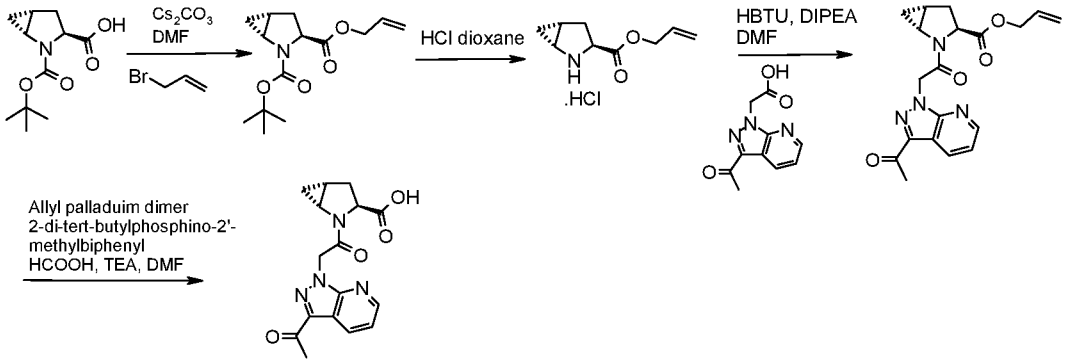
To a solution of (1R,3S,5S)-3-(2-fluoro-3-trifluoromethoxy-phenylcarbamoyl)-5-(tetrahydro-pyran-2-yloxymethyl)-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester (105 mg, 0.19 mmol) in dioxane (0.5 mL) was added HCl (4 N in dioxane, 481 µL, 1.92 mmol). The mixture was stirred at RT for 4 h, solvent was removed under reduced pressure and the material thus obtained was used without further purification in the next step. MS (UPLC/MS): 335.2 [M+H]+, 333.2 [M-H]-, 379.6 [M+HCOO]-.

(1R,3S,5R)-3-[3-(3-Chloro-2-fluoro-phenyl)-oxetan-3-ylcarbamoyl]-2-aza-bicyclo[3.1.0] hexane-2-carboxylic acid tert-butyl ester



To a solution of (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester (220 mg, 0.968 mmol), propylphosphonic anhydride (50% in EtOAc, 0.856 ml, 1.45 mmol) and 3-(3-chloro-2-fluoro-phenyl)-oxetan-3-ylamine (prepared as described in Part C, 358 mg, 1.06 mmol) in CH_2Cl_2 (10 mL) was added DIPEA (0.507 ml, 2.90 mmol) under nitrogen atmosphere. The reaction mixture was stirred 2 h at RT and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 3:2). MS (LC/MS): 411.2/413.2 [M+H]+, 455.2/457.2 [M+HCOO]-; t_R (HPLC conditions f): 2.02 min.

Scheme B30: Preparation of (1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-b]pyridin-1-yl)-acetyl]-2-azabicyclo[3.1.0]- hexane-3-carboxylic acid



A. (1R,3S,5R)-2-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-allyl ester 2-tert-butyl ester

To a solution of (1R,3S,5R)-2-azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester (1.5 g, 3.6 mmol) and Cs_2CO_3 (2.26 g, 6.9 mmol) in DMF (20 mL) allyl bromide (0.6 mL, 3.9 mmol) was added. The reaction mixture was stirred for 40 h at RT. DMF was evaporated. The residue was dissolved in EtOAc and washed with HCl 1N, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 4:6). MS (LCMS):167.9 [MH-Boc]+, 290.0 [M+Na]+.

B. (1R,3S,5R)-2-Azabicyclo[3.1.0]hexane-3-carboxylic acid allyl ester hydrochloride

To (1R,3S,5R)-2-azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-allyl ester 2-tert-butyl ester (1.69 g, 6.32 mmol) was added HCl 4N in dioxane (15.8 mL, 63.2 mmol). The reaction mixture was stirred for 6 h at RT and subsequently lyophilized. MS:168.0 [M+H]+.

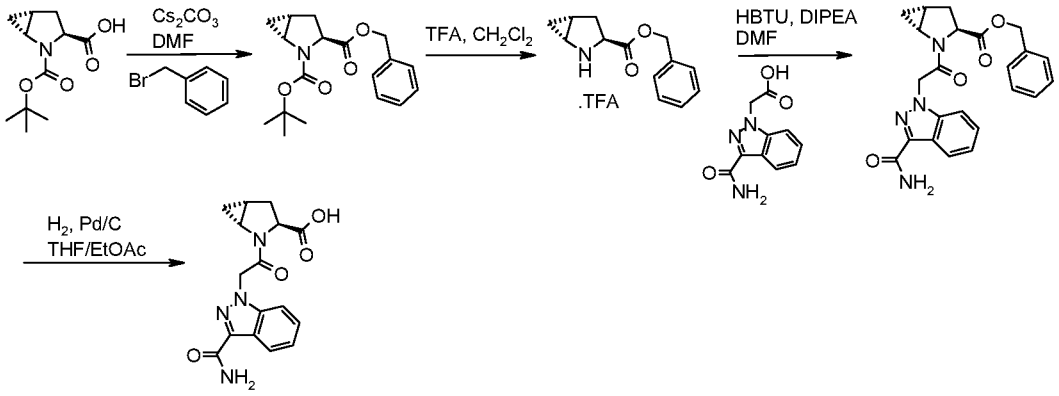
C. (1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0] hexane-3-carboxylic acid allyl ester

To a solution of (1R,3S,5R)-2-azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-allyl ester hydrochloride (1.03 g, 6.43 mmol), (3-acetyl-pyrazolo[3,4-b]pyridin-1-yl)-acetic acid (prepared as described in Part A, 1.3 g, 5.93 mmol) and HBTU (2.70 g, 7.12 mmol) in DMF (19.7 mL) was added DIPEA (3.11 mL, 17.8 mmol). The reaction mixture was stirred for 16 h at RT. DMF was evaporated. The residue was poured into NH_4Cl (saturated aqueous solution) and extracted with EtOAc (3 x 50 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 0:10). R_f, TLC (EtOAc) = 0.6; MS (LCMS): 369.0 [M+H]+, 391.0 [MH+Na]+; t_R (HPLC conditions k): 2.78 min.

D. (1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0] hexane-3-carboxylic acid

Allyl palladium chloride dimer (0.084 g, 0.231 mmol) and 2-di-tert-butylphosphino-2'-methylbiphenyl (0.288 g, 0.923 mmol) were dissolved in DMF (7.69 mL) under argon atmosphere. The reaction mixture was stirred at RT for 10 min. After cooling the reaction mixture to 10°C, formic acid (0.513 mL, 13.38 mmol) was added followed by TEA (1.865 mL, 13.38 mmol) and a solution of (1R,3S,5R)-2-[2-(3-acetyl-pyrazolo[3,4-b]pyridin-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carboxylic acid allyl ester (1 g, 2.3 mmol) in DMF (15.38 mL). The reaction mixture was stirred at 10°C during 1 h. DMF was evaporated. The residue was poured into NH_4Cl (saturated aqueous solution) and extracted with EtOAc (3 x 50 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in MeOH and filtered over a PL-Thiol cartridge. The filtrate was concentrated. The crude residue was purified by preparative HPLC (Waters Sunfire C18-OBD, 5 µm, 30x100mm, flow: 40 mL/min, eluent: 5% to 80% CH_3CN in H_2O in 20 min, CH_3CN and H_2O containing 0.1% TFA) and the pure fractions were combined and lyophilized. White solid. MS (LCMS): 328.9 [M+H]+, 351.0 [MH+Na]; t_R (HPLC conditions l): 1.84 min. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.66 (dd, *J*=4.52, 1.59 Hz, 1 H), 8.58 (m, *J*=6.36 Hz, 1 H), 7.35 - 7.50 (m, 1 H), 8.54 - 8.61 (m, 1 H), 5.88 (d, *J*=16.87 Hz, 1 H), 5.55 (d, *J*=17.12 Hz, 1 H), 4.14 - 4.24 (m, 1 H), 3.75 - 3.83 (m, 1 H), 2.64 (s, 3 H), 2.26 - 2.36 (m, 1 H), 2.10 - 2.23 (m, 1 H), 1.80 - 1.95 (m, 1 H), 0.95 - 1.07 (m, 1 H), 0.67 - 0.81 (m, 1 H).

Scheme B31: Preparation of (1R,3S,5R)-2-[2-(3-Carbamoyl-indazol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid



A. (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-benzyl ester 2-tert-butyl ester

To a solution of (1R,3S,5R)-2-azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester (2.5 g, 11.0 mmol) and Cs_2CO_3 (3.94 g, 12.1 mmol) in DMF (50 mL) at 0°C benzylbromide (2.26 g, 13.2 mmol) was added dropwise. The reaction mixture was stirred overnight at RT. DMF was evaporated. The residue was dissolved in EtOAc and washed with a saturated aqueous solution of $NaHCO_3$, the layers were separated and the aqueous phase was extracted with EtOAc (x2). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 100:0 to 0:100) to give the desired material as a colorless oil. MS (LCMS): 318.2 [M+H]+; t_R (HPLC conditions f): 2.23 min.

B. (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester trifluoroacetate

To (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-benzyl ester 2-tert-butyl ester (3.27 g, 9.79 mmol) in CH_2Cl_2 (50 mL) was added was added TFA (7.54 mL, 98 mmol). The reaction mixture was stirred overnight at RT and subsequently concentrated under reduced pressure to give the desired material as a yellow oil. MS (UPLC): 218.1 [M+H]+; t_R (HPLC conditions f): 1.24 min.

C. (1R,3S,5R)-2-[2-(3-Carbamoyl-indazol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester

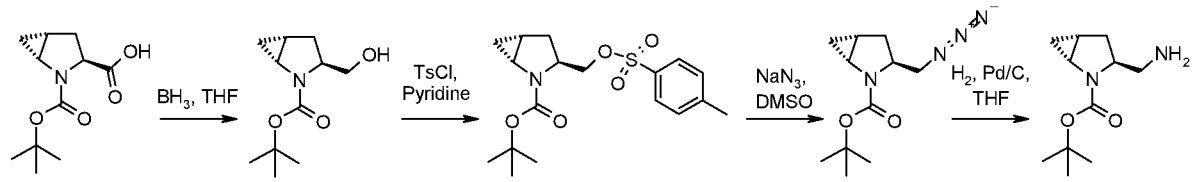
To a solution of (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester trifluoroacetate (3.9 g, 9.77 mmol), (3-carbamoyl-indazol-1-yl)-acetic acid (prepared as

described in Scheme A25, 2.26 g, 9.77 mmol), HBTU (5.56 g, 14.66 mmol) in CH_2Cl_2 (60 mL) was added DIPEA (5.12 mL, 29.3 mmol). The reaction mixture was stirred for 48 h at RT. The reaction mixture was poured into water and extracted with CH_2Cl_2 (x3). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 10:0 to 0:10). R_f, TLC (EtOAc) = 0.85; MS (UPLC): 436.3 $[M+NH_4]+$, 463.2 [M+HCOO]-; t_R (HPLC conditions f): 1.82 min.

D. (1R,3S,5R)-2-[2-(3-Carbamoyl-indazol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid

(1R,3S,5R)-2-[2-(3-carbamoyl-indazol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester (3.9 g, 8.85 mmol) was dissolved in THF (120 mL) and EtOAc (120 mL). Air was removed from the flask and replaced with nitrogen three times. Pd/C 10 % (390 mg) was added to the solution which was again degassed, placed under a hydrogen atmosphere, and stirred at RT for 4 h. The catalyst was removed through a pad of Celite and washed with EtOAc. Solvents were removed under reduced pressure and the foam thus obtained was used without further purification in the next step. MS (LCMS): 346.2 $[M+NH_4]+$, 327.1 [M-H]-; t_R (HPLC conditions f): 1.12 min.

Scheme B32: (1R,3S,5R)-3-aminomethyl-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester



A. (1R,3S,5R)-3-Hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester

To a solution of (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester (0.5 g, 2.2 mmol) in dry THF (10 mL), cooled to 0°C, was added under an argon atmosphere dropwise a 1M solution of boran-tetrahydrofuran-complex (4.40 mL, 4.40 mmol). The reaction mixture was kept at 0°C for an additional 2 h and then allowed to warm up to RT overnight. The reaction was quenched by careful addition of water and subsequently EtOAc. The organic layer was subsequently washed with saturated aqueous solutions of NaCl, $NaHCO_3$, water and NaCl. The organic phase was dried (phase separator) and concentrated to give the title compound as a colorless oil. MS (LC-MS): 214.0 $[M+H]+$; t_R (HPLC conditions k): 2.99 min. The material thus obtained was used in the next step without further purification.

B. (1R,3S,5R)-3-(Toluene-4-sulfonyloxymethyl)-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester

To an ice-cooled solution of (1R,3S,5R)-3-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester (0.480 g, 2.15 mmol) in pyridine (5 mL) was added 4-toluenesulfonyl chloride (0.490 g, 2.58 mmol). The reaction mixture was stirred at RT for 6 h and then diluted with Et_2O. The organic phase was washed with 1N HCl (3x), aqueous $NaHCO_3$ (3x) and NaCl, then dried (phase separator) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent gradient: c-hexane to c-hexane/EtOAc 4:1) to afford the title compound as a colorless wax. TLC, R_f (c-hexane/EtOAc 4:1) = 0.2. MS (LC-MS): 390.0 [M+Na]+, 757.0 [2M+H]+. t_R (HPLC conditions k): 4.07 min.

C. (1R,3S,5R)-3-Azidomethyl-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester

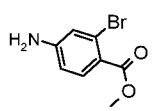
A mixture of (1R,3S,5R)-3-(toluene-4-sulfonyloxymethyl)-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester (0.400 g, 1.08 mmol) and NaN_3 (0.420 g, 6.47 mmol) in dry DMSO (8 mL) was stirred at 65°C overnight. After cooling, the mixture was diluted with Et_2O and washed with water (x3) and brine (x2). The organics were dried (phase separator) and concentrated in vaccuo to give the title compound as a colorless oil. MS (LC-MS): 239.0 [M+H]+; t_R (HPLC conditions k): 3.78 min. The material thus obtained was used in the next step without further purification.

D. (1R,3S,5R)-3-Aminomethyl-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester

(1R,3S,5R)-3-azidomethyl-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester (195 mg, 0.82 mmol) was suspended in THF (10 mL). Air was removed from the flask and replaced with nitrogen three times. Pd/C 10 % (20 mg) was added to the solution which was again degassed, placed under a hydrogen atmosphere, and stirred at RT overnight. The catalyst was removed through a 0.45 microns filter, and the filtrate was concentrated in vacuo to give the title compound. MS (LC-MS): 213.0 [M+H]+; t_R (HPLC conditions k): 2.51 min. The material thus obtained was used in the next step without further purification.

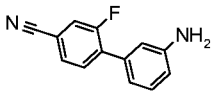
Part C: Synthesis of aniline and benzylamine intermediates:

4-Amino-2-bromo-benzoic acid methyl ester



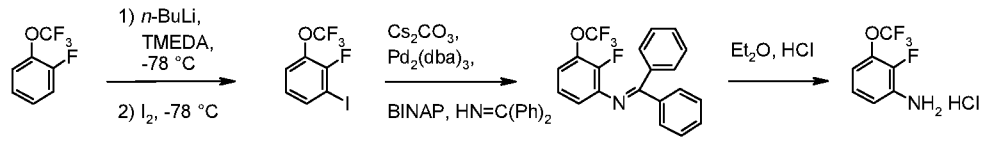
To a suspension of 2-bromo-4-nitro-benzoic acid methyl ester [100959-22-6] (350 mg, 1.35 mmol) in MeOH (60 mL) were subsequently added tin powder (1.6 g, 13.5 mmol) and 3N aqueous HCl (27.8 mL, 83 mmol). The mixture was stirred overnight at RT. The liquid phase was decanted from the excess tin and neutralized by adding a saturated aqueous $NaHCO_3$ solution. An equal amount of water by volume was added and the water phase was extracted with EtOAc (3x). The combined organics were dried (Phase Separator) and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc/c-hexane 1:4) to give the title compound as yellow solid. MS (LC/MS): 230 [M+H]+; t_R (HPLC conditions b): 2.89 min.

3'-Amino-2-fluoro-biphenyl-4-carbonitrile



3-Aminophenylboronic acid (200 mg, 1.29 mmol), 3-fluoro-4-iodobenzonitrile (319 mg, 1.29 mmol), TBACl (35.9 mg, 0.129 mmol) and $Pd(PPh_3)_4$ (74.6 mg, 0.064 mmol) were suspended in a mixture of toluene (4mL) and K_2CO_3 1M in water (4mL). The biphasic mixture was vigorously stirred under argon at 90°C for 20 h. The organic layer was separated and the aqueous phase was extracted with toluene (x2). The organic layers were combined, washed with water, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by column chromatography (c-hexane/EtOAc 3:1) to give the desired material. MS (LC/MS) [M+H]+ = 213; t_R (HPLC, Waters Atlantis, 2.1x30mm, flow 0.6mL/min, CH_3CN/H_2O 5 to 95% in 2.5 min, 95% CH_3CN 2 min, 95 to 5% CH_3CN, H_2O and CH_3CN both containing 0.1% HCOOH): 2.84 min.

2-Fluoro-3-(trifluoromethoxy)aniline hydrochloride



A. 2-Fluoro-1-iodo-3-(trifluoromethoxy)benzene

To a solution of 1-fluoro-2-(trifluoromethoxy)benzene [2106-18-5] (20.0 g, 111 mmol) in dry THF (200 mL), cooled to -78°C, was added dropwise *n*-BuLi (2.5 M solution in *n*-hexane; 65 mL, 160 mmol) and subsequently TMEDA (60 mL). The reaction mixture was stirred for additional 60 min at -78°C, followed by addition of a solution of iodine (30.2 g, 120 mmol) in dry THF (50 mL). The resulting mixture was stirred for 1 h and then quenched by addition of a saturated aqueous NH_4Cl solution (20 mL). The organic layer was washed with 1N HCl, water and brine, and dried over $MgSO_4$. Volatiles were removed in vacuo to afford the title compound as yellow oil. The product was used in the next reaction step without further purification. MS (LC/MS): 306.0 [M+H]+.

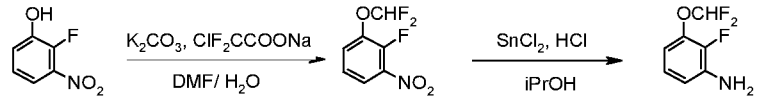
B. Benzhydrylidene-(2-fluoro-3-trifluoromethoxy-phenyl)-amine

To a solution of 2-fluoro-1-iodo-3-(trifluoromethoxy)benzene (25 g, 81 mmol) in dry toluene (200 mL) was added Cs_2CO_3 (38.7 g, 120 mmol), $Pd_2(dba)_3$ (7.42 g, 8.1 mmol), BINAP (10.8 g, 16.2 mmol) and benzhydrylideneamine (19.6 g, 108 mmol). The reaction mixture was refluxed for 8 h with stirring and then cooled to RT. The organic layer was washed with water and brine and then dried over $MgSO_4$. After removal of solvent in vacuo, the residue was purified by column chromatography on silica gel (solvent gradient from 100% *n*-hexane to *n*-hexane/EtOAc 20:1) to afford the title compound as a pale yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) : δ 7.72 (s, 1H, ArH,), 7.70 (s, 1H, ArH), 7.45-7.42 (m, 1H, ArH,), 7.37-7.33 (m, 2H, ArH), 7.25-7.17 (m, 3H, ArH), 7.06 (s, 1H, ArH), 7.05 (s, 1H, ArH,), 6.84 (t, 1H, J = 8 Hz, ArH), 6.78 (t, 1H, J = 8 Hz, ArH), 6.67-6.64 (m, 1H, ArH).

C. 2-Fluoro-3-(trifluoromethoxy)aniline hydrochloride

To a mixture of benzhydrylidene-(2-fluoro-3-trifluoromethoxy-phenyl)-amine (7.5 g, 20 mmol) in Et_2O (40 mL) was added 3N aqueous HCl (10 mL). The reaction mixture was stirred for 4 h at RT, followed by addition of water. The aqueous layer was extracted with Et_2O (2x10 mL), the combined organic layers were washed with brine and then dried over $MgSO_4$. After removal of solvent in vacuo, the residue was purified by preparative HPLC (stationary phase: Gimini 300x50 mm, particle size 10 μm; solvent: A H_2O + B CH_3CN, pressure: 60-70 bar). The product was extracted with Et_2O as the free base from the combined fractions. HCl gas was bubbled through the organic phase, and the solvent was removed under vacuum to afford the title compound. Recrystallisation from EtOH/diisopropylether gave a white solid. ^1H NMR (D_2O, 400 MHz) : δ 7.40-7.35 (m, 1H, ArH), 7.32-7.27 (m, 1H, ArH), 7.27-7.19 (m, 1H, ArH). HRMS: 196.03801 [M]+ (calcd. 196.03800 for $C_7H_5F_4NO$); Anal. Calcd. for $C_7H_5F_4NO$: C, 36.31; H, 2.61; N, 6.05; Cl, 15.31; F, 32.82; Found: C, 35.78; H, 2.63; N, 6.14; Cl, 15.69; F, 31.99.

3-Difluoromethoxy-2-fluoro-phenylamine



A. 1-Difluoromethoxy-2-fluoro-3-nitro-benzene

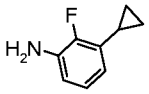
To a mixture of sodium 2-chloro-2,2-difluoroacetate (7.14 g, 46.8 mmol) and potassium carbonate (3.50 g, 25.3 mmol) in DMF (10 mL) and water (2.5 mL) at 110°C was added a solution of 2-fluoro-3-nitrophenol (2 g, 12.65 mmol) in DMF (10 mL) and the mixture was stirred at 110°C for 6 h. After cooling down, the mixture was quenched with water and extracted with EtOAc. The organic layer was then washed with water, brine and dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash column

chromatography on silica gel (c-hexane to c-hexane/EtOAc 1:1). 1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.79 (td, 1H), 7.45 (t, 1H), 5.15 (m, 1H), 7.44 (m, 1H). t_R (HPLC conditions f): 2.09 min.

B. 3-Difluoromethoxy-2-fluoro-phenylamine

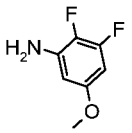
To a mixture of 1-difluoromethoxy-2-fluoro-3-nitro-benzene (2.16 g, 10.43 mmol) and tin(II) chloride (6.92 g, 36.5 mmol) in 2-propanol (100 ml) was added carefully HCl (37%, 10.28 ml, 125 mmol) and the mixture was stirred for 30 min at 110°C. The reaction mixture was cooled to RT, diluted with water and the pH adjusted to 10 by addition of 2N NaOH. The mixture was extracted with EtOAc and the organic layer was dried over Na_2SO_4, filtered and concentrated to afford the titled compound. 1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.06 (t, 1H), 6.95 (m, 1H), 6.87 (m, 1H), 6.55 (td, 1H), 5.04 (bs, 2H). t_R (HPLC conditions f): 1.93 min.

3-Cyclopropyl-2-fluoro-phenylamine



To a solution of 3-bromo-2-fluoroaniline (200 mg, 1.05 mmol), cyclopropylboronic acid (118 mg, 1.37 mmol), potassium phosphate (782 mg, 3.68 mmol), and tricyclohexylphosphine (29.5 mg, 0.105 mmol) in toluene (2.4 mL) and water (120 µL) was added $Pd(OAc)_2$ (11.8 mg, 0.05 mmol). The reaction mixture was degassed by repeating alternating application of vacuum and positive nitrogen pressure (3x), and then heated at 100°C under nitrogen overnight. The mixture was cooled to RT, diluted with water, and extracted twice with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 93-7). TLC, R_f (c-hexane/ EtOAc 2:1) = 0.7; MS (UPLC/MS): 152.0 [M+H]+.

2,3-Difluoro-5-methoxy-benzylamine



A. 2,3-Difluoro-5-methoxy-benzoic acid methyl ester

To a solution of 2,3-difluoro-5-hydroxy-benzoic acid [749230-51-1] (1.00 g, 5.74 mmol; Melford Laboratories Ltd) in DMF (20 mL) was added K_2CO_3 (1.99 g, 14.4 mmol) and MeI (0.79 mL, 12.6 mmol), followed by stirring at RT overnight. The reaction mixture was diluted with EtOAc, the organics were washed with a saturated aqueous NH_4Cl solution (50 mL) and a saturated aqueous $NaHCO_3$ solution, dried (Phase separator) and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 3:1)

to afford the title compound as a colorless oil. TLC, R_f (c-hexane/EtOAc 3:1) = 0.37; MS (LC/MS): 203.0 [M+H]+; t_R (HPLC conditions c): 4.72 min.

B. (2,3-Difluoro-5-methoxy-phenyl)-methanol

To a solution of 2,3-difluoro-5-methoxy-benzoic acid methyl ester (925 mg, 4.58 mmol) in THF (25 mL), cooled to 0°C, was added a solution of $LiBH_4$ (199 mg, 9.15 mmol) in THF (5 mL). The reaction mixture was stirred at RT for overnight. An additional aliquot of $LiBH_4$ (4 equiv) was added and stirring was continued at RT for 6 h, and subsequently at 60°C overnight. The mixture was diluted with EtOAc, the organics were washed with 1N aqueous NaOH solution (50 mL), dried (Phase separator) and evaporated in vacuo to afford the title compound as a white solid. TLC R_f (c-hexane/EtOAc 1:1) = 0.57; MS (LC/MS): 198.0 [M+Na]+; t_R (HPLC conditions c): 3.74 min.

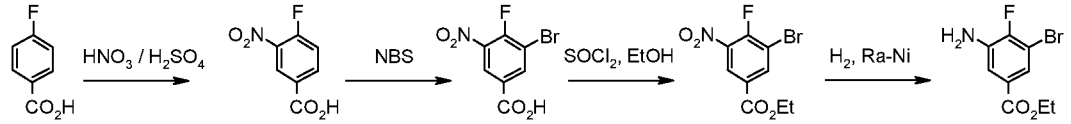
C. 1-Azidomethyl-2,3-difluoro-5-methoxy-benzene

To a solution of (2,3-difluoro-5-methoxy-phenyl)-methanol (715 mg, 4.11 mmol) in toluene (10 mL) was added DPPA (1.04 mL, 4.93 mmol) and DBU (0.805 mL, 5.34 mmol), followed by stirring at RT for 1 h. The reaction mixture was diluted with EtOAc, the organics were washed with diluted brine (20 mL), dried (Phase separator) and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 9:1) to afford the title compound as a colorless oil. TLC R_f (c-hexane/EtOAc 3:1) = 0.55; MS (LC/MS): 208.0 [M+NH_4]+; t_R (HPLC conditions c): 5.46 min.

D. 2,3-Difluoro-5-methoxy-benzylamine

To a solution of 1-azidomethyl-2,3-difluoro-5-methoxy-benzene (710 mg, 3.57 mmol) in EtOH (20 mL) was added Pd/C 10% (70 mg) and the reaction mixture was stirred at RT overnight under an H_2 atmosphere. The reaction mixture was filtered through Celite, followed by washing with EtOH and CH_2Cl_2. The combined filtrates were evaporated in vacuo and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2/acetone 9:1, then CH_2Cl_2/MeOH 9:1) to afford the title compound as a yellowish oil. TLC R_f (CH_2Cl_2/MeOH 9:1) = 0.32; MS (LC/MS): 174.0 [M+H]+; t_R (HPLC conditions c): 2.30 min.

3-Amino-5-bromo-4-fluoro-benzoic acid ethyl ester



A. 4-Fluoro-3-nitro-benzoic acid

Conc. HNO_3 (79 mL) was dropwise added to a solution of 4-fluoro-benzoic acid (70 g, 0.5 mol) in conc. H_2SO_4 (500 mL) at 0°C. The mixture was stirred for 4 h at RT and then poured into ice-water (3.0 L). The precipitate was filtered off, washed twice with water (0.5 L) and dried to give the title compound as a white solid. 1H-NMR (300 MHz, $CDCl_3$): δ (ppm) 11.0 (s, br, 1H), 8.86 (m, 1H), 8.42 (m, 1H), 7.47 (m, 1H).

B. 3-Bromo-4-fluoro-5-nitro-benzoic acid

NBS (47.9 g, 0.268 mol) was added portion-wise to a solution of 4-fluoro-3-nitro-benzoic acid (41.5 g, 0.224 mol) in conc. H_2SO_4 (0.35 L). The reaction mixture was stirred for 5 h at 65°C and then poured into ice-water (1.5 L). The precipitate was filtered off, washed twice with water (300 mL) and dried to give the title compound as a white solid. 1H-NMR (300 MHz, $CDCl_3$): δ (ppm) 10.7 (s, br, 1H), 8.76 (m, 1H), 8.62 (m, 1H).

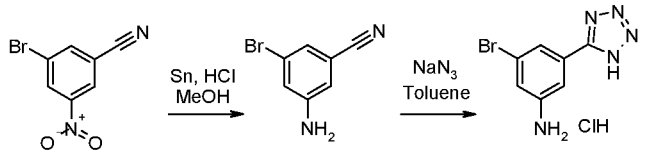
C. 3-Bromo-4-fluoro-5-nitro-benzoic acid ethyl ester

$SOCl_2$ (33.7 g, 0.283 mol) was added dropwise to a solution of 3-bromo-4-fluoro-5-nitro-benzoic acid (37.4 g, 0.142 mol) in EtOH (300 mL). The reaction mixture was refluxed overnight, cooled to RT and subsequently concentrated under reduced pressure. The residue was dissolved in EtOAc (300 mL), washed twice with water (50 mL), dried (Na_2SO_4) and concentrated to give the title compound as yellow solid. 1H-NMR (300 MHz, $CDCl_3$): δ (ppm) 8.65 (m, 1H), 8.53 (m, 1H), 4.46 (m, 2H), 1.45 (m, 3H).

D. 3-Amino-5-bromo-4-fluoro-benzoic acid ethyl ester

A mixture of 3-bromo-4-fluoro-5-nitro-benzoic acid ethyl ester (20 g, 2.2 mol) and 3 g of Raney-Ni in EtOH (250 mL) was hydrogenated at RT (1 atm) overnight. The reaction mixture was filtered, the filtrate was concentrated under reduced pressure and the residue was washed with petrol ether to afford the title compound as a white solid. (400 MHz, DMSO-d_6): δ (ppm) 7.38 (dd, 1H), 7.26 (dd, 1H), 5.81 (s, 2H), 4.26 (q, 2H), 1.29 (t, 3H).

3-Bromo-5-(1H-tetrazol-5-yl)-phenylamine dihydrochloride



A. 3-Amino-5-bromo-benzonitrile

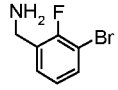
To a solution of 3-bromo-5-nitrobenzonitrile (1 g, 4.4 mmol) in MeOH (50 mL) was added tin (5.23 g, 44 mmol) and 3N HCl (44 mL, 132 mmol). The reaction mixture was stirred at RT for 2 h, the filtered off and washed with MeOH. The filtrate was concentrated in vacuo, and the remaining water phase was basified to pH=12 by addition of 4N NaOH. The aqueous layer was

extracted twice with EtOAc (100 mL), the combined organics were dried (Na_2SO_4) and evaporated in vacuo to afford the title compound as a yellowish solid. MS (LC/MS): 197.0 [M+H]+; t_R (HPLC conditions c): 4.30 min.

B. 3-Bromo-5-(1H-tetrazol-5-yl)-phenylamine hydrochloride

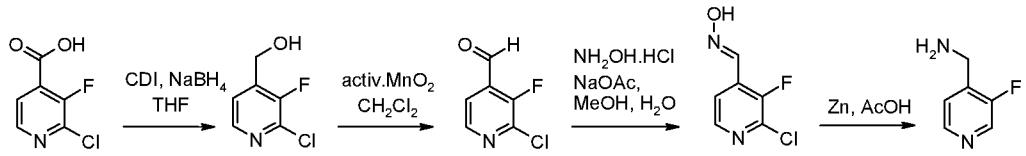
To a solution of 3-amino-5-bromo-benzonitrile (200 mg, 1.02 mmol) in toluene (2 mL) was added 6N HCl (0.220 mL, 1.32 mmol), triethylamine (0.184 mL, 1.32 mmol) and sodium azide (86.0 mg, 1.32 mmol). The reaction mixture was stirred at 100°C for 30 min in a microwave apparatus (Personal Chemistry, Biotage), and after cooling to RT was then diluted with CH_2Cl_2/MeOH (4:1) and washed with 10 mL of water. The organic phase was discarded, and the water phase was acidified to pH=1 by adding 12N HCl. The aqueous layer was freeze-dried overnight to afford the title compound as a yellowish solid. MS (LC/MS): 239.3 [M+H]+; t_R (HPLC conditions c): 3.23 min.

3-Bromo-2-fluoro-benzylamine, hydrochloride



A mixture of 3-bromo-2-fluoro-benzonitrile (1.0 g, 5.0 mmol) and Raney-Ni in EtOH (4% NH_3) (30 mL) was stirred under a hydrogen atmosphere (1 atm) at RT for 6.5 h. The reaction mixture was filtered through Celite, rinsed down with CH_2Cl_2, and the filtrate was concentrated under reduced pressure. The crude mixture was taken up in 1M aqueous HCl, the organic layer was separated, and the water phase was freeze-dried overnight to afford the title compound as a white solid. MS (LC/MS): 206.0 [M+H]+; t_R (HPLC conditions c): 2.21 min.

C-(3-Fluoro-pyridin-4-yl)-methylamine



A. (2-Chloro-3-fluoro-pyridin-4-yl)-methanol

Carbonyldiimidazole (1.80 g, 11.1 mmol) was added to a solution of 2-chloro-3-fluoro-isonicotinic acid (1.3 g, 7.41 mmol) in THF (21.2 mL). The reaction mixture was stirred at RT overnight and was then added to a cold (0°C) solution of $NaBH_4$ (1.40 g, 37 mmol) in water (52.9 mL). The mixture was stirred for 10 min at 0°C, and 1M HCl was then added carefully to quench the reaction (caution: H_2 evolving). Volatiles were removed via rotary evaporation and the residue was dissolved in saturated aqueous $NaHCO_3$. The mixture was extracted repeatedly with CH_2Cl_2, the combined organics were dried (phase separator) and concentrated in vaccuo. Purification by flash column chromatography on silica gel (eluent gradient: c-

hexane/EtOAc 4:1 to 2:1) afforded the title compound as a white solid. TLC, R_f (c-hexane/EtOAc 1:1) = 0.37; MS (LC/MS): 162.0 [M+H]+; t_R (HPLC conditions b): 1.60 min.

B. 2-Chloro-3-fluoro-pyridine-4-carbaldehyde

A mixture of (2-chloro-3-fluoro-pyridin-4-yl)-methanol (0.9 g, 5.76 mmol) and activated MnO_2 (5.76 g, 66.2 mmol) in CH_2Cl_2 was stirred at RT overnight. The solid was filtered off and washed with CH_2Cl_2, and the filtrate was concentrated under mildly reduced pressure to afford the title compound as a colorless liquid. MS (LC/MS): 191.0 [M+MeOH]+; t_R (HPLC conditions b): 2.02 min.

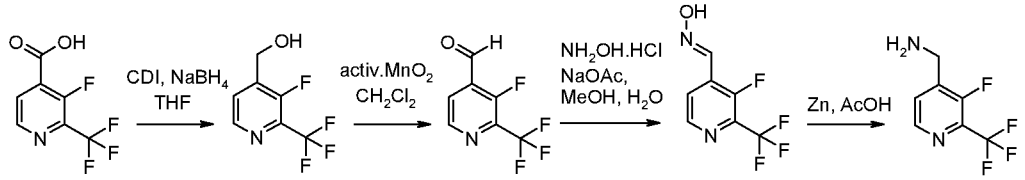
C. 2-Chloro-3-fluoro-pyridine-4-carbaldehyde oxime

To a solution of 2-chloro-3-fluoro-pyridine-4-carbaldehyde (1.20 g, 5.64 mmol) in MeOH (48 mL) and water (8 mL) were added hydroxylamine hydrochloride (0.59 g, 8.46 mmol) and ammonium acetate (1.30 g, 16.9 mmol), and stirring was continued at RT overnight. The reaction mixture was concentrated in vacuo, and the residue was suspended in CH_2Cl_2/MeOH 9:1. The precipitate was filtered off, washed with CH_2Cl_2 and dried to afford the title compound as a white solid. MS (LC/MS): 175.0 [M+H]+; t_R (HPLC conditions b): 2.78 min.

D. C-(3-Fluoro-pyridin-4-yl)-methylamine

Zinc dust (2.52 g, 38.6 mmol) was added at RT to a solution of 2-chloro-3-fluoro-pyridine-4-carbaldehyde oxime (1.34 g, 6.29 mmol) in acetic acid (30 mL). The reaction mixture was stirred at RT for 2 h, then concentrated in vacuo. The colored oily residue was partitioned between CH_2Cl_2 and 1N HCl. The layers were separated and the aqueous phase was extracted twice with CH_2Cl_2. The pH of the aqueous layer was then adjusted to pH=9 with 1N NaOH, and the resulting white suspension was extracted repeatedly with CH_2Cl_2. The combined organics were dried (phase separator) and concentrated in vacuo to afford the title compound as a yellow oil. MS (LC/MS): 127.0 [M+H]+; t_R (HPLC conditions c): 0.50 min.

C-(3-Fluoro-2-trifluoromethyl-pyridin-4-yl)-methylamine



A. (3-Fluoro-2-trifluoromethyl-pyridin-4-yl)-methanol

Carbonyldiimidazole (1.16 g, 7.17 mmol) was added to a solution of 3-fluoro-2-trifluoromethyl-isonicotinic acid (1.00 g, 4.78 mmol) in THF (13.7 mL). The reaction mixture was stirred at RT overnight and was then added to a cold (0°C) solution of $NaBH_4$ (0.905 g, 23.9 mmol) in water

(34.2 mL). The mixture was stirred for 10 min at 0°C, and 1M HCl was then added carefully (caution: H_2 evolving). Volatiles were removed under reduced pressure, and the residue was dissolved in saturated aqueous $NaHCO_3$. The mixture was extracted repeatedly with CH_2Cl_2, the combined organics were dried (phase separator) and concentrated in vacuo. Purification by flash column chromatography on silica gel (eluent gradient: c-hexane/EtOAc 1:1 to 0:1) afforded the title compound as a yellow oil. TLC, R_f (c-hexane/EtOAc 1:1) = 0.27; MS (LC/MS): 196.0 [M+H]+; t_R (HPLC conditions b): 2.62 min.

B. 3-Fluoro-2-trifluoromethyl-pyridine-4-carbaldehyde

A mixture of (3-fluoro-2-trifluoromethyl-pyridin-4-yl)-methanol (0.620 g, 3.18 mmol) and activated MnO_2 (3.20 g, 36.5 mmol) in CH_2Cl_2 was stirred at RT overnight. The solid was filtered off, washed with CH_2Cl_2, and the filtrate was concentrated under mildly reduced pressure to afford the title compound as a yellow liquid. MS (LC/MS): 212.0 [M+NH_4]+, 226.0 [M+MeOH]+. t_R (HPLC conditions c): 3.26 min.

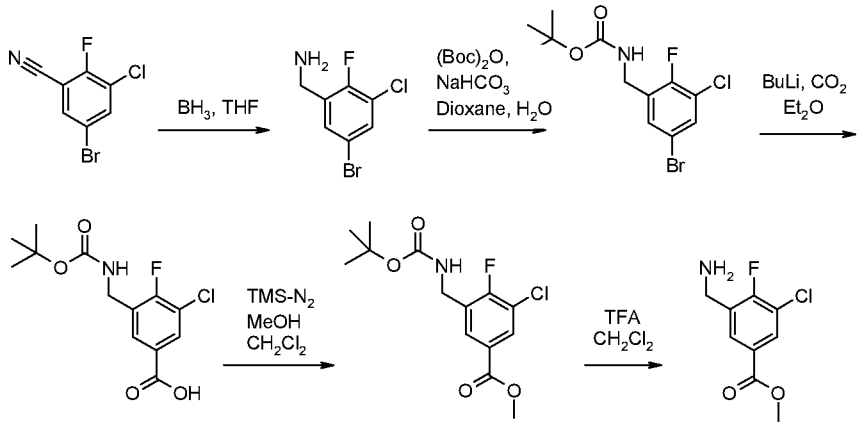
C. 3-Fluoro-2-trifluoromethyl-pyridine-4-carbaldehyde oxime

To a solution of 3-fluoro-2-trifluoromethyl-pyridine-4-carbaldehyde (0.495 g, 2.05 mmol) in MeOH (17.6 mL) and water (2.9 mL) were added hydroxylamine hydrochloride (0.214 g, 3.08 mmol) and ammonium acetate (0.474 g, 6.15 mmol), and the resulting mixture was stirred ar RT overnight. Volatile were removed in vacuo, and the residue was suspended in CH_2Cl_2/MeOH 9:1. The precipitate was filtered off, washed with CH_2Cl_2 and dried to afford the title compound as a white solid. MS (LC/MS): 209.0 [M+H]+; t_R (HPLC conditions c): 4.28 min.

D. C-(3-Fluoro-2-trifluoromethyl-pyridin-4-yl)-methylamine

Zinc dust (0.63 g, 9.62 mmol) was added at RT to a solution of 3-fluoro-2-trifluoromethyl-pyridine-4-carbaldehyde oxime (0.460 g, 1.57 mmol) in acetic acid (8 mL). The reaction mixture was stirred at RT for 3 h, then filtered through a 0.45 microns filter, and the filtrate was concentrated in vacuo. The colored oily residue was partitioned between CH_2Cl_2 and 1N HCl, the layers were separated and the aqueous phase was extracted twice with CH_2Cl_2. The pH of the aqueous layer was then adjusted to pH=9 by adding a saturated aqueous $NaHCO_3$ solution, and the resulting white suspension was extracted four times with CH_2Cl_2. The combined organics were dried (phase separator) and concentrated in vacuo to afford the title compound as a yellow oil. MS (LC/MS): 195.0 [M+H]+; t_R (HPLC conditions c): 2.47 min.

3-Aminomethyl-5-chloro-4-fluoro-benzoic acid methyl ester



A. 5-Bromo-3-chloro-2-fluoro-benzylamine

To a solution of 5-bromo-3-chloro-2-fluorobenzonitrile (13.2 g, 56.3 mmol) in THF (200 mL) was added under an argon atmosphere a 1M solution of boran-tetrahydrofuran-complex (70.4 mL, 70.4 mmol) dropwise over 30 min. The reaction mixture was then heated at 65°C for 1.5 h. After cooling to RT, a 2N HCl solution (70.4 mL, 141 mmol) was added dropwise over 30 min. The reaction mixture was then again heated at 65°C for 1 h and subsequently cooled to RT. Volatiles were evaporated and the residue was taken up in 1M aqueous HCl solution, followed by extraction with EtOAc (3x150 mL). The combined organics were washed with 1M aqueous HCl solution. The combined acid phases were basified to pH=12 by addition of 4M aqueous NaOH solution and then extracted with EtOAc (3x150 mL). The organics were dried (Na_2SO_4), filtered and evaporated in vacuo to afford the title compound as a yellowish oil. MS (LC/MS): 238.0 [M+H]+; t_R (HPLC conditions c): 3.25 min. The material thus obtained was used directly in the next step without further purification

B. (5-Bromo-3-chloro-2-fluoro-benzyl)-carbamic acid tert-butyl ester

To a solution of 5-bromo-3-chloro-2-fluoro-benzylamine (10.6 g, 44.3 mmol) in dioxane/H_2O 3:1 (280 mL) was added Boc_2O (10.3 mL, 44.3 mmol) and $NaHCO_3$ (11.2 g, 133 mmol). The reaction mixture was stirred at RT for 60 h. Volatiles were then removed under reduced pressure, the residue was taken up in water, and the aqueous layer was extracted twice with EtOAc (200 mL). The organics were dried (Na_2SO_4), filtered and evaporated in vacuo to afford the title compound as a white solid. MS (LC/MS): 284.0 [M+H]+; t_R (HPLC conditions c): 5.98 min. The material thus obtained was used directly in the next step without further purification.

C. 3-(tert-Butoxycarbonylamino-methyl)-5-chloro-4-fluoro-benzoic acid

To a solution of (5-bromo-3-chloro-2-fluoro-benzyl)-carbamic acid tert-butyl ester (8 g, 23.6 mmol) in Et_2O (300 mL), cooled to -78°C, was added under an argon atmosphere n-BuLi (1.6M in hexane; 37.5 mL, 60.1 mmol) dropwise over 30 min. The reaction mixture was stirred at -78°C for 15 min, then CO_2 gas was bubbled through the mixture over 1 min. After stirring for 15 min, a saturated solution of NH_4Cl (50 mL) added dropwise over 15 min, and the reaction

mixture was allowed to warm up to RT. The aqueous phase was basified to pH= 12 by addition of a 4M aqueous NaOH solution and then washed with EtOAc (100mL). The aqueous layer was acidified to pH=1 by addition of a 4M aqueous HCl solution and extracted with EtOAc (3x200 mL). The combined organics were dried (Na_2SO_4) and concentrated under vacuo to give the title compound as an off-white solid. MS (LC/MS): 302.0 [M-H]- ; t_R (HPLC conditions c): 4.79 min.

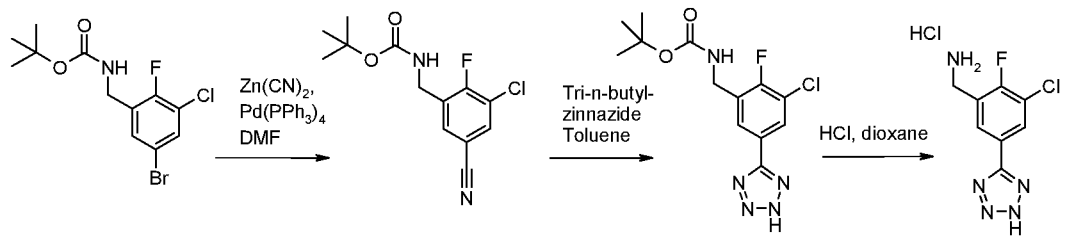
D. 3-(tert-Butoxycarbonylamino-methyl)-5-chloro-4-fluoro-benzoic acid methyl ester

To a solution of 3-(tert-butoxycarbonylamino-methyl)-5-chloro-4-fluoro-benzoic acid (4.00 g, 13.2 mmol) in CH_2Cl_2 (100 mL) were added MeOH (6.94 mL, 171 mmol) and subsequently trimethylsilyldiazomethane (8.56 mL, 17.1 mmol) in a dropwise manner over 15 min. Stirring was continued at RT for 4.5 h. Volatiles were then evaporated under reduced pressure to afford the title compound as a colorless oil, which was used directly in the next step without further purification. TLC R_f (c-hexane/EtOAc 6:1) = 0.40 ; t_R (HPLC conditions c): 5.56 min.

E. 3-Aminomethyl-5-chloro-4-fluoro-benzoic acid methyl ester

To a solution of 3-(tert-butoxycarbonylamino-methyl)-5-chloro-4-fluoro-benzoic acid methyl ester (4.25 g, 13.4 mmol) in CH_2Cl_2 (70 mL) was added TFA (10.3 mL, 134 mmol), and stirring was continued at RT overnight. Methanol was then added to the reaction mixture, and volatiles were removed in vacuo. The residue was taken up in methanol and concentrated again under reduced pressure to afford the title compound as a beige solid. MS (LC/MS): 218.0 [M+H]+; t_R (HPLC conditions c): 3.10 min. The material thus obtained was used in the next reaction step without further purification.

3-Chloro-2-fluoro-5-(2H-tetrazol-5-yl)-benzylamine



A. (3-Chloro-5-cyano-2-fluoro-benzyl)-carbamic acid tert-butyl ester

To a solution of (5-bromo-3-chloro-2-fluoro-benzyl)-carbamic acid tert-butyl ester (3 g, 8.86 mmol) in DMF (45 mL) was added zinc cyanide (1.04 g, 8.86 mmol) and $Pd(Ph_3P)_4$ (1.02 g, 0.886 mmol). The reaction mixture was stirred at 120°C for 15 min in a microwave apparatus (Personal Chemistry, Biotage). After cooling to RT, the mixture was filtered through Celite and rinsed down with EtOAc. The filtrate was washed with saturated aqueous NH_4Cl solution (4x75 mL), dried (Na_2SO_4) and evaporated in vacuo. Purification by flash column chromatography on

silica gel (eluent gradient: c-hexane/EtOAc 9:1 to 3:1) afforded the title compound as white solid. TLC R_f (c-hexane/EtOAc 3:1) = 0.35 ; t_R (HPLC conditions c): 5.28 min.

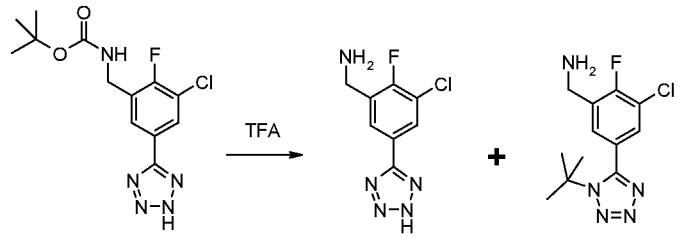
B. [3-Chloro-2-fluoro-5-(2H-tetrazol-5-yl)-benzyl]-carbamic acid tert-butyl ester

To a solution of (3-chloro-5-cyano-2-fluoro-benzyl)-carbamic acid tert-butyl ester (1.30 g, 4.57 mmol) in toluene (35 mL) was added tri-n-butyl-tinazide (6.26 mL, 22.8 mmol). The reaction mixture was stirred at 135°C for 90 min in a microwave (Personal Chemistry, Biotage). After cooling to RT, the mixture was diluted with EtOAc and washed with saturated aqueous NH_4Cl solution (3x100 mL). After washing the organic phase with 70 mL of a 1M aqueous NaOH solution and separation of the phases, three layers were obtained: the upper organic phase was discarded, the middle oily layer was isolated and diluted with EtOAc. The water phase was acidified with 4M aqueous HCl solution, extracted twice with EtOAc (50 mL). All organics were combined, dried (phase separator) and evaporated in vacuo to afford the title compound. Yellowish solid. MS (LC/MS): 328.0 [M+H]+, 349.9 [M+Na]+, 271.9 [MH-tBu]+ ; t_R (HPLC conditions c): 4.74 min. The material thus obtained was used in the next reaction step without further purification.

C. 3-Chloro-2-fluoro-5-(2H-tetrazol-5-yl)-benzylamine, hydrochloride

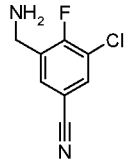
To a solution of [3-chloro-2-fluoro-5-(2H-tetrazol-5-yl)-benzyl]-carbamic acid tert-butyl ester (1.06 g, 3.23 mmol) in dioxane (20 mL) was added a 4M HCl solution in dioxane (8.09 mL, 32.3 mmol). The reaction mixture was stirred at RT for 72 h and then freeze-dried overnight to afford the title compound as a white solid. MS (LC/MS): 228.0 [M+H]+ ; t_R (HPLC conditions c): 2.68 min.

5-(1-tert-Butyl-1H-tetrazol-5-yl)-3-chloro-2-fluoro-benzylamine



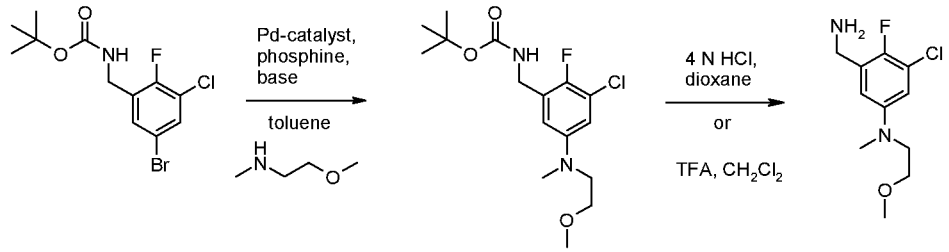
To a solution of [3-chloro-2-fluoro-5-(2H-tetrazol-5-yl)-benzyl]-carbamic acid tert-butyl ester (0.15 g, 0.46 mmol) in CH_2Cl_2 (4 mL) was added TFA (1.5 mL). The reaction mixture was stirred at RT for 2 h and the solvent was removed in vacuo to give the title compound as a 2:1 mixture of 5-(1-tert-butyl-1H-tetrazol-5-yl)-3-chloro-2-fluoro-benzylamine and 3-chloro-2-fluoro-5-(2H-tetrazol-5-yl)-benzylamine which was used in the next steps without separation. MS (LC/MS): 228.0 and 284.0 [M+H]+. t_R (HPLC conditions c): 2.16 and 2.99 min.

3-Aminomethyl-5-chloro-4-fluoro-benzonitrile



To a solution of (3-chloro-5-cyano-2-fluoro-benzyl)-carbamic acid tert-butyl ester (645 mg, 2.27 mmol) in CH_2Cl_2 (15 mL) was added TFA (1.75 mL, 22.7 mmol), and stirring was continued at RT overnight. Volatiles were removed under reduce pressure, water was added and the mixture was washed with EtOAc. The aqueous layer was basified to pH=12 by addition of 4M NaOH solution and extracted twice with EtOAc. The combined organics were dried (phase separator) and evaporated to afford the title compound as a beige solid. MS (LC/MS): 185.0 [M+H]+; t_R (HPLC conditions c): 2.62 min.

Scheme C1: preparation of (3-Aminomethyl-5-chloro-4-fluoro-phenyl)-(2-methoxy-ethyl)-methyl-amine



A. {3-Chloro-2-fluoro-5-[(2-methoxy-ethyl)-methyl-amino]-benzyl}-carbamic acid tert-butyl ester

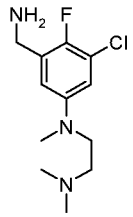
A suspension of (5-bromo-3-chloro-2-fluoro-benzyl)-carbamic acid tert-butyl ester (250 mg, 0.7 mmol), N-methoxyethyl-methylamine (99 mg, 1.1 mmol), sodium tert-butoxide (142 mg, 1.5 mmol) and di-μ-bromobis(tri-tert-butylphosphino)dipalladium (I) [CAS 185812-86-6] (29 mg, 0.04 mmol) in toluene (5 mL) was sealed in a microwave vial and heated for 30 min at 140°C (Emrys Optimizer; personal chemistry). The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$, extracted with EtOAc, dried (Na_2SO_4) and evaporated in vacuo. The crude product was purified by RP-preparative HPLC (Waters Sunfire, C18-ODB, 5 μm, 30x100 mm, 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 mL/min) to give the title compound after lyophilization. MS (LC/MS): 347.0 [M]+. t_R (HPLC conditions c): 5.23 min.

B. (3-Aminomethyl-5-chloro-4-fluoro-phenyl)-(2-methoxy-ethyl)-methyl-amine

To a mixture of {3-chloro-2-fluoro-5-[(2-methoxy-ethyl)-methyl-amino]-benzyl}-carbamic acid tert-butyl ester (60 mg, 0.17 mmol) in MeOH (2 mL) was added a solution of 4N HCl in dioxane (2 mL). The reaction mixture was stirred for 1 h at ambient temperature and the solvent was

removed in vacuo to give the title compound. MS (LC/MS): 247.0 [M]+. t_R (HPLC conditions c): 3.15 min.

N-(3-Aminomethyl-5-chloro-4-fluoro-phenyl)-N,N',N'-trimethyl-ethane-1,2-diamine

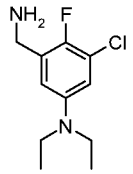


was prepared according to Scheme C1 (step B) from {3-chloro-5-[(2-dimethylamino-ethyl)-methyl-amino]-2-fluoro-benzyl}-carbamic acid tert-butyl ester and 4N HCl in dioxane. MS (LC-MS): 260.0 [M]+

{3-Chloro-5-[(2-dimethylamino-ethyl)-methyl-amino]-2-fluoro-benzyl}-carbamic acid tert-butyl ester

was prepared according to Scheme C1 (step A) from (5-bromo-3-chloro-2-fluoro-benzyl)-carbamic acid tert-butyl ester (300 mg, 0.89 mmol), N,N,N'-trimethyl-ethylenediamine (136 mg, 1.3 mmol), sodium tert-butoxide (170 mg, 1.8 mmol) and di-μ-bromobis(tri-tert-butylphosphino)dipalladium (I) [CAS 185812-86-6] (34 mg, 0.04 mmol). MS (LC-MS): 360.3 [M]+; t_R (HPLC conditions c): 4.15 min.

(3-Aminomethyl-5-chloro-4-fluoro-phenyl)-diethyl-amine

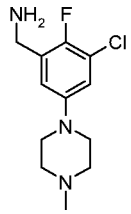


was prepared according to Scheme C1 (step B) from (3-chloro-5-diethylamino-2-fluoro-benzyl)-carbamic acid tert-butyl ester and TFA in CH_2Cl_2. MS (LC-MS): 231.0 [M]+; t_R (HPLC conditions c): 2.29 min.

(3-Chloro-5-diethylamino-2-fluoro-benzyl)-carbamic acid tert-butyl ester

was prepared according to Scheme C1 (step A) from (5-bromo-3-chloro-2-fluoro-benzyl)-carbamic acid tert-butyl ester (300 mg, 0.89 mmol), diethylamine (0.14 mL, 1.3 mmol), sodium tert-butoxide (170 mg, 1.8 mmol) and di-μ-bromobis(tri-tert-butylphosphino)dipalladium (I) [CAS 185812-86-6] (34 mg, 0.04 mmol). MS (LC-MS): 331.2 [M]+; t_R (HPLC conditions c): 4.08 min.

3-Chloro-2-fluoro-5-(4-methyl-piperazin-1-yl)-benzylamine

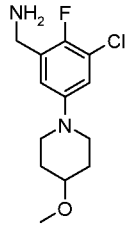


was prepared according to Scheme C1 (step B) from [3-chloro-2-fluoro-5-(4-methyl-piperazin-1-yl)-benzyl]-carbamic acid tert-butyl ester and 4N HCl in dioxane. MS (LC-MS): 258.0 [M]+; t_R (HPLC conditions f): 0.74 min.

[3-Chloro-2-fluoro-5-(4-methyl-piperazin-1-yl)-benzyl]-carbamic acid tert-butyl ester

was prepared according to Scheme C1 (step A) from (5-bromo-3-chloro-2-fluoro-benzyl)-carbamic acid tert-butyl ester (200 mg, 0.59 mmol), 1-methylpiperazine (71 mg, 0.71 mmol), caesium carbonate (269 mg, 0.83 mmol), palladium (II) acetate (6.6 mg, 0.03 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (24 mg, 0.04 mmol). MS (LC-MS): 358.0 [M]+; t_R (HPLC conditions c): 3.98 min.

3-Chloro-2-fluoro-5-(4-methoxy-piperidin-1-yl)-benzylamine

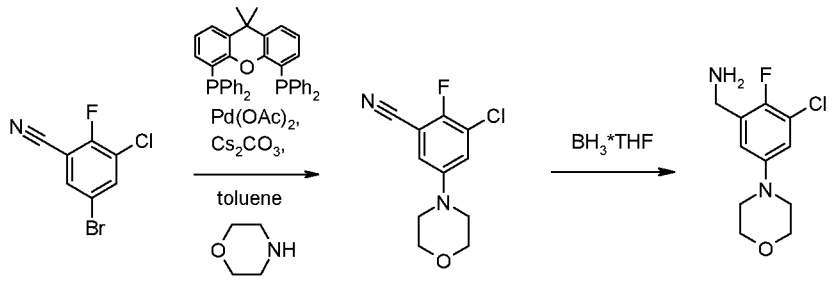


was prepared according to Scheme C1 (step B) from [3-chloro-2-fluoro-5-(4-methyl-piperazin-1-yl)-benzyl]-carbamic acid tert-butyl ester and 4N HCl in dioxane. MS (LC-MS): 273.0 [M]+; t_R (HPLC conditions c): 2.97 min.

[3-Chloro-2-fluoro-5-(4-methoxy-piperidin-1-yl)-benzyl]-carbamic acid tert-butyl ester

was prepared according to Scheme C1 (step A) from (5-bromo-3-chloro-2-fluoro-benzyl)-carbamic acid tert-butyl ester (250 mg, 0.74 mmol), 1-methoxypiperidine (102 mg, 0.89 mmol), caesium carbonate (337 mg, 1.0 mmol), palladium (II) acetate (8.3 mg, 0.04 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (30 mg, 0.05 mmol). MS (LC-MS): 373.0 [M]+; t_R (HPLC conditions c): 4.68 min.

3-Chloro-2-fluoro-5-morpholin-4-yl-benzylamine



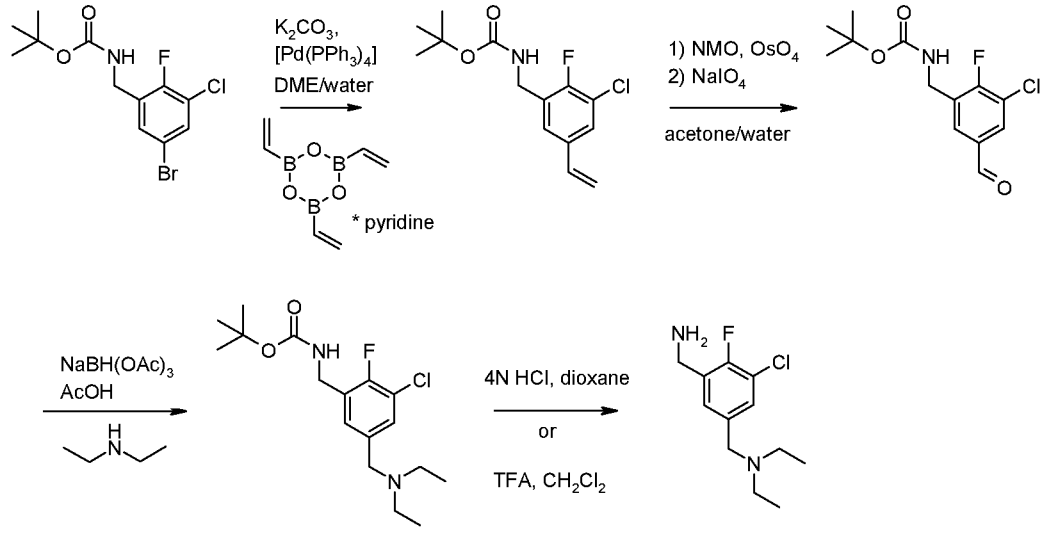
A. 3-Chloro-2-fluoro-5-morpholin-4-yl-benzonitrile

A suspension of 5-Bromo-3-chloro-2-fluoro-benzonitrile (200 mg, 0.85 mmol), morpholine (74 mg, 0.85 mmol), caesium carbonate (389 mg, 1.2 mmol), palladium(II) acetate (10 mg, 0.04 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (35 mg, 0.06 mmol) in toluene (5 mL) was sealed in a microwave vial and heated for 30 min at 140°C (Emrys Optimizer; personal chemistry). The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$, extracted with EtOAc, dried (Na_2SO_4) and the solvent was removed in vacuo to give the title compound which was used without further purification in the next step. TLC R_f (hexane/EtOAc 1:1) = 0.60 ; t_R (HPLC conditions c): 5.28 min.

B. 3-Chloro-2-fluoro-5-morpholin-4-yl-benzylamine

To a solution of 3-Chloro-2-fluoro-5-morpholin-4-yl-benzonitrile (215 mg, 0.85 mmol) in THF (2 mL) was added dropwise a solution of BH_3-THF. The reaction mixture was heated under reflux for several hours, cooled to ambient temperature and quenched carefully by addition of methanol. The solvent was removed in vacuo and the crude product was purified by RP-preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 mL/min) to give the title compound. MS (LC/MS): 244.9 [M]+ ; t_R (HPLC conditions c): 3.02 min.

Scheme C2: preparation of (3-Aminomethyl-5-chloro-4-fluoro-benzyl)-diethyl-amine



A. (3-Chloro-2-fluoro-5-vinyl-benzyl)-carbamic acid tert-butyl ester

To a solution of (5-bromo-3-chloro-2-fluoro-benzyl)-carbamic acid tert-butyl ester (6 g, 17.7 mmol) in DME (100 mL) was added $Pd(Ph_3)_4$ (1.0 g, 0.9 mmol) under argon atmosphere and the mixture was stirred for 30 min at ambient temperature. After addition of vinyl boronic anhydride pyridine complex (4.3 g, 17.7 mmol), water (25 mL) and K_2CO_3 (2.45 g, 17.7 mmol) the reaction was heated under reflux for 7 h. The reaction mixture was concentrated in vacuo to half of the volume, quenched by addition of saturated aqueous $NaHCO_3$ and extracted wit EtOAc. After drying (Na_2SO_4) the solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc 9:1 to 4:1) to afford the title compound as a colorless oil. 1H-NMR (500 MHz, DMSO): δ (ppm) 7.62 (d, 1H), 7.45 (m, 1H,-*NH*), 7.35 (d, 1H), 6.68 (dd, 1H), 5.82 (d, 1H), 5.32 (d, 1H), 4.18 (d, 2H), 1.39 (s, 9H).

B. (3-Chloro-2-fluoro-5-formyl-benzyl)-carbamic acid tert-butyl ester

To a solution of (3-chloro-2-fluoro-5-vinyl-benzyl)-carbamic acid tert-butyl ester (2.7 g, 9.5 mmol) in acetone (20 mL) was added N-methylmorpholine-N-oxide monohydrate (1.5 g, 11 mmol) and a solution of 4% aq. osmiumtetraoxide (3.7 mL, 0.5 mmol). The reaction was stirred for 1 h, saturated aqueous $Na_2S_2O_3$-solution was added and stirring was continued for one hour. After extraction with EtOAc and removal of the solvent in vacuo, the residue was dissolved in acetone/water (3:1, 40 mL) and $NaIO_4$ (4.0 g, 19 mmol) was added. After stirring for 2 h at ambient temperature, the reaction mixture was filtered, washed with EtOAc, extracted with EtOAc, dried (Na_2SO_4) and the solvent was removed in vacuo to give the title compound which was used without further purification. t_R (HPLC conditions c): 5.22 min.

C. (3-Chloro-5-diethylaminomethyl-2-fluoro-benzyl)-carbamic acid tert-butyl ester

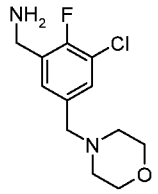
A solution of (3-chloro-2-fluoro-5-formyl-benzyl)-carbamic acid tert-butyl ester (200 mg, 0.7 mmol), diethylamine (51 mg, 0.7 mmol) and acetic acid (0.06 mL) in THF (mL) was stirred for 30 min at ambient temperature. After addition of sodium triacetoxyborohydride (368 mg, 1,7

mmol) the reaction was stirred overnight, quenched by addition of of saturated aqueous $NaHCO_3$ and extracted wit EtOAc. The solvent was removed in vacuo and the residue was purified by RP-preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 mL/min) to give the title compound. MS (LC-MS): 345.0 [M]+; t_R (HPLC conditions c): 4.09 min.

D. (3-Aminomethyl-5-chloro-4-fluoro-benzyl)-diethyl-amine

To a mixture of (3-chloro-5-diethylaminomethyl-2-fluoro-benzyl)-carbamic acid tert-butyl ester (115 mg, 0.33 mmol) in MeOH (1 mL) was added a solution of 4N HCl in dioxane (3 mL). The reaction mixture was stirred for 2 h at ambient temperature and the solvent was removed in vacuo to give the title compound. MS (LC/MS): 245.0 [M]+ ; t_R (HPLC conditions c): 2.13 min.

3-Chloro-2-fluoro-5-morpholin-4-ylmethyl-benzylamine

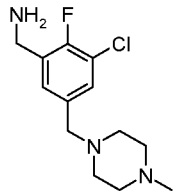


was prepared according to Scheme C2 (step D) from (3-chloro-2-fluoro-5-morpholin-4-ylmethyl-benzyl)-carbamic acid tert-butyl ester (231 mg, 0.64 mmol) and 4N HCl in dioxane. MS (LC-MS): 259.0 [M]+.

(3-Chloro-2-fluoro-5-morpholin-4-ylmethyl-benzyl)-carbamic acid tert-butyl ester

was prepared according to Scheme C2 (step C) from (3-chloro-2-fluoro-5-formyl-benzyl)-carbamic acid tert-butyl ester (220 mg, 0.65 mmol), morpholine (57 mg, 0.65 mmol), acetic acid (0.056 mL, 0.9 mmol) and sodium triacetoxyborohydride (344 mg, 1.6 mmol) in THF (8 mL). TLC, R_f (EtOAc) = 0.44 ; MS (LC-MS): 359.0 [M]+.

3-Chloro-2-fluoro-5-(4-methyl-piperazin-1-ylmethyl)-benzylamine

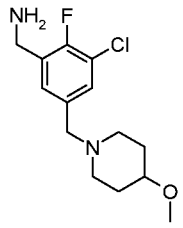


was prepared according to Scheme C2 (step D) from [3-chloro-2-fluoro-5-(4-methyl-piperazin-1-ylmethyl)-benzyl]-carbamic acid tert-butyl ester (225 mg, 0.61 mmol) and 4N HCl in dioxane. MS (LC-MS): 272.0 [M]+; t_R (HPLC conditions c): 2.07 min.

[3-Chloro-2-fluoro-5-(4-methyl-piperazin-1-ylmethyl)-benzyl]-carbamic acid tert-butyl ester

was prepared according to Scheme C2 (step C) from (3-chloro-2-fluoro-5-formyl-benzyl)-carbamic acid tert-butyl ester (200 mg, 0.59 mmol), 1-methylpiperazine (59 mg, 0.59 mmol), acetic acid (0.053 mL, 0.89 mmol) and sodium triacetoxyborohydride (313 mg, 1.5 mmol) in THF (8 mL). MS (LC-MS): 372.0 [M]+; t_R (HPLC conditions c): 3.64 min.

3-Chloro-2-fluoro-5-(4-methoxy-piperidin-1-ylmethyl)-benzylamine

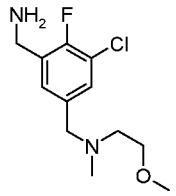


was prepared according to Scheme C2 (step D) from [3-chloro-2-fluoro-5-(4-methoxy-piperidin-1-ylmethyl)-benzyl]-carbamic acid tert-butyl ester (225 mg, 0.61 mmol) and 4N HCl in dioxane. MS (LC-MS): 287.0 [M]+; t_R (HPLC conditions c): 2.34 min.

[3-Chloro-2-fluoro-5-(4-methoxy-piperidin-1-ylmethyl)-benzyl]-carbamic acid tert-butyl ester

was prepared according to Scheme C2 (step C) from (3-chloro-2-fluoro-5-formyl-benzyl)-carbamic acid tert-butyl ester (200 mg, 0.59 mmol), 1-methoxypiperidine (68 mg, 0.59 mmol), acetic acid (0.051 mL, 0.89 mmol) and sodium triacetoxyborohydride (313 mg, 1.5 mmol) in THF (8 mL). MS (LC-MS): 387.0 [M]+

(3-Aminomethyl-5-chloro-4-fluoro-benzyl)-(2-methoxy-ethyl)-methyl-amine



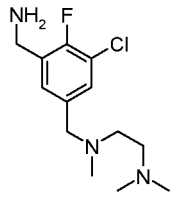
was prepared according to Scheme C2 (step D) from (3-chloro-2-fluoro-5-{[(2-methoxy-ethyl)-methyl-amino]-methyl}-benzyl)-carbamic acid tert-butyl ester (222 mg, 0.47 mmol) and 4N HCl in dioxane. MS (LC-MS): 261.0 [M]+.

(3-Chloro-2-fluoro-5-{[(2-methoxy-ethyl)-methyl-amino]-methyl}-benzyl)-carbamic acid tert-butyl ester

was prepared according to Scheme C2 (step C) from (3-chloro-2-fluoro-5-formyl-benzyl)-carbamic acid tert-butyl ester (200 mg, 0.59 mmol), N-methoxyethyl-methylamine (74 mg, 0.83

mmol), acetic acid (0.06 mL, 1.0 mmol) and sodium triacetoxyborohydride (368 mg, 1.7 mmol) in THF (8 mL). MS (LC-MS): 362.3 [M+H]+; t_R (HPLC conditions c): 4.04 min.

N-(3-Aminomethyl-5-chloro-4-fluoro-benzyl)-N,N',N'-trimethyl-ethane-1,2-diamine

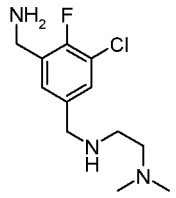


was prepared according to Scheme C2 (step D) from (3-chloro-5-{[(2-dimethylamino-ethyl)-methyl-amino]-methyl}-2-fluoro-benzyl)-carbamic acid tert-butyl ester (228 mg, 0.51 mmol) and 4N HCl in dioxane. MS (LC-MS): 274.0 [M]+.

(3-Chloro-5-{[(2-dimethylamino-ethyl)-methyl-amino]-methyl}-2-fluoro-benzyl)-carbamic acid tert-butyl ester

was prepared according to Scheme C2 (step C) from (3-chloro-2-fluoro-5-formyl-benzyl)-carbamic acid tert-butyl ester (200 mg, 0.59 mmol), N,N,N'-trimethyl-ethylendiamine (71 mg, 0.70 mmol), acetic acid (0.06 mL, 1.0 mmol) and sodium triacetoxyborohydride (368 mg, 1.7 mmol) in THF (8 mL). MS (LC-MS): 374.0 [M]+; t_R (HPLC conditions c): 3.53 min.

N-(3-Aminomethyl-5-chloro-4-fluoro-benzyl)-N',N'-dimethyl-ethane-1,2-diamine

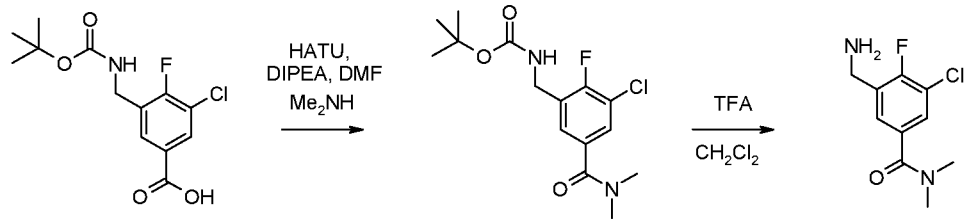


was prepared according to Scheme C2 (step D) from (3-chloro-5-{[(2-dimethylamino-ethyl)-methyl-amino]-methyl}-2-fluoro-benzyl)-carbamic acid tert-butyl ester (165 mg, 0.46 mmol) and 4N HCl in dioxane (3 mL). MS (LC-MS): 260.0 [M]+.

{3-Chloro-5-[(2-dimethylamino-ethylamino)-methyl]-2-fluoro-benzyl}-carbamic acid tert-butyl ester

was prepared according to Scheme C2 (step C) from (3-chloro-2-fluoro-5-formyl-benzyl)-carbamic acid tert-butyl ester (200 mg, 0.70 mmol), N,N-dimethyl-ethylendiamine (67 mg, 0.77 mmol), acetic acid (0.06 mL, 1.0 mmol) and sodium triacetoxyborohydride (368 mg, 1.7 mmol) in THF (8 mL). MS (LC-MS): 360.3 [M+H]+; t_R (HPLC conditions c): 3.49 min.

Scheme C3 : preparation of 3-Aminomethyl-5-chloro-4-fluoro-N,N-dimethyl-benzamide



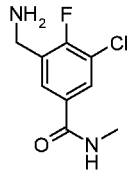
A. (3-Chloro-5-dimethylcarbamoyl-2-fluoro-benzyl)-carbamic acid tert-butyl ester

A mixture of 3-(tert-butoxycarbonylamino-methyl)-5-chloro-4-fluoro-benzoic acid (100 mg, 0.3 mmol), HATU (188 mg, 0.5 mmol), dimethylamine (0.2 mL, 2M in THF) and DIPEA (0.23 mL, 1.3 mmol) in DMF (2 mL) was stirred for 16 h at ambient temperature. The crude product was purified without aqueous workup by RP-preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 ml/min) to give the title compound. MS (LC-MS): 275.0 [M-55]+; t_R (HPLC conditions c): 4.68 min.

B. 3-Aminomethyl-5-chloro-4-fluoro-N,N-dimethyl-benzamide

To a mixture of (3-chloro-5-dimethylcarbamoyl-2-fluoro-benzyl)-carbamic acid tert-butyl ester (115 mg, 0.33 mmol) in CH_2Cl_2 (4 mL) was added TFA (1 mL). The reaction mixture was stirred for 1 h at ambient temperature and the solvent was removed in vacuo to give the title compound. MS (LC/MS): 231.0 [M]+. t_R (HPLC conditions c): 2.59 min.

3-Aminomethyl-5-chloro-4-fluoro-N-methyl-benzamide

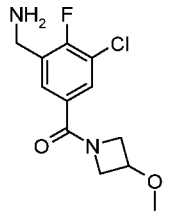


was prepared according to Scheme C3 (step B) from (3-chloro-2-fluoro-5-methylcarbamoyl-benzyl)-carbamic acid tert-butyl ester (99 mg, 0.3 mmol) and TFA (0.5 mL) in CH_2Cl_2. MS (LC-MS): 217.0 [M]+; t_R (HPLC conditions c): 2.39 min.

(3-Chloro-2-fluoro-5-methylcarbamoyl-benzyl)-carbamic acid tert-butyl ester

was prepared according to Scheme C3 (step A) from 3-(tert-butoxycarbonylamino-methyl)-5-chloro-4-fluoro-benzoic acid (125 mg, 0.41 mmol), HATU (235 mg, 0.6 mmol), methylamine (0.25 mL, 2M in THF) and DIPEA (0.29 mL, 1.6 mmol) in DMF (2 mL). MS (LC-MS): 633.0 [2M]+; t_R (HPLC conditions c): 4.55 min.

(3-Aminomethyl-5-chloro-4-fluoro-phenyl)-(3-methoxy-azetidin-1-yl)-methanone

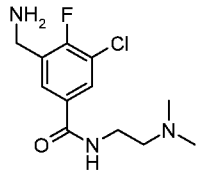


was prepared according to Scheme C3 (step B) from [3-chloro-2-fluoro-5-(3-methoxy-azetidine-1-carbonyl)-benzyl]-carbamic acid tert-butyl ester (99 mg, 0.3 mmol) and TFA (0.5 mL) in CH_2Cl_2. MS (LC-MS): 273.0 [M]+; t_R (HPLC conditions c): 2.73 min.

[3-Chloro-2-fluoro-5-(3-methoxy-azetidine-1-carbonyl)-benzyl]-carbamic acid tert-butyl ester

was prepared according to Scheme C3 (step A) from 3-(tert-butoxycarbonylamino-methyl)-5-chloro-4-fluoro-benzoic acid (116 mg, 0.38 mmol), HATU (218 mg, 0.46 mmol), 3-methoxy-azetidine (57 mg, 0.57 mmol) and DIPEA (0.27 mL, 1.5 mmol) in DMF (2 mL). MS (LC-MS): 373.0 [M]+

3-Aminomethyl-5-chloro-N-(2-dimethylamino-ethyl)-4-fluoro-benzamide

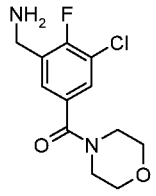


was prepared according to Scheme C3 (step B) from [3-chloro-5-(2-dimethylamino-ethylcarbamoyl)-2-fluoro-benzyl]-carbamic acid tert-butyl ester (120 mg, 0.3 mmol) and TFA (1 mL) in CH_2Cl_2. MS (LC-MS): 274.0 [M]+; t_R (HPLC conditions c): 2.17 min.

[3-Chloro-5-(2-dimethylamino-ethylcarbamoyl)-2-fluoro-benzyl]-carbamic acid tert-butyl ester

was prepared according to Scheme C3 (step A) from 3-(tert-butoxycarbonylamino-methyl)-5-chloro-4-fluoro-benzoic acid (116 mg, 0.38 mmol), HATU (218 mg, 0.46 mmol), N,N-dimethylethylenediamine (40 mg, 0.46 mmol) and DIPEA (0.2 mL, 1.1 mmol) in DMF (2 mL). MS (LC-MS): 374.2 [M]+; t_R (HPLC conditions c): 3.87 min.

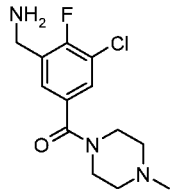
(3-Aminomethyl-5-chloro-4-fluoro-phenyl)-morpholin-4-yl-methanone



was prepared according to Scheme C3 (step B) from [3-chloro-2-fluoro-5-(morpholine-4-carbonyl)-benzyl]-carbamic acid tert-butyl ester (72 mg, 0.19 mmol) and TFA (1 mL) in CH_2Cl_2. MS (LC-MS): 273.0 [M]+; t_R (HPLC conditions c): 2.64 min.

[3-Chloro-2-fluoro-5-(morpholine-4-carbonyl)-benzyl]-carbamic acid tert-butyl ester
was prepared according to Scheme C3 (step A) from 3-(tert-butoxycarbonylamino-methyl)-5-chloro-4-fluoro-benzoic acid (125 mg, 0.41 mmol), HATU (235 mg, 0.62 mmol), morpholine (43 mg, 0.49 mmol) and DIPEA (0.22 mL, 1.2 mmol) in DMF (2 mL). MS (LC-MS): 317.0 [M-55]+; t_R (HPLC conditions c): 4.65 min.

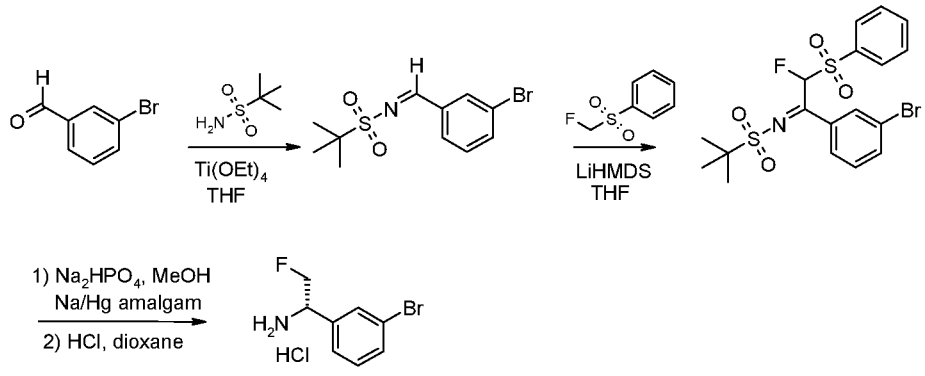
(3-Aminomethyl-5-chloro-4-fluoro-phenyl)-(4-methyl-piperazin-1-yl)-methanone



was prepared according to Scheme C3 (step B) from [3-chloro-2-fluoro-5-(4-methyl-piperazine-1-carbonyl)-benzyl]-carbamic acid tert-butyl ester (165 mg, 0.43 mmol) and TFA (2 mL) in CH_2Cl_2. MS (LC-MS): 286.0 [M]+; t_R (HPLC conditions c): 1.47 min.

[3-Chloro-2-fluoro-5-(4-methyl-piperazine-1-carbonyl)-benzyl]-carbamic acid tert-butyl ester
was prepared according to Scheme C3 (step A) from 3-(tert-butoxycarbonylamino-methyl)-5-chloro-4-fluoro-benzoic acid (150 mg, 0.49 mmol), HATU (282 mg, 0.74 mmol), 4-methylpiperazine (59 mg, 0.59 mmol) and DIPEA (0.26 mL, 1.5 mmol) in DMF (2 mL). MS (LC-MS): 386.0 [M]+; t_R (HPLC conditions c): 3.77 min.

(S)-1-(3-Bromo-phenyl)-2-fluoro-ethylamine hydrochloride



A. 2-Methyl-propane-2-sulfonic acid 1-(3-bromo-phenyl)-meth-(Z)-ylideneamide

To a solution of 3-bromo-benzaldehyde (1.27 mL, 10.8 mmol) in THF (50 mL) were added titanium(IV) ethoxide (0.786 mL, 21.6 mmol) and tert-butylsulfonamide (1.31 g, 10.8 mmol), and stirring was continued for 16 h at 65°C. After cooling to RT, volatiles were evaporated, and the residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 3:1) to afford the title compound. MS (LC/MS): 289 [M+H]+; t_R (HPLC conditions f): 2.35 min.

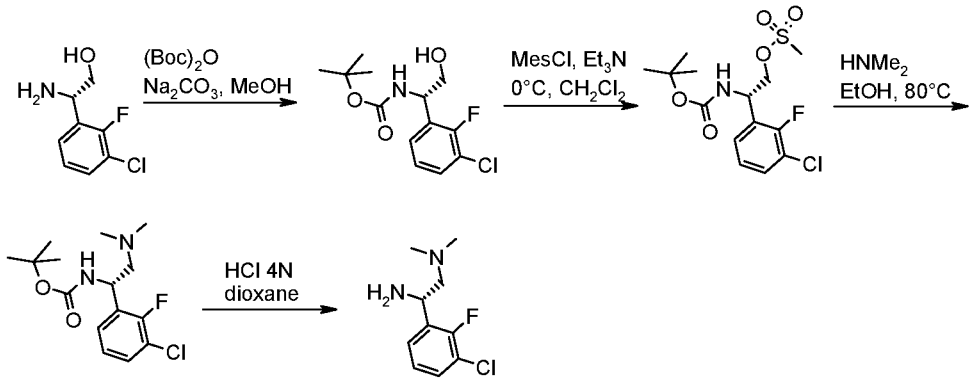
B. 2-Methyl-propane-2-sulfonic acid [2-benzenesulfonyl-1-(3-bromo-phenyl)-2-fluoro-eth-(Z)-ylidene]-amide

To a mixture of 2-methyl-propane-2-sulfonic acid 1-(3-bromo-phenyl)-meth-(Z)-ylideneamide (2.16 g, 7.49 mmol) and (fluoromethylsulfonyl)benzene (1.31 g, 7.49 mmol) in THF (50 mL), cooled to -78°C, was added LiHMDS (1M in THF; 7.87 mL, 7.87 mmol). The reaction mixture was stirred for 40 min at -78°C, followed by quenching saturated aqueous NH_4Cl (10 mL) at -78°C. The mixture was extracted with EtOAc (3x), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (c-hexane/EtOAc 3:1) afforded the title compound. MS (LC/MS): 462/464 [M+H]+; t_R (HPLC conditions f): 2.20 min.

C. (S)-1-(3-Bromo-phenyl)-2-fluoro-ethylamine hydrochloride

To a mixture of 2-methyl-propane-2-sulfonic acid [2-benzenesulfonyl-1-(3-bromo-phenyl)-2-fluoro-eth-(Z)-ylidene]-amide (1.74 g, 3.76 mmol) and sodium phosphate dibasic (4.27 g, 30.1 mmol) in methanol (50 mL), cooled to -20°C, was added Na/Hg amalgam (6.92 g, 30.1 mmol). The reaction mixture was stirred for 1 h at -20°C, followed by filtration. To the filtrate was added a 4N HCl solution in dioxane (9.41 mL, 37.6 mmol), followed by stirring for 30 min at 25°C. After evaporation of volatiles, Et_2O was added to the residue and the resulting precipitate was filtered off. The title compound thus obtained was used in the next reaction step without further purification. MS (LC/MS): 218/220 [M+H]+; t_R (HPLC conditions f): 1.05 min.

Scheme C4: preparation of (S)-1-(3-Chloro-2-fluoro-phenyl)-N*2*,N*2*-dimethyl-ethane-1,2-diamine



A. [(S)-1-(3-Chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-carbamic acid tert-butyl ester

To a solution of (2S)-2-amino-2-(3-chloro-2-fluorophenyl)ethan-1-ol (517 mg, 2.29 mmol) in MeOH (35 mL) were added $(Boc)_2O$ (0.54 mL, 2.31 mmol) and sodium carbonate (970 mg, 9.15 mmol) and the reaction mixture was stirred at RT overnight. Organic volatiles were removed and the crude material was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 1:1). TLC, R_f (c-hexane/EtOAc 1:1): 0.55; MS (UPLC/MS): 290.2/292.2 [M+H]+, 334.2/336.3 [M+HCOO]-; t_R (HPLC conditionsa): 3.36 min.

B. Methanesulfonic acid (S)-2-tert-butoxycarbonylamino-2-(3-chloro-2-fluoro-phenyl)-ethyl ester

To a solution of [(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-carbamic acid tert-butyl ester (550 mg, 1.9 mmol) and triethylamine (0.29 mL, 2.09 mmol) in CH_2Cl_2 (5.5 mL) cooled at -10°C was added under nitrogen atmosphere mesylchloride (0.16 mL, 2.09 mmol) and the reaction mixture was stirred at 0°C for 1.5 h. The reaction mixture was quenched with ice and water then extracted twice with EtOAc. The combined organic layers were washed with water, dried (Na_2SO_4), filtered and concentrated. The crude material was used without purification in the next step. MS (UPLC/MS): 412.3/414.3 [M+HCOO]-; t_R (HPLC conditions a): 3.66 min.

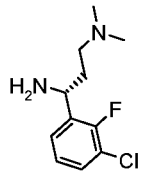
C. [(S)-1-(3-Chloro-2-fluoro-phenyl)-2-dimethylamino-ethyl]-carbamic acid tert-butyl ester

A solution of methanesulfonic acid (S)-2-tert-butoxycarbonylamino-2-(3-chloro-2-fluoro-phenyl)-ethyl ester (690 mg, 1.88 mmol) in 33% dimethylamine in EtOH (5.6 M, 7.5 mL, 42 mmol) was heated at 80°C for 2 h in a sealed tube. The reaction mixture was concentrated and the crude material was purified by flash column chromatography on silica gel (c-hexane/EtOAc 1:1 to EtOAc) to give a pale yellow oil. TLC, R_f (EtOAc): 0.60; MS (UPLC/MS): 317.3/319.3 [M+H]+; t_R (HPLC conditions a): 3.19 min.

D. (S)-1-(3-Chloro-2-fluoro-phenyl)-N*2*,N*2*-dimethyl-ethane-1,2-diamine

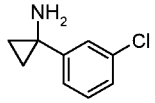
To a solution of [(S)-1-(3-chloro-2-fluoro-phenyl)-2-dimethylamino-ethyl]-carbamic acid tert-butyl ester (315 mg, 0.99 mmol) in dioxane (6 mL) was added HCl 4N in dioxane (9.94 mL, 39.8 mmol). The reaction mixture was stirred at RT for 1 h and concentrated to give the desired material as a HCL salt which was used without further purification in the next step. MS (UPLC/MS): 217.2/219.2 [M+H]+; 1H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.17 (bs, 2H), 7.75 (m, 2H), 7.40 (t, 1H), 5.16 (m, 1H), 3.85 (m, 1H), 3.60 (m, 1H), 2.87 (s, 3H).

(R)-1-(3-Chloro-2-fluoro-phenyl)-N*3*,N*3*-dimethyl-propane-1,3-diamine



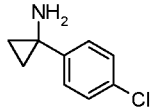
was prepared using similar procedures as described for the synthesis of (3-acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetic acid in Scheme C4 from (R)-3-amino-3-(3-chloro-2-fluoro-phenyl)-propan-1-ol. 1H-NMR (400 MHz, DMSO): δ (ppm): 8.89 (m, 2H), 7.73 (m, 2H), 7.39 (t, 1H), 4.69 (m, 1H), 3.13 (m, 1H), 2.98 (m, 1H), 2.73 (s, 6H), 2.47 (m, 1H), 2.34 (, 1H).

1-(3-chloro-phenyl)-cyclopropylamine



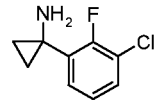
To a solution of 3-chlorobenzonitrile (1 g, 7.27 mmol) and titanium (IV) isopropoxide (2.34 mL, 8 mmol) in Et_2O (35 mL) at -78°C was added ethyl magnesium chloride in THF (5.71 mL, 15.99 mmol). The solution was stirred for 10 min at -78°C then at 25°C for 1 h. $BF_3.Et_2O$ (1.82 mL, 14.54 mmol) was added and the solution was stirred for 1 h at 25°C. The reaction mixture was quenched with 1N HCl (22 mL) Et_2O was added (100 mL). Then 10% aq. NaOH (70 mL) was added and the layers were separated. The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by preparative HPLC (Waters SunFire C18-ODB, 5 µm, 19x50 mm, 5% CH_3CN/H_2O 2.5 min, 5-100% CH_3CN/H_2O in 10 min, CH_3CN/H_2O containing 0.1 % HCOOH flow: 20 mL/min) to give after lyophilization of the purified fractions the title compound. MS (UPLC-MS): 170 [M+H]+, 168 [M-H]-; t_R (HPLC conditions f): 1.22 min.

1-(4-chloro-phenyl)-cyclopropylamine



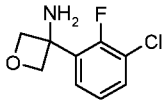
was prepared using the same procedure as for the preparation of 1-(3-chloro-phenyl)-cyclopropylamine starting from 4-chlorobenzonitrile. MS (UPLC-MS): 170 [M+H]+, 168 [M-H]; t_R (HPLC conditions f): 1.21 min.

1-(3-Chloro-2-fluoro-phenyl)-cyclopropylamine



was prepared using the same procedure as for the preparation of 1-(3-chloro-phenyl)-cyclopropylamine starting from 3-chloro-2-fluroro-benzonitrile. MS (UPLC-MS): 186/188 [M+H]+; t_R (HPLC conditions f): 1.13 min.

3-(3-Chloro-2-fluoro-phenyl)-oxetan-3-ylamine hydrochloride

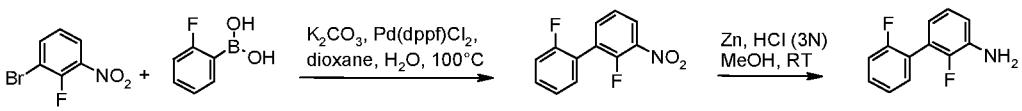


A solution of 2-methyl-propane-2-sulfinic acid [3-(3-chloro-2-fluoro-phenyl)-oxetan-3-yl]-amide (940 mg, 2.46 mmol) and hydrochloric acid (4 N in dioxane, 0.922 ml, 3.69 mmol) in MeOH (5 mL) was stirred 30 min at 0°C and concentrated. The material thus obtained was used without further purification in the next step. MS (UPLC-MS): 202/204 [M+H]+; t_R (HPLC conditions f): 0.86 min.

2-methyl-propane-2-sulfinic acid [3-(3-chloro-2-fluoro-phenyl)-oxetan-3-yl]-amide

To a solution of 1-bromo-3-chloro-2-fluorobenzene (896 mg, 4.28 mmol) in THF (100 mL) was added at -78°C under nitrogen atmosphere n-butyllithium (1.6 N in hexanes, 2.67 ml, 4.28 mmol). The reaction mixture was stirred 1 h at -78°C and a solution of 2-methyl-N-(oxetan-3-ylidene)propane-2-sulfinamide (500 mg, 2.85 mmol) in THF (17.5 ml) was added dropwise. The reaction mixture was further stirred 1 h at -78°C then allowed to reach RT and quenched by slow addition of a saturated aqueous solution of NH_4Cl, extracted with EtOAc (x2). The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and concentrated. The material thus obtained was used without further purification in the next step. MS (UPLC-MS): 306.1/308.1 [M+H]+; t_R (HPLC conditions f): 1.85 min.

Scheme C5: Preparation of 2,2'-difluoro-biphenyl-3-ylamine



A. 2,2'-Difluoro-3-nitro-biphenyl

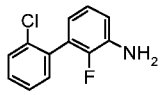
To a solution of 1-bromo-2-fluoro-3-nitrobenzene [58534-94-4] (150 mg, 0.68 mmol) and 2-fluorophenylboronic acid [1193-03-9] (191 mg, 1.36 mmol) in dioxane (4 mL) and water (1 mL) was added potassium carbonate (236 mg, 1.70 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ adduct (55.7 mg, 0.068 mmol). The solution was heated for 30 min at 100°C under microwave irradiation.

The reaction mixture was diluted with CH_2Cl_2 and the resulting solution was washed successively with saturated aqueous $NaHCO_3$ solution, 1N HCl solution and brine, then dried (Phase separator) and concentrated under reduced pressure. The residue was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, flow: 40 mL/min, eluent: 20-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) to give after lyophilization of the purified fractions the title compound. MS (LC-MS): 236 [M+H]+; t_R (HPLC conditions k): 3.81 min.

B. 2,2'-Difluoro-biphenyl-3-ylamine

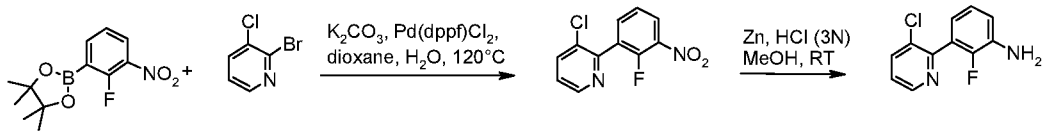
To a suspension of 2,2'-difluoro-3-nitro-biphenyl (100 mg, 0.36 mmol) in methanol (5 mL) were added a 3N aqueous HCl solution (7.23 mL, 21.7 mmol) and Zn powder (426 mg, 6.51 mmol). The mixture was stirred 4 h at RT. The reaction mixture was concentrated and neutralized with saturated aqueous $NaHCO_3$ solution, then diluted with an equal volume of water and extracted (x3) with CH_2Cl_2 .The combined organics were dried (Phase Separator) and concentrated in vacuo to give the title compound. MS (LC-MS): 206 [M+H]+; t_R (HPLC conditions k): 3.30 min.

2'-Chloro-2-fluoro-biphenyl-3-ylamine



was prepared by using the same procedures as described for the preparation of 2,2'-difluoro-biphenyl-3-ylamine in Scheme C5, starting from 2-chlorophenylboronic acid [1679-18-1]. MS (LC-MS): 222 [M+H]+; t_R (HPLC conditions k): 3.42 min.

Scheme C6: Preparation of 3-(3-chloro-pyridin-2-yl)-2-fluoro-phenylamine



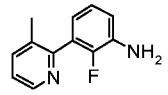
A. 3-Chloro-2-(2-fluoro-3-nitro-phenyl)-pyridine

To a solution of 2-bromo-3-chloropyridine [96424-68-9] (144 mg, 0.75 mmol) and 2-fluoro-3-nitrophenylboronic acid pinacol ester [1189042-70-3] (200 mg, 0.75 mmol) in dioxane (4 mL) and water (1 mL) was added potassium carbonate (259 mg, 1.87 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ adduct (61.2 mg, 0.075 mmol). The solution was heated for 60 min at 120°C under microwave irradiation. The reaction mixture was diluted with EtOAc and the resulting solution was washed successively with saturated aqueous $NaHCO_3$ solution and brine, then dried (Phase separator) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (c-hexane/EtOAc 4:1) to give the title compound. MS (LC-MS): 253 [M+H]+; t_R (HPLC conditions k): 3.45 min.

B. 3-(3-Chloro-pyridin-2-yl)-2-fluoro-phenylamine

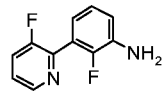
was prepared by using the same procedure as described for the preparation of 2,2'-difluoro-biphenyl-3-ylamine in Scheme C5 step B. MS (LC-MS): 223 [M+H]+; t_R (HPLC conditions k): 2.63 min.

2-Fluoro-3-(3-methyl-pyridin-2-yl)-phenylamine



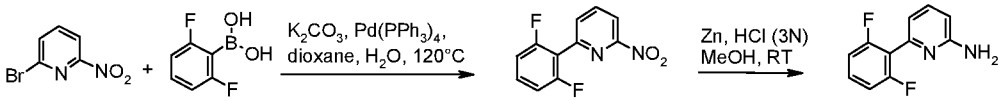
was prepared by using the same procedures as described for the preparation of 3-(3-chloro-pyridin-2-yl)-2-fluoro-phenylamine in Scheme C6, starting from 2-bromo-3-methylpyridine [3430-17-9]. MS (LC-MS): 203 [M+H]+; t_R (HPLC conditions k): 1.36 min.

2-Fluoro-3-(3-fluoro-pyridin-2-yl)-phenylamine



was prepared by using the same procedures as described for the preparation of 3-(3-chloro-pyridin-2-yl)-2-fluoro-phenylamine in Scheme C6, starting from 2-bromo-3-fluoropyridine [40273-45-8] and 2-fluoro-3-nitrophenylboronic acid [1150114-29-6]. MS (LC-MS): 207 [M+H]+; t_R (HPLC conditions k): 2.39 min.

6-(2,6-difluoro-phenyl)-pyridin-2-ylamine



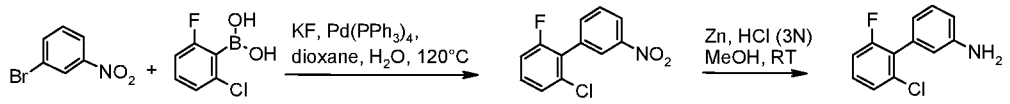
A. 2-(2,6-Difluoro-phenyl)-6-nitro-pyridine

To a solution of 2-bromo-6-nitropyridine [21203-78-1] (200 mg, 0.99 mmol) and 2,6-difluorophenylboronic acid [162101-25-9] (311 mg, 1.97 mmol) in dioxane (4 mL) and water (1 mL) was added potassium carbonate (340 mg, 2.46 mmol) and $Pd(PPh_3)_4$ (114 mg, 0.099 mmol). The solution was heated for 60 min at 120°C under microwave irradiation. More 2,6-difluorophenylboronic acid (622 mg, 3.94mmol) was added to the mixture followed by heating at 120°C for 120 min under microwave irradiation. The reaction mixture was then diluted with EtOAc and the resulting solution was washed successively with saturated aqueous $NaHCO_3$ solution and brine, the organics were then dried (Phase separator) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 9:1) to give the title compound. MS (LC-MS): 237 [M+H]+, 259 [M+Na]+; t_R (HPLC conditions k): 3.44 min.

B. 6-(2,6-Difluoro-phenyl)-pyridin-2-ylamine

was prepared by using the same procedure as described for the preparation of 2,2'-difluoro-biphenyl-3-ylamine in Scheme C5 step B. MS (LC-MS): 207 [M+H]+; t_R (HPLC conditions k): 2.39 min.

2'-chloro-6'-fluorobiphenyl-3-amine



A. 2-Chloro-6-fluoro-3'-nitro-1,1'-biphenyl

To a solution of 1-bromo-3-nitrobenzene [585-79-5] (400 mg, 1.98 mmol) and 2-chloro-6-fluorophenylboronic acid [313545-32-3] (414 mg, 2.37 mmol) in dioxane (12 mL) and water (3 mL) was added potassium fluoride (460 mg, 7.92 mmol) and $Pd(PPh_3)_4$ (229 mg, 0.20 mmol). The solution was heated for 60 min at 120°C under microwave irradiation. More 2-chloro-6-fluorophenylboronic acid (414 mg, 2.37 mmol) was added to the mixture followed by heating at 120°C for 45 min under microwave irradiation. The reaction mixture was then diluted with EtOAc and the resulting solution was washed successively with saturated aqueous $NaHCO_3$ solution and brine, the organics were then dried (Phase separator) and concentrated under reduced pressure. The residue was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, flow: 50 mL/min, eluent: 20-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) to give the title compound. t_R (HPLC conditions c): 5.42 min.

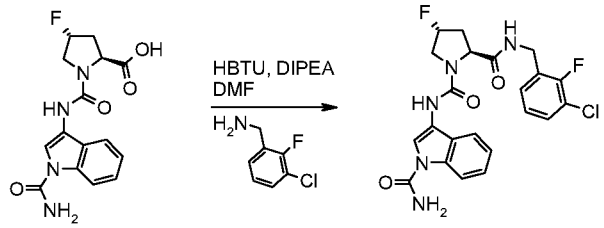
B. 2'-Chloro-6'-fluorobiphenyl-3-amine

was prepared by using the same procedure as described for the preparation of 2,2'-difluoro-biphenyl-3-ylamine in Scheme C5 step B. MS (LC-MS): 222 [M+H]+; t_R (HPLC conditions c): 3.58 min.

Part D: Synthesis of examples 1 to 773

1H NMR and HRMS data for selected compounds can be found at the end of Part D.

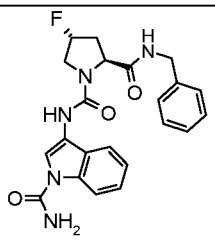
Scheme D1: general protocol described for the preparation of Example 1: (2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)

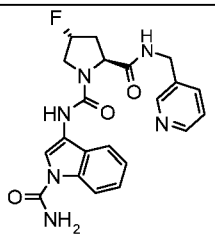
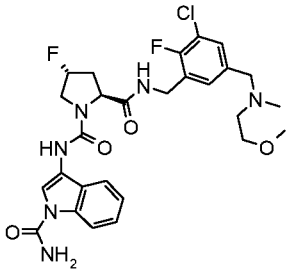
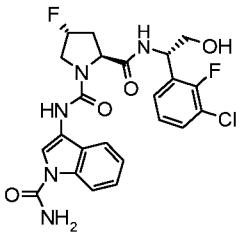
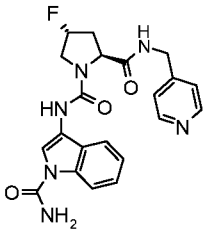
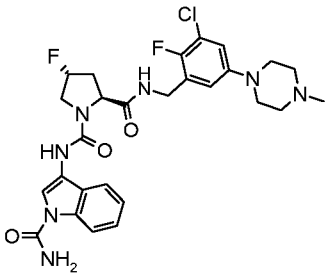
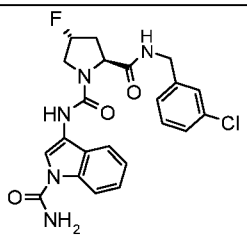


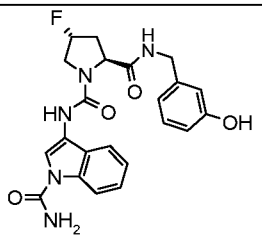
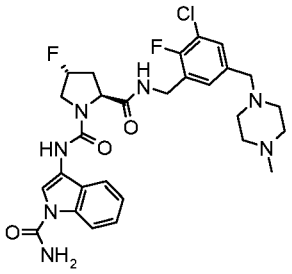
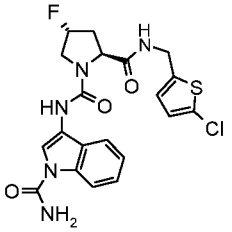
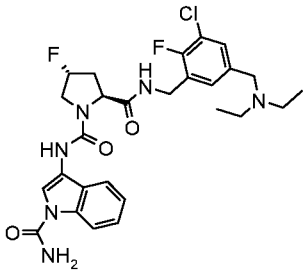
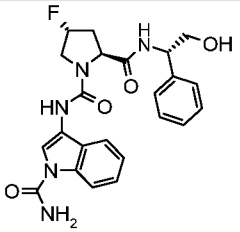
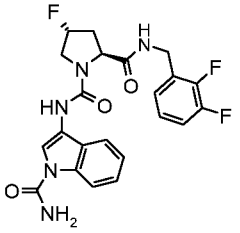
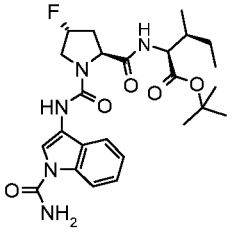
(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carboxylic acid (80 mg, 0.24 mmol, prepared as described in PartB), 3-chloro-2-fluorobenzylamine (76 mg, 0.48 mmol) and HBTU (136 mg, 0.36 mmol) were dissolved in DMF (7.98 mL). DIPEA (125 µl, 0.718 mmol) was added and the reaction mixture was stirred at 25°C for 1 h. The crude reaction mixture was diluted with EtOAc and successively washed with HCl 1N and $NaHCO_3$ (5% in water). The organic layer was dried (Na_2SO_4), filtered and concentrated. The crude material was purified by preparative HPLC (Waters Sunfire C18-ODB, 5um, 19x50mm, flow: 20 mL/min, gradient: 0-2.5 min 20% CH_3CN, 2.5-12.5 min 20 to 100% CH_3CN, 12.5-15 min 100% CH_3CN, H_2O and CH_3CN containing 0.1% HCOOH) the pure fractions were combined, extracted with EtOAc and concentrated. The residue was finally taken up in Et_2O and the desired compound was obtained after filtration. MS: 475.9 [M+H]+, 498 [M+Na]+; t_R (HPLC conditions b): 3.64 min.

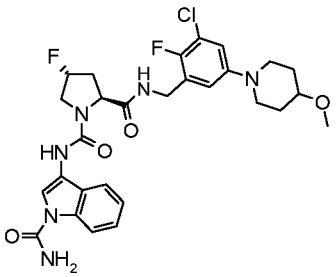
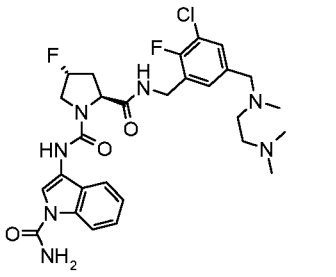
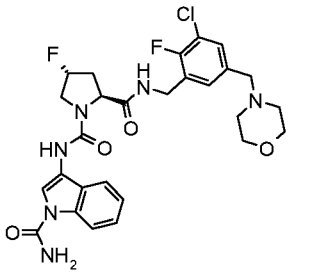
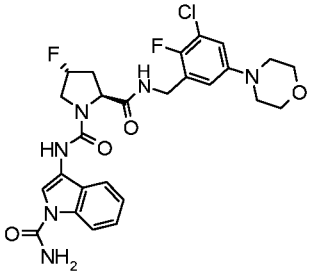
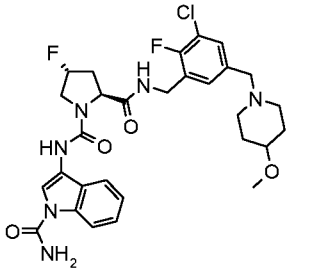
The examples below were prepared according to the general procedures described in Scheme D1 for **Example 1** *using commercially available building blocks, if not otherwise stated (see notes at the end of table 1):*

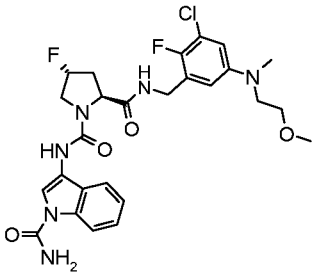
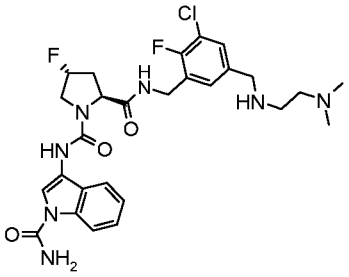
Table 1:

Example	Structure	Name	Characterization (end–table notes), TLC, R_f (eluent); MS (LC/MS); t_R (HPLC conditions)
2		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzylamide 1-[(1-carbamoyl-1H-indol-3-yl)-amide]	424 [M+H]+; t_R (b): 3.15 min.

3		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(pyridin-3-ylmethyl)-amide]	425.0 [M+H]+, 423.1 [M-H]-; t_R (a): 1.05 min.
4		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-5-{[(2-methoxy-ethyl)-methyl-amino]-methyl}-benzylamide)	(1 [C2]) 577.3 [M]+; t_R (c): 3.67 min.
5		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide}	506.4 [M+H], 504.3 [M-H]-; t_R (a): 2.87 min.
6		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(pyridin-4-ylmethyl)-amide]	425.2 [M+H]+, 447.1 [M+Na]+, 871.3 [2M+Na]+, 423.1 [M-H]-, 380 [M-$CONH_2$]-; t_R (a): 1.27 min.
7		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(4-methyl-piperazin-1-yl)-benzylamide]	(1[C1]) 574.2/577.3 [M+H]+; t_R (c): 3.63 min.
8		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide)	458.2 [M+H]+ 456.1 [M-H]-; t_R (a): 3.05 min; t_R (b): 3.34 min.

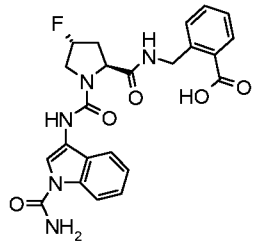
9		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-hydroxy-benzylamide)	440 [M+H]+; t_R (b): 2.66 min.
10		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(4-methyl-piperazin-1-ylmethyl)-benzylamide]	(1[C2]) 588 [M+H]+; t_R (c): 3.31 min.
11		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-chloro-thiophen-2-ylmethyl)-amide]	463.9 [M+H]+; t_R (b): 3.55 min.
12		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-5-diethylamino-methyl-2-fluoro-benzyl-amide)	(1[C2]) 561.3 [M]+; t_R (c): 3.72 min.
13		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((S)-2-hydroxy-1-phenyl-ethyl)-amide]	454.3 [M+H]+, 452.3 [M-H]-; t_R (a): 2.63 min.
14		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2,3-difluoro-benzylamide)	460.1 [M+H]+; 415 [M-$CONH_2$]-; t_R (a): 2.95 min.
15		(2S,3S)-2-{[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-3-methyl-pentanoic	R_f (EtOAc) = 0.7; 504.3 [M+H]+, 526.3 [M+Na]+, 448.1 [MH-tBu]+, 502.2 [M-H]-, 459.2

		acid tert-butyl ester	[M-$CONH_2$]-; t_R (a): 3.42 min.
16		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(4-methoxy-piperidin-1-yl)-benzylamide]	(1[C1]) 589.3/592.3 [M+H]+, t_R (c): 3.76 min.
17		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-5-{[(2-dimethylamino-ethyl)-methyl-amino]-methyl}-2-fluoro-benzylamide)	(1[C2]) 590.2 [M]+; t_R (c): 3.25 min.
18		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-5-morpholin-4-ylmethyl-benzylamide)	(1[C2]) 575.2 [M]+; t_R (c): 3.57 min.
19		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-5-morpholin-4-yl-benzylamide)	(1) 561.3/564 [M+H]+,t_R (c): 4.26 min.
20		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(4-methoxy-piperidin-1-ylmethyl)-benzylamide]	(1[C2]) 603 [M+H]+; t_R (c): 3.72 min.

21		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{3-chloro-2-fluoro-5-[(2-methoxy-ethyl)-methyl-amino]-benzylamide}	(1[C1]) 563.3/566.3 [M+H]+, t_R (c): 3.99 min.
22		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{3-chloro-5-[(2-dimethylamino-ethylamino)-methyl]-2-fluoro-benzylamide}	(1[C2]) 576.2/579.2 [M+H]+, t_R (c): 3.27 min.

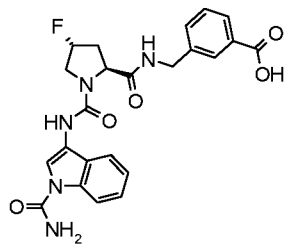
(1) The substituted benzylamine or aniline derivative used in step A was prepared as described in Part C [Scheme].

Example 23: 2-({[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-methyl)-benzoic acid



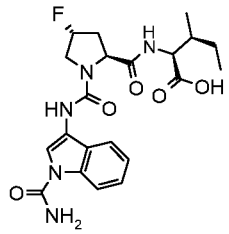
To a solution of 2-({[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-methyl)-benzoic acid tert-butyl ester (prepared according to Scheme D1 using 2-aminomethyl-benzoic acid tert-butyl ester) (76 mg, 0.145 mm) in CH_2Cl_2 (1 mL) was added TFA (168 µl, 2.18 mmol) and the resulting solution was stirred at RT overnight. The crude mixture was concentrated to give a solid which was suspended in Et_2O and filtered to give the desired material. MS (LC-MS): 468.1 [M+H]+, 490.1 [M+Na]+, 957.2 [2M+Na]+, 466.1 [M-H]-, 423.1 [M-$CONH_2$]-, t_R (HPLC conditions a): 2.64 min.

Example 24: 2-({[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-3-carbonyl]-amino}-methyl)-benzoic acid



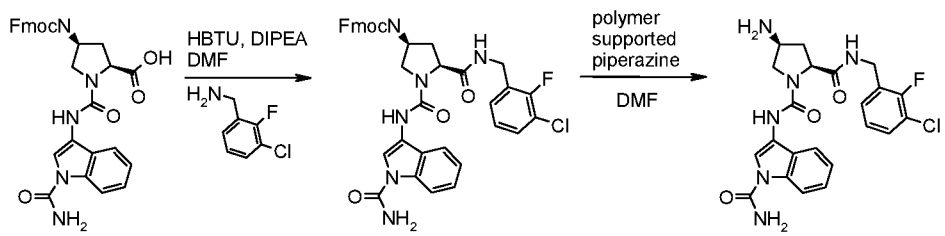
To a solution of 3-({[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-methyl)-benzoic acid tert-butyl ester (prepared according to Scheme D1 using 3-aminomethyl-benzoic acid tert-butyl ester) (21 mg, 0.04 mmol) in CH_2Cl_2 (0.5 mL) was added TFA (31 µl, 0.4 mmol) and the solution was stirred at RT for 24 h. The solvent was concentrated and the crude residue was purified by preparative HPLC (C18-ODB, 5 µm, 19x50 mm, waters, eluent: CH_3CN/H_2O + 0.1 % HCOOH flow: 20 mL/min, standard 20 % method) to give after lyophilization of the purified fractions the desired material. MS (LC-MS): 468 [M+H]+, 490 [M+Na]+, 466 [M-H]-, 423.0 [M-$CONH_2$]-; t_R (HPLC conditions a): 2.57 min.

Example 25: (2S,3S)-2-{[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-3-methyl-pentanoic acid



To a suspension of (2S,3S)-2-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-3-methyl-pentanoic acid tert-butyl ester **Example 15** (64 mg, 0.127 mmol) in CH_2Cl_2 (1 mL) was added TFA (97 µl, 1.27 mmol) and the resulting solution was stirred at RT for 20 h. TFA (1.27 mmol) was added again to ensure completion of the reaction. CH_2Cl_2 was concentrated and the crude residue was purified by preparative HPLC (C18-ODB, 5 µm, 19x50 mm, waters, eluent: CH_3CN/H_2O + 0.1% HCOOH flow: 20 mL/min, standard 20 % method) to give after lyophilization of the purified fractions the desired material which was dissolved in CH_3CN and was purified again on trimethylaminopropyl cartridge (Mega Bond Elut-SAX, 1 g, from Varian, conditioned with 20 mL of CH_3CN). The column was eluted with CH_3CN and the compound was finally released with 10 mL of HCl 0.1 N in CH_3CN, concentration led to a residue which was taken up in Et_2O and filtered-off to give the desired material. MS (LC-MS): 448.1 [M+H]+, 446 [M-H]-; t_R (HPLC conditions a): 2.67 min.

Scheme D2: general protocol described for the preparation of Example 26: (2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



A. (2S,4S)- 4-(9H-fluoren-9-ylmethoxycarbonylamino)-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)

(2S,4S)-1-[(1-carbamoyl-1H-indol-3-yl)-amide]-4-(9H-fluoren-9-ylmethoxycarbonylamino)-pyrrolidine-2-carboxylic acid (400 mg, 0.723 mmol, prepared as described in Scheme B10), 3-chloro-2-fluorobenzylamine (230 mg, 1.45 mmol) and HBTU (411 mg, 1.08 mmol) were dissolved in DMF (2.5 mL). DIPEA (0.378 mL, 2.18 mmol) was added and the reaction mixture was stirred at 25°C for 16 h. The reaction mixture was diluted in EtOAc and successively washed with HCl 1N and $NaHCO_3$ (5% in water). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to dryness. The crude residue was purified by preparative HPLC (Waters Sunfire C18-ODB, 5 um, 30x100mm, 20% CH_3CN/2 min, 20-100% CH_3CN/H_2O/18 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 mL/min) to give the desired compound. MS (LC/MS): 695 [M+H]+, 717 [M+Na]+; t_R (HPLC conditions b): 5.16 min.

Alternative protocol:

(2S,4S)-1-[(1-carbamoyl-1H-indol-3-yl)-amide]-4-(9H-fluoren-9-ylmethoxycarbonylamino)-pyrrolidine-2-carboxylic acid (40 mg, 0.072 mmol, prepared as described in Scheme B10) and amine (0.08 mmol) were dissolved in NMP (0.7 mL). DIPEA (0.025 mL, 0.143 mmol) and HBTU (40.6 mg, 0.107 mmol) were added and the reaction mixture was stirred at 25°C for 90 min. The reaction mixture was diluted with MeOH (1 mL) and filtered over a PTFE membrane (0.45 um). The resulting filtrate was purified by preparative HPLC (Waters Sunfire C18-ODB, 5 um, 30x150mm, 45% CH_3CN/3.0 min, 45-70% CH_3CN/H_2O/12 min, 70-95% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 50 mL/min) to give the desired compound.

Alternative protocol 2:

(2S,4S)-1-[(1-carbamoyl-1H-indol-3-yl)-amide]-4-(9H-fluoren-9-ylmethoxycarbonylamino)-pyrrolidine-2-carboxylic acid (70 mg, 0.126 mmol, prepared as described in Scheme B10), amine (0.253 mmol) and HBTU (100 mg, 0.264 mmol) were dissolved in DMF (2 mL). DIPEA (0.066 mL, 0.379 mmol) was added and the reaction mixture was stirred at 25°C for 90 min. The reaction mixture was diluted with MeOH (2 mL), filtered over a PTFE membrane (0.45 um) and washed with MeOH. The resulting filtrate was purified by preparative HPLC (Waters Sunfire C18-ODB, 5 um, 30x150mm, 20% CH_3CN/1.5 min, 20-88% CH_3CN/9 min, 88-100% CH_3CN/3 min, H_2O containing 0.1% TFA, flow: 50 mL/min) to give the desired compound.

B. (2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)

To a solution of (2S,4S)-4-(9H-fluoren-9-ylmethoxycarbonylamino)-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide) (209 mg, 0.3 mmol) in DMF (15 mL) was added piperazine polymer bound (Aldrich CAS 526290, loading = 1.5 mmol/g, 2 g, 3.01 mmol) and the reaction mixture was stirred at 25°C for 16 h. The reaction mixture was filtered, the polymer was washed with CH_2Cl_2 and the filtrate was concentrated to dryness. The crude residue was purified by preparative HPLC (Waters Sunfire C18-ODB, 5 um, 30x100mm, 20% CH_3CN/2 min, 20-100% CH_3CN/H_2O/18 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 40 mL/min) to give the title compound as a formate salt. MS (LC/MS): 473 [M+H]+; t_R (HPLC conditions b): 2.52 min.

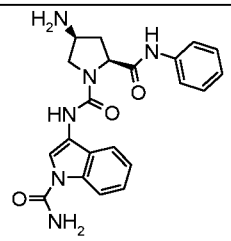
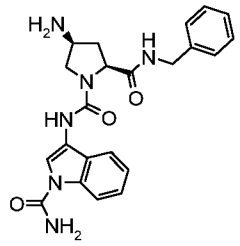
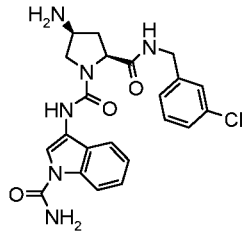
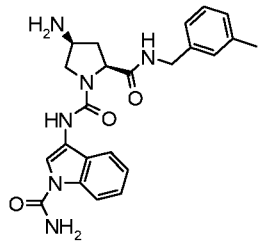
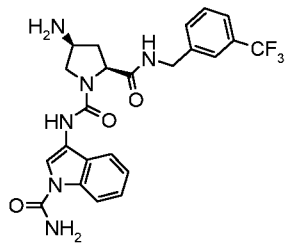
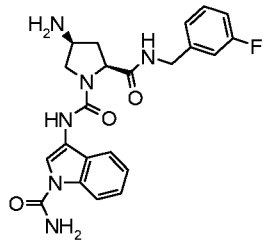
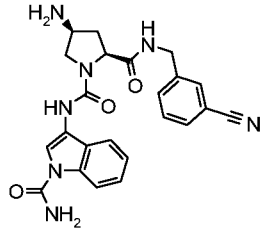
Alternative protocol:
Alternatively the crude residue can be purified by catch release using silicaPrep Tosic Acid-1g column (SPE-R60530B-06S from Silicycle). The column was conditioned with MeOH (10 mL), and the crude residue dissolved in MeOH was added. The column was washed MeOH (10 mL) and the compound released by elution with 2M ammonia in MeOH (10 mL).

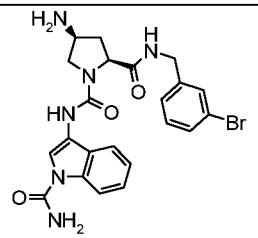
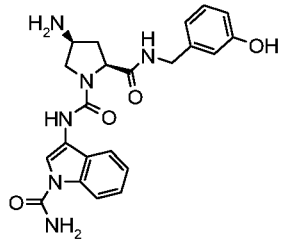
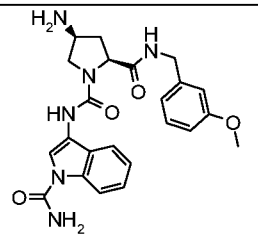
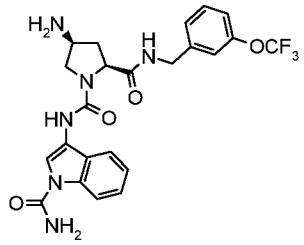
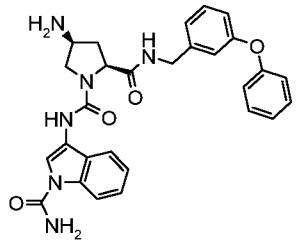
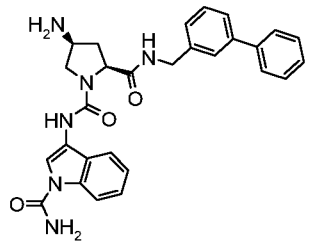
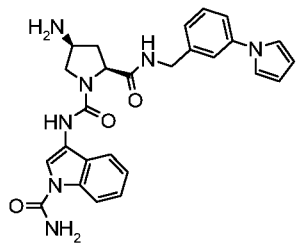
Alternative protocol 2:
To solutions of (2S,4S)-4-(9H-fluoren-9-ylmethoxycarbonylamino)-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] amides in DMF (2.0 mL) was added piperazine polymer bound (Aldrich CAS 526290, loading = 1.5 mmol/g, 2 g, 3.01 mmol), the reaction vessels were flushed with argon and the reaction mixtures were stirred at 25°C for 48 h. The resulting solutions were poured onto cartridges containing 500 mg of silicaPrep Tosic Acid (SPE-R60530B-06S from Silicycle), conditioned with MeOH (10 mL). The columns were washed with MeOH (20 mL) and the compounds were then released by elution with 2M ammonia in MeOH (10 mL).

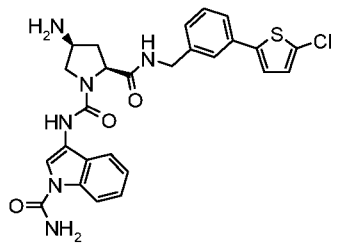
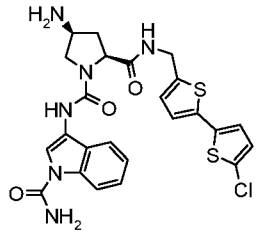
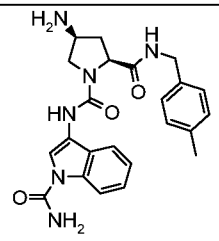
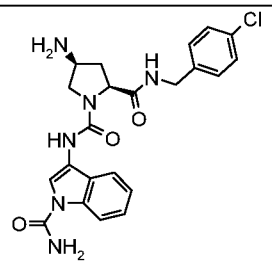
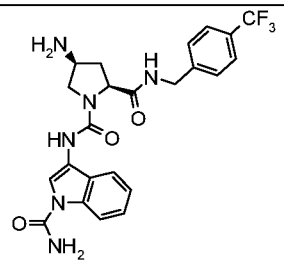
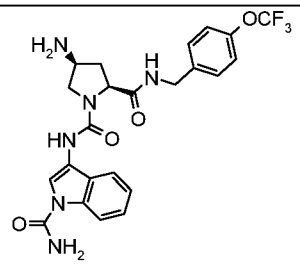
The examples below were prepared according to the general procedure described for **Example 26** *Scheme D2, using various amines in step A:*

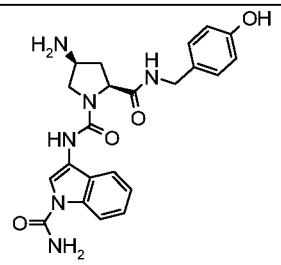
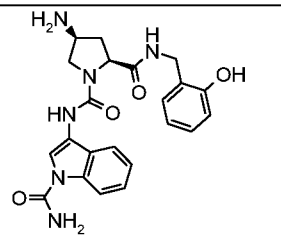
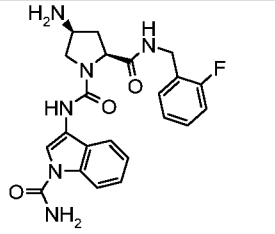
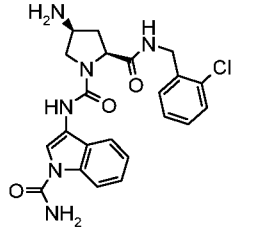
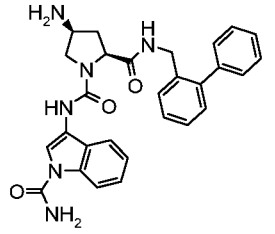
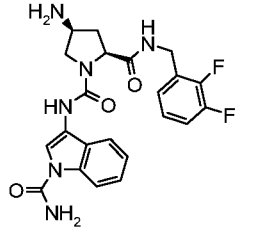
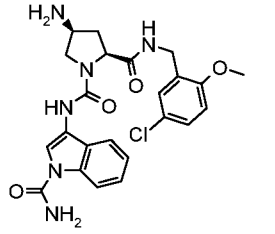
Table 2:

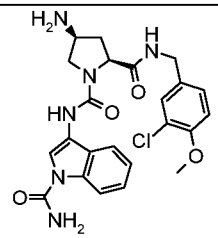
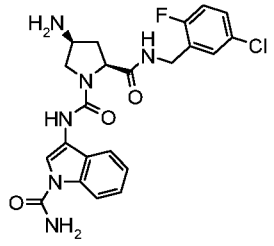
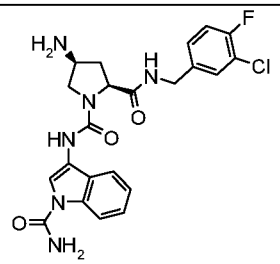
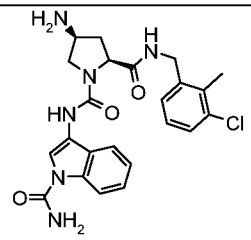
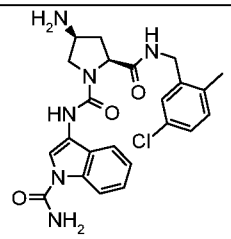
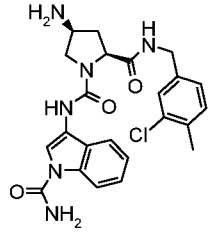
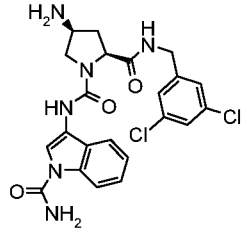
Example	Structure	Name	Characterization (end–table notes), TLC, R_f (eluent); MS (LC/MS); t_R (HPLC conditions)

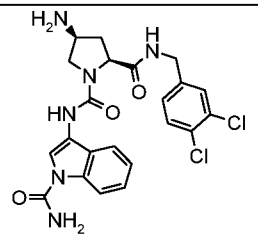
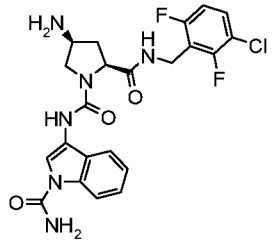
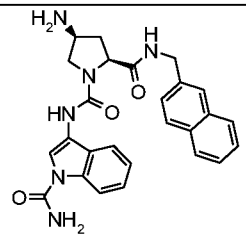
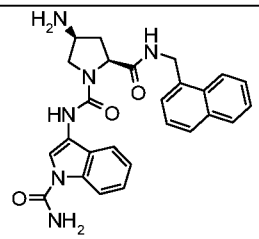
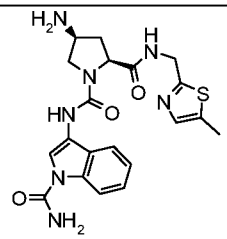
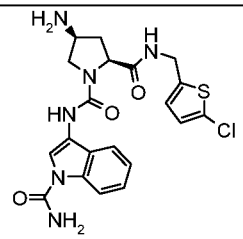
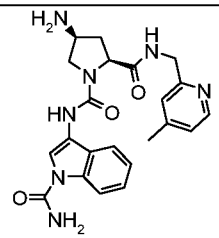
27		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-phenylamide	(1) 407 [M+H]+; t_R (d): 0.6 min.
28		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 2-benzylamide 1-[(1-carbamoyl-1H-indol-3-yl)-amide]	(2) 421.3 [M+H]+; t_R (d): 0.62 min.
29		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide) as a formate salt	(1) 454/456.1 [M+H]+, 932.2 [2M+Na]+, 453.1 [M-H]-; t_R (d): 2.51 min.
30		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-methyl-benzylamide)	(1) 435 [M+H]+; t_R (b): 2.62 min.
31		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-trifluoromethyl-benzylamide)	(1) 489 [M+H]+; t_R (b): 2.95 min.
32		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-fluoro-benzylamide)	(2) 439.1 [M+H]+; t_R (d): 0.75 min.
33		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-cyano-benzylamide)	(1) 446 [M+H]+; t_R (b) : 2.09 min.

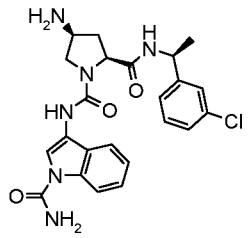
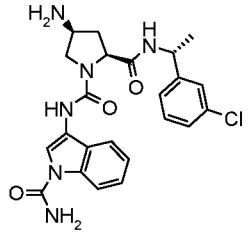
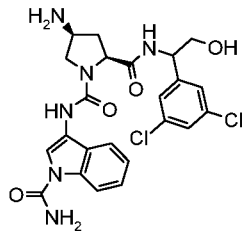
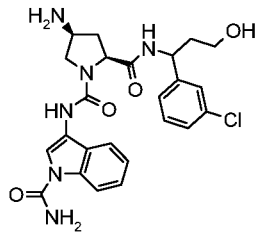
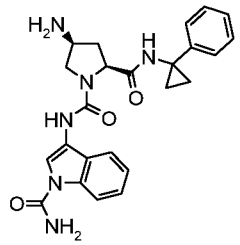
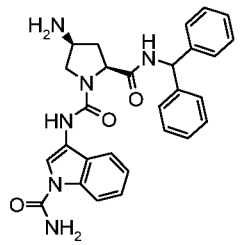
34		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 2-(3-bromo-benzylamide) 1-[(1-carbamoyl-1H-indol-3-yl)-amide]	(1) 499/501 [M+H]+; t_R (b) : 2.78 min.
35		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-hydroxy-benzylamide)	(2) 437.1 [M+H]+; t_R (d): 0.52 min.
36		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-methoxy-benzylamide)	(1) 451 [M+H]+; t_R (b) : 2.36.
37		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-trifluoromethoxy-benzylamide)	(2) 505.1 [M+H]+; t_R (d): 0.90 min.
38		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-phenoxy-benzylamide)	(2) 513.2 [M+H]+; t_R (d): 0.95 min.
39		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 2-[(biphenyl-3-ylmethyl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide] as a formate salt	(1) 497.2 [M+H]+, 495.2 [M-H]-; t_R (a): 2.8 min.
40		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-pyrrol-1-yl-benzylamide)	(2) 486.2 [M+H]+; t_R (d): 0.87 min.

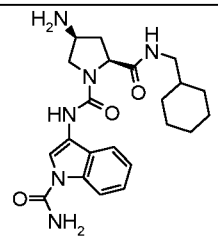
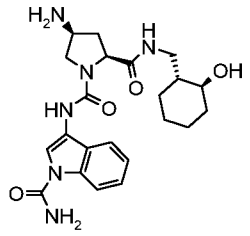
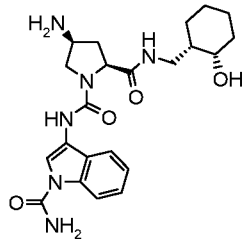
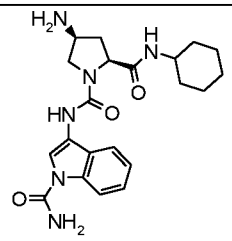
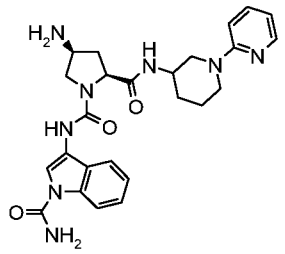
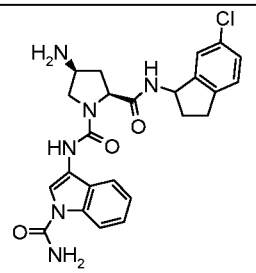
41		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-(5-chloro-thiophen-2-yl)-benzylamide]	(1) R_f (MeOH) = 0.25; 537.1/539.2 [M+H]+, 536/538 [M-H]-; t_R (a): 2.92 min.
42		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-amide]	(1) R_f (MeOH) = 0.28; 543.1/545 [M+H]+, 541/543.2 [M-H]-; t_R (a): 2.90 min.
43		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(4-methyl-benzylamide)	(3) 435.2 [M+H]+; t_R (d): 0.87 min.
44		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(4-chloro-benzylamide)	(2) 455 [M+H]+; t_R (d): 0.82 min.
45		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(4-trifluoromethyl-benzylamide)	(2) 489.1 [M+H]+; t_R (d): 0.88 min.
46		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(4-trifluoromethoxy-benzylamide)	(2) 505.1 [M+H]+; t_R (d): 0.91 min.

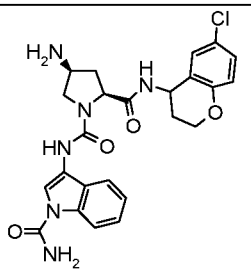
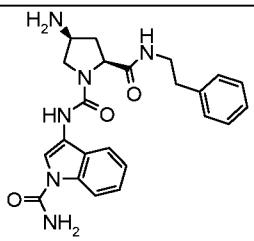
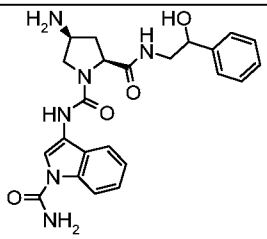
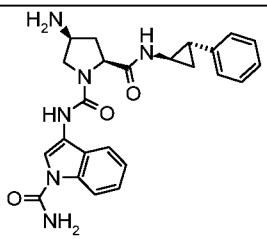
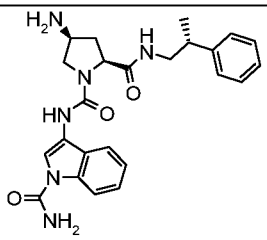
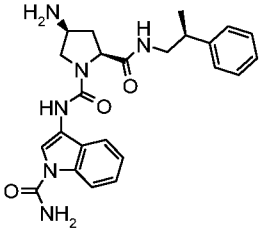
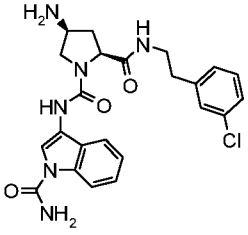
47		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(4-hydroxy-benzylamide)	(2) 437.1 [M+H]+; t_R (d): 0.52 min.
48		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2-hydroxy-benzylamide)	(3) 437.1 [M+H]+; t_R (d): 0.72 min.
49		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2-fluoro-benzylamide)	(1) 439.3 [M+H]+; t_R (b) : 2.12 min.
50		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2-chloro-benzylamide)	(3) 455.1 [M+H]+; t_R (d): 0.88 min.
51		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 2-[(biphenyl-2-ylmethyl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide]	(3) 497.1 [M+H]+; t_R (d): 1.02 min.
52		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2,3-difluoro-benzylamide)	(1) 457.2 [M+H]+; t_R (b): 2.24 min.
53		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(5-chloro-2-methoxy-benzylamide)	(1) 485 [M+H]+; t_R (b) : 2.80 min.

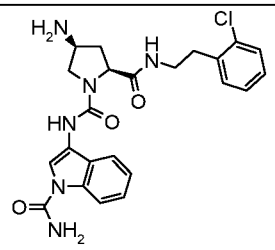
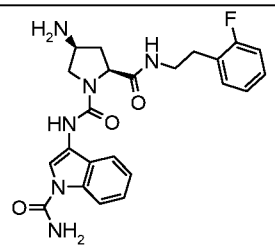
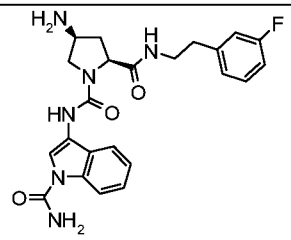
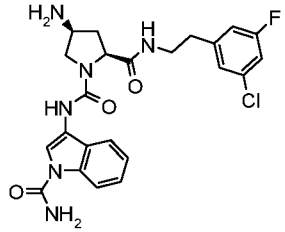
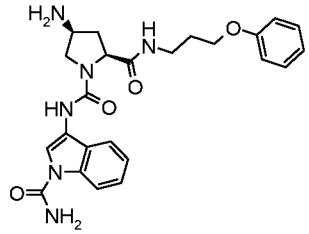
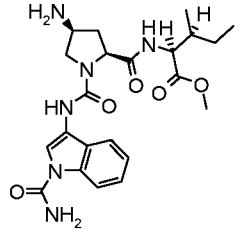
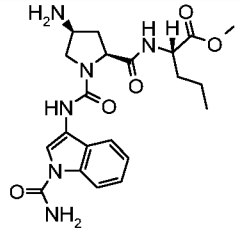
54		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-4-methoxy-benzylamide)	(1) 485 [M+H]+; t_R (b): 2.67 min.
55		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(5-chloro-2-fluoro-benzylamide)	(1) 473 [M+H]+; t_R (b): 2.68 min.
56		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-4-fluoro-benzylamide)	(1) 473 [M+H]+; t_R (b): 2.77 min.
57		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-methyl-benzylamide)	(1) 469 [M+H]+; t_R (b): 2.82 min.
58		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(5-chloro-2-methyl-benzylamide)	(1) 469 [M+H]+; t_R (b): 2.84 min.
59		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-4-methyl-benzylamide)	(1) 469 [M+H]+; t_R (b) : 2.93 min.
60		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3,5-dichloro-benzylamide)	(3) 489.1 [M+H]+; t_R (d): 0.96 min.

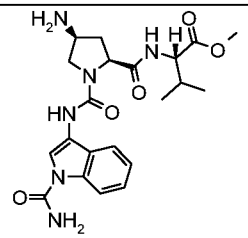
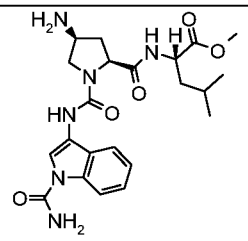
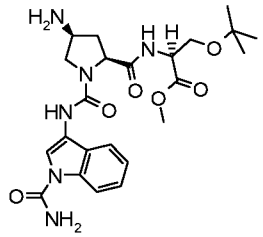
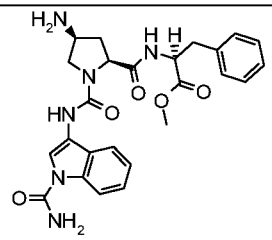
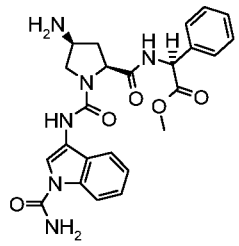
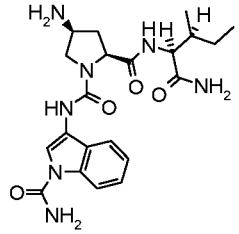
61		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3,4-dichloro-benzylamide)	(3) 489.1 [M+H]+; t_R (d): 0.96 min.
62		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2,6-difluoro-benzylamide)	(3) 491.1 [M+H]+; t_R (d): 0.88 min.
63		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(naphthalen-2-ylmethyl)-amide]	(3) 471.2 [M+H]+; t_R (d): 0.95 min.
64		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(naphthalen-1-ylmethyl)-amide]	(3) 471.2 [M+H]+; t_R (d): 0.94 min.
65		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-methyl-thiazol-2-ylmethyl)-amide]	(3,4) 442.1 [M+H]+; t_R (d): 0.60 min.
66		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-chloro-thiophen-2-ylmethyl)-amide]	(1) 461 [M+H]; t_R (b) : 2.37 min.
67		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(4-methyl-pyridin-2-ylmethyl)-amide]	(3,4) 436.2 [M+H]+; t_R (e): 1.13 min.

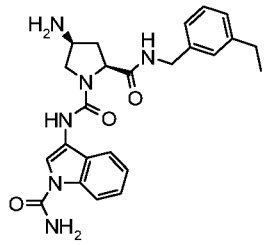
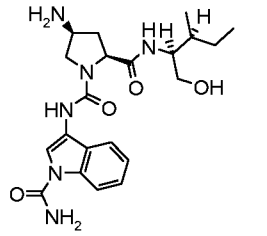
68		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-phenyl)-ethyl]-amide} as a formate salt	(1) 469/471 [M+H]+, 424/426 [M-$CONH_2$]-; t_R (a): 2.57 min.
69		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(R)-1-(3-chloro-phenyl)-ethyl]-amide} as a formate salt	(1) 469/471 [M+H]+, 424/426 [M-$CONH_2$]-; t_R (a): 2.59 min.
70		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[1-(3,5-dichloro-phenyl)-2-hydroxy-ethyl]-amide}	(1) mixture of 2 diastereosiomers. 519 [M+H]+; t_R (b): 2.72/2.76 min.
71		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[1-(3-chloro-phenyl)-3-hydroxy-propyl]-amide}	(3) 499.1 [M+H]+; t_R (d): 0.82 min.
72		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(1-phenyl-cyclopropyl)-amide]	(2) 447.1 [M+H]+; t_R (d): 0.77 min.
73		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 2-benzhydryl-amide 1-[(1-carbamoyl-1H-indol-3-yl)-amide] as a formate salt	(1) 497.2 [M+H]+, 495.2 [M-H]-; t_R (a): 2.80 min.

74		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-cyclohexylmethyl-amide	(2) 427.1 [M+H]+, t_R (d): 0.83 min.
75		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((1R*,2S*)-2-hydroxy-cyclohexylmethyl)-amide]	(2) mixture of trans diastereoisomers: 443.2 [M+H]+, 465.2 [M+Na]+, 441.2 [M-H]-; t_R (a): 1.84/1.36 min.
76		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((1S,2S)-2-hydroxy-cyclohexylmethyl)-amide]	(3) 443.2 [M+H]+; t_R (d): 0.70 min.
77		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-cyclohexylamide	(2) 413.1 [M+H]+, t_R (d): 0.75 min.
78		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3-yl)-amide]	(2) Mixture of diastereoisomers 491.2 [M+H]+, t_R (e): 1.12/1.19 min.
79		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(6-chloro-indan-1-yl)-amide]	(3) 481.1 [M+H]+; t_R (d): 0.94 min.

80		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(6-chloro-chroman-4-yl)-amide]	(3) 497.1 [M+H]+; t_R (d): 0.92 min.
81		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(phenethyl-amide)	(2) 435.1 [M+H]+, t_R (d): 0.77 min.
82		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-hydroxy-2-phenyl-ethyl)-amide]	(3) 451.2 [M+H]+; t_R (d): 0.71 min.
83		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((1R,2S)-2-phenyl-cyclopropyl)-amide]	(3) 447.2 [M+H]+; t_R (d): 0.90 min.
84		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((R)-2-phenyl-propyl)-amide]	(3) 449.2 [M+H]+; t_R (d): 0.90 min.
85		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((S)-2-phenyl-propyl)-amide]	(3) 449.2 [M+H]+; t_R (d): 0.90 min.
86		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[2-(3-chloro-phenyl)-ethyl]-amide}	(3) 469.1 [M+H]+; t_R (d): 0.91 min.

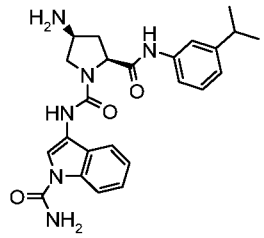
87		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1Hindol-3-yl)-amide] 2-{[2-(2-chloro-phenyl)-ethyl]-amide}	(3) 469.1 [M+H]+; t_R (d): 0.91 min.
88		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1Hindol-3-yl)-amide] 2-{[2-(2-fluoro-phenyl)-ethyl]-amide}	(3) 453.1 [M+H]+; t_R (d): 0.86 min.
89		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1Hindol-3-yl)-amide] 2-{[2-(3-fluoro-phenyl)-ethyl]-amide}	(3) 453.1 [M+H]+; t_R (d): 0.86 min.
90		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[2-(3-chloro-5-fluoro-phenyl)-ethyl]-amide}	(3) 473.1 [M+H]+; t_R (d): 0.90 min.
91		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-phenoxy-ethyl)-amide]	(2) 451.1 [M+H]+, t_R (d): 0.78 min.
92		(2S,3S)-2-{[(2S,4S)-4-Amino-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-3-methyl-pentanoic acid methyl ester	(2) 459.1 [M+H]+, t_R (d): 0.79 min.
93		(S)-2-{[(2S,4S)-4-Amino-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-pentanoic acid methyl ester	(3) 445.2 [M+H]+; t_R (d): 0.80 min.

94		(R)-2-{[(2S,4S)-4-Amino-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-3-methyl-butyric acid methyl ester	(3) 445.2 [M+H]+; t_R (d): 0.76 min.
95		(S)-2-{[(2S,4S)-4-Amino-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-4-methyl-pentanoic acid methyl ester	(3) 459.2 [M+H]+; t_R (d): 0.87 min.
96		(S)-2-{[(2S,4S)-4-Amino-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-3-tert-butoxy-propionic acid methyl ester	(3) 489.2 [M+H]+; t_R (d): 0.87 min.
97		(S)-2-{[(2S,4S)-4-Amino-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-3-phenyl-propionic acid methyl ester	(3) 493.2 [M+H]+; t_R (d): 0.88 min.
98		(S)-{[(2S,4S)-4-Amino-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-phenyl-acetic acid methyl ester	(3) 479.1 [M+H]+; t_R (d): 0.84 min.
99		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((1S,2S)-1-carbamoyl-2-methyl-butyl)-amide]	(2) 444.1 [M+H]+, t_R (d): 0.61 min.

100		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-ethyl-benzylamide)	(2) 449.1 [M+H]+; t_R (d): 0.86 min.
101		(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((1S,2S)-1-hydroxymethyl-2-methyl-butyl)-amide]	(2) 431.1 [M+H]+, t_R (d): 0.69 min.

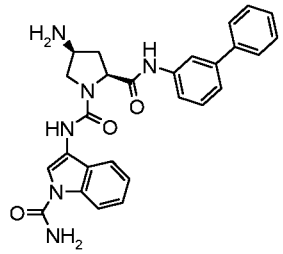
(1) Compound prepared according to the general procedure described for **Example 26** Scheme D2; (2) Compound prepared according to the alternative protocol described for step A and using silica gel derivatized piperazine (SPE-R60530B-06S from Silicycle) in step B; (3) Compound prepared using the alternative protocols 2 for both step A and B ; (4) In Step B stirring was continued at 60°C for additional 30 h.

Example 102: (2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-isopropyl-phenyl)-amide]



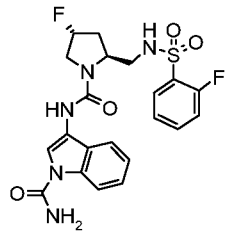
was prepared according to the general procedure described in Scheme D2 using 5 equivalents of 3-isopropylaniline in step A and silica gel derivatized piperazine (Silicycle, loading = 0.9 mmol/g, cat. Number: SPE-R60030B) in step B. MS (LC/MS): 449.2 [M+H]+, 920.3 [2M+Na]+, 447.3 [M-H]-; t_R (HPLC conditions a): 2.74 min.

Example 103: (2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 2-biphenyl-3-ylamide 1-[(1-carbamoyl-1H-indol-3-yl)-amide]



was prepared according to the general procedures described in Scheme D2 using 10 equivalents of biphenyl-3-ylamine in step A. MS (LC/MS): 483.3 [M+H]+, 481.2 [M-H]-; t_R (HPLC conditions a): 2.83 min.

Scheme D3: general protocol described for the preparation Example 104: 3-({(2S,4R)-4-Fluoro-2-[(2-fluoro-benzenesulfonylamino)-methyl]-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide

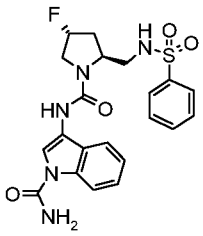
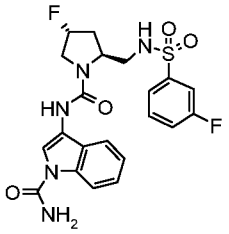
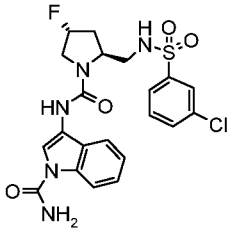
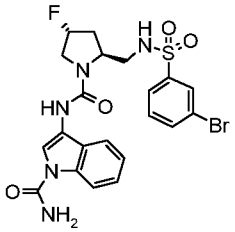
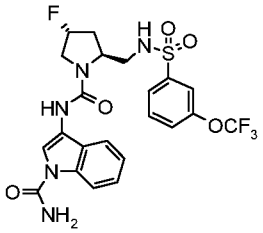
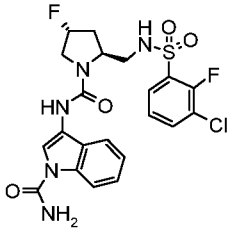


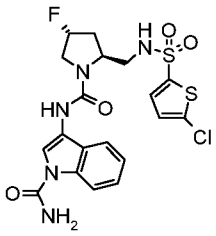
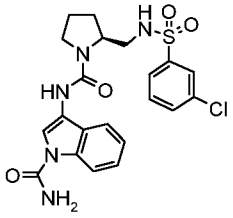
To a mixture of 3-[((2S,4R)-2-aminomethyl-4-fluoro-pyrrolidine-1-carbonyl)-amino]-indole-1-carboxylic acid amide (52 mg, 0.163 mmol) (prepared as described Scheme B11) and 2-fluorobenzenesulfonyl chloride (24 µL, 0.179 mmol) in CH_2Cl_2 (0.5 mL), was added triethylamine (25 µL, 0.179 mmol) and the resulting suspension was stirred at RT under nitrogen overnight. The mixture was poured into water and extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 19x50 mm, eluent: 20% to 100% CH_3CN in H_2O in 15 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 20 mL/min) to give after lyophilization of the purified fractions the desired material. R_f, TLC (EtOAc) = 0.55; MS (LC-MS): 478.1 [M+H]+, 500 [M+Na]+, 516 [M+K]+, 977.2 [2M+Na]+, 476 [M-H]-; t_R (HPLC conditions f): 1.73 min.

The examples below were prepared according to the procedure described in Scheme D3 for **Example 104,** *using various sulfonyl chlorides:*

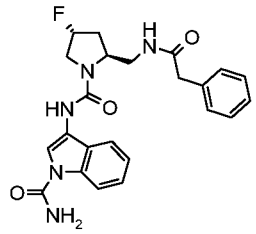
Table 3:

Example	Structure	Name	Characterization TLC, R_f (eluent); MS (LC/MS); t_R (HPLC conditions)

105		3-{[(2S,4R)-2-(Benzenesulfonylamino-methyl)-4-fluoro-pyrrolidine-1-carbonyl]-amino}-indole-1-carboxylic acid amide	R_f (EtOAc) = 0.65; 460 [M+H]+, 482 [M+Na]+, 919 [2M+H]+, 941 [2M+Na]+, 458.2 [M-H]-; t_R (f): 1.71 min.
106		3-({(2S,4R)-4-Fluoro-2-[(3-fluoro-benzenesulfonylamino)-methyl]-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide	R_f (EtOAc) = 0.7; 478 [M+H]+, 476 [M-H]-; t_R (f): 1.79 min.
107		3-({(2S,4R)-4-Fluoro-2-[(3-chloro-benzenesulfonylamino)-methyl]-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide	R_f (EtOAc) = 0.7; 494/496 [M+H]+, 516.1/518.2 [M+Na]+, 492/494 [M-H]-; t_R (f): 1.99 min.
108		3-({(2S,4R)-4-Fluoro-2-[(3-bromo-benzenesulfonylamino)-methyl]-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide	R_f (EtOAc) = 0.70; 537.9/539.9 [M+H]+, 559.9/561.8 [M+Na]+, 356/538 [M-H]-; t_R (f): 1.89 min.
109		3-({(2S,4R)-4-Fluoro-2-[(3-trifluoromethoxy-benzenesulfonylamino)-methyl]-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide	R_f (EtOAc) = 0.75; 544.2 [M+H]+, 566 [M+Na]+, 542 [M-H]-; t_R (f): 2.08 min.
110		3-({(2S,4R)-2-[(3-Chloro-2-fluoro-benzenesulfonylamino)-methyl]-4-fluoro-pyrrolidine-1-carbonyl}-amino)-indole-1-	512/514 [M+H]+, 534.1/536 [M+Na]+, 510/512 [M-H]-; t_R (f): 1.92 min.

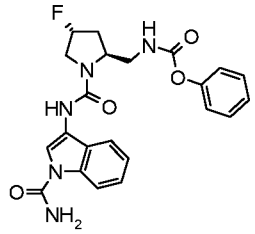
		carboxylic acid amide	
111		3-({(2S,4R)-2-[(5-Chloro-thiophene-2-sulfonylamino)-methyl]-4-fluoro-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide	R_f (EtOAc) = 0.7; 500/502 [M+H]+, 522/524 [M+Na]+, 498/500 [M-$CONH_2$]-; t_R (f): 1.88 min.
112		3-({(S)-2-[(3-Chloro-benzenesulfonylamino)-methyl]-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide	476.0 [M+H]+, 474.1 [M-H]-; t_R (a): 3.34 min.

Example 113: 3-{[(2S,4R)-4-Fluoro-2-(phenylacetylamino-methyl)-pyrrolidine-1-carbonyl]-amino}-indole-1-carboxylic acid amide



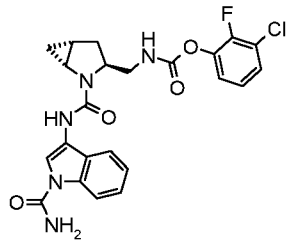
To a mixture of 3-[((2S,4R)-2-aminomethyl-4-fluoro-pyrrolidine-1-carbonyl)-amino]-indole-1-carboxylic acid amide (50 mg, 0.16 mmol, prepared as described in Scheme B11) and phenylacetyl chloride (23 µL, 0.17 mmol) in CH_2Cl_2 (0.5 mL), was added triethylamine (24 µL, 0.17 mmol) and the resulting suspension was stirred at RT under N_2 overnight. The mixture was poured into water and extracted with CH_2Cl_2 (x2). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 19x50 mm, eluent: 20% to 100% CH_3CN in H_2O in 15 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 20 mL/min) to give after lyophilization of the purified fractions the desired material. R_f, TLC (EtOAc) = 0.1; MS (LC-MS): 438.1 [M+H]+, 897.2 [2M+Na]+, 393.1 [M-$CONH_2$]-; t_R (HPLC conditions f): 1.70 min.

Example 114: [(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidin-2-ylmethyl]-carbamic acid phenyl ester



To a mixture of 3-[((2S,4R)-2-aminomethyl-4-fluoro-pyrrolidine-1-carbonyl)-amino]-indole-1-carboxylic acid amide (50 mg, 0.157 mmol, prepared as described in Scheme B11) and phenyl chloroformate (22 µL, 0.17 mmol) in CH_2Cl_2 (0.5 mL), was added triethylamine (24 µL, 0.17 mmol) and the resulting suspension was stirred at RT under nitrogen overnight. The mixture was poured into water and extracted with CH_2Cl_2 (x2). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 19x50 mm, eluent: 20% to 100% CH_3CN in H_2O in 15 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 20 mL/min) to give after lyophilization of the purified fractions the desired material. R_f, TLC (EtOAc) = 0.45; MS (LC-MS): 440 [M+H]+, 901.3 [2M+Na]+; t_R (HPLC conditions f): 1.77 min.

Example 115: [(1R,3S,5R)-2-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-3-ylmethyl]-carbamic acid 3-chloro-2-fluoro-phenyl ester



To a solution of [(1R,3S,5R)-1-(2-aza-bicyclo[3.1.0] hex-3-yl)methyl]-carbamic acid 3-chloro-2-fluoro-phenyl ester, trifluoroacetate (60.0 mg, 0.211 mmol) and Et_3N (88 µl, 0.62 mmol) in THF (5 mL) was added 3-isocyanato-indole-1-carboxylic acid amide (43.0 mg, 0.211 mmol ; prepared as described in Scheme A1). The solution was stirred at RT under a nitrogen atmosphere for 3 days. Purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, eluent: 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 mL/min) afforded after lyophilization of the purified HPLC fractions the title compound. MS (LC/MS): 486.0 [M+H]+; t_R (HPLC conditions k): 3.57 min.

(1R,3S,5R)-3-[(3-Chloro-2-fluoro-phenoxycarbonylamino)-methyl]-2-aza-icyclo[3.1.0]-hexane-2-carboxylic acid tert-butyl ester

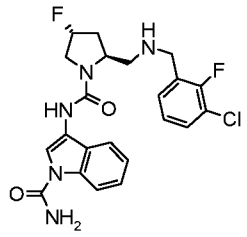
To a solution of 3-chloro-2-fluorophenol (180 mg, 1.20 mmol) in dry CH_2Cl_2 (10 mL), cooled to at 0°C, was added triphosgene (120 mg, 0.4 mmol) followed by dropwise addition of a solution of DIPEA (210 µL, 1.20 mmol) in CH_2Cl_2 (5 mL). The mixture was allowed to warm to RT and

stirring was continued for 1 h. The reaction mixture was then added dropwise to a solution of (1R,3S,5R)-3-aminomethyl-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester (170 mg, 0.80 mmol) (prepared as described in Part B) and DIPEA (168 µL, 0.96 mmol) in CH_2Cl_2 (10 mL) at RT. After stirring for 2 h, the reaction was quenched by addition of methanol (2 mL) and water with vigorous stirring. The mixture was extracted with CH_2Cl_2 (2x), the combined organics were washed with brine, dried (phase separator) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (eluent gradient: c-hexane/EtOAc 9:1 to c-hexane/EtOAc 1:1) afforded the title compound as a colorless wax. MS (LC/MS): 385.0 [M+H]+; t_R (HPLC conditions k): 4.03 min.

[(1R,3S,5R)-1-(2-Aza-bicyclo[3.1.0] hex-3-yl)methyl]-carbamic acid 3-chloro-2-fluoro-phenyl ester, trifluoroacetate

To a solution of (1R,3S,5R)-3-[(3-chloro-2-fluoro-phenoxycarbonylamino)-methyl]-2-aza-icyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester (130 mg, 0.34 mmol) in CH_2Cl_2 (4 mL) was added TFA (2 mL, 26 mmol) and solution was stirred at RT for 2 h. Methanol was then added and volatiles were removed under reduced pressure. The residue was taken up in MeOH and concentrated in vacuo to afford the crude title compound as a colorless wax. MS (LC/MS): 285.0 [M+H]+; t_R (HPLC conditions k): 2.66 min. The material thus obtained was used directly in the next step without further purification.

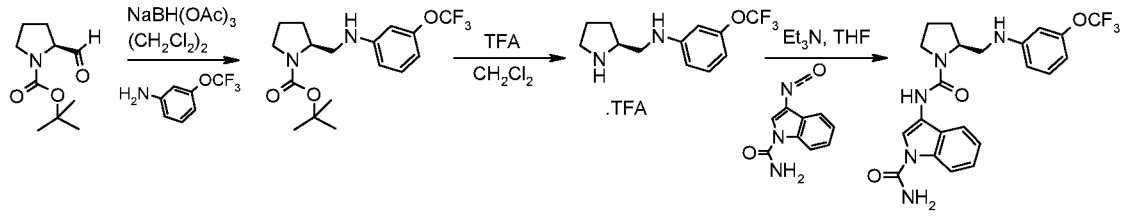
Example 116: 3-({(2S,4R)-2-[(3-Chloro-2-fluoro-benzylamino)-methyl]-4-fluoro-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide



3-[((2S,4R)-2-Aminomethyl-4-fluoro-pyrrolidine-1-carbonyl)-amino]-indole-1-carboxylic acid amide (50 mg, 0.157 mmol) and 3-chloro-2-fluorobenzaldehyde (25 mg, 0.157 mmol, prepared as described in Scheme B11) were mixed in dichloroethane (1 mL), sodium triacetoxyborohydride (46.5 mg, 0.22 mmol) was added and the mixture was stirred at RT under nitrogen for 2 days. 3-Chloro-2-fluorobenzaldehyde (25 mg, 0.157 mmol) and triacetoxyborohydride (46.5 mg, 0.219 mmol) were added to complete the reaction. The reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered and condentrated. The crude residue diluted in MeOH was purified by SiliaPrep Tosic Acid-1g (SPE-R60530B-06S from Silicycle), the column was washed with 10 mL of MeOH and the compound released with

10 mL of 2M ammonia in MeOH to give after concentration the desired material which was further purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 19x50 mm, eluent: 20% to 100% CH_3CN in H_2O in 15 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 20 mL/min) to give after lyophilization of the purified fractions the desired material as a formic acid salt. MS (LC-MS): 462.1/464 [M+H]+, 460/462 [M-H]-; t_R (HPLC, condditons f): 1.54 min.

Example 117: 3-({(S)-2-[(3-Trifluoromethoxy-phenylamino)-methyl]-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide



A. (S)-2-[(3-Trifluoromethoxy-phenylamino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

N-(tert-Butoxycarbonyl)-L-prolinal (200 mg, 1,00 mmol) and 3-trifluoromethoxy-phenylamine (186,8 mg, 1,05 mmol) were mixed in 1,2-dichloroethane (10 mL) and treated with sodium triacetoxyborohydride (314 mg, 1,41 mmol). The mixture was stirred at RT under nitrogen overnight, then quenched by addition of water, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated. The crude oil was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 1:1) to give the desired material. MS (LC/MS): 361,1 [M+H]+.

B. (S)-1-Pyrrolidin-2-ylmethyl-(3-trifluoromethoxy-phenyl)-amine

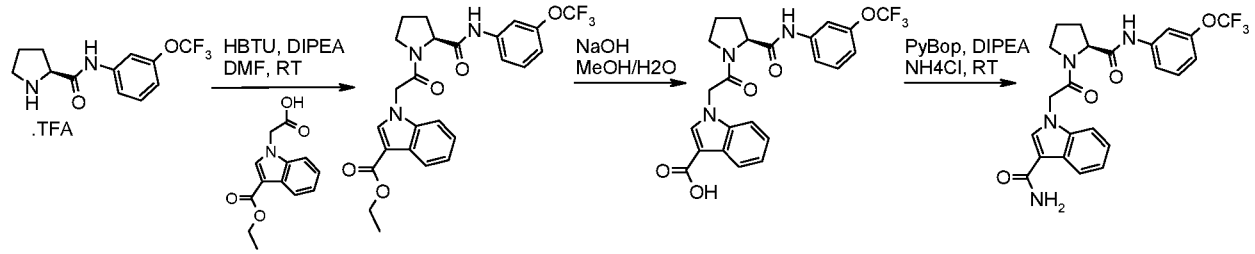
A solution of (S)-2-[(3-trifluoromethoxy-phenylamino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (100 mg, 0.277 mmol) and TFA (1 mLl) in CH_2Cl_2 (2 mL) was stirred at RT for 2 h. Solvent was concentrated and the residue was co-evaporated twice with CH_2Cl_2 and dried under high vacuum overnight to give the crude title compound as a TFA salt. MS: 261.1 [MH-Boc]+, t_R (HPLC conditions a): 2.61 min.

C. 3-({(S)-2-[(3-Trifluoromethoxy-phenylamino)-methyl]-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide

To a solution of (S)-1-pyrrolidin-2-ylmethyl-(3-trifluoromethoxy-phenyl)-amine (49 mg, 0.131 mmol) and Et_3N (55 µl, 0.393 mmol) in THF (1.5 mL) was added a solution of 3-isocyanato-1-methyl-1H-indole (26 mg, 0.393 mmol, prepared as described in Scheme A1) in THF (1.5 mL). The resulting solution was stirred at RT under nitrogen for 1 h. The mixture was poured into water and extracted twice with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by preparative HPLC (Waters C18-

ODB, 5 µm, 19x50 mm, eluent: CH_3CN /H_2O + 0.1 % HCOOH, flow: 20 ml/min) to give after lyophilisation of the purified fraction the title compound. TLC, R_f (c-hexane/EtOAc 1:2) = 0.23; MS (LC/MS): 462.1 [M+H]+, 484.1 [M+Na]+; t_R (HPLC conditions a): 3.75 min.

Example 118: 1-{2-Oxo-2-[(S)-2-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidin-1-yl]-ethyl}-1H-indole-3-carboxylic acid amide



A. 1-{2-Oxo-2-[(S)-2-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidin-1-yl]-ethyl}-1H-indole-3-carboxylic acid ethyl ester

The title compound was prepared according to the general procedure described in Scheme D6 using 1-carboxymethyl-1H-indole-3-carboxylic acid ethyl ester (prepared as described in Part A) and DMF as solvent. TLC, R_f (EtOAc) = 0.56; MS (LC/MS): 526 [M+Na]+, 502 [M-H]-; t_R (HPLC conditions a): 3.90 min.

B. 1-{2-Oxo-2-[(S)-2-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidin-1-yl]-ethyl}-1H-indole-3-carboxylic acid

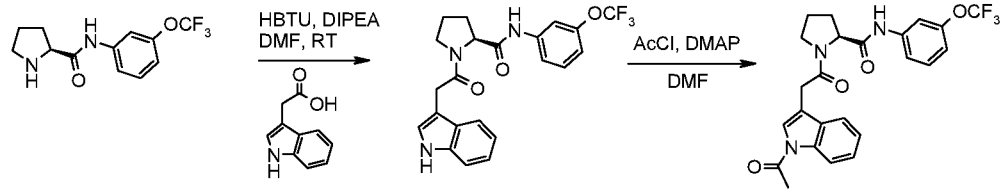
To a solution of 1-{2-oxo-2-[(S)-2-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidin-1-yl]-ethyl}-1H-indole-3-carboxylic acid ethyl ester (314 mg, 0.62 mmol) in MeOH (12 mL) and water (1.2 mL) was added NaOH 1N (1.87 mL, 1.87 mmol) and the mixture was heated at 80°C for 6 h. MeOH was concentrated, HCl 1N was added and the residue was extracted with EtOAc. The organic extracts were dried with Na_2SO_4, filtered and concentrated. The crude residue was purified by preparative HPLC (Interchrom C18-ODB, 10 µm, 28x250 mm, 20% CH_3CN in H_2O 2.5 min, then 20% to 100 % CH_3CN in H_2O in 32.5 min, CH_3CN and H_2O containing 0.1 % HCOOH; flow: 40 mL/min) to give after lyophilization of the purified fractions the desired compound. TLC, R_f (EtOAc) = 0.05; MS (LC/MS): 498.1 [M+Na]+, 474.1 [M-H]- ; t_R (HPLC conditions a): 3.48 min.

C. Example 118: 1-{2-Oxo-2-[(S)-2-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidin-1-yl]-ethyl}-1H-indole-3-carboxylic acid amide

1-{2-Oxo-2-[(S)-2-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidin-1-yl]-ethyl}-1H-indole-3-carboxylic acid (11 mg, 0.023 mmol), was treated with PyBOP (12 mg, 0.023 mmol), HOBt (3.54 mg, 0.023 mmol), DIPEA (16 µL, 0.092 mmol), and NH_4Cl (1 mg, 0.069 mmol) in DMF (1 mL) and the reaction mixture was stirred at RT under nitrogen for 3 h, then poured into an

aqueous saturated solution of $NaHCO_3$, EtOAc (20 mL) was added and the layers were separated. The aqueous layer was back-extracted twice with EtOAc and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by preparative HPLC (Waters SunFire C18-ODB, 5 µm, 19x50 mm, 20% CH_3CN/H_2O 2.5 min, 20-100% CH_3CN/H_2O in 10 min, CH_3CN/H_2O containing 0.1 % HCOOH flow: 20 mL/min) to give after lyophilization of the purified fractions the desired compound. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.17; MS (LC/MS): 473.2 [M-H]-; t_R (HPLC conditions a): 3.24 min.

Example 119 (S)-1-[2-(1-Acetyl-1H-indol-3-yl)-acetyl]-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide



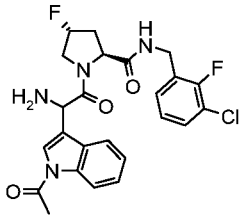
A. (S)-1-(2-1H-Indol-3-yl-acetyl)-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide

The title compound was prepared according to the general procedure described in Scheme D6 using (1H-indol-3-yl)-acetic acid using DMF as solvent. TLC, R_f (c-hexane/EtOAc 1:1) = 0.14; MS (LC/MS): 432.3 [M+H]+, 454.1 [M+Na]+; t_R (HPLCconditions a): 3.68 min.

B. Example 119: (S)-1-[2-(1-Acetyl-1H-indol-3-yl)-acetyl]-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide

To a solution of (S)-1-(2-1H-indol-3-yl-acetyl)-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide (100 mg, 0.232 mmol) in DMF (1.5 mL) under nitrogen atmosphere were added acetyl chloride (148 µl, 2.09 mmol) followed by DMAP (85 mg, 0.7 mmol) and the reaction mixture was heated at 80°C for 18 h. After completion of the reaction, the mixture was poured into citric acid (10% solution), and extracted three times with EtOAc. The combined organic layers were washed twice with water, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by preparative HPLC (Waters SunFire C18-ODB, 5 µm, 19x50 mm, 20% CH_3CN/H_2O 2.5 min, 20-100% CH_3CN/H_2O in 10 min, CH_3CN/H_2O containing 0.1 % HCOOH flow: 20 mL/min) to give after lyophilization of the purified fractions the desired compound. TLC, R_f (c-hexane/EtOAC 3:7) = 0.16; MS (LC/MS): 474.1 [M+H]+, 496 [M+Na]+, 472 [M-H]- ; t_R (HPLC conditions a): 3.80 min.

Example 120: (2S,4R)-1-[2-(1-Acetyl-1H-indol-3-yl)-2-amino-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide

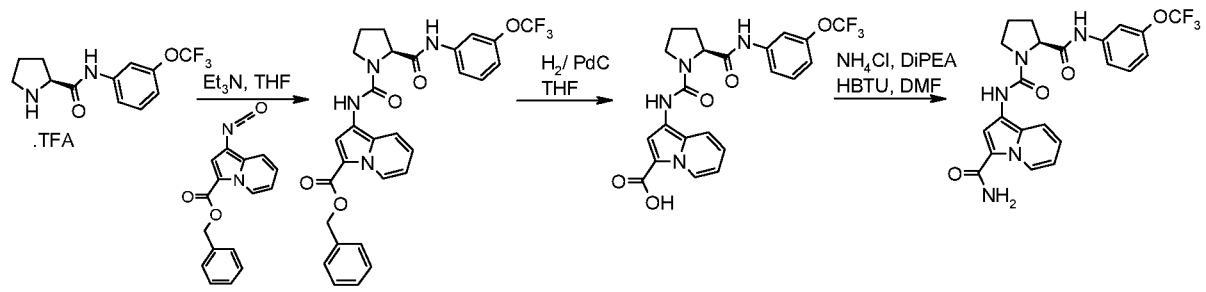


A solution of {1-(1-acetyl-1H-indol-3-yl)-2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-carbamic acid tert-butyl ester (102 mg, 0.173 mmol) and TFA (66.7 µL, 0.866 mmol) in CH_2Cl_2 (0.58 mL) was stirred at 23°C overnight. TFA (66.7 µL, 0.866 mmol) was again added and the reaction mixture was stirred at 23°C for an additional 4 h to complete the reaction. Solvents were removed in vacuo and the crude residue was purified by preparative HPLC (Waters SunFire C18ODB, 5 µm, 19x50, eluent: 5% CH_3CN /95% H_2O to 100% CH_3CN in 17 min, CH_3CN and H_2O containing 0.1% of TFA, flow 20 mL/min) to give after lyophilization of the purified fractions the desired material. MS (LC-MS): 487.1 [M-H]-; t_R (HPLC conditions b): 3.19 min.

{1-(1-Acetyl-1H-indol-3-yl)-2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-carbamic acid tert-butyl ester

To a solution of [2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-1-(1H-indol-3-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester diastereosiomer P2 (prepared as described in Part B) (150 mg, 0.274 mmol) in dry THF (1.37 mL) was added under argon and at 0°C, tBuOK (40 mg, 0.356 mmol). The reaction mixture was stirred 5 min at 0°C then acetyl chloride (25.3 µL, 0.356 mmol) was added and the reaction mixture was allowed to warm up to 23°C and stirred overnight. The mixture was quenched by addition of an aqueous saturated solution of $NaHCO_3$ and extracted with EtOAc (x3). The organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc gradient 100:0 to 0:100) to give the desired material. TLC, R_f (EtOAc) = 0.65; MS (LC-MS): 587.2 [M-H]-, 611 [M+Na]+; t_R (HPLC conditions b) : 5.18 min.

Scheme D4: preparation of Example 121: (S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(3-carbamoyl-indolizin-1-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]



A. 1-{[(S)-2-(3-Trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carbonyl]-amino}-indolizine-3-carboxylic acid benzyl ester

To a solution of (S)-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide TFA salt (328 mg, 0.845 mmol) and triethylamine (353 µl, 2.54 mmol) in THF (10 mL) was added the crude 1-isocyanato-indolizine-3-carboxylic acid benzyl ester (247 mg, 0.845 mmol, prepared as described in Scheme A6). The resulting mixture was stirred at RT under nitrogen over the week-end then poured into HCl 1 N and extracted with EtOAc (x3). The combined organic extracts were washed with an aqueous saturated solution of $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The crude mixture was purified by flash column chromatography on silica gel (c-hexane/EtOAc 1:1 to c-hexane/EtOAc 3:7) to afford the desired compound. TLC, R_f (c-hexane/EtOAc 1:1) = 0.3; MS (LC/MS): 567.3 [M+H]+ 565.2 [M-H]-; t_R (HPLC conditions a): 4.16 min.

B. 1-{[(S)-2-(3-Trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carbonyl]-amino}-indolizine-3-carboxylic acid

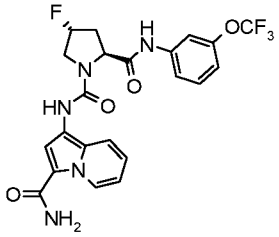
To 1-{[(S)-2-(3-Trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carbonyl]-amino}-indolizine-3-carboxylic acid benzyl ester (100 mg, 0.177 mmol) dissolved in THF (3 mL) was added Pd/C 10% (20 mg). Air was removed from the flask under vacuum and replaced with nitrogen three times, finally nitrogen was removed and replaced with hydrogen and the mixture was stirred at RT for 5 h. Hydrogen was removed and replaced by nitrogen, the catalyst was removed by filtration through a pad of Celite and washed with THF. Solvents were concentrated to give a mixture containing the desired compound contaminated with 20% of the decarboxylated analog. The mixture was used without further purification in the next step. LC/MS : 475 [M-H]-; t_R (HPLC conditions a): 3.41 min.

C. Example 121: (S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(3-carbamoyl-indolizin-1-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]

To a solution of 1-{[(S)-2-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carbonyl]-amino}-indolizine-3-carboxylic acid containing 20% of the decarboxylated analog (65 mg, 0.136 mmol), NH_4Cl (8.80 mg, 0.164 mmol) and HBTU (78 mg, 0.205 mmol) in DMF (2.5 mL) was added DIPEA (49 µl, 0.287 mmol) and the resulting solution was stirred at RT under nitrogen overnight. After completion of the reaction, the mixture was poured into HCl 1 N and extracted with EtOAc (x3). The combined organic extracts were washed with water (x2), dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by preparative HPLC (Waters SunFire C18-ODB, 5 µm, 19x50 mm, 20% CH_3CN/H_2O 2.5 min, 20-100% CH_3CN/H_2O in 10 min, CH_3CN/H_2O containing 0.1 % HCOOH flow: 20 mL/min) to give after lyophilization of the

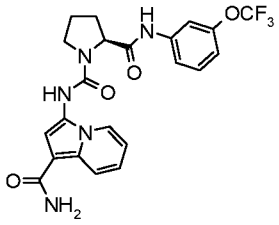
purified fractions the desired compound as a powder. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.4; MS (LC/MS): 476 [M+H]+, 498.1 [M+Na]+, 474.1 [M-H]-; t_R (HPLC conditions a): 3.30 min.

Example 122: (2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(3-carbamoyl-indolizin-1-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]



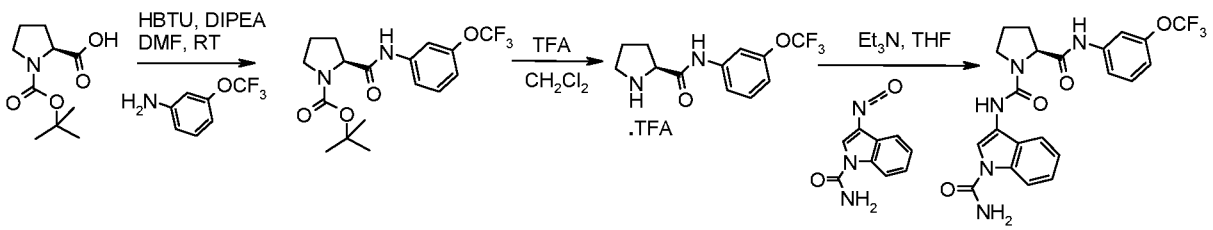
The title compound was prepared according to the same procedure as described in Scheme D4 starting from (S)-pyrrolidine-1,2-dicarboxylic acid 1-[(3-carbamoyl-indolizin-1-yl)-amide] 2-[(3-trifluoro methoxy-phenyl)-amide]. MS: 494 [M+H]+, 492.1 [M-H]-; t_R (HPLC conditions a): 1.87 min.

Example 123: (S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-indolizin-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]



The title compound was prepared from 3-isocyanato-indolizine-1-carboxylic acid benzyl ester (prepared as described in Scheme A7) using the protocol described in Scheme D4. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.4; MS (LC/MS): 476 [M+H]+, 498.1 [M+Na]+, 474.1 [M-H]-; t_R (HPLC conditions a): 3.13 min.

<u>Scheme D5: general protocol described for the preparation of Example 124: (S)-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]</u>



A. (S)-2-(3-Trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a mixture of Boc-L-proline (5 g, 23.23 mmol), 3-(trifluoromethoxy)aniline (3.73 mL, 27.88 mmol) and HBTU (13.2 g, 34.8 mmol) in DMF (60 mL) was added DIPEA (7.95 mL, 46.5 mmol) and the resulting yellow solution was stirred at RT under nitrogen. The solvent was concentrated under vacuum and the residue dissolved in EtOAc and washed with HCl 1N. The combined organic layers were neutralized by addition of an aqueous saturated solution of $NaHCO_3$. The layers were separated and the aqueous one back-extracted twice with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 3:1 to 2:1) to give the desired compound. TLC, R_f (c-hexane/EtOAc 1:1) = 0.57; MS (LC/MS): 397.1 [M+Na]+, 275.2 [MH-Boc]+, 373.3 [M-H]-; t_R (HPLC conditions a) 3.81 min.

Dichloromethane can also be used instead of DMF.

B. (S)-Pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide

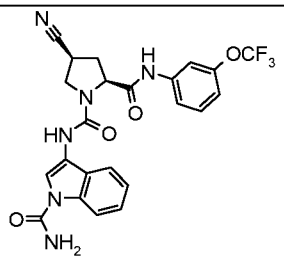
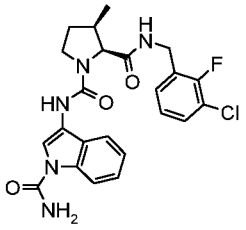
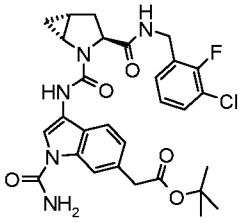
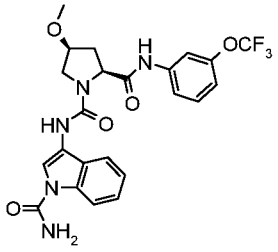
To a solution of (S)-2-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (8.52 g, 22.6 mmol) in CH_2Cl_2 (50 mL) was added TFA (8.65 mL, 113 mmol) and solution was stirred at RT for 12 h. The crude reaction mixture was concentrated under vacuum, Et_2O was added and the white precipitate was filtered off to give the desired compound as a TFA salt. MS (LC/MS): 275.2 [M+H]+, 273.3 [M-H]-; t_R (HPLC conditions a) 2.47 min.

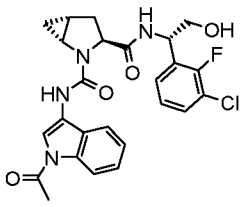
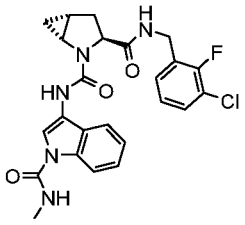
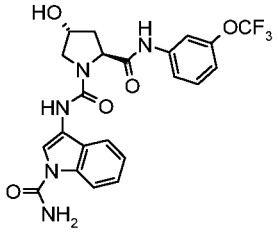
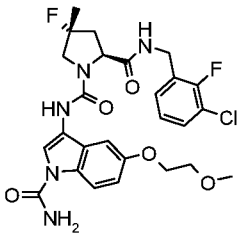
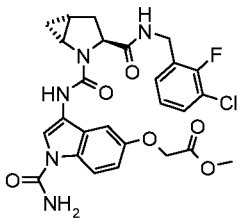
C. Example 124: (S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]

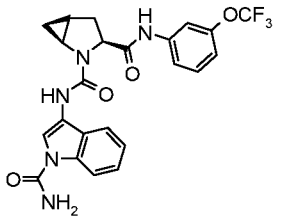
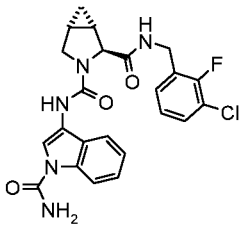
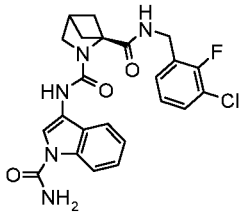
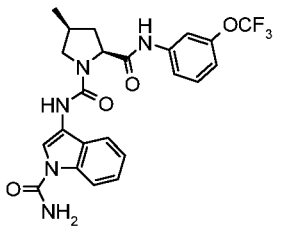
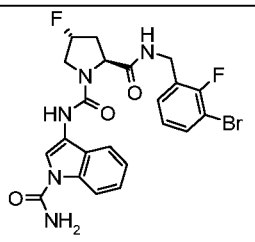
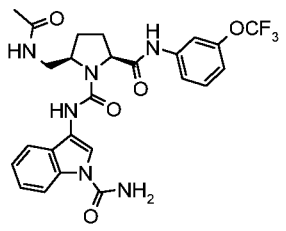
To a solution of (S)-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide trifluoroacetate (328 mg, 0.845 mmol) and Et_3N (353 µl, 2.53 mmol) in THF (7.5 mL) was added a suspension of 3-isocyanato-indole-1-carboxylic acid amide (170 mg, 0.845 mmol, prepared as described in Scheme A1) in THF (7.5 mL). The resulting solution was stirred at RT under nitrogen for 1 h, poured into water and the mixture was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by preparative HPLC (Waters SunFire C18-ODB, 5 µm, 19x50 mm, 20% CH_3CN/H_2O 2.5 min, 20-100% CH_3CN/H_2O in 10 min, CH_3CN/H_2O containing 0.1 % HCOOH flow: 20 mL/min) to give after lyophilization of the purified HPLC fractions the title compound. TLC, R_f (c-hexane/EtOAc 1:2) = 0.11; MS (LC/MS): 476.2 [M+H]+, 973.2 [2M+Na]+.

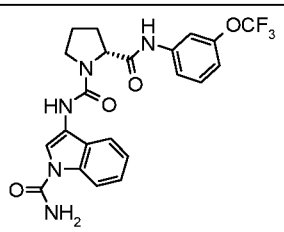
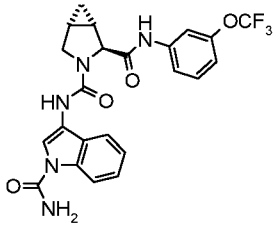
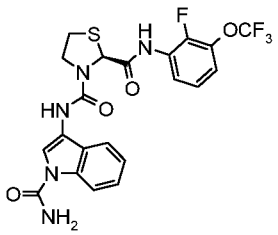
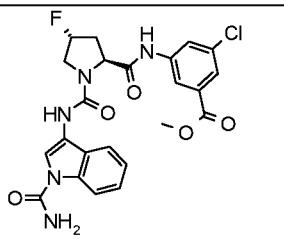
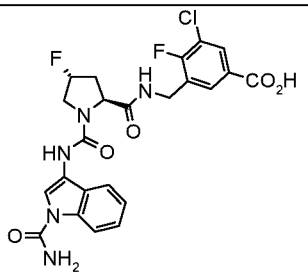
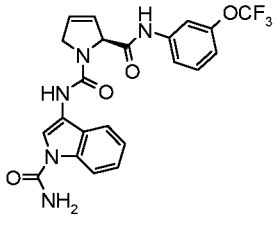
The examples below were prepared according to the general procedures described in Scheme D5 for the preparation of **Example 124** *from commercially available building blocks, if not otherwise stated (see notes at the end of table 4):*

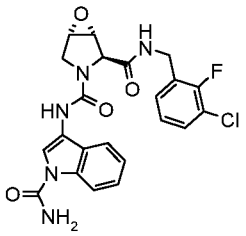
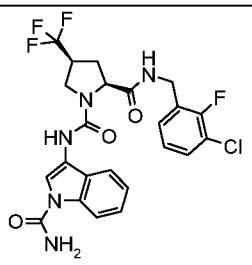
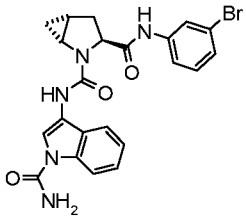
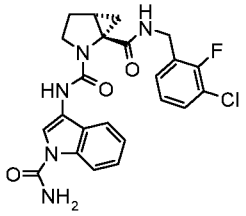
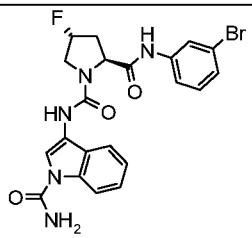
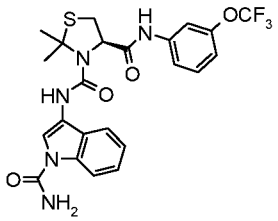
Table 4:

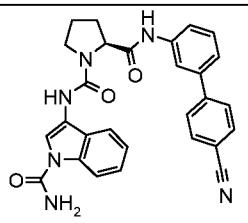
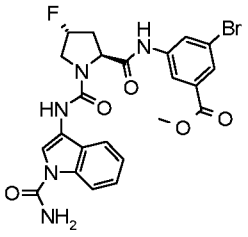
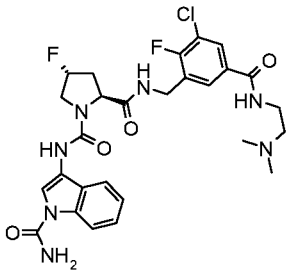
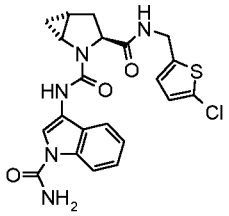
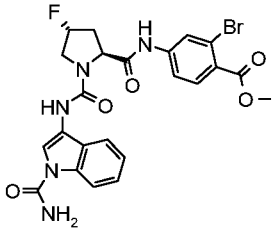
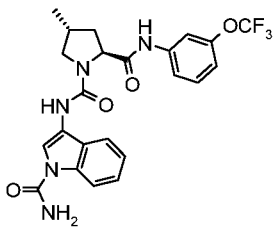
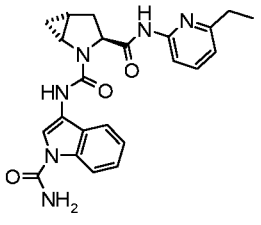
Example	Structure	Name	Characterization (end–table notes), TLC, R_f (eluent); MS (LC/MS); t_R (HPLC conditions); 19F NMR (100 MHz, solvent) δ (ppm):
125		(2S,4S)-4-Cyano-pyrrolidine-1,2 dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	501.1 [M+H]+; t_R (b): 4.07 min.
126		(2S,3R)-3-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(7) R_f (EtOAc) = 0.5; 472.1/474.2 [M+H]+, 427/429 [M-$CONH_2$]-; t_R (a): 3.24 min.
127		(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-6-yl)-acetic acid tert-butyl ester	(9) R_f (EtOAc) = 0.44; 584.4/586.4 [M+H]+, 582.7/584.4 [M-H]-, 539.4/541.4 [M-$CONH_2$]-, 628.4/630.4 [M+HCOO]-; t_R (f): 2.20 min.
128		(2S,4S)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	506.2 [M+H]+, 504.1 [M-H]-; t_R (a): 3.43 min.

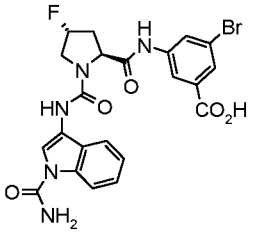
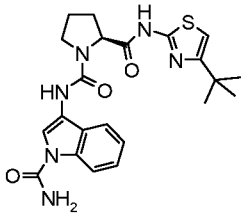
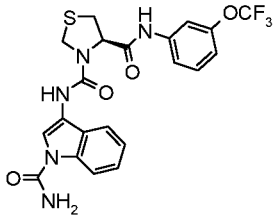
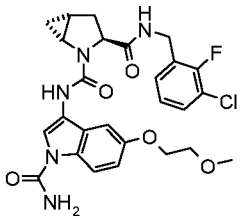
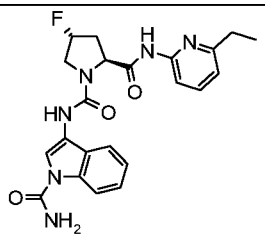
129		(1R,3S,5R)-2-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-acetyl-1H-indol-3-yl)-amide] 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2hydroxy-ethyl]-amide}	(5, 8[B9],9[A1]) R_f (EtOAc) = 0.45; 499.4/501.3 [M+H]+, 521.3/523.4 [M+Na]+, 543.3/545.4 [M+HCOO]-, 497.5/499.8 [M-H]-; t_R (a): 1.95 min.
130		(1R,3S,5R)-2-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-(3-chloro-2-fluoro-benzylamide) 2-[(1-methylcarbamoyl-1H-indol-3-yl)-amide]	(9[A2]) R_f (EtOAc) = 0.3; 484.4 [M+H]+, 484.4 [M+HCOO]-; t_R (a): 3.34 min.
131		(2S,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	492.1 [M+H]+, 490.1 [M-H]-; t_R (a): 3.08 min.
132		(2S,4R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-{[1-carbamoyl-5-(2-methoxy-ethoxy)-1H-indol-3-yl]-amide} 2-(3-chloro-2-fluoro-benzylamide)	(8[B13],9) R_f (EtOAc) = 0.35; 550.5/552.4 [M+H]+, 572.3/574.5 [M+Na]+, 548.4/550.4 [M-H]-, 594.4/596.4 [M+HCOO]-; t_R (f): 1.82 min.
133		(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid methyl ester	(9) R_f (EtOAc) = 0.2; 558.1/560.2 [M+H]+, 580/582.1 [M+Na]+, 513.1/515 [M-$CONH_2$]-; t_R (f): 1.87 min.

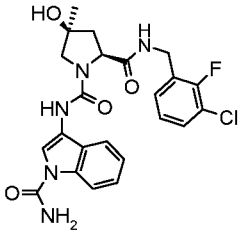
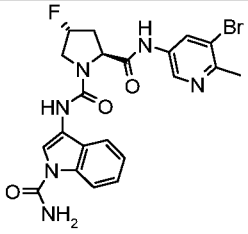
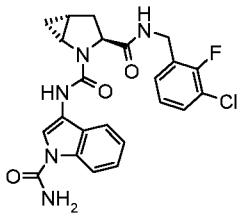
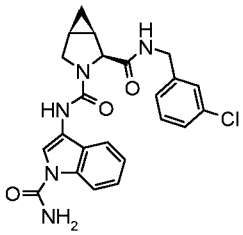
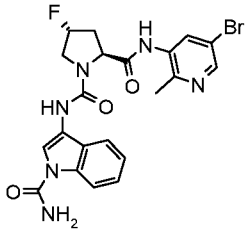
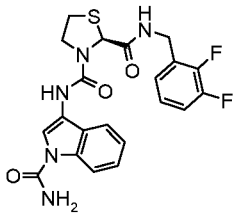
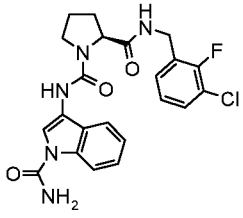
134		(1S,3S,5S)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-trifluoromethoxy-phenyl)-amide]	R_f (c-hexane/EtOAc 1:2) = 0.15, 488.2 [M+H]+, 486.1 [M-H]-; t_R (a): 3.59 min.
135		(1S,2S,5R)-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	470 [M+H]+, 425 [M-$CONH_2$]-; t_R (f): 1.84 min.
136		2-Aza-bicyclo[2.1.1]hexane-1,2-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 1-(3-chloro-2-fluoro-benzylamide)	(1) White solid. R_f (EtOAc) = 0.2; 470/473 [M]+; t_R (c): 4.51 min.
137		(2S,4S)-4-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	(8[B2]) R_f (c-hexane/EtOAc 1:3) = 0.44; 487.9 [M-H]-, 446.0 [M-$CONH_2$]-; t_R (c): 4.51 min.
138		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-(3-bromo-2-fluoro-benzylamide) 1-[(1-carbamoyl-1H-indol-3-yl)-amide]	(1,6) 522.0 [M+H]+; t_R (c): 4.38 min.
139		(2S,5R)-5-(Acetylamino-methyl)-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	(8[B4]) 547 [M+H]+; t_R (b): 4.05 min.

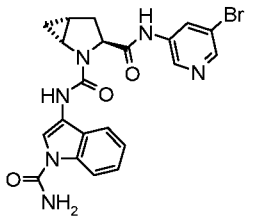
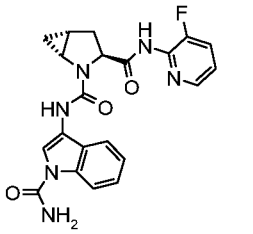
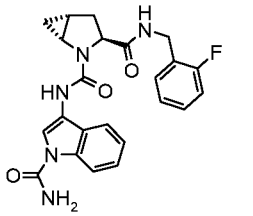
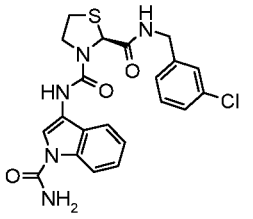
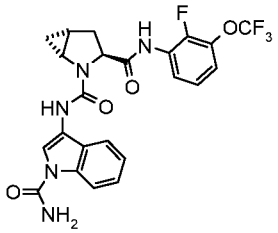
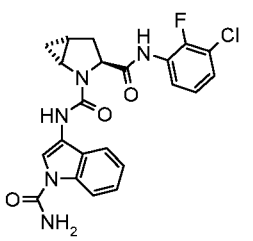
140		(R)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	476.1 [M+H]+, 498.1 [M+Na]+, 474.1 [M-H]-; t_R (a): 3.47 min.
141		(1S*,2S*,5R*)-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	488.2 [M+H]+, 510.1 [M+Na]+; t_R (a): 3.52 min
142		(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-fluoro-3-trifluoromethoxy-phenyl)-amide]	(1,6) White solid. 510 [M+H]+; t_R (b) 4.36 min.
143		3-Chloro-5-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-benzoic acid methyl ester	(1) 500 [M+H]+; t_R (b): 3.96 min.
144		3-({[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-methyl)-5-chloro-4-fluoro-benzoic acid	(8) 520.0 [M]+; t_R (c): 3.05 min
145		(S)-2,5-Dihydro-pyrrole-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	474.1 [M+H]+, 969.2 [2MH+Na]+, 472.1 [M-H]-; t_R (a): 3.38 min.

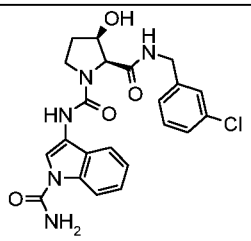
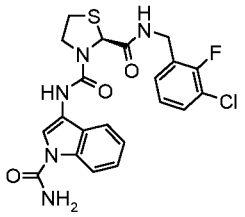
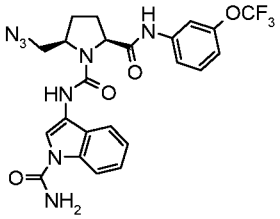
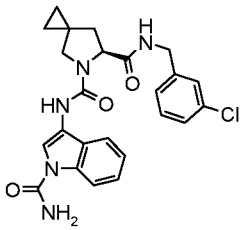
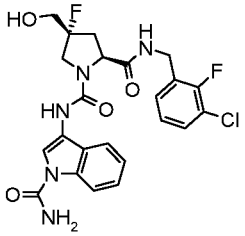
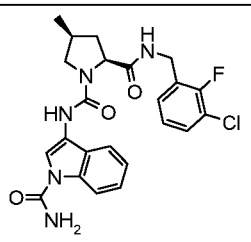
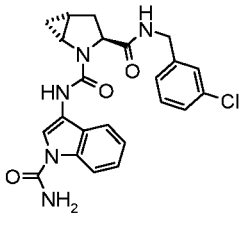
146		(1R,2S,5S)-6-Oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(8[B19]) 472 [M+H]+; t_R (f): 1.76 min; 19F NMR (CD_3OD): -124.
147		(2S,4S)-4-Trifluoromethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(1) Off-white solid. R_f (EtOAc) = 0.30; 526.0 [M+H]+; t_R (c): 4.88 min.
148		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(3-bromo-phenyl)-amide] 2-[(1-carbamoyl-1H-indol-3-yl)-amide]	(1) 481.9/483.0 [M+H]+, 481.9/482.8 [M-H]-, 436.9/438.9 [M-$CONH_2$]-; t_R (b) 4.20 min.
149		(1S,5R)-2-Aza-bicyclo[3.1.0]hexane-1,2-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 1-(3-chloro-2-fluoro-benzylamide)	(1) White solid. R_f (EtOAc) = 0.43; 470 [M+H]+; t_R (c): 4.49 min.
150		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-[(3-bromo-phenyl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide]	(1) 487/489 [M+H]+; t_R (b): 3.64 min.
151		(R)-2,2-Dimethyl-thiazolidine-3,4-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 4-[(3-trifluoromethoxy-phenyl)-amide]	R_f (c-hexane/EtOAc 1:3) = 0.51; 522.1 [M+H]+, 520.2 [M-H]-; t_R (c): 5.39 min.

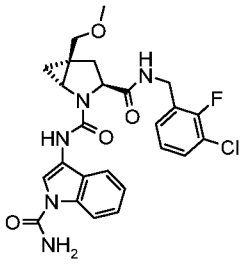
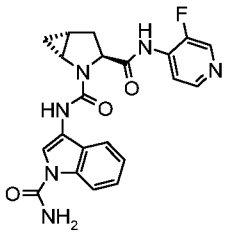
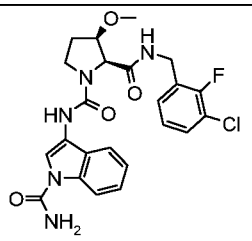
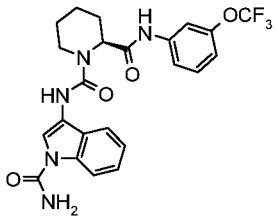
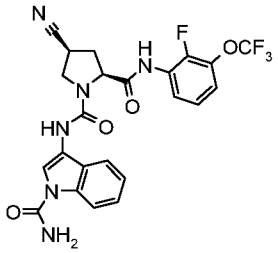
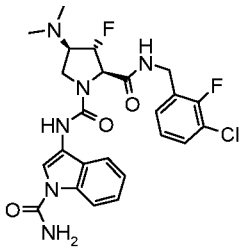
152		(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(4'-cyano-biphenyl-3-yl)-amide]	493 [M+H]+; t_R (j) 2.90 min.
153		3-Bromo-5-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-benzoic acid methyl ester	R_f (EtOAc) = 0.75; 546.1/548.1 [M+H]+, 568.1/570 [M+Na]+, 544/546 [M-H]-, 500/502 [M-$CONH_2$]-; t_R (a): 3.33 min.
154		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-5-(2-dimethylamino-ethylcarba-moyl)-2-fluoro-benzylamide]	(3,6[C3]) 590.2 [M]+; t_R (c): 3.59 min.
155		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(5-chloro-thiophen-2-ylmethyl)-amide]	458 [M+H]+, 456 [M-H]-, 413 [M-$CONH_2$]; t_R (f): 1.99 min.
156		2-Bromo-4-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-benzoic acid methyl ester	(1) 546/548 [M+H]+; t_R (b): 3.55 min.
157		(2S,4R)-4-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	(8[B2]) R_f (c-hexane/EtOAc 1:3) = 0.44; 489.1 [M-H], 445.0 [M-$CONH_2$]-; t_R (c): 4.65 min.
158		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-	433.1 [M+H]+ 432.1 [M-H]-; t_R (a): 2.49 min.

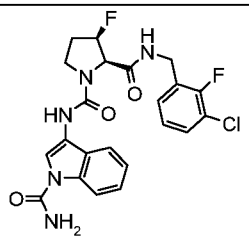
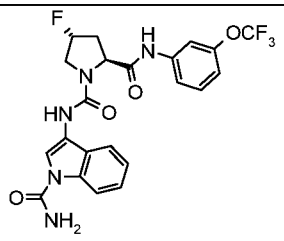
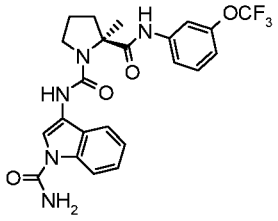
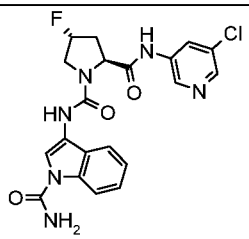
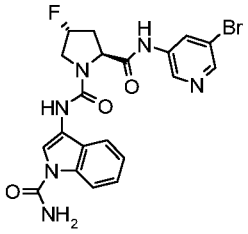
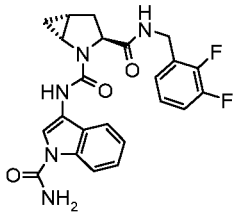
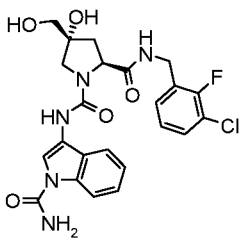
		amide] 3-[(6-ethyl-pyridin-2-yl)-amide]	
159		3-Bromo-5-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-benzoic acid	(8[B7]) R_f (CH_2Cl_2/MeOH 4:1) = 0.23; 532.0/534.0 [M+H]+, 554.0/556.0 [M+Na]+, 530.2/532.2 [M-H]-, 486.9/489.0 [M-$CONH_2$]-; t_R (a): 2.98 min.
160		(S)-Pyrrolidine-1,2-dicarboxylic acid 2-[(4-tert-butyl-thiazol-2-yl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide]	R_f (c-hexane/EtOAc 1:2) = 0.32; 455.2 [M+H]+, 909.2 [2M+H]+, 453.1 [M-H]-; t_R (H a): 3.5 min.
161		(R)-Thiazolidine-3,4-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 4-[(3-trifluoromethoxy-phenyl)-amide]	R_f (c-hexane/EtOAc 1:3) = 0.42; 494.0 [M+H]+, 492.1 [M-H]-; t_R (c): 5.03 min.
162		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-methoxy-ethoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide)	(9) R_f (EtOAc) = 0.3; 544.2/546.1 [M+H]+, 566/568.1 [M+Na]+, 542 [M-H]-, 499.1 [M-$CONH_2$]-; t_R (f): 1.85 min.
163		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(6-ethyl-pyridin-2-yl)-amide]	439.1 [M+H]+, 899.2 [2M+Na]+, 437.0 [M-H]-; t_R (a): 2.32 min.

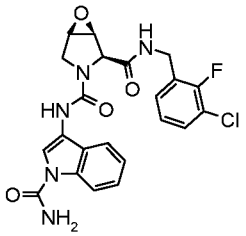
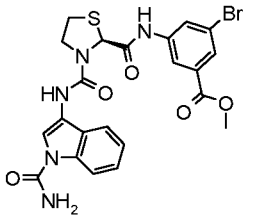
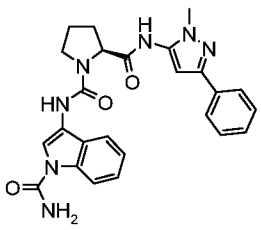
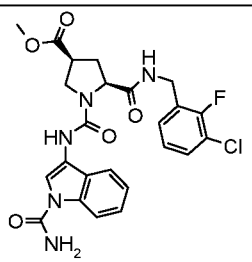
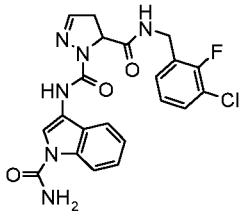
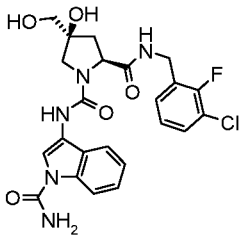
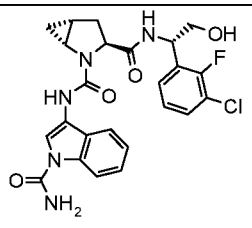
164		(2S,4S)-4-Hydroxy-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(8[B13]) R_f (EtOAc) = 0.21; 488.2/490.1 [M+H]+, 486.1/488.1 [M-H]-; t_R (f): 1.75 min.
165		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-bromo-4-methyl-pyridin-3-yl)-amide]	(4) R_f (EtOAc) = 0.38; 503/505 [M+H]+; t_R (c): 3.70 min
166		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide)	470 [M+H]+; t_R (b): 3.87 min.
167		(1R*,2S*,5S*)-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide)	452.0 [M+H]+, 407.0 [M-$CONH_2$]-; t_R (a): 3.16 min.
168		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-[(5-bromo-2-methyl-pyridin-3-yl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide]	505.0 [M+H]+; t_R (c): 3.67 min.
169		(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2,3-difluoro-benzylamide)	460.1 [M+H]+, 941.2 [2M+Na]+, 415.0 [M-$CONH_2$]-; t_R (a): 3.11 min.
170		(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	458.0 [M+H]+, t_R (b): 3.70 min.

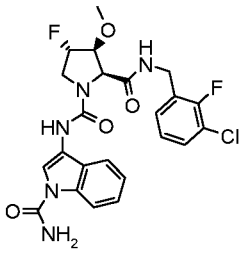
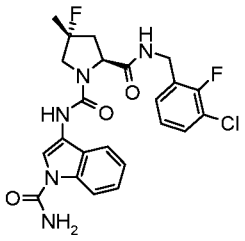
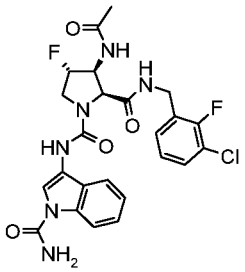
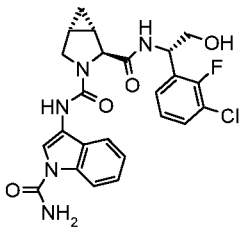
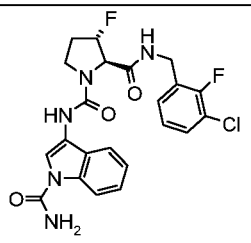
171		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(5-bromo-pyridin-3-yl)-amide]	(4) White solid. R_f (EtOAc) = 0.48; 483/485 [M+H]+; t_R (c): 4.08 min.
172		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-fluoro-pyridin-2-yl)-amide]	(4) Off-white solid. R_f (CH_2Cl_2/MeOH 95/5) = 0.21; 423 [M+H]+; t_R (c): 3.59 min.
173		(1R,3S,5R)-2-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(2-fluoro-benzylamide)	R_f (EtOAc) = 0.5; 436.4/438.5 [M+H]+, 871.7/873.7 [2M+H]+, 480.4/482.4 [M+HCOO]-; t_R (f): 1.77 min.
174		(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide)	458 [M+H]+; t_R (a): 3.17 min.
175		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(2-fluoro-3-trifluoromethoxy-phenyl)-amide]	(1,6) White solid. 506 [M+H]+; t_R (b) 4.47 min.
176		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-chloro-2-fluoro-phenyl)-amide]	(1) White solid. 456 [M+H]+; t_R (b): 4.14 min.

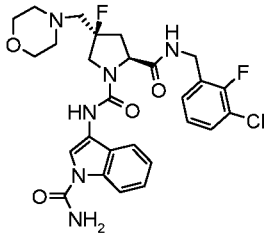
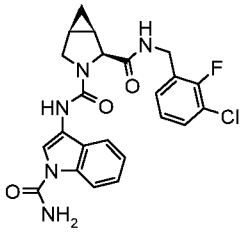
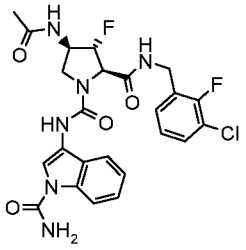
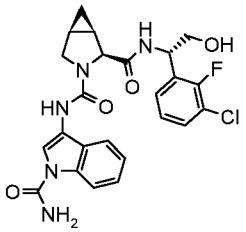
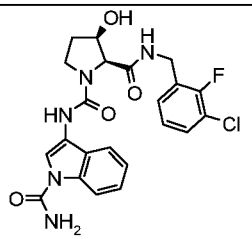
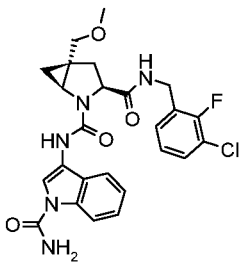
177		(2S,3R)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide)	(1) White solid. 456 [M+H]+; t_R (b): 2.84 min.
178		(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	475.9 [M+H]+, 498 [M+Na]+; t_R (b): 3.89 min.
179		(2S,5R)-5-Azidomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	(8[B3]) 531.1 [M+H]+; t_R (b): 4.85 min.
180		(S)-5-Aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-[(1-carbamoyl-1H-indol-3-yl)-amide] 6-(3-chloro-benzylamide)	466.1 [M+H]+, 421.1 [M-$CONH_2$]-; t_R (a): 3.26 min.
181		(2S,4R)-4-Fluoro-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(8[B12]) R_f (EtOAc) = 0.15; 506.2/508.1 [M+H]+, 528.1/530.2 [M+Na]+, 504.1/506 [M-H]-; t_R (f): 1.69 min.
182		(2S,4S)-4-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(1, 8[B2]) R_f (EtOAc) = 0.51; 472.0 [M+H]+; t_R (c): 4.62 min.
183		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-	452/454 [M+H]+; t_R (a): 3.16 min; t_R (b): 3.78 min.

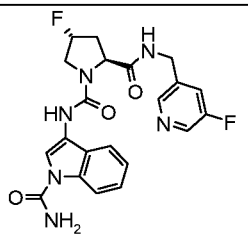
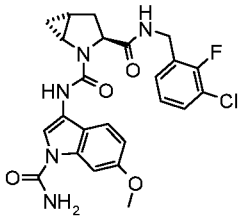
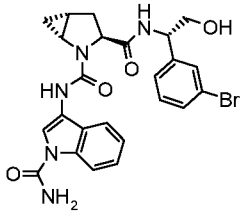
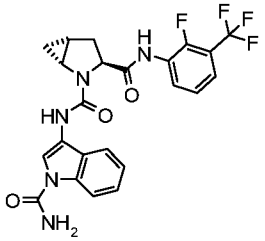
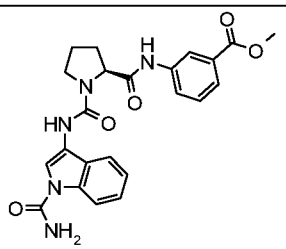
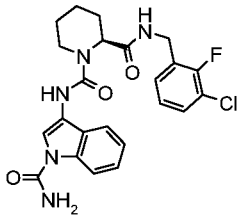
		benzylamide)	
184		(1R,3S,5S)-5-Methoxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide)	(5,8) Rf (EtOAc) = 0.20; 514.4/516.4 [M+H]+, 512.3 [M-H]-; t_R (a): 3.27 min.
185		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-fluoro-pyridin-4-yl)-amide]	(4) R_f (EtOAc) = 0.23; 423 [M+H]+; t_R (c): 3.4 min.
186		(2S,3R)-3-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(8) White solid. 488 [M+H]+; t_R (b): 3.61 min.
187		(S)-Piperidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	R_f (c-hexane/EtOAc 1:2) = 0.21; 490.1 [M+H]+, 1001.2 [2M+Na]+, 488.1 [M-H]-; t_R (a): 3.75 min.
188		(2S,4S)-4-Cyano-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-fluoro-3-trifluoromethoxy-phenyl)-amide]	(2 at 50°C,3,6) R_f (EtOAc) = 0.45; 519.1 [M+H]+, 541.0 [M+Na]+, 517.2 [M-H]-; t_R (f): 1.93.
189		(2R,3S,4R)-4-Dimethylamino-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(8[B20]) R_f (CH_2Cl_2/MeOH 95/5) = 0.26; 519 [M+H]+, 563 [M-HCOO]-; t_R (f): 1.51 min.

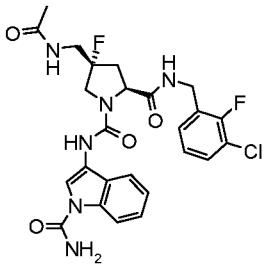
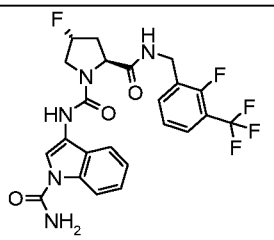
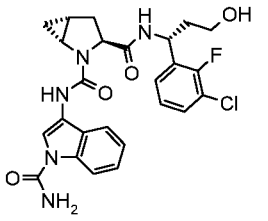
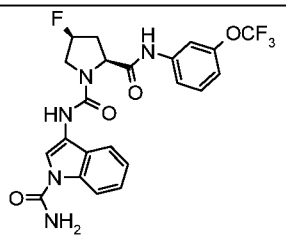
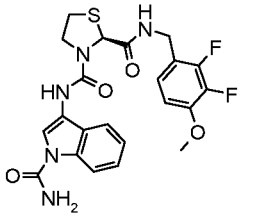
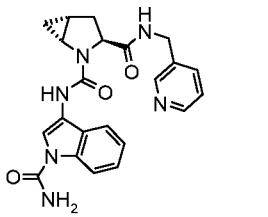
190		(2R,3R)-3-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(8) White solid. 476 [M+H]+; t_R (b): 3.66 min.
191		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	R_f (c-hexane/EtOAc 1:2) = 0.33; 494.0 [M+H]+, 492.1 [M-H]-; t_R (a): 3.41 min.
192		(S)-2-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	490.1 [M+H]+, 512.2 [M+Na]+; t_R (a): 3.61 min.
193		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-chloro-pyridin-3-yl)-amide]	(4) R_f (c-hexane/EtOAc 1:3) = 0.12; 445 [M+H]+; t_R (b): 3.79 min.
194		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-bromo-pyridin-3-yl)-amide]	(4) R_f (c-hexane/EtOAc 1:3) = 0.1; 491 [M+H]+; t_R (c): 3.85 min.
195		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(2,3-difluoro-benzylamide)	454.1 [M+H]+, 929.3 [2M+Na]+, 409.1 [M-$CONH_2$]-; t_R (a): 3.09 min.
196		(2S,4R)-4-Hydroxy-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(8[B12]) 504 [M+H]+, 502 [M-H]-; t_R (f): 1.57 min.

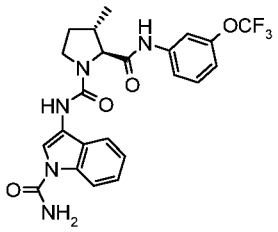
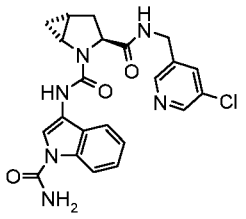
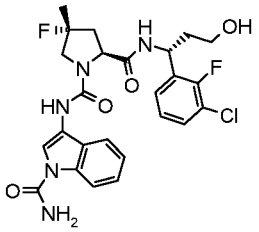
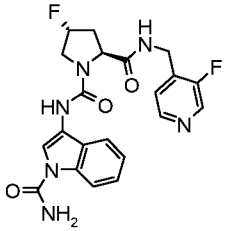
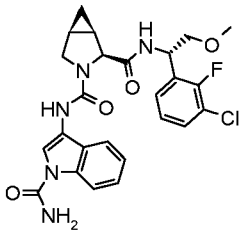
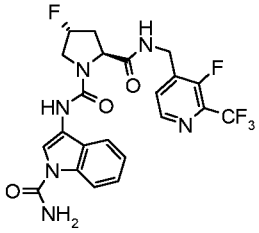
197		(1S,2S,5R)-6-Oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(8[B19]) 472 [M+H]+; t_R (f): 1.54 min; 19F NMR (CD_3OD): -124.
198		3-Bromo-5-{[(S)-3-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-thiazolidine-2-carbonyl]-amino}-benzoic acid methyl ester	(1) 544.2/546.2 [M+H]+; t_R (b): 4.26 min.
199		(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-methyl-5-phenyl-2H-pyrazol-3-yl)-amide]	R_f (EtOAc) = 0.26; 472.1 [M+H]+, 470.2 [M-H]-; t_R (a): 3.07 min.
200		(3S,5S)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-5-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrrolidine-3-carboxylic acid methyl ester	(8) 516 [M+H]+, 540 [M+Na]+; t_R (b): 3.37 min.
201		4,5-Dihydro-pyrazole-1,5-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 5-(3-chloro-2-fluoro-benzylamide)	(8[B5]) R_f (CH_2Cl_2/acetone 1:1) = 0.53; 457.0 [M+H]+; t_R (b) : 3.77 min.
202		(2S,4S)-4-Hydroxy-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(8[B12]) 504 [M+H]+, 502 [M-H]-; t_R (f): 1.60 min.
203		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-	(5,8[B9]) R_f (CH_2Cl_2/MeOH 95:5) = 0.2; 498.1/500.4 [M-H]-, 543.8

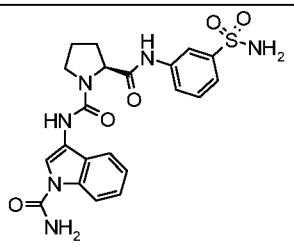
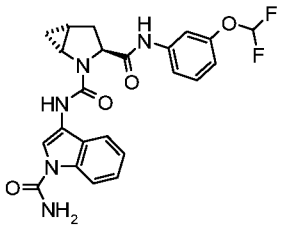
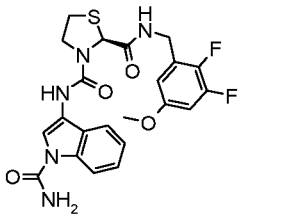
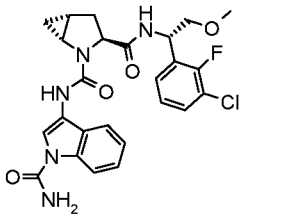
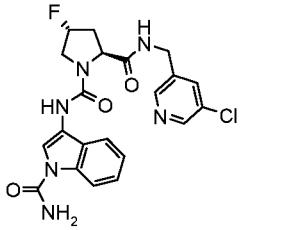
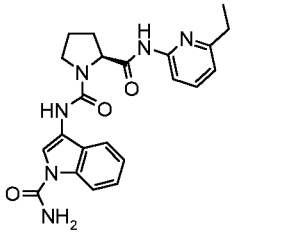
		amide] 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide}	[M+HCOO]-, 500.2 [M+H]+, 522/522.7 [M+Na]+; t_R (a): 1.81 min.
204		(2S,3S,4S)-4-Fluoro-3-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(8[B24]) 506 [M+H]+, 550 [M+HCOO]-; t_R (f): 1.87 min.
205		(2S,4R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(8[B13]) TLC, R_f (EtOAc) = 0.45; 490.1/492.1 [M+H]+, 488/490 [M-H]-, 445/447.1 [M-$CONH_2$]-; t_R (f): 1.89 min.
206		(2S,3S,4S)-3-Acetylamino-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(8[B23]) R_f (CH_2Cl_2/MeOH 95/5) = 0.26 ; 531 [M+H]+, 533 [M-H]-; t_R (f): 1.72 min.
207		(1S,2S,5R)-3-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S) -1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide}	(5,8[B9]) R_f (EtOAc) = 0.25; 500.3 [M+H]+, 544.3/546.4 [M+HCOO]-; t_R (a): 2.93 min.
208		(2R,3S)-3-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(8) White solid. 476 [M+H]+; t_R (b): 3.86 min.

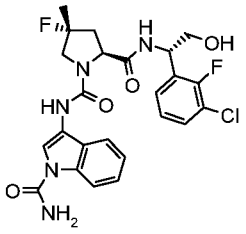
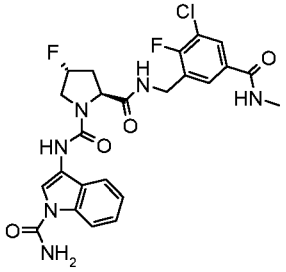
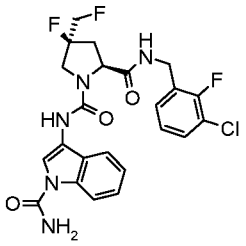
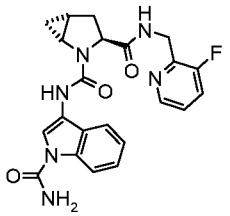
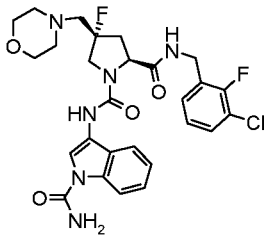
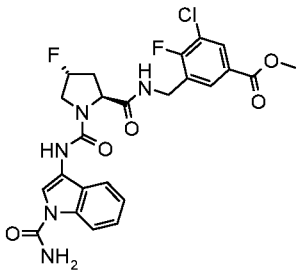
209		(2S,4R)-4-Fluoro-4-morpholin-4-ylmethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(8[B14]) 575 [M+H]+, 502 [M-H]-; t_R (f): 1.53 min.
210		(1R,2S,5S)-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	R_f (EtOAc) = 0.45; 470.4/472.4 [M+H]+, 468.3/470.3 [M-H]-, 514.4/516.5 [M+HCOO]-; t_R (a): 3.21 min.
211		(2R,3S,4R)-4-Acetylamino-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(8[B23]) R_f (EtOAc) = 0.26 ; 531 [M+H]+, 533 [M-H]-; t_R (f): 1.74 min.
212		(1R,2S,5S)-3-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide}	(5,8[B9]) R_f (EtOAc) = 0.3; 520.3 [M+H]+, 564.3/566.3 [M+HCOO]-; t_R (a): 3.0 min.
213		(2S,3R)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(1) White solid. 474 [M+H]+; t_R (b): 3.11 min.
214		(1S,3S,5R)-5-Methoxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide)	(5,8) White solid. Rf (EtOAc) = 0.20; 514.4/516.4 [M+H]+, 512.4 [M-H]-, 558.3/560.3 [M+HCOO]-; t_R (a): 3.27 min.

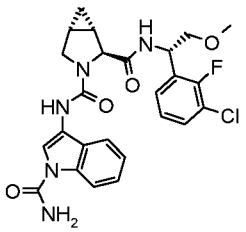
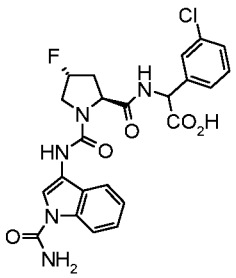
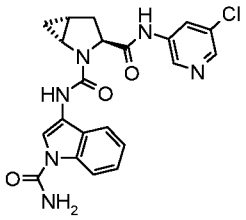
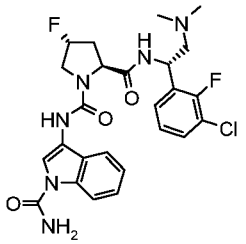
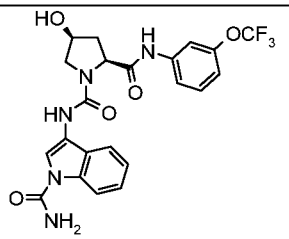
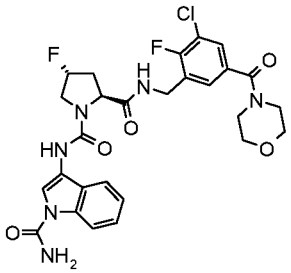
215		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-fluoro-pyridin-3-ylmethyl)-amide]	(1) White solid. 443 [M+H]+; t_R (b): 3.15 min.
216		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-6-methoxy-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide)	(9[A1]) R_f (EtOAc) = 0.45; 500/502.2 [M+H]+, 455.2/457.2 [M-$CONH_2$]-; t_R (f): 1.90 min.
217		(1R,3S,5R)-2-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[(S)-1-(3-bromo-phenyl)-2-hydroxy-ethyl]-amide} 2-[(1-carbamoyl-1H-indol-3-yl)-amide]	(5) R_f (EtOAc) = 0.25; 526.3/528.3 [M+H]+, 570.4/572.4 [M+HCOO]-; t_R (a): 3.1 min.
218		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(2-fluoro-3-trifluoromethyl-phenyl)-amide]	(1) White solid. 490 [M+H]+; t_R (b): 4.39 min.
219		3-{[(S)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-benzoic acid methyl ester	450.1 [M+H]+, 473.0 [M+Na]+, 899.2 [2M+H]+, 448.1 [M-H]-; t_R (a): 3.03 min.
220		(S)-Piperidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(1) 472 [M+H]+, 494 [M+Na]+; t_R (c): 4.72 min.

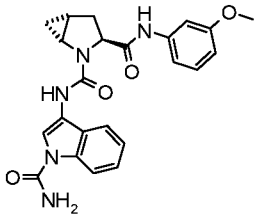
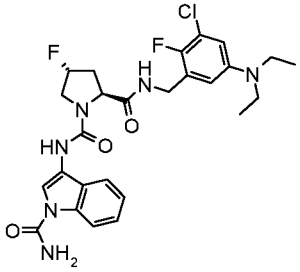
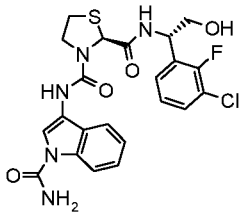
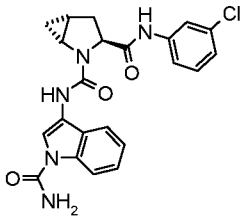
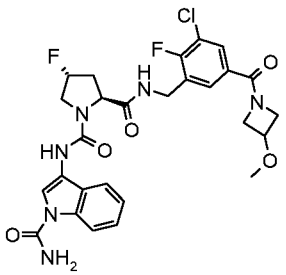
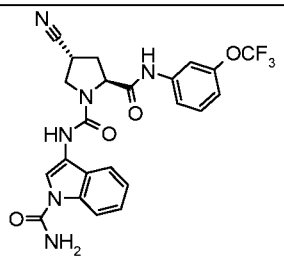
221		(2S,4S)-4-(Acetylamino-methyl)-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(8) 531 [M+H]-, 533 [M+H]+; t_R (f): 0.56 min; 19F NMR (DMSO-d_6): -121, -150.
222		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2-fluoro-3-trifluoromethyl-benzylamide)	(1) White solid. 510 [M+H]+; t_R (b): 3.88 min.
223		(1R,3S,5R)-2-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-{[(R) -1-(3-chloro-2-fluoro-phenyl)-3-hydroxy-propyl]-amide}	(5,8[B9]) R_f (EtOAc) = 0.1; 514.3/516.3 [M+H]+, 558.3/560.2 [M+HCOO]-; t_R (a): 3.15 min.
224		(2S,4S)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	(1) R_f (c-hexane/EtOAc 1:3) = 0.19; 494 [M+H]+; t_R (c): 4.78 min.
225		(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2,3-difluoro-4-methoxy-benzylamide)	(2,3) White solid. R_f (c-hexane/EtOAc 1:3) = 0.33; 490.1 [M+H]+; t_R (c): 4.39 min.
226		(1R,3S,5R)-2Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)amide] 3-[(pyridin-3-ylmethyl)-amide]	(1) 419.3 [M+H]+; t_R (a): 1.83 min.

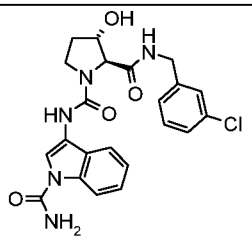
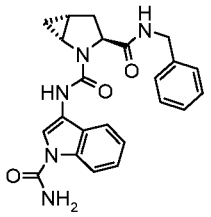
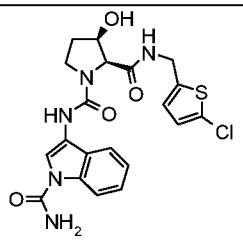
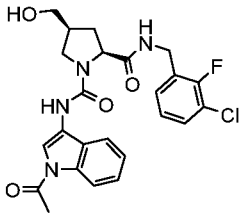
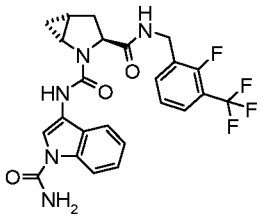
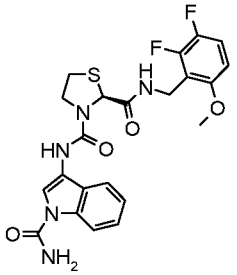
227		(2S,3S)-3-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	490 [M+H]+; t_R (b): 4.51 min.
228		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(5-chloro-pyridin-3-ylmethyl)-amide]	453 [M+H]+; t_R (a): 2.70 min.
229		(2S,4R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(R)-1-(3-chloro-2-fluoro-phenyl)-3-hydroxy-propyl]-amide}	(5,8[B9]) R_f (EtOAc) = 0.1; 514.3/516.3 [M+H]+, 558.3/560.2 [M+HCOO]-; t_R (a): 3.15 min.
230		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-fluoro-pyridin-4-ylmethyl)-amide]	(1,6). 443.0 [M+H]+; t_R (c): 3.05 min.
231		(1R,2S,5S)-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-methoxy-ethyl]-amide}	(5,8[B9]) White powder. R_f (CH_2CL_2/MeOH 9:1): 0.60; 514.3/516.3 [M+H]+, 558.3/560.3 [M+HCOO]-; t_R (a): 3.31 min.
232		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-fluoro-2-trifluoromethyl-pyridin-4-ylmethyl)-amide]	(1,6). 511.0 [M+H]+; t_R (c): 4.16 min.

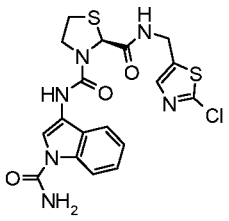
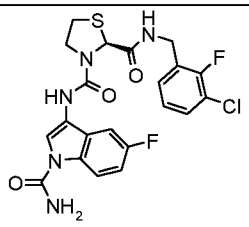
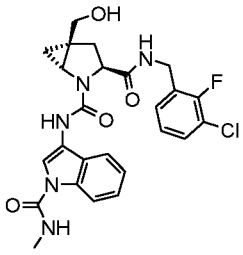
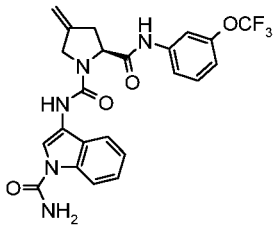
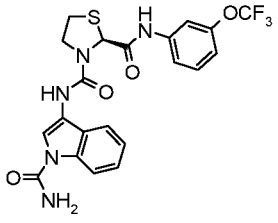
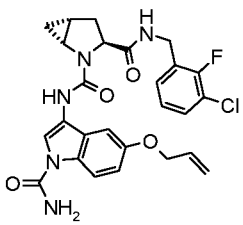
233		(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-sulfamoyl-phenyl)-amide]	471.1 [M+H]+, 963.3 [2M+Na]+; t_R (a): 2.58 min.
234		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-difluoromethoxy-phenyl)-amide]	(1) 470.0 [M+H]+, 468.9 [M-H]- , 425.0 [M-$CONH_2$]-; t_R (b) 4.05 min. HCO_2
235		(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2,3-difluoro-5-methoxy-benzylamide)	(2,3,6) Solid. R_f (c-hexane/EtOAc 1:3) = 0.33; 490 [M+H]+; t_R (c): 4.48 min.
236		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-methoxy-ethyl]-amide}	(5,8[B9]) White powder. 514.4/516.4 [M+H]+, 531.4/533.4 [M+Na]+, 558.4/560.4 [M+HCOO]-; t_R (f): 1.97 min.
237		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-chloro-pyridin-3-ylmethyl)-amide]	459.1/461 [M+H]+; t_R (f): 1.30 min.
238		(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(6-ethyl-pyridin-2-yl)-amide]	R_f (CH_2Cl_2/iPrOH 95:5) = 0.13; 421.1 [M+H]+, 419.2 [M-H]-; t_R (a): 2.42 min.

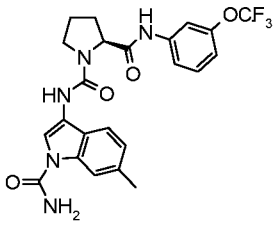
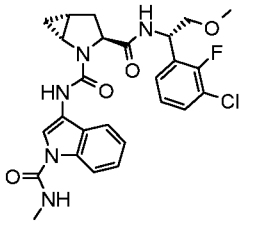
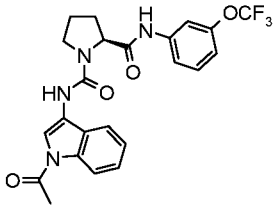
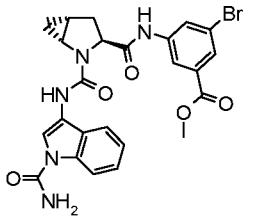
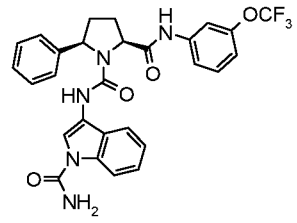
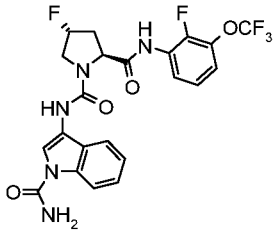
239		(2S,4R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S) -1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide}	(5,8[B9]) R_f (CH_2Cl_2/MeOH 9:1) = 0.3; 500.3/502.4 [M+H]+, 544.2/546.2 [M+HCOO]-; t_R (a): 3.02 min.
240		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-5-methylcarbamoyl-benzylamide)	(3,6[C3]) 533.0 [M]+; t_R (c): 3.86 min.
241		(2S,4S)-4-Fluoro-4-fluoromethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(8) R_f (EtOAc) = 0.38; 508/510 [M+H]+, 530/532 [M+Na]+, 506/508 [M-H]-, 463.1/465.1 [M-$CONH_2$]-; t_R (f): 1.92 min.
242		1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-fluoro-pyridin-2-ylmethyl)-amide]	437.2 [M+H]+, 895.3 [2M+Na]+; t_R (a): 2.36 min.
243		(2S,4S)-4-Fluoro-4-morpholin-4-ylmethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(8[B14]) 575 [M+H]+, 502 [M-H]-; tR (f): 1.51 min.
244		3-({[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-methyl)-5-chloro-4-fluoro-benzoic acid methyl ester	(3,6) 534.0 [M]+; t_R (c): 3.24 min.

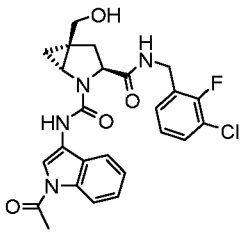
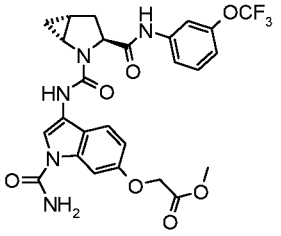
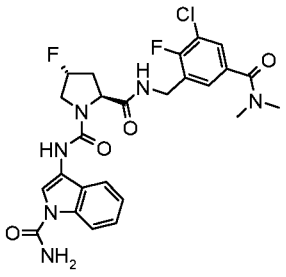
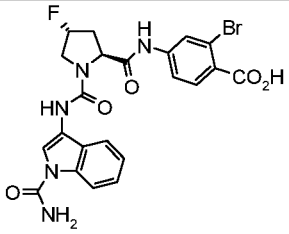
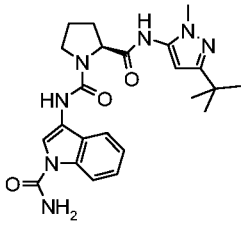
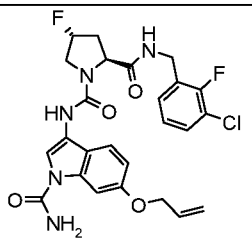
245		(1S,2S,5R)-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-methoxy-ethyl]-amide}	(5,8[B9]) White powder. R_f (EtOAc): 0.20; 514.4/516.4 [M+H]+, 558.4/560.3 [M+HCOO]-; t_R (a): 3.25 min.
246		{[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-(3-chloro-phenyl)-acetic acid	(8) (mixture of diastereosisomers) R_f (CH_2Cl_2/MeOH 4:1) = 0.2; 502/504, [M+H]+, 500/502 [M-H]-; t_R (a): 2.86 and 2.92 min.
247		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(5-chloro-pyridin-3-yl)-amide]	(4) White solid. R_f (EtOAc) = 0.46; 439.0 [M+H]+; t_R (c): 4.01 min.
248		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-dimethylamino-ethyl]-amide}	(5,6[C4]) 533.4/535.5 [M+H]+, 577.5/579.4 [M+HCOO]; t_R (a): 2.60 min.
249		(2S,4S)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	492.1 [M+H]+, 514.2 [M+H]+, 490.1 [M-H]-; t_R (a): 3.19 min.
250		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(morpholine-4-carbonyl)-benzylamide]	(3,6[C3]) 589.3 [M]+; t_R (c): 3.96 min.

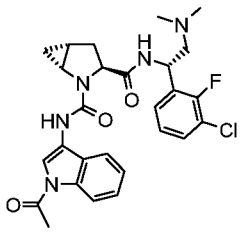
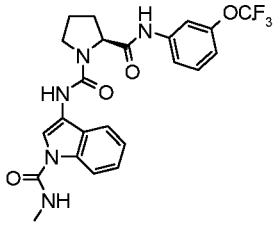
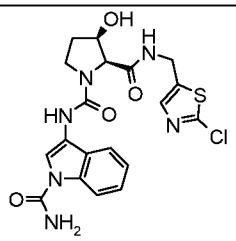
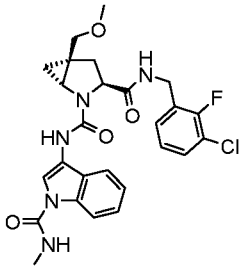
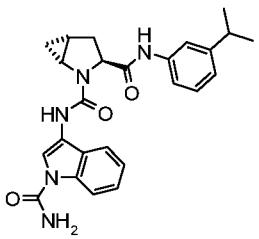
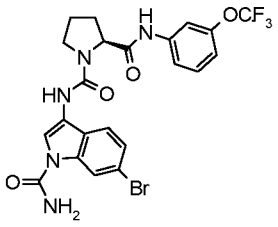
251		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-methoxy-phenyl)-amide]	(1) 434.0 [M+H]+, 388.9 [M-$CONH_2$]-; t_R (b) 3.64 min.
252		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-5-diethylamino-2-fluoro-benzylamide)	(3,6[C1]) 547.2 [M]+; t_R (c): 3.67 min.
253		(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide}	(5) R_f (EtOAc) = 0.2; 506.3/508.2 [M+H]+, 550.2/552.2 [M+HCOO]-; t_R (a): 3.06 min.
254		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-chloro-phenyl)-amide]	(1) 438.0/440.0 [M+H]+, 437.8 [M-H]-, 393/395 [M-$CONH_2$]-; t_R (b) 4.12 min.
255		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(3-methoxy-azetidine-1-carbonyl)-benzylamide]	(3,6[C3]) 589.3 [M]+; t_R (c): 4.06 min.
256		(2S,4R)-4-Cyano-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	501.1 [M+H]+; t_R (b): 4.22 min.

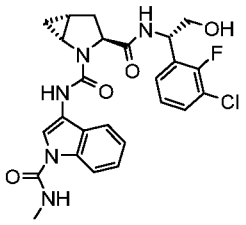
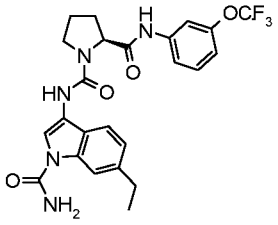
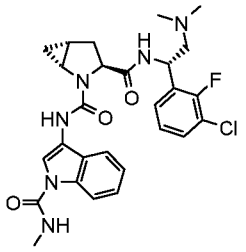
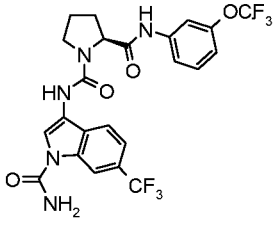
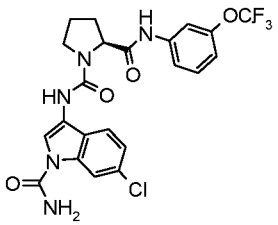
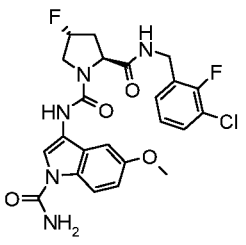
257		(2S,3S)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide)	(1) White solid. 456 [M+H]+; t_R (b): 2.99 min.
258		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-benzylamide 2-[(1-carbamoyl-1H-indol-3-yl)-amide]	418.3 [M+H]+, 416.3 [M-H]-; t_R (a): 2.94 min.
259		(2S,3R)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-chloro-thiophen-2-ylmethyl)-amide]	(1) White solid. 462/463 [M+H]+; t_R (b): 2.92 min.
260		(2S,4S)-4-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(8,9[A1]) R_f (EtOAc) = 0.15; 487.4/489.4 [M+H], 485.4/486.4 [M-H]-; t_R (a): 3.11 min.
261		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(2-fluoro-3-trifluoromethyl-benzylamide)	(1) White solid. 504 [M+H]+; t_R (b): 4.08 min.
262		(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2,3-difluoro-6-methoxy-benzylamide)	(2,3) White solid. R_f (c-hexane/EtOAc 1:3) = 0.19; 490.1 [M+H]+; t_R (c): 4.45 min.

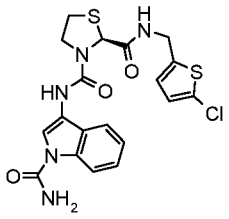
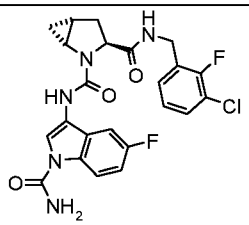
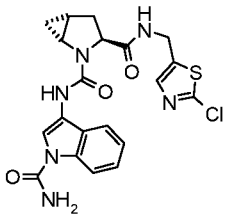
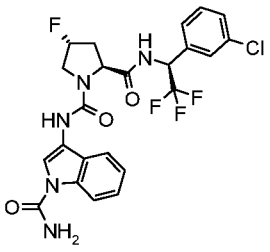
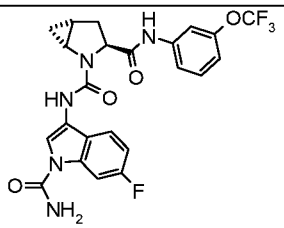
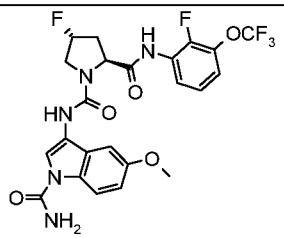
263		(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-chloro-thiazol-5-ylmethyl)-amide]	(1) White solid. 465 [M+H]+; t_R (b): 3.06 min.
264		(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-5-fluoro-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(9[A4]) 494 [M+H]+; t_R (b): 4.01 min.
265		(1R,3S,5S)-5-Hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-(3-chloro-2-fluoro-benzylamide) 2-[(1-methylcarbamoyl-1H-indol-3-yl)-amide]	(5,8[B28],9[A2]) White solid. R_f (EtOAc) = 0.20; 514.4/516.4 [M+H]+, 558.4/560.3 [M+HCOO]-; t_R (f): 1.80 min.
266		(S)-4-Methylene-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	(1) R_f (c-hexane/EtOAc 1:3) = 0.38; 486. [M-H]-, 443 [M-$CONH_2$]-; t_R (i): 3.52 min.
267		(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	494.0 [M+H]+, 492.1 [M-H]-; t_R (a): 3.52 min.
268		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(5-allyloxy-1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide)	(9) R_f (EtOAc) = 0.47; 526/528 [M+H]+, 481.1/483.3 [M-$CONH_2$]-; t_R (f): 2.01 min.

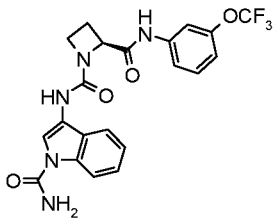
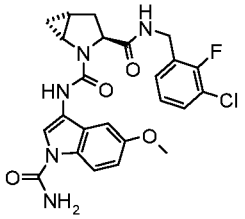
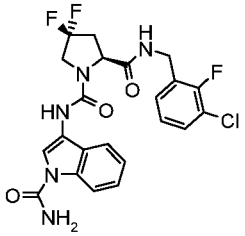
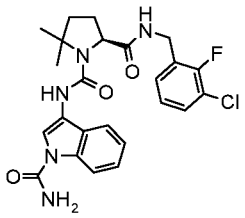
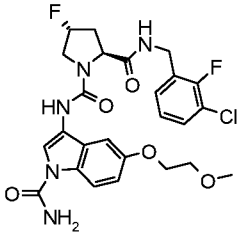
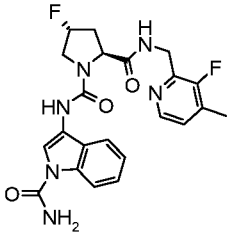
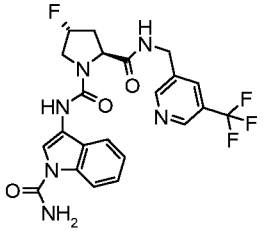
269		S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-6-methyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	(9[A4]) R_f (c-hexane/EtOAc 8:2)= 0.4; 490.1 [M+H]+, 488 [M-H]-; t_R (a): 3.57 min.
270		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-methoxy-ethyl]-amide} 2-[(1-methylcarbamoyl-1H-indol-3-yl)-amide]	(5,8[B9],9[A2]) White powder. R_f (EtOAc): 0.30; 528.4/530.4 [M+H]+, 572.4 [M+HCOO]-; t_R (a): 3.41 min.
271		(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	(9[A1]) R_f (c-hexane/EtOAc 1:2) = 0.35; 475.1 [M+H]+, 473.2 [M-H]-; t_R (a): 3.94 min.
272		3-Bromo-5-{[(1R,3S,5R)-2-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-3-carbonyl]-amino}-benzoic acid methyl ester	(1) White solid. 538.0 [M+H]+; t_R (b): 4.3 min.
273		(2S,5R)-5-Phenyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide	(1) 552.1 [M+H]+; t_R (c): 5.53 min.
274		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-fluoro-3-trifluoromethoxy-phenyl)-amide]	(1,6) 512 [M+H]+; t_R (b) 4.15 min.

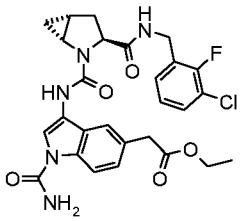
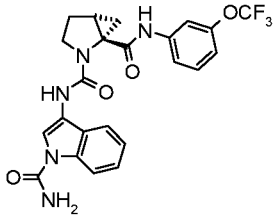
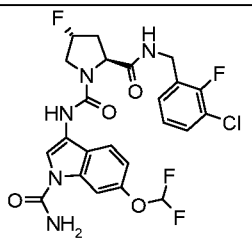
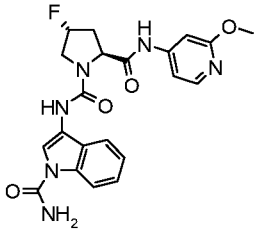
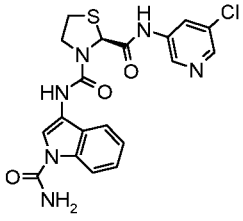
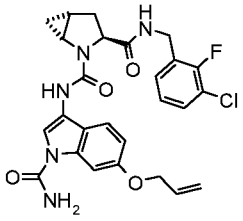
275		(1R,3S,5S)-5-Hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-acetyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide)	(5,8[B28],9[A1]) White solid. R_f (EtOAc) = 0.25; 499.3/501.3 [M+H]+, 521.3/523.2 [M+Na]+, 497.3/499.3 [M-H]-, 543.2/545.3 [M+HCOO]-; t_R (f): 1.90 min.
276		(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-trifluoromethoxy-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-6-yloxy)-acetic acid methyl ester	(9) R_f (EtOAc) = 0.6; 576.3 [M+H]+, 574.3 [M-H]-, 620.3 [M+HCOO]-; t_R (f): 2.12 min.
277		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-5-dimethylcarbamoyl-2-fluoro-benzylamide)	(3,6[C3]) 547.2 [M]+; t_R (c): 3.97 min.
278		2-Bromo-4-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-benzoic acid	(8) 530/531 [M+H]+; t_R (b): 3.0 min.
279		(S)-Pyrrolidine-1,2-dicarboxylic acid 2-[(5-tert-butyl-2-methyl-2H-pyrazol-3-yl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide]	452.2 [M+H]+, 450.2 [M-H]-; t_R (a): 2.79 min.
280		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(6-allyloxy-1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(9[A4]) R_f (EtOAc) = 0.55; 532 [M+H]+; t_R (b): 4.08 min.

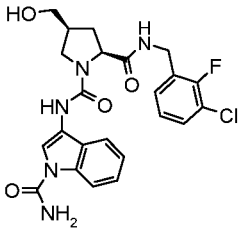
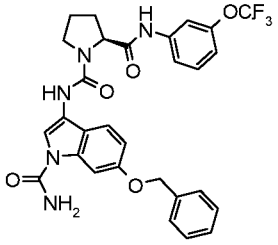
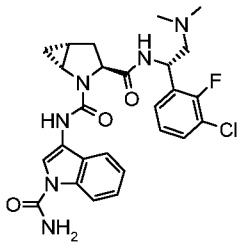
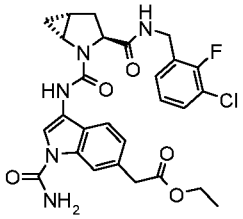
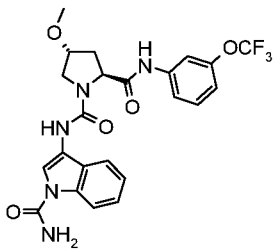
281		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-acetyl-1H-indol-3-yl)-amide] 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-dimethylamino-ethyl]-amide}	(5,6[C4],9[A1]) R_f (CH_2Cl_2/MeOH 9:1) = 0.65; 526.3/528.3 [M+H]+, 570.3/572.3 [M+HCOO]; t_R (a): 3.06 min.
282		(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-methylcarbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	(9[A2]) 490.1 [M+H]+, 488.2 [M-H]-; t_R (a): 3.65 min.
283		(2S,3R)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-chloro-thiazol-5-ylmethyl)-amide]	(1) White solid. 463 [M+H]+; t_R (b): 2.03 min.
284		(1R,3S,5S)-5-Methoxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-(3-chloro-2-fluoro-benzylamide) 2-[(1-methylcarbamoyl-1H-indol-3-yl)-amide]	(5,8,9[A2]) White solid. 528.4 [M+H]+, 526.2 [M+H]-, 572.3 [M+HCOO]-; t_R (a): 3.34 min.
285		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-isopropyl-phenyl)-amide]	R_f (c-hexane/EtOAc 1:2) = 0.29; 446.2 [M+H]+, 891.3 [2M+H]+, 913.3 [2M+Na]+, 401.2 [M-$CONH_2$]-; t_R (a): 3.54 min.
286		(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(6-bromo-1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	(9[A4]) R_f (c-hexane/EtOAc 1:1) = 0.5; 554/556 [M+H]+; t_R (a): 3.74 min.

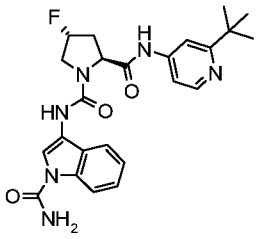
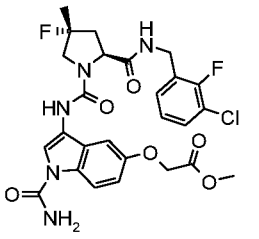
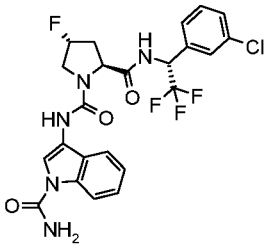
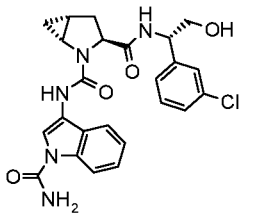
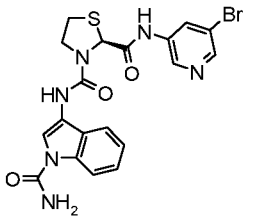
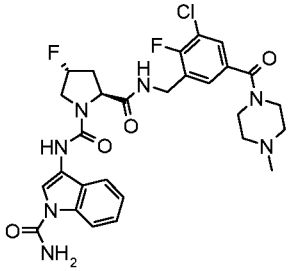
287		(1R,3S,5R)-2-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide}2-[(1-methylcarbamoyl-1H-indol-3-yl)-amide]	(5, 8[B9],9[A2]) R_f (EtOAc) = 0.2; 514.4 [M+H]+ 558.4 [M+HCOO]-; t_R (a): 3.12 min.
288		(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-6-ethyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	(9[A3]) 504.1 [M+H]+, 526.2 [M+Na]+, 502 [M-H]-; t_R (a): 3.68 min.
289		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-dimethylamino-ethyl]-amide} 2-[(1-methylcarbamoyl-1H-indol-3-yl)-amide]	(5,6[C4],9 [A2]) White solid. R_f (EtOAc) = 0.25; 541.4/543.4 [M+H]+, 585.3/587.2 [M+HCOO]; t_R (a): 2.88 min.
290		(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-6-trifluoromethyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	(9) 499 [M-H]- ; t_R (a): 4.15 min.
291		(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-6-chloro-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	(9[A4]) R_f (c-hexane/EtOAc 1:1)= 0.5; 510.1 [M+H]+, 532 [M+Na]+, 508 [M-H]-; t_R (a): 3.67 min.
292		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-5-methoxy-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(9[A4]) R_f (EtOAc) = 0.45; 506.0/508.0 [M+H]+, 504.1/506.1 [M-H]-, 461.0/463.0 [M-$CONH_2$]-; t_R (f): 1.80 min.

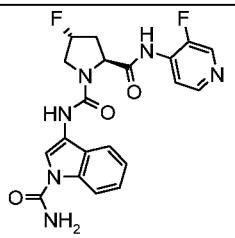
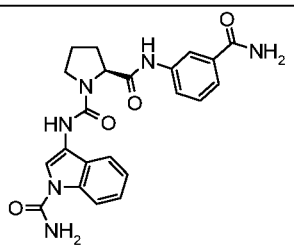
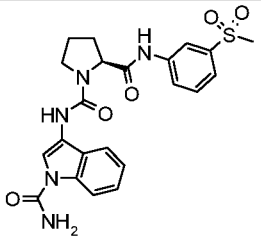
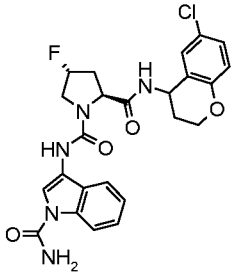
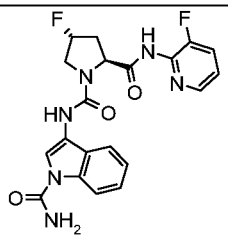
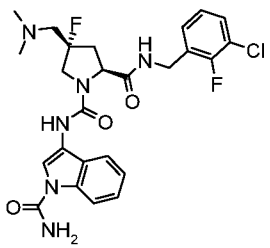
293		(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-chloro-thiophen-2-ylmethyl)-amide]	464.0 [M+H]+, 462.0 [M-H]-, 419.0 [M-$CONH_2$]-; t_R (f): 2.02 min.
294		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-5-fluoro-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide)	(9[A4]) R_f (EtOAc) = 0.47; 488 [M+H]+; t_R (b): 4.01 min.
295		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(2-chloro-thiazol-5-ylmethyl)-amide]	(1) White solid. 459 [M+H]+; t_R (b): 3.11 min.
296		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-phenyl)-2,2,2-trifluoro-ethyl]-amide}	(4) R_f (c-hexane/EtOAc 25/75)= 0.55; 526.0 [M+H]+; t_R (c): 4.80 min.
297		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-6-fluoro-1H-indol-3-yl)-amide] 3-[(3-trifluoromethoxy-phenyl)-amide]	(9[A4]) 506 [M+H]+; t_R (b): 4.62 min.
298		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-5-methoxy-1H-indol-3-yl)-amide] 2-[(2-fluoro-3-trifluoromethoxy-phenyl)-amide]	(6,9[A4]) 542.0 [M+H]+, 564.0 [M+Na]+; t_R (k): 3.47 min

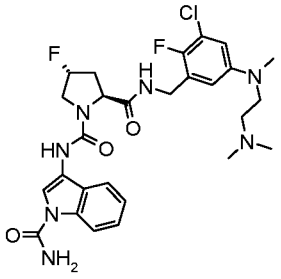
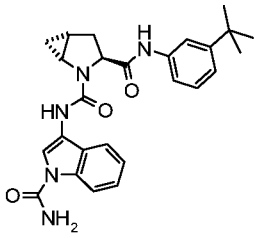
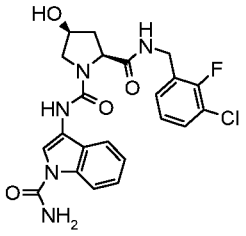
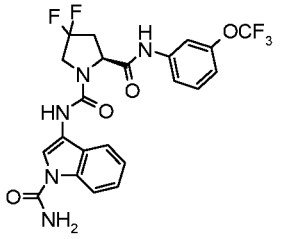
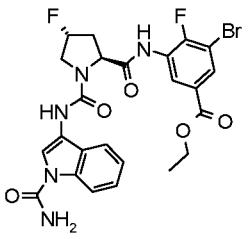
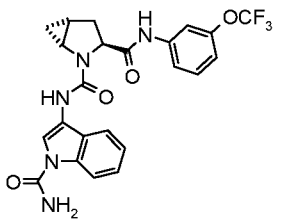
299		(S)-Azetidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	462.1 [M+H]+, 460.1 [M-H]-; t_R (a): 3.52 min.
300		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-5-methoxy-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide)	(9[A4]) R_f (EtOAc) = 0.45; 500/502.1 [M+H]+, 455/457 [M-$CONH_2$]-; t_R (f): 1.91 min.
301		(S)-4,4-Difluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	R_f (EtOAc) = 0.65; 492 [M+H]+, 494 [M-H]-; t_R (f): 1.96 min.
302		(S)-5,5-Dimethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(1) Off-white solid. R_f (EtOAc) = 0.53; 486.2 [M+H]+; t_R (c): 4.87 min.
303		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-{[1-carbamoyl-5-(2-methoxy-ethoxy)-1H-indol-3-yl]-amide} 2-(3-chloro-2-fluoro-benzylamide)	(9) R_f (EtOAc) = 0.3; 550.2/552.1 [M+H]+, 572/574.1 [M+Na]+, 548 [M-H]-, 505 [M-$CONH_2$]-; t_R (f): 1.76 min.
304		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-fluoro-4-methyl-pyridin-2-ylmethyl)-amide]	(1) 457.0 [M+H]+; t_R (c): 3.20 min.
305		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-trifluoromethyl-pyridin-3-ylmethyl)-amide]	(1) White solid. 493 [M+H]+; t_R (b): 3.76 min.

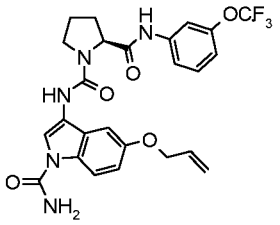
306		(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yl)-acetic acid ethyl ester	(9) R_f (EtOAc) = 0.45; 556.3/558.4 [M+H]+, 554.3/556.3 [M-H]-, 511.3/513.3 [M-$CONH_2$]-; t_R (f): 2.02 min.
307		(1S,5R)-2-Aza-bicyclo[3.1.0]hexane-1,2-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 1-[(3-trifluoromethoxy-phenyl)-amide]	R_f (c-hexane/EtOAc 1:2) = 0.15; 488 [M+H]+, 486.1 [M-H]-; t_R (a): 3.51 min.
308		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-6-difluoromethoxy-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(9[A4]) White solid. 542.0 [M+H]+; 564.0 [M+Na]+; t_R (k): 3.41 min.
309		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-methoxy-pyridin-4-yl)-amide]	(3,4) Off-white solid. R_f (c-hexane/EtOAc 1:1) = 0.42; 441.2 [M+H]+; t_R (c): 3.28 min.
310		(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-chloro-pyridin-3-yl)-amide]	(3,4) Off-white solid. R_f (EtOAc) = 0.47; 445.0 [M+H]+; t_R (c): 4.03 min.
311		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(6-allyloxy-1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide)	(9[A4]) R_f (EtOAc) = 0.4; 526 [M+H]+; t_R (b) : 4.33 min.

312		(2S,4S)-4-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(8) 488.2 [M+H]+, 433.0 [M-$CONH_2$]-; t_R (f): 1.63 min.
313		(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(6-benzyloxy-1-carbamoyl-1H-indol-3-yl)-amide]2-[(3-trifluoromethoxy-phenyl)-amide]	(9[A4]) R_f (EtOAc)= 0.44; 582.1 [M+H]+, 580.2 [M-H]-; t_R (a): 3.91 min.
314		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-dimethylamino-ethyl]-amide}	(5,6[C4]) White solid. R_f (EtOAc) = 0.1; 527.3/529.3 [M+H]+, 571.3 [M+HCOO]; t_R (a): 2.84 min.
315		(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-6-yl)-acetic acid ethyl ester	(9) R_f (EtOAc) = 0.4; 556.3/558.4 [M+H]+, 573.4/575.2 [M+H_3O]+, 1111.7/1113.7 [2M+H]+, 554.3/556.4 [M-H]-, 600.3/602.8 [M+HCOO]-; t_R (f): 2.02 min.
316		(2S,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	R_f (c-hexane/EtOAc 1:2) = 0.1; 506.0 [M+H]+, 504.1 [M-H]; t_R (a): 3.36 min.

317		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-[(2-tert-butyl-pyridin-4-yl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide]	(4) Off-white solid. R_f (c-hexane/EtOAc 1:1) = 0.42; 467.3 [M+H]+; t_R (c): 3.58 min.
318		(1-Carbamoyl-3-{[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidine-1-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid methyl ester	(8[B13],9) R_f (EtOAc) = 0.6; 578.4/580.4 [M+H]+, 576.3/578.2 [M-H]-, 533.5/535.5 [M-$CONH_2$]-; t_R (f): 1.90 min.
319		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(R)-1-(3-chloro-phenyl)-2,2,2-trifluoro-ethyl]-amide}	(4) R_f (c-hexane/EtOAc 1:3)= 0.56; 526.0 [M+H]+; t_R (c): 4.79 min.
320		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-{[(S)-1-(3-chloro-phenyl)-2-hydroxy-ethyl]-amide}	(5) 482.4 [M+H]+; t_R (a): 3.05 min.
321		(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-bromo-pyridin-3-yl)-amide]	(3,4) Off-white solid. R_f (EtOAc) = 0.38; 489.0 [M+H]+; t_R (c): 4.10 min.
322		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(4-methyl-piperazine-1-carbonyl)-benzylamide]	(3,6[C3]) 602.2 [M]+; t_R (c): 3.47 min.

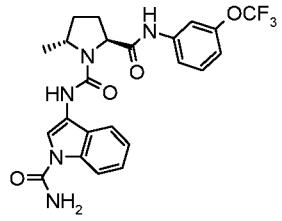
323		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-fluoro-pyridin-4-yl)-amide]	(4) White foam. R_f (EtOAc) = 0.18; 429.0 [M+H]+; t_R (c): 3.14 min.
324		(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-carbamoyl-phenyl)-amide]	435.1 [M+H]+, 891.3 [2M+Na]+, 433.1 [M-H]-; t_R (a): 2.39 min.
325		(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-methanesulfonyl-phenyl)-amide]	470.0 [M+H]+, 939.1 [2MH]+, 961.2 [2M+Na]+, 468.1 [M-H]-; t_R (a): 2.70 min.
326		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(6-chloro-chroman-4-yl)-amide] (mixture of 2 diastereoisomers)	(3) 500.0 [M]+; t_R (c): 4.39 min.
327		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-fluoro-pyridin-2-yl)-amide]	(4) White solid. R_f (EtOAc) = 0.25; 429.0 [M+H]+; t_R (c): 3.42 min.
328		(2S,4S)-4-Dimethylaminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	(8[B15]) 532 [M+H]+, 530 [M-H]-; t_R (f): 1.62 min, 19F NMR (DMSO-d_6): -120, -149.

329		(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{3-chloro-5-[(2-dimethylamino-ethyl)-methyl-amino]-2-fluoro-benzylamide}	(3,6[C1]) 576.2 [M]+; t_R (c): 3.91 min.
330		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(3-tert-butyl-phenyl)-amide] 2-[(1-carbamoyl-1H-indol-3-yl)-amide]	(1) 460.1 [M+H]+, 415.1 [M-$CONH_2$]-; t_R (b) 4.68 min.
331		(2S,4S)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)	R_f (EtOAc) = 0.2; 474.1/476.2 [M+H]+, 496.1/498 [M+Na]+, 472/474.1 [M-H]-, 429.1/431 [M-$CONH_2$]-; t_R (a): 2.88 min.
332		(S)-4,4-Difluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	512.2 [M+H]+, 510.1 [M-H]-; t_R (a): 3.63 min.
333		3-Bromo-5-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-4-fluoro-benzoic acid ethyl ester	(4,6) 578/580 [M+H]+, 576/578 [M-H]-; t_R (b): 4.3 min.
334		(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-trifluoromethoxy-phenyl)-amide]	R_f (c-hexane/EtOAc 1:2) = 0.40; 488 [M+H]+, 997.2 [2M+Na]+, 486.1 [M-H]-, 443.2 [M-$CONH_2$]-; t_R (a): 3.55 min.

335		(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(5-allyloxy-1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]	(9[A4]) R_f (EtOAc)= 0.51; 532.2 [M+H]+, 530 [M-H]-; t_R (a): 3.64 min.

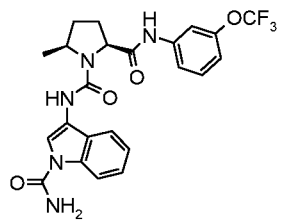
(1) CH_2Cl_2 was used instead of DMF in step A; (2) CH_3CN was used instead of DMF in step A; (3) HATU was used as the coupling reagent in step A; (4) The reaction mixture in step A was heated at 70°C; (5) HCl (4 M in dioxane) in dioxane was used instead of TFA in CH_2Cl_2 in step B; (6) The substituted benzylamine or aniline derivative used in step A was prepared as described in Part C [Scheme]; (7) The substituted proline derivative used in step A was prepared as described in Part B [Scheme]; (8) The title compound was prepared according to the general procedure described in Scheme D5 steps B and C starting from the substituted proline derivative prepared as described in Part B [Scheme]; (9) The isocyanate reagent used in step C was prepared as described in Part A.

Example 336: (2S,5R)-5-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]



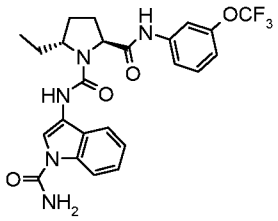
The title compound was prepared according to the general procedure described in Scheme D5 except that CH_2Cl_2 was used instead of DMF in step A, starting from a mixture of (2S,5R)- and (2S,5S)-5-methyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester in a 7:1 ratio (prepared as described in Scheme B1). The diastereoisomers were separated by chiral HPLC (Chiracel OJ, 20 μM, 185 x 48 mm, flow: 100 mL/min, mobile phase: n-hexane/EtOH 9:1) to give the title compound: TLC, R_f (c-hexane/EtOAc 1:3) = 0.45; MS (LC/MS): 490.0 [M+H]+, 488.0 [M-H]-; t_R (HPLC conditions c): 4.99 min.

Example 337: (2S,5S)-5-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]



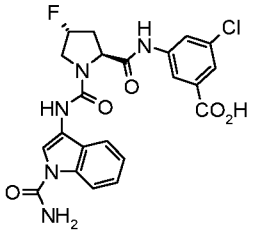
The title compound was prepared according to the general procedure described in Scheme D5 except that CH_2Cl_2 was used instead of DMF in step A, starting from a (7:1)-mixture of (2S,5R)- and (2S,5S)-5-methyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (prepared as described in Scheme B1). The diastereoisomeric product was separated by chiral HPLC (Chiracel OJ, 20 μM, 185 x 48 mm, flow: 100 mL/min, mobile phase: n-hexane/EtOH 9:1) to give the title compound. TLC R_f (c-hexane/EtOAc 1:3) = 0.45; MS (LC/MS): 490.0 [M+H]+, 488.0 [M-H]-; t_R (HPLC conditions c): 5.21 min.

Example 338: (2S,5R)-5-Ethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromthoxy-phenyl)-amide]



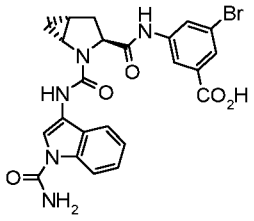
The title compound was prepared according to the general procedure described in Scheme D5 except that CH_2Cl_2 was used instead of DMF in step A, starting from a >9:1 diastereoisomeric mixture of (2S,5R)- and (2S,5S)-5-ethyl-pyrrolidine-1,2-diarboxylic acid 1-tert-butyl ester (prepared as described in Part B). Purification of the product in the final reaction step by chiral preparative HPLC (Chiralcel OJ H 5 μM stationary phase) gave the title compound as single diastereomer. TLC R_f (EtOAc) = 0.60; MS (LC/MS): 504.1 [M+H]+; t_R (Chiralcel OJ H 5 μM, column 250 x 4.0 mm, n-hexane/EtOH 8:2, flow 1.1 mL/min, 25°C, detection 200 nm): 4.73 min; t_R (HPLC conditions c): 5.21 min.

Example 339: 3-Chloro-5-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-benzoic acid



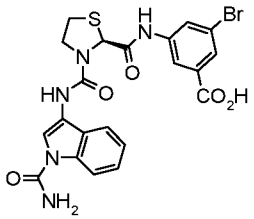
The title compound was prepared according to the general procedure described in Scheme D5 (Steps B and C) starting from (2S,4R)-2-(3-carboxy-5-chloro-phenylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester)(prepared by using similar protocols as described in Scheme B7). White solid. MS (LC/MS): 486 [M-H]+; t_R (HPLC conditions b): 3.31 min.

Example 340: 3-Bromo-5-{[(1R,3S,5R)-2-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-3-carbonyl]-amino}-benzoic acid



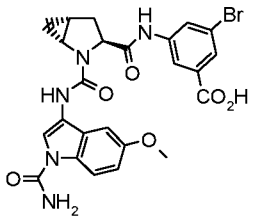
The title compound (White solid) was prepared according to the general procedure described in Scheme D5 (Steps B and C) starting from (1R,3S,5R)-3-(3-bromo-5-carboxy-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester)(prepared by using similar protocols as described in Scheme B7, except that the reaction mixture was heated at 65°C in step A and dioxane was used instead of MeOH in step B). White solid. MS (LC/MS): 524.3/525.3 [M+H]+; t_R (HPLC conditions b): 3.6 min.

Example 341: 3-Bromo-5-{[(S)-3-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-thiazolidine-2-carbonyl]-amino}-benzoic acid



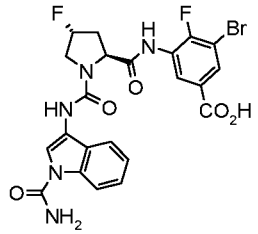
The title compound was prepared according to the general procedure described in Scheme D5 (Steps B and C) starting from (S)-2-(3-bromo-5-carboxy-phenylcarbamoyl)-thiazolidine-3-carboxylic acid tert-butyl ester) (prepared by using similar protocols as described in Scheme B7). MS (LC/MS): 530.2/532.2/533.1 [M-H]-; t_R (HPLC conditions b): 3.55 min.

Example 342: 3-Bromo-5-{[(1R,3S,5R)-2-(1-carbamoyl-5-methoxy-1H-indol-3-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-3-carbonyl]-amino}-benzoic acid



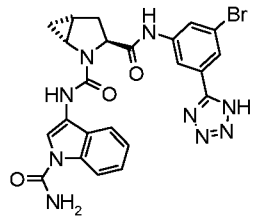
The title compound (White solid) was prepared according to the general procedure described in Scheme D5 (Steps B and C) using (1R,3S,5R)-3-(3-bromo-5-carboxy-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester)(prepared by using similar protocols as described in Scheme B7, except that the reaction mixture was heated at 65°C in step A and dioxane was used instead of MeOH in step B) and 3-Isocyanato-5-methoxy-indole-1-carboxylic acid amide (prepared as described in Scheme A1). MS (LC/MS): 556.0 [M+H]+; t_R (HPLC conditions c): 4.32 min.

Example 343: 3-Bromo-5-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-4-fluoro-benzoic acid



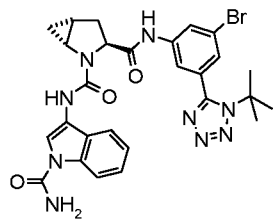
The title compound was prepared according to the general procedure described in Scheme D5 (Steps B and C) starting from (2S,4R)-2-(3-bromo-5-carboxy-2-fluoro-phenylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared by using similar protocols as described in Scheme B7 starting from 3-amino-5-bromo-4-fluoro-benzoic acid ethyl ester described Part C). MS (LC/MS): 550/552 [M+H]+; t_R (HPLC conditions b): 3.3 min.

Example 344: (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[3-bromo-5-(1H-tetrazol-5-yl)-phenyl]-amide} 2-[(1-carbamoyl-1H-indol-3-yl)-amide]



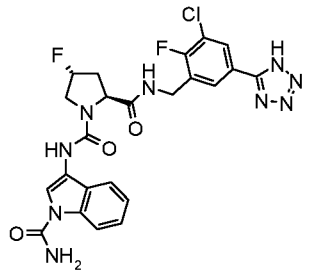
The title compound was prepared according to the general procedure described in Scheme D5 step C from a mixture of (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [3-bromo-5-(1H-tetrazol-5-yl)-phenyl]-amide and (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [3-bromo-5-(1-tert-butyl-1H-tetrazol-5-yl)-phenyl]-amide (ratio 2:3, prepared as described in Scheme B8). Purification by preparative HPLC (Sunfire, C18-ODB, 5 µm, 30x100 mm, flow: 40 mL/min, eluent: 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) afforded the title compound (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[3-bromo-5-(1H-tetrazol-5-yl)-phenyl]-amide} 2-[(1-carbamoyl-1H-indol-3-yl)-amide] as a white powder, MS (LC/MS): 550.0 [M+H]+; t_R (HPLC conditions c): 4.35 min.

Example 345: (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[3-bromo-5-(1-tert-butyl-1H-tetrazol-5-yl)-phenyl]-amide} 2-[(1-carbamoyl-1H-indol-3-yl)-amide]



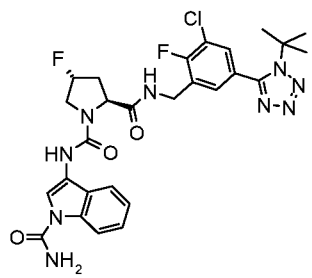
The title compound was prepared according to the general procedure described in Scheme D5 step C from a mixture of (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [3-bromo-5-(1H-tetrazol-5-yl)-phenyl]-amide and (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [3-bromo-5-(1-tert-butyl-1H-tetrazol-5-yl)-phenyl]-amide (ratio 2:3, prepared as described in Scheme B8). Purification by preparative HPLC (Sunfire, C18-ODB, 5 µm, 30x100 mm, flow: 40 mL/min, eluent: 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) afforded the title compound (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[3-bromo-5-(1-tert-butyl-1H-tetrazol-5-yl)-phenyl]-amide} 2-[(1-carbamoyl-1H-indol-3-yl)-amide] as a white solid. MS (LC/MS): 606.0 [M+H]+; t_R (HPLC conditions c): 5.60 min.

Example 346: (2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(1H-tetrazol-5-yl)-benzylamide]



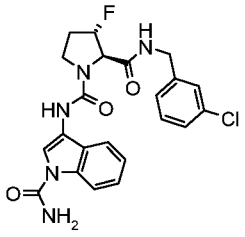
The title compound was prepared according to the general procedure described in Scheme D5 step C from a 2:1 mixture of (2S,4R)-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-5-(2H-tetrazol-5-yl)-benzylamide and (2S,4R)-4-fluoro-pyrrolidine-2-carboxylic acid 5-(1-tert-butyl-1H-tetrazol-5-yl)-3-chloro-2-fluoro-benzylamide (prepared as described in Part B). The crude products were purified without aqueous workup by RP-preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, 5-80% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 mL/min) to give the title compound (2S,4R)-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(1H-tetrazol-5-yl)-benzylamide]: MS (LC/MS): 544.0 [M]+; t_R (HPLC conditions c): 3.09 min.

Example 347: (2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-[5-(1-tert-butyl-1H-tetrazol-5-yl)-3-chloro-2-fluoro-benzylamide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide]



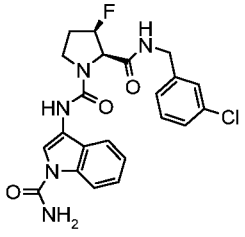
The title compound was prepared according to the general procedure described in Scheme D5 step C from a 2:1 mixture of (2S,4R)-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-5-(2H-tetrazol-5-yl)-benzylamide and (2S,4R)-4-fluoro-pyrrolidine-2-carboxylic acid 5-(1-tert-butyl-1H-tetrazol-5-yl)-3-chloro-2-fluoro-benzylamide (prepared as described in Part B). The crude products were purified without aqueous workup by RP-preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, 5-80% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 mL/min) to give the title compound (2S,4R)-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-[5-(1-tert-butyl-1H-tetrazol-5-yl)-3-chloro-2-fluoro-benzylamide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide]: MS (LC/MS): 600.2 [M]+; t_R (HPLC conditions c): 3.63 min.

Example 348: (2R,3S)-3-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide)



The title compound was prepared according to the general procedure described in Scheme D5 (Steps B and C) starting from (2R,3S)-2-(3-chloro-benzylcarbamoyl)-3-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared by using similar protocols as described for the preparation of (2R,3S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester in Part B). White solid. MS (LC/MS): 458 [M+H]+; t_R (HPLC conditions b): 3.56 min.

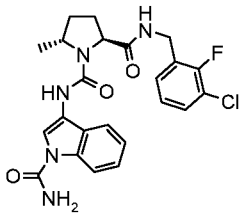
Example 349: (2R,3R)-3-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide)



The title compound was prepared according to the general procedure described in Scheme D5 (Steps B and C) by starting from (2R,3R)-2-(3-chloro-benzylcarbamoyl)-3-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared by using similar protocols as described for the preparation of (2R,3R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-fluoro-pyrrolidine-1-carboxylic

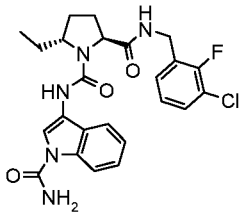
acid tert-butyl ester in Part B). White solid. MS (LC/MS): 458 [M+H]+; t_R (HPLC conditions b): 3.42 min.

Example 350: (2S,5R)-5-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



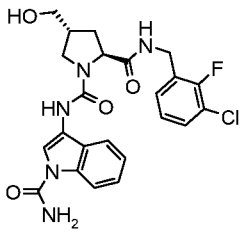
The title compound (cis/trans ratio 1:11) was prepared according to the general procedure described in Scheme D5 except that CH_2Cl_2 was used instead of DMF in step A, and starting (2S,5R)-5-methyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (prepared in cis/trans ratio of 1:11 as described in Scheme B1). White solid. TLC R_f (EtOAc) = 0.35; MS (LC/MS): 472 [M+H]+, 494 [M+Na]+; t_R (HPLC conditions c): 4.52 min.

Example 351: (2S,5R)-5-Ethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



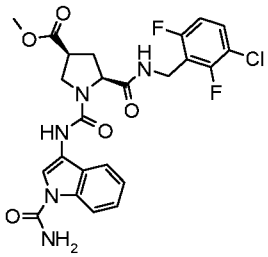
The title compound was prepared according to the general procedure described in Scheme D5 except that CH_2Cl_2 was used instead of DMF in step A, starting from a >9:1 diastereoisomeric mixture of (2S,5R)- and (2S,5S)-5-ethyl-pyrrolidine-1,2-diarboxylic acid 1-tert-butyl ester (prepared as described in Part B). The crude diastereoisomeric product mixture was purified by chiral preparative HPLC (Chiracel OJ, 10 μM, 250 x 4.6 mm, flow: 1.0 mL/min, mobile phase: heptane/EtOH 8:2; t_R = 5.61 min (major) and 14.3 min (minor) in a peak ratio of 87:13) to give the title compound as single diastereomer. TLC, R_f (EtOAc/c-hexane 4:1) = 0.31; MS (LC/MS): 486.1 [M+H]+; t_R (HPLC conditions c): 4.76 min.

Example 352: (2S,4R)-4-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



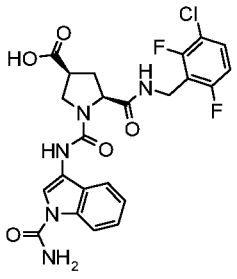
The title compound was prepared according to Scheme D5 (steps B and C) from (2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester prepared using the same protocol as for the preparation of (2S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared as described in Part B). TLC, R_f (EtOAc) = 0.05; MS (LC/MS): 488.1/490.1 [M+H]+, 510.1/512.1 [M+Na]+, 443.0/445.0 [M-$CONH_2$]-; t_R (HPLC conditions a): 2.87 min.

Example 353: (3S,5S)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-5-(3-chloro-2,6-difluoro-benzylcarbamoyl)-pyrrolidine-3-carboxylic acid methyl ester



The title compound was prepared according to Scheme D5 (steps B and C) from (3S,5S)-5-(3-chloro-2,6-difluoro-benzylcarbamoyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester prepared using the protocols described for the preparation of (3S,5S)-5-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester in Part B. R_f, TLC (CH_2Cl_2/MeOH, 95:5) = 0.2; MS (LC-MS): 534.3/536.2 [M+H]+, 532.2 [M-H]-; t_R (HPLC conditions a): 2.96 min.

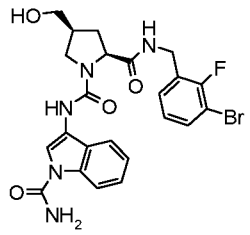
Example 354: (3S,5S)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-5-(3-chloro-2,6-difluoro-benzylcarbamoyl)-pyrrolidine-3-carboxylic acid



To a solution of (3S,5S)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-5-(3-chloro-2,6-difluoro-benzylcarbamoyl)-pyrrolidine-3-carboxylic acid methyl ester **Example 353** (50 mg, 0.094 mmol) in THF (0.3 mL)/ Et_2O (3 mL)/ H_2O (0.3 mL) was added potassium trimethylsilanolate

(19.5 mg, 0.2 mmol) and the resulting suspension was stirred at RT for 1.30 h. The reaction was diluted with EtOAc (15 mL) and H_2O (3 mL), and the biphasic mixture was vigorously stirred for 5 min. The layers were separated, and the aqueous one was extracted with EtOAc (x2). The aqueous layer was acidified by addition of 1N HCl and extracted with EtOAc, the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude material was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 19x50 mm, eluent: 20% to 100% CH_3CN in H_2O in 25 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 20 mL/min) to give, after lyophilization of the purified fractions the title compound as a white solid. MS (LC-MS): 518.4 [M-H]-, 520.1 [M+H]+, 1039.3 [2M+H]+; t_R (HPLC conditions f): 1.70 min.

Example 355: (2S,4S)-4-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 2-(3-bromo-2-fluoro-benzylamide) 1-[(1-carbamoyl-1H-indol-3-yl)-amide]

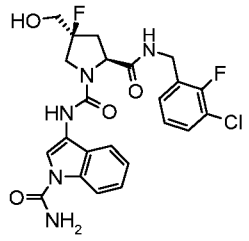


To a solution of (3S,5S)-5-(3-bromo-2-fluoro-benzylcarbamoyl)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-3-carboxylic acid methyl ester (85 mg, 0.14 mmol) in THF (1.5 mL) under nitrogen atmosphere was added $LiBH_4$ (2 M in THF, 0.14 mL, 0.29 mmol). The reaction mixture was stirred at RT for 30 min, and then it was slowly poured into an aqueous saturated solution of $NaHCO_3$ and extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (eluent: 100% CH_2Cl_2 to CH_2Cl_2/ MeOH 91-9) to give the desired material as white solid. R_f, TLC (EtOAc) = 0.2; MS (UPLC-MS): 532.3/534.4 [M+H]+, 576.3/578.3 [M+HCOO]-, 530.4/532.5 [M-H]-; t_R (HPLC conditions f): 1.69 min.

(3S,5S)-5-(3-Bromo-2-fluoro-benzylcarbamoyl)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-3-carboxylic acid methyl ester

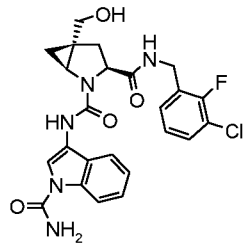
The title compound was prepared according to Scheme D5 (steps B and C) from (3S,5S)-5-(3-bromo-2-fluoro-benzylcarbamoyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester prepared using the protocols as for the preparation of (3S,5S)-5-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester described in Part B. R_f, TLC (EtOAc) = 0.45, MS (UPLC-MS): 560.5/562.4 [M+H]+, 577.3/579.4 [M+NH4]+, 582.3/584.3 [M+Na]+, 604.4/606.3 [M+HCOO]-, 558.2/560.2 [M-H]-; t_R (HPLC conditions f): 1.88 min.

Example 356: (2S,4S)-4-Fluoro-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



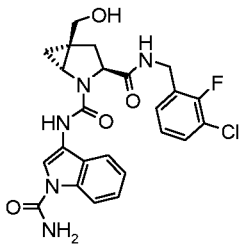
The title compound was prepared according to Scheme D5 (steps B and C) from (2S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared using similar protocols as described in Scheme B12). TLC, R_f (EtOAc) = 0.15; MS (LC-MS): 506.0/508.0 [M+H]+, 528.1/530.1 [M+Na]+, 504.1/506.1 [M-H], 461.0/463.0 [M-$CONH_2$]-; t_R (HPLC conditions f): 1.71 min.

Example 357: (1S,3S,5R)-5-Hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide)



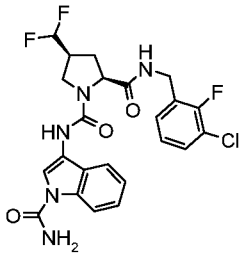
The title compound was prepared according to Scheme D5 (steps B and C) using in step B HCl 4N in dioxane instead of TFA from a mixture of (1S,3S,5R) and (1R,3S,5S)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide.HCl salt (prepared as described in Part B Scheme B28). The mixture of diastereoisomers was purified by flash column chromatography on silica gel (CH_2Cl_2 to CH_2Cl_2/MeOH:90:10) to give: (1R,3S,5S)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide) and (1S,3S,5R)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide) which was again purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 19x50 mm, eluent: 20% to 100% (CH_3CN/MeOH 1:4)/H_2O in 30 min, (CH_3CN/MeOH 1:4) and H_2O containing 0.1% HCOOH, flow: 20 mL/min): UPLC-MS: 500 [M+H]+, 544.3/546.4 [M+HCOO-]-; t_R (HPLC conditions f): 1.78 min. The absolute stereochemistry was tentatively assigned by NMR and based on the test results for the final compounds **Example 357** and **Example 358.**

Example 358: (1R,3S,5S)-5-Hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide)



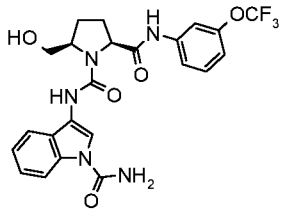
The title compound was prepared according to Scheme D5 (steps B and C) using in step B HCl 4N in dioxane instead of TFA from a mixture of (1S,3S,5R) and (1R,3S,5S)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide.HCl salt (prepared as described in Part B Scheme B28). The mixture of diastereoisomers was purified by flash column chromatography on silica gel (CH_2Cl_2 to CH_2Cl_2/MeOH:90:10) to give: (1R,3S,5S)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide) which was again purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 19x50 mm, eluent: 20% to 100% (CH_3CN/MeOH 1:4)/H_2O in 30 min, (CH_3CN/MeOH 1:4) and H_2O containing 0.1% HCOOH, flow: 20 mL/min) to give a white solid: 500.4/502.4 [M+H]+, 544.4/546.5 [M+HCOO]-; t_R (HPLC conditions f): 1.72 min. The absolute stereochemistry was tentatively assigned by NMR and based on the test results for the final compounds **Example 357** and **Example 358.**

Example 359: (2S,4S)-4-Difluoromethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



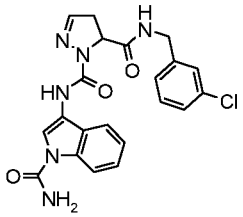
The title compound was prepared according to Scheme D5 from (2S,4S)-4-difluoromethyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (prepared following the procedure described in *J. Org. Chem.* **2002**, *67*, 7162). White solid. MS (LC/MS): 508 [M+H]+; t_R (HPLC conditions b) 4.03 min.

Example 360: (2S,5R)-5-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]



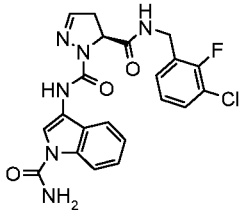
was prepared according to Scheme D5 (step C) using (2S,5R)-5-(tert-butyl-dimethyl-silanyloxymethyl)-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide (prepared as described in Part B). Except that after completion of the reaction, the mixture was poured into HCl 1N and EtOAc was added. The layers were separated and the aqueous one was back extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by preparative HPLC (Waters SunFire C18-ODB, 5 µm, 19x50 mm, 20% CH_3CN/H_2O 2.5 min, 20-100% CH_3CN/H_2O in 10 min, CH_3CN/H_2O containing 0.1 % HCOOH flow: 20 mL/min) to give after lyophilization of the purified HPLC fractions the title compound. MS (LC-MS): 506 [M+H]+; t_R (HPLC conditions b) 4.13 min.

Example 361: 4,5-Dihydro-pyrazole-1,5-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 5-(3-chloro-benzylamide)



The title compound was prepared according to Scheme D5 (step C) from 3,4-dihydro-2H-pyrazole-3-carboxylic acid 3-chloro-benzylamide (prepared using similar protocols as described in Scheme B5). MS (LC-MS): 439.0 [M+H]; t_R (HPLC conditions b): 3.55 min.

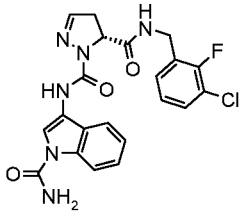
Example 362: ($S^{\S}$)-4,5-Dihydro-pyrazole-1,5-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 5-(3-chloro-2-fluoro-benzylamide)



Obtained from racemic 4,5-dihydro-pyrazole-1,5-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 5-(3-chloro-2-fluoro-benzylamide) **Example 201** by separation by chiral HPLC (Chiralpak ADi 5µm, 1mL/min, solvent: TBME/CH_2Cl_2/EtOH 50:30:20, t_R = 9.08 min). MS (LC-MS): 457 [M+H]+; t_R (HPLC conditions b): 3.73 min. The absolute stereochemistry has been

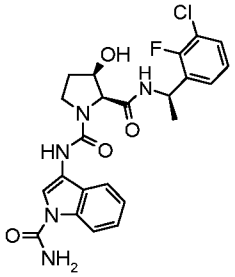
assigned tentatively based on the test results for the final compounds **Example 362** and **Example 363** in the biological assay.

Example 363: ($R^{\S}$)-4,5-Dihydro-pyrazole-1,5-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 5-(3-chloro-2-fluoro-benzylamide)



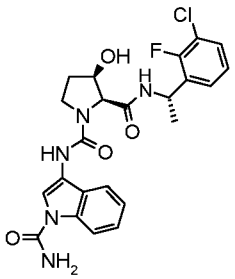
Obtained from racemic 4,5-dihydro-pyrazole-1,5-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 5-(3-chloro-2-fluoro-benzylamide) **Example 201** by separation by chiral HPLC (Chiralpak ADi 5μm, 1mL/min, solvent: TBME/CH_2Cl_2/EtOH 50:30:20, t_R = 6.49 min). MS (LC-MS): 457 [M+H]+; t_R (HPLC conditions b): 3.73 min. The absolute stereochemistry has been assigned tentatively based on the test results for the final compounds **Example 362** and **Example 363** in the biological assay.

Example 364: (2S,3R)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[($R^{\S}$)-1-(3-chloro-2-fluoro-phenyl)-ethyl]-amide}



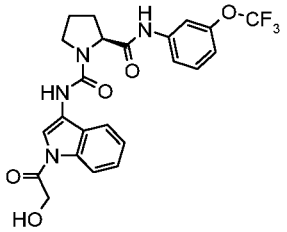
The title compound was prepared according to the general procedure described in Scheme D5 (CH_2Cl_2 was used instead of DMF in step A) from a ca. (1:1)-mixture of diastereomers (2S,3R)-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(R) and (S)-1-(3-chloro-2-fluoro-phenyl)-ethyl]-amide} and purification of the title compound by preparative chromatographic separation on a Chiralpak IA 5 μm stationary phase (column 250 x 10 mm) using heptane/TBME/MeOH/TFA 50:35:15:0.05 as the eluent (flow: 8 mL/min, detection 254 nm, 25°C). White solid. MS (LC/MS): 488 [M+H]+; t_R (HPLC conditions b): 3.28 min. t_R (chiral HPLC conditions: Chiralpak IA 5 μm; column 250 x 4.6 mm; heptane/TBME/MeOH/TFA 50:35:15:0.05; flow: 2.00 mL/min; detection 254 nm, 25°C): 10.1 min. The absolute stereochemistry has been assigned tentatively based on the test results for the final compounds **Example 364** and **Example 365** in the biological assay.

Example 365: (2S,3R)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S§)-1-(3-chloro-2-fluoro-phenyl)-ethyl]-amide}



The title compound was prepared according to the general procedure described in Scheme D5 (CH_2Cl_2 was used instead of DMF in step A) from a ca. (1:1)-mixture of diastereomers (2S,3R)-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(R) and (S)-1-(3-chloro-2-fluoro-phenyl)-ethyl]-amide} by preparative chromatographic separation on a Chiralpak IA 5 μm stationary phase (column 250 x 10 mm) using heptane/TBME/MeOH/TFA 50:35:15:0.05 as the eluent (flow: 8 mL/min, detection 254 nm, 25°C). White solid. MS (LC/MS): 488 [M+H]+; t_R (HPLC conditions b): 3.28 min. t_R (chiral HPLC conditions: Chiralpak IA 5 μm; column 250 x 4.6 mm; heptane/TBME/MeOH/TFA 50:35:15:0.05; flow: 2.00 mL/min; detection 254 nm, 25°C): 14.3 min. The absolute stereochemistry has been assigned tentatively based on the test results for the final compounds **Example 364** and **Example 365** in the biological assay.

Example 366: (S)-Pyrrolidine-1,2-dicarboxylic acid 1-{[1-(2-hydroxy-acetyl)-1H-indol-3-yl]-amide} 2-[(3-trifluoromethoxy-phenyl)-amide]

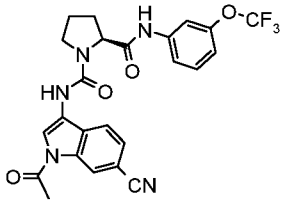


(S)-Pyrrolidine-1,2-dicarboxylic acid 1-{[1-(2-benzyloxy-acetyl)-1H-indol-3-yl]-amide} 2-[(3-trifluoromethoxy-phenyl)-amide] (55 mg, 0.095 mmol) was dissolved in MeOH (1 mL) and Pd/C 10% (12 mg) was added and the solution was degassed 3 times replacing air by nitrogen and finally nitrogen by hydrogen. The reaction mixture was further stirred under hydrogen atmosphere overnight and the catalyst was removed through a pad of Celite and washed with MeOH. Solvent was concentrated and the crude residue was purified by preparative HPLC (Waters SunFire C18-ODB, 5 μm, 19x50 mm, 20% CH_3CN/H_2O 2.5 min, 20-100% CH_3CN/H_2O in 10 min, CH_3CN/H_2O containing 0.1 % HCOOH flow: 20 mL/min) to give after lyophilization of the pure fractions the desired compound. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.49; MS (LC/MS): 491.1 [M+H]+, 513.2 [M+Na]+, 489.1 [M-H]-; t_R (HPLC conditions a): 3.47 min.

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-{[1-(2-benzyloxy-acetyl)-1H-indol-3-yl]-amide} 2-[(3-trifluoromethoxy-phenyl)-amide]

To a solution of (S)-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide TFA salt (177 mg, 0.457 mmol) and Et_3N (191 µl, 1.37 mmol) in dry THF (3.5 mL) was added a solution of 2-benzyloxy-1-(3-isocyanato-indol-1-yl)-ethanone (140 mg, 0.457 mmol, prepared as described in Scheme A5) in dry THF (3.5 mL). The solution was stirred at RT under nitrogen for 15 min until completion. The mixture was poured into water, extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 65:35) to afford the desired compound. TLC, R_f (c-hexane/EtOAc 1:1) = 0.3; MS (LC/MS): 581.2 [M+H]+, 579.1 [M-H]-; t_R (HPLC conditions a): 4.18 min.

Example 367: (S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-6-cyano-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]



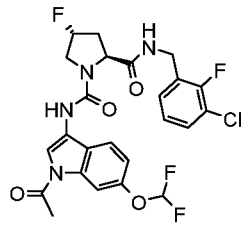
To a solution of (S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(6-cyano-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide] (60 mg, 0.131 mmol) in dry THF (1 mL) at 0°C under nitrogen atmosphere was added potassium tert-butoxide (17.7 mg, 0.157 mmol). The suspension was stirred at 0°C for 5 minutes before addition of acetyl chloride (0.011 mL, 0.157 mmol) and the resulting solution was stirred at RT under nitrogen overnight. The mixture was poured into an aqueous saturated solution of $NaHCO_3$ and extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude material was successively purified by flash column chromatography on silica gel (CH_2Cl_2 to CH_2Cl_2/MeOH 95:5) and preparative HPLC (Waters Sunfire C18-ODB, 5um, 19x50mm, flow: 20 mL/min, gradient: 0-2.5 min 20% CH_3CN, 2.5-12.5 min 20 to 100% CH_3CN, 12.5-15 min 100% CH_3CN, H_2O and CH_3CN containing 0.1% HCOOH) to give after lyophilization of the purified fractions the desired compound. MS (LC/MS): 500 [M+H]+, 498.1 [M-H]-; t_R (HPLC conditions a): 3.69 min.

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(6-cyano-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]

A solution of (S)-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide TFA salt (315 mg, 0.81 mmol) in THF (10 mL) was added to a solution of 3-isocyanato-1H-indole-6-

carbonitrile (270 mg, prepared as described in Part A, 70% purity as measured by NMR) in toluene (4 mL). Triethylamine (338 µl, 2.43 mmol) was added and the resulting solution was stirred at RT under nitrogen overnight. The mixture was poured into HCl 1 N and extracted with EtOAc (x3). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 1:1) to give the title compound. TLC, R_f (c-hexane/EtOAc 1:1) = 0.5; MS (LC-MS): 554.0 [M+H]+, 556.0 [M-H]-; t_R (HPLC conditions a): 3.74 min.

Example 368: (2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-6-difluoromethoxy-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)

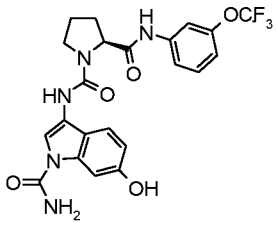


To a solution of (2S,4R)-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-(3-chloro-2-fluoro-benzylamide) 1-[(6-difluoromethoxy-1H-indol-3-yl)-amide] (105 mg, 0.210 mmol) in dry THF (5 mL) was added Ac_2O (1 mL, 10.5 mmol) and DMAP (26 mg, 0.210 mmol). The reaction mixture was stirred at 60°C for 18 h. The volatiles were evaporated under reduced pressure, and the residue was purified by preparative HPLC (Macherey-Nagel Nucleosil 100-10 C18, 5 µm, 40x250 mm, flow: 40 mL/min, eluent: 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) to afford after lyophilization of purified fractions the title compound as a white solid. MS (LC/MS): 541 [M+H]+, 563 [M+Na]+; t_R (HPLC conditions k): 3.65 min.

(2S,4R)-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-(3-chloro-2-fluoro-benzylamide) 1-[(6-difluoromethoxy-1H-indol-3-yl)-amide]

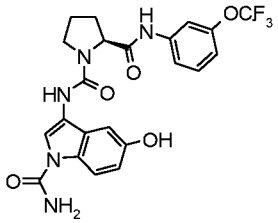
The title compound was prepared according to the general protocol described in Scheme D5. In Step C, 6-difluoromethoxy-3-isocyanato-1H-indole (prepared as described in Part A) was used and after completion of the reaction, the mixture was concentrated and directly purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, flow: 40 ml/min, eluent: 5-100% CH_3CN/H_2O/20 min, 100% CH3CN/2 min, CH_3CN and H_2O containing 0.1% TFA). White solid. MS (LC/MS): 499 [M+H]+, 521 [M+Na]+; t_R (HPLC conditions k): 3.49 min).

Example 369: (S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-6-hydroxy-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]



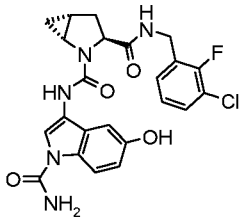
(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(6-benzyloxy-1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide] **Example 313** (75 mg, 0.129 mmol) was dissolved in a mixture of THF/DMF 1-1 (3 mL), Pd/C 10 % (20 mg) was added to the solution and the solution was degassed 3 times replacing air by nitrogen and finally nitrogen by hydrogen. The reaction mixture was further stirred under hydrogen atmosphere for 3 h and the catalyst was removed through a pad of Celite and washed with THF. Solvents were concentrated and the resulting oil was poured into water and extracted with EtOAc (x3). The combined organic layers were washed twice with water, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by preparative HPLC (Waters SunFire C18-ODB, 5 µm, 19x50 mm, 20% to 100 % CH_3CN in H_2O in 25 min, CH_3CN/H_2O containing 0.1 % HCOOH flow: 20 mL/min) to give after lyophilization of the purified fractions the desired compound. TLC, R_f (EtOAc) = 0.39; MS (LC/MS): 492.1 [M+H]+, 490.1 [M-H]-; t_R (HPLC conditions a): 3.22 min.

Example 370: (S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-5-hydroxy-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]



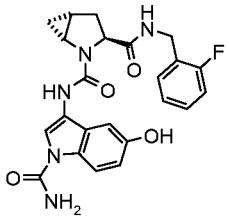
A mixture of (S)-pyrrolidine-1,2-dicarboxylic acid 1-[(5-allyloxy-1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide] **Example 335** (30 mg, 0.056 mmol), palladium acetate (1.4 mg, 2.82 µmol) and triphenylphosphine (1.5 mg, 5.64 µmol) in formic acid (0.7 mL) was heated at 90°C for 30 min under nitrogen. The mixture was poured into water and extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash column chromatography on silica gel (c-hexane/EtOAc 1:1 to EtOAc) to give the desired compound. TLC, R_f (EtOAc) = 0.56; MS (LC/MS): 492 [M+H]+, 514.2 [M+Na]+, 490 [M-H]-, 447.1 [M-$CONH_2$]-; t_R (HPLC conditions a): 3.13 min.

Example 371: (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-5-hydroxy-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide)



Allyl palladium chloride dimer (4.9 mg, 0.013 mmol) and 2-di-tert-butylphosphino-2'-methylbiphenyl (16.6 mg, 0.053 mmol) were dissolved in DMF (0.4 mL) and the mixture was stirred for 5 min under nitrogen atmosphere. Formic acid (30 µL, 0.772 mmol), triethylamine (107 µL, 0.772 mmol) and (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(5-allyloxy-1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide) **Example 268** (70 mg, 0.133 mmol) in DMF (1 mL) were added in that order. The mixture was stirred at 10°C for 1 h, then at RT for 2 days. The mixture was poured into water and extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude material was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 19x50 mm, eluent: 20% to 100% CH_3CN in H_2O in 15 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 20 mL/min) to give the desired compound after lyophilization of the purified fractions. TLC, R_f (EtOAc) = 0.4 ; MS (LC-MS): 486.0 [M+H]+, 441.1 [M-$CONH_2$]-; t_R (HPLC conditions f): 1.65 min.

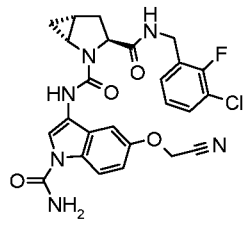
Example 372: (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-5-hydroxy-1H-indol-3-yl)-amide] 3-(2-fluoro-benzylamide)



Allyl palladium chloride dimer (17.8 mg, 0.048 mmol) and 2-di-tert-butylphosphino-2'-methylbiphenyl (60.6 mg, 0.194 mmol) were dissolved in DMF (2 mL) and the mixture was stirred for 5 min. Formic acid (108 µL, 2.81 mmol), triethylamine (391 µL, 2.81 mmol) and (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(5-allyloxy-1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide) **Example 268** (255 mg, 0.485 mmol) in DMF (3 mL) were added in that order and the resulting solution was stirred at RT overnight under nitrogen. The mixture was poured into water and extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane 100% to 100% EtOAc to CH_2Cl_2/MeOH 90-10) to give a mixture of the desired compound together with the deschlorinated analog. The mixture was purified by preparative HPLC (Interchrom, C18-ODB, 10 µm, 28x250 mm, eluent: 20% to 100% CH_3CN in H_2O in 40 min, CH_3CN and H_2O

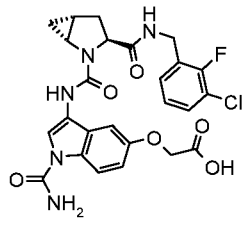
containing 0.1% HCOOH, flow: 40 mL/min) to give after extraction of the purified fractions with EtOAc (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-5-hydroxy-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide) and (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-5-hydroxy-1H-indol-3-yl)-amide] 3-(2-fluoro-benzylamide). TLC, R_f (EtOAc) = 0.3; MS (LC-MS): 452.1 [M+H]+, 474.1 [M+Na]+, 407 [M-$CONH_2$]-; t_R (HPLC conditions f): 1.81 min.

Example 373: (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-5-cyanomethoxy-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide)



To a solution of **Example 371** (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-5-hydroxy-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide) (50 mg, 0.103 mmol) in acetone (0.5 mL) were added cesium carbonate (36.9 mg, 0.11 mmol) and bromoacetonitrile (8.13 µL, 0.11 mmol) and the reaction mixture was stirred at RT under nitrogen for 4 h. Acetone was concentrated. The residue was dissolved in water and extracted twice with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude material was purified by prep HPLC (Waters Sunfire, C18-ODB, 5 µm, 19x50 mm, eluent: 20% to 100% (CH_3CN/MeOH 1-4) / H_2O in 15 min, (CH_3CN/MeOH 1-4) and H_2O containing 0.1% HCOOH, flow: 20 mL/min). TLC, Rf (EtOAc) = 0.45; MS (UPLC/MS): 525.4/527.2 [M+H]+, 542.4/544.7 [M+NH_4]+, 569.4/571.4 [M+HCOO]-; t_R (HPLC conditions f): 1.89 min.

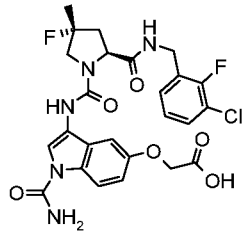
Example 374: (1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid



To a solution of (1-carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid methyl ester **Example 133** (85 mg, 0.145 mmol) in THF (1.2 mL) and H_2O (120 µL) was added NaOH 1N (290 µL, 0.29 mmol) and the reaction mixture was stirred at RT for 20 min. The crude was directly purified using trimethylaminopropyl cartridge (Mega Bond Elut-SAX, 1 g from Varian) pre-

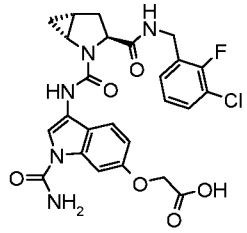
washed with CH_3CN (10 mL) and the compound was released with 10 mL of HCl 0.1 N in CH_3CN. The resulting solution was concentrated and purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 19x50 mm, eluent: 20% to 100% CH_3CN in H_2O in 15 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 20 mL/min) to give the desired material after lyophilization of the purified fractions. MS (UPLC-MS): 544.3/546.3 [M+H]+, 566.4/568.3 [M+Na]+, 542.3/544.4 [M-H]-; t_R (HPLC conditions f): 1.72 min.

Example 375: (1-Carbamoyl-3-{[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidine-1-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid



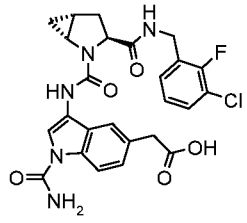
The title compound was prepared according to the protocol described for the preparation of **Example 374** from (1-carbamoyl-3-{[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methylpyrrolidine-1-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid methyl ester **Example 318**. MS (UPLC): 564.2 [M+H]+, 562.3 [M-H]-; t_R (HPLC conditions f): 1.72 min.

Example 376: (1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-6-yloxy)-acetic acid



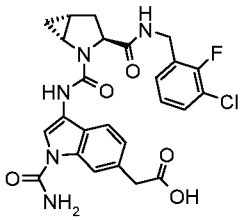
The title compound was prepared according to the protocol described for the preparation of **Example 374** from (1-carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza bicyclo[3.1.0] hexane-2-carbonyl]-amino}-1H-indol-6-yloxy)-acetic acid methyl ester **Example 394**. MS (UPLC): 544.3/546.3 [M+H]+, 542.3/544.3 [M-H]-; t_R (HPLC conditions f): 1.78 min.

Example 377: (1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yl)-acetic acid



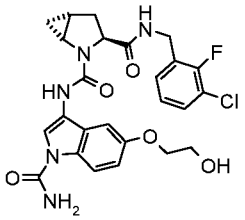
The title compound was prepared according to the protocol described for the preparation of **Example 374** from (1-carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-3 **Example 306**. TLC, R_f (EtOAc) = 0.2; MS (UPLC): 528.3/530.2 [M+H]+, 526.3/528.6 [M-H]-, 483.3/485.3 [M-$CONH_2$]-; t_R (HPLC conditions f): 1.74 min.

Example 378: (1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-6-yl)-acetic acid



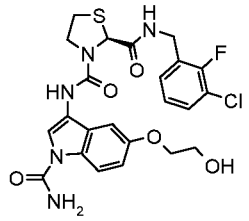
to a solution of (1-carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0] hexane-2-carbonyl]-amino}-1H-indol-6-yl)-acetic acid tert-butyl ester **Example 127** (30 mg, 0.051 mmol) in CH_2Cl_2 (0.5 mL) was added TFA (157 µL, 2.05 mmol) and the mixture was stirred at RT for 1 h. Then concentrated and the crude residue was taken up in Et_2O and filtered-off to give the desired material. MS (UPLC): 528.2/530.3 [M+H]+, 1055.6/1057.2 [2M+H]+, 483.1/485.1 [M-$CONH_2$]-, 1053.6/1055.6 [2M-H]-; t_R (HPLC conditions f): 1.75 min.

Example 379: (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-hydroxy-ethoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide)



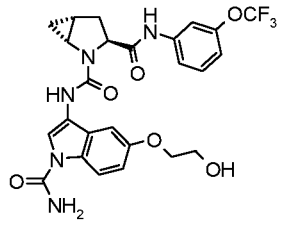
To a solution of (1-carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid methyl ester **Example 133** (344 mg, 0.573 mmol) in THF (3 mL) under nitrogen was added $LiBH_4$ 2M in THF (573 µL, 1.15 mmol). The resulting solution was stirred at RT under nitrogen for 30 min, then slowly poured into an aqueous saturated solution of $NaHCO_3$ and extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was taken up in CH_2Cl_2 and filtered-off then purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 19x50 mm, eluent: 20% to 100% CH_3CN in H_2O in 15 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 20 mL/min) to give the desired material after lyophilization of the purified fractions. R_f, TLC (EtOAc) = 0.15; MS (LC-MS): 530/532 [M+H]+, 552.1/554.1 [M+Na]+, 528.1/530.1 [M-H]-, 485/487 [M-$CONH_2$]-; t_R (HPLC conditions f): 1.64 min.

Example 380: (S)-Thiazolidine-2,3-dicarboxylic acid 3-{[1-carbamoyl-5-(2-hydroxy-ethoxy)-1H-indol-3-yl]-amide} 2-(3-chloro-2-fluoro-benzylamide)



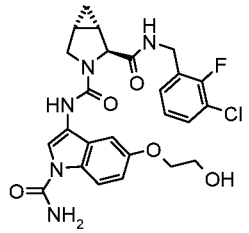
The title compound was prepared according to the protocol described for the preparation of **Example 379** from (1-carbamoyl-3-{[(S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-thiazolidine-3-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid methyl ester (prepared using similar protocols as for **Example 133**). TLC, R_f (EtOAc) = 0.45; MS (UPLC): 564.2/566.2 [M+H]+, 581.2/583.2 [M+NH_4]+, 562.3/564.3 [M-H]-, 608.4/610.4 [M+HCOO]-; t_R (HPLC conditions f): 1.82 min.

Example 381: (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-hydroxy-ethoxy)-1H-indol-3-yl]-amide} 3-[(3-trifluoromethoxy-phenyl)-amide]



The title compound was prepared according to the protocol described for the preparation of **Example 379** from (1-carbamoyl-3-{[(1R,3S,5R)-3-(3-trifluoromethoxy-phenylcarbamoyl)-2-aza-bicyclo[3.1.0] hexane-2-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid methyl ester (prepared using similar protocols as for **Example 133**). MS (UPLC): 548.3 [M+H]+, 546.3 [M-H]-, 592.3 [M+HCOO]-; t_R (HPLC conditions f): 1.80 min.

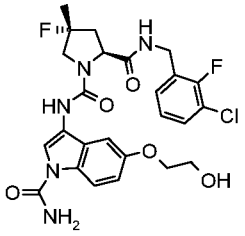
Example 382: (1S*,2S*,5R*)-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[1-carbamoyl-5-(2-hydroxy-ethoxy)-1H-indol-3-yl]-amide} 2-(3-chloro-2-fluoro-benzylamide)



The title compound was prepared according to the protocol described for the preparation of **Example 379** from (1-carbamoyl-3-{[(1S*,2S*,5R*)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-aza-bicyclo[3.1.0] hexane-3-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid methyl ester ester

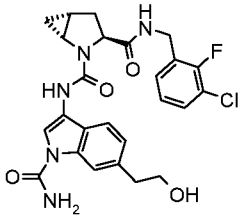
(prepared using similar protocols as for **Example 133**). MS (UPLC): 530.3/532.2 [M+H]+, 528.2/530.4 [M-H]-, 574.3/576.3 [M+HCOO]-; t_R (HPLC conditions f): 1.58 min.

Example 383: (2S,4R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-{[1-carbamoyl-5-(2-hydroxy-ethoxy)-1H-indol-3-yl]-amide} 2-(3-chloro-2-fluoro-benzylamide)



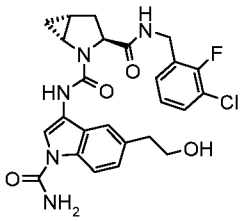
The title compound was prepared according to the protocol described for the preparation of **Example 379** from (1-carbamoyl-3-{[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidine -1-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid methyl ester **Example 318**. TLC, R_f (EtOAc) = 0.30; MS (UPLC): 550.3/552.5 [M+H]+, 505.7/507.1 [M-$CONH_2$]-; t_R (HPLC conditions f): 1.72 min.

Example 384: (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-6-(2-hydroxy-ethyl)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide)



The title compound was prepared according to the protocol described for the preparation of **Example 379** from (1-carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0] hexane-2-carbonyl]-amino}-1H-indol-6-yl)-acetic acid ethyl ester **Example 315**. MS (UPLC): 514.3/516.3 [M+H]+, 512.3/514.3 [M-H]-, 558.3/560.2 [M+HCOO]-; t_R (HPLC conditions f): 1.75 min.

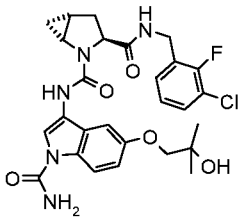
Example 385: (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-hydroxy-ethyl)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide)



The title compound was prepared according to the protocol described for the preparation of **Example 379** from (1-carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-

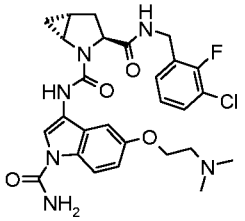
bicyclo[3.1.0] hexane-2-carbonyl]-amino}-1H-indol-5-yl)-acetic acid ethyl ester **Example 306**. TLC, R_f (EtOAc) = 0.2; MS (UPLC): 514.2/516.3 [M+H]+, 512.3/514.1 [M-H]-, 558.3/560.2 [M+HCOO]-, 469.2/471.4 [M-$CONH_2$]-; t_R (HPLC conditions f): 1.72 min.

Example 386: (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-hydroxy-2-methyl-propoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide)



To a solution of (1-carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid methyl ester **Example 133** (50 mg, 0.083 mmol) in dry THF (0.5 mL) at 0°C was added methylmagnesium bromide (3M in Et_2O, 61 µL, 0.183 mmol). The mixture was stirred under nitrogen at 0°C for 10 min, then allowed to reach RT and further stirred for 24 h. Water was added (2 mL) and the precipitate was filtered-out. The filtrate was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 19x50 mm, eluent: 20% to 100% CH_3CN in H_2O in 15 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 20 mL/min) to give the desired material after lyophilization of the purified fractions. TLC, R_f (EtOAc) = 0.25; MS (LC-MS): 558/560 [M+H]+, 513.1/515.2 [M-$CONH_2$]-; t_R (HPLC conditions f): 1.84 min.

Example 387: (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-dimethylamino-ethoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide)



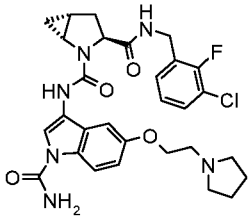
A solution of methanesulfonic acid 2-(1-carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yloxy)-ethyl ester (35 mg, 0.054 mmol) and dimethylamine 5.6 M in EtOH (0.5 mL) was heated at 70°C for 4 h in a sealed tube. The reaction was poured into an aqueous saturated solution of $NaHCO_3$ and extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by preparative HPLC (Nucleosil, C18-HD, 5 µm,

21x50 mm, eluent: 20% to 100% CH3CN in H_2O in 15 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 20 mL/min) to give after lyophilization of the purified fractions the desired material as a formic acid salt. MS (UPLC): 557.3/559.3 [M+H]+, 555.6/558.4 [M-H]-, 512.3/514.5 [M-$CONH_2$]-; t_R (HPLC conditions f): 1.47 min.

Methanesulfonic acid 2-(1-carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yloxy)-ethyl ester

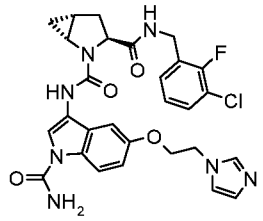
To a solution of (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-hydroxy-ethoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide) **Example 379** (50 mg, 0.09 mmol) and Et_3N (62 µL, 0.448 mmol) in CH_2Cl_2 (1 mL) at 0°C under nitrogen atmosphere, was added methanesulfonyl chloride (35 µL, 0.448 mmol). The resulting solution was stirred at RT overnight. Et_3N (31 µL, 0.224 mmol) and methanesulfonyl chloride (17 µL, 0.224 mmol) were added and the mixture was further stirred at RT for 1.5 h to complete the reaction. The reaction was poured into a saturated aqueous solution of $NaHCO_3$, extracted twice with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 1-1 to 100% EtOAc) to give the desired material. TLC, R_f (EtOAc) = 0.25; MS (UPLC): 608.5/610.2 [M+H]+, 563.4 [M-$CONH_2$]-, 606.4/608.0 [M-H]-; t_R (HPLC conditions f): 1.88 min.

Example 388: (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-pyrrolidin-1-yl-ethoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide)



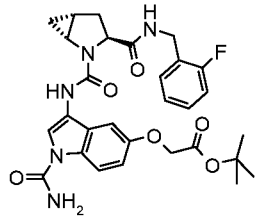
The title compound was prepared as a formic acid salt from methanesulfonic acid 2-(1-carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yloxy)-ethyl ester and pyrrolidine according to the procedure described for the preparation of **Example 387**: (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-dimethylamino-ethoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide). TLC, R_f (CH_2Cl_2/ MeOH 8-2) = 0.3; MS (UPLC/MS): 583.5/585.5 [M+H]+, 627.5/629.3 [M+HCOO]-; t_R (HPLC conditions f): 1.51 min.

Example 389: (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-imidazol-1-yl-ethoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide)



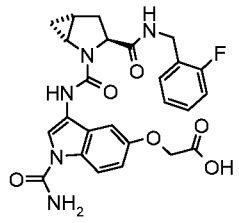
The title compound was prepared from methanesulfonic acid 2-(1-carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yloxy)-ethyl ester and imidazole according to the procedure described for the preparation of **Example 387**: (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-dimethylamino-ethoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide). TLC, R_f (CH_2Cl_2/ MeOH 8-2) = 0.60; MS (UPLC/MS): 580.5/582.5 [M+H]+, 578.5/580.7 [M-H]-, 624.5/626.5 [M+HCOO]-; t_R (HPLC conditions f): 1.49 min.

Example 390: (1-Carbamoyl-3-{[(1R,3S,5R)-3-(2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid tert-butyl ester



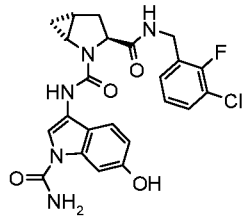
To (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-5-hydroxy-1H-indol-3-yl)-amide] 3-(2-fluoro-benzylamide) **Example 372** (38 mg, 0.084 mmol) in acetone (0.45 mL) was added cesium carbonate (30.2 mg, 0.093 mmol) and tert-butyl bromoacetate (14 µL, 0.093 mmol), and the resulting suspension was stirred at RT under nitrogen overnight. Acetone was concentrated and to the residue water was added and the mixture was extracted twice with EtOAc. The combined oragnic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 19x50 mm, eluent: 20% to 100% CH_3CN in H_2O in 15 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 20 mL/min) to give the desired material after lyophilization of the purified fractions. MS (LC-MS): 588.3 [M+Na]+, 510.1 [MH-tBu]+, 521.2 [M-$CONH_2$]-; t_R (HPLC conditions f): 2.04 min.

Example 391: (1-Carbamoyl-3-{[(1R,3S,5R)-3-(2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid



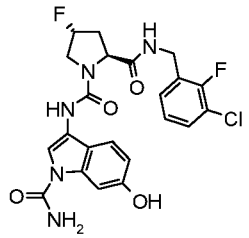
To (1-carbamoyl-3-{[(1R,3S,5R)-3-(2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid tert-butyl ester **Example 390** (18 mg, 0.032 mmol) in CH_2Cl_2 (0.5 mL) was added TFA (97 µL, 1.27 mmol) and the mixture was stirred at RT overnight. Then concentrated, taken up in CH_2Cl_2 and filtered-off to give the desired material which was further dried under high vacuum. MS (LC-MS): 510.1 [M+H]+, 532.2 [M+Na]+, 508.1 [M-H]-, 465.1 [M-$CONH_2$]-; t_R (HPLC conditions f): 1.52 min.

Example 392: (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-6-hydroxy-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide)



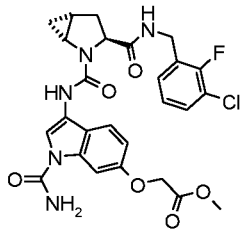
The title compound was prepared from (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(6-allyloxy-1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide) according to the procedure described for the preparation of (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-5-hydroxy-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide) **Example 371**. MS (LC-MS): 486.0 [M+H]+; t_R (HPLC conditions b) : 3.39 min.

Example 393: (2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-6-hydroxy-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



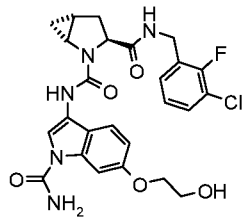
The title compound was prepared from (2S,4R)-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(6-allyloxy-1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide) according to the procedure described for the preparation of (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-5-hydroxy-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide) **Example 371**. MS (LC-MS): 492 [M+H]+; t_R (HPLC conditions b): 3.12 min.

Example 394: (1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-6-yloxy)-acetic acid methyl ester



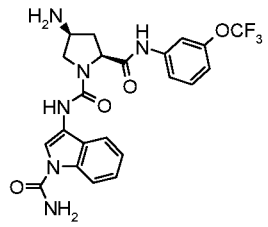
To (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-6-hydroxy-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide) **Example 392** (70 mg, 0.144 mmol) in acetone (720 µL) were added Cs_2CO_3 (56.3 mg, 0.173 mmol) and methyl bromoacetate (16.4 µL, 0.173 mmol) and the reaction mixture was stirred at 23°C overnight. 0.5 eq of methyl bromoacetate and 0.5 eq of Cs_2CO_3 were added and the reaction mixture was stirred at 23°C for 4 hr to complete the reaction. The crude mixture was poured in water and extracted with EtOAc (x2). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to dryness. The crude material was purified by preparative HPLC (Waters SunFire C18ODB, 5 µm, 30x100, eluent: 20% CH_3CN/80% H_2O to 100% CH_3CN in 20 min, CH_3CN and H_2O containing 0.1% of TFA, flow 40 mL/min) to give the desired material after lyophilization of the purified fractions. MS (LC-MS): 558 [M+H]+; t_R (HPLC conditions b) : 3.84 min.

Example 395: (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-6-(2-hydroxy-ethoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide)



The title compound was prepared from (1-carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-6-yloxy)-acetic acid methyl ester **Example 394** according to the procedure described for the preparation of (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-hydroxy-ethoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide) **Example 379**. TLC, Rf (EtOAc) = 0.12; MS (UPLC): 530.3/532.3 [M+H]+, 528.2/530.5 [M-H]-, 574.2/576.4 [M+HCOO]-; t_R (HPLC conditions f): 1.71 min.

Example 396: (2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]

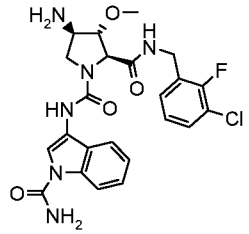


(2S,4S)-4-N-fmoc-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide] (380 mg, 0.533 mmol) was dissolved in a solution of piperidine 20 % in DMF (2 mL). The mixture was stirred at RT for 1 h and directly purified by preparative HPLC (Interchrom C18-ODB, 10 µm, 28x250 mm, 5% CH_3CN in H_2O 2.5 min, then 5% to 100 % CH_3CN in H_2O in 32.5 min, CH_3CN and H_2O containing 0.1 % HCOOH; flow: 40 mL/min). To the purified HPLC fractions was added NaOH 1 N and the compound was extracted with EtOAc (x3). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated and this material was purified again by preparative HPLC (Water SunFire C18-ODB, 5 µm, 19x50 mm, eluent: 5 % to 60% CH_3CN in H_2O in 18 min, CH_3CN and H_2O containing 0.1 % HCOOH; flow: 20 mL/min) to give after lyophilization of the purified fractions the desired compound as a formate salt. MS (LC-MS): 491.2 [M+H]+, 489.1 [M-H]-.

(2S,4S)-4-N-fmoc-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]

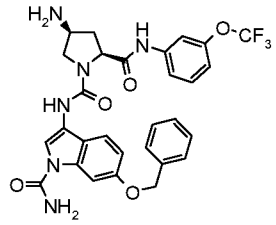
The title compound was prepared as described in Scheme D5 from (4S)-4-N-Fmoc-amino-1-Boc-L-proline. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.45; t_R (HPLC conditions a): 4.20 min.

Example 397: (2S,3S,4R)-4-Amino-3-methoxy-pyrrolidine-1,2-dicarboxylicacid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



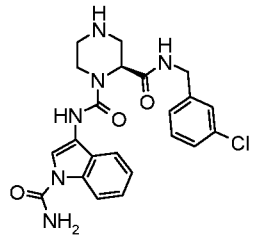
The title compound was prepared according to Scheme D5 (steps B and C) from (2S,3S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-(9H-fluoren-9-ylmethoxycarbonylamino)-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester (described in Scheme B21) followed by Fmoc deprotection using the same protocol as described for **Example 396**. MS (UPLC-MS): 547 [M+H]+; t_R (HPLC conditions f): 1.50 min; 19F NMR (100 MHz, DMSO-d_6) δ (ppm): -120.

Example 398: (2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(6-benzyloxy-1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]



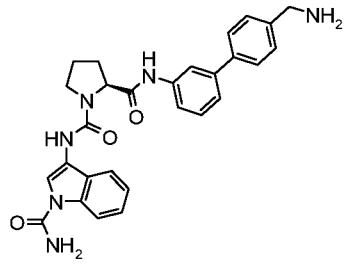
The title compound was prepared as described in Scheme D5 using (4S)-4-N-Fmoc-amino-1-Boc-L-proline in step A and 6-benzyloxy-3-isocyanato-indole-1-carboxylic acid amide (prepared as described in Part A4) in step C, followed by Fmoc deprotection as described in Scheme D2 step B. MS (LC/MS): 597.1 [M+H]+, 595.2 [M-H]; t_R (HPLC conditions a): 3.16 min.

Example 399: (S)-Piperazine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide)



The title compound as a formate salt was prepared as described in Scheme D5 using (S)-1-N-Boc-4-N-Fmoc-piperazine-2-carboxylic acid and 1 equivalent of 3-chlorobenzylamine in step A followed by Fmoc deprotection as described in Scheme D2 step B. MS (LC/MS): 455.2/457.2 [M+H]+, 410/412 [M-$CONH_2$]-; t_R (HPLC conditions a): 2.58 min.

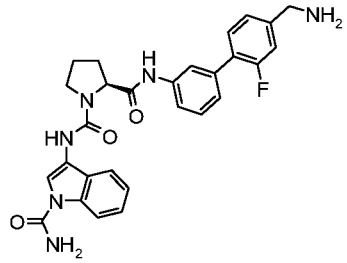
Example 400: (S)-Pyrrolidine-1,2-dicarboxylic acid 2-[(4'-aminomethyl-biphenyl-3-yl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide]



Ta solution of (S)-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(4'-cyano-biphenyl-3-yl)-amide] **Example 152** (25 mg, 0.051 mmol) in EtOH (1 mL) containing 5% of NH_3, was added a drop of Ni Raney dissolved in EtOH (0.5 mL). The resulting mixture was stirred at RT under hydrogen atmosphere for 26 h, then filtered through Celite, and concentrated. The crude residue was purified by preparative HPLC (Waters SunFire C18ODB, 5 µm, flow 20 mL/min, eluent: 5% CH_3CN/95% H_2O to 100% CH_3CN in 15 min, CH_3CN and H_2O containing1% of HCOOH) to give after lyophilization of the purified fractions the desired compound as a formate salt. MS (LC/MS): 497 [M+H]+; t_R (Waters Symmetry C18, 3.5um,

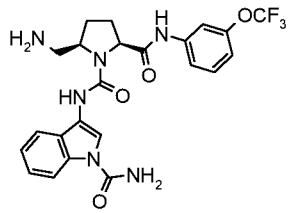
2.1x50mm, 5-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min) 3.04 min.

Example 401: (S)-Pyrrolidine-1,2-dicarboxylic acid 2-[(4'-aminomethyl-2'-fluoro-biphenyl-3-yl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide]



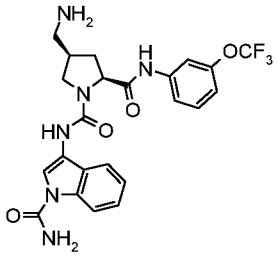
To a solution of (S)-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(4'-cyano-2'-fluoro-biphenyl-3-yl)-amide] (140 mg, 0.274 mmol) (prepared according to the general procedure described in Scheme D5, using in step A 3'-Amino-2-fluoro-biphenyl-4-carbonitrile (prepared as described in Part C) in EtOH (15 mL) containing 4% of NH_3 was added Ra-nickel (70 mg) and the mixture was stirred under H_2 atmosphere for 18 h. The reaction mixture was filtered on Celite and concentrated. The crude residue was purified by preparative HPLC (Waters Sunfire (C18 ODB, 5µm, 19x50, flow = 20mL/min, 20% CH_3CN/ 80% water to 100% CH_3CN) to give the desired compound. MS (LC/MS): 515 [M+H]+; t_R (Waters Symmetry C18, 3.5um, 2.1x50mm, 5-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min) 3.1 min.

Example 402: (2S,5R)-5-Aminomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]



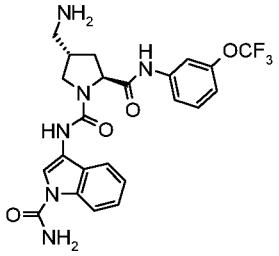
A mixture of (2S,5R)-5-azidomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide] **Example 179** (50 mg, 0.094 mmol) and triphenylphosphine (29.7 mg, 0.113 mmol) in THF (1 mL) was stirred at RT overnight. After completion of the reaction MeOH (1 mL) and water (1 mL) were added and the solution was stirred for 1 h, then the crude reaction mixture was concentrated and purified by preparative HPLC (Waters SunFire C18-ODB 5 µm, 19x50, 5-100% CH_3CN/H_2O in 17 min, 100% CH_3CN for 3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 20 mL/min) to give the title compound. MS: 505 [M+H]+; t_R (HPLC conditions b): 3.24 min.

Example 403: (2S,4R)-4-Aminomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]



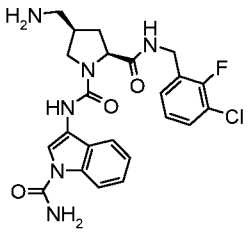
(2S,4S)-4-Cyano-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide] **Example 125** (20 mg, 0.04 mmol) was dissolved in MeOH (0.2 mL). Ammonia (25% in water, 0.02 mL) and Raney Nickel (7.11 mg) were added. Air was removed from the flask and replaced with nitrogen three times. Finally the flask was again degassed and the mixture was placed under a hydrogen atmosphere, and stirred at RT overnight. The catalyst was removed through a pad of Celite and washed with MeOH. The filtrate was concentrated, and the residue purified by preparative HPLC (Waters SunFire C18-ODB, 5 µm, 19x50 mm, eluent: 5-100 % CH_3CN/H_2O in 17 min, CH_3CN and H_2O containing 0.1% TFA, flow: 20 mL/min) to give the title compound as a TFA salt. MS (LC-MS): 505 [M+H]+; t_R (HPLC conditions b): 3.1 min.

Example 404: (2S,4S)-4-Aminomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]



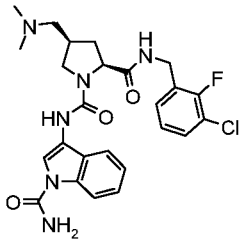
The title compound was obtained from (2S,4R)-4-cyano-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide] **Example 256** using the protocol described for the preparation of **Example 403**. MS (LC/MS): 505 [M+H]+; t_R (HPLC conditions b): 3.1 min.

Example 405: (2S,4R)-4-Aminomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



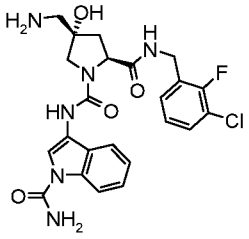
The title compound was prepared analogously as described for the title compound **Example 403** using (2S,4S)-4-cyano-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide) prepared according to scheme D5. MS (LC/MS): 487 [M+H]+, 442 [M-$CONH_2$]-; t_R (HPLC conditions f): 1.46 min.

Example 406: (2S,4R)-4-Dimethylaminomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



To a solution of **Example 405** (132 mg, 0.271 mmol) in MeOH (0.9 mL) was added formaldehyde 20 % in MeOH (373 µL, 2.71 mmol), sodium cyanoborohydride (56 mg, 0.895 mmol) and acetic acid (31.5 µL, 0.542 mmol). The reaction mixture was stirred for 16 h at RT then concentrated. The crude material was purified by preparative HPLC (Waters SunFire C18-ODB, 5 µm, 19x50 mm, eluent: 10-100 % CH_3CN/H_2O in 30 min, CH_3CN and H_2O containing 0.1% TFA, flow: 20 mL/min) to give the desired material. TLC, R_f (EtOAc)= 0.02; MS (LC/MS): 515 [M+H]+, 470 [M-$CONH_2$]-; t_R (HPLC conditions f): 1.47 min.

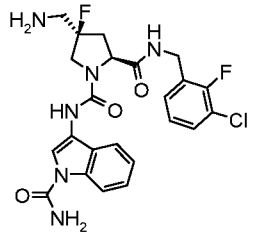
Example 407: (2S,4S)-4-Aminomethyl-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



To a solution of (2S,4R)-4-azidomethyl-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide) (300 mg, 0.567 mmol) (prepared according to Scheme D5 from (2S,4R)-4-azidomethyl-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (described in Part B) in EtOAc (10 mL) was added Pd/C (10 mg). Air was removed from the flask and replaced with nitrogen three times. Finally the flask was again degassed and the mixture was placed under a hydrogen atmosphere, and stirred at RT overnight. The catalyst was removed through a pad of Celite and washed with EtOAc. The filtrate was concentrated, and the residue purified by preparative HPLC (Waters SunFire C18-ODB, 5 µm, 19x50 mm, eluent: 5-100 % CH_3CN/H_2O in 17 min, CH_3CN and H_2O containing 0.1% TFA, flow: 20 mL/min) to give the title compound

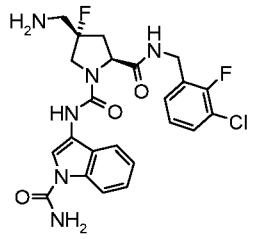
as a TFA salt. MS (LC-MS): 503 [M+H]+; t_R (HPLC conditions c): 3.57 min; 19F NMR (100 MHz, DMSO-d_6) δ (ppm): -122.

Example 408: (2S,4R)-4-Aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



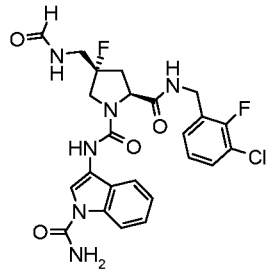
The title compound was prepared analogously as described for **Example 407** using (2S,4S)-4-azidomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide) prepared according to scheme D5 from (2S,4S)-4-azidomethyl-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (described in Part B). MS (LC-MS): 505/507 [M+H]+; t_R (HPLC conditions f): 1.46 min; 19F NMR (100 MHz, DMSO-d_6) δ (ppm): -121, -150.

Example 409: (2S,4S)-4-Aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



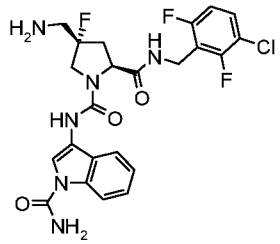
The title compound was prepared analogously as described for **Example 407** using (2S,4R)-4-azidomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide) prepared according to scheme D5 from (2S,4R)-4-azidomethyl-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (described Scheme B15). MS (LC-MS): 505/507 [M+H]+; t_R (HPLC conditions f): 1.47 min; 19F NMR (100 MHz, DMSO-d_6) δ (ppm): -121, -150.

Example 410: (2S,4S)-4-Fluoro-4-formylaminomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



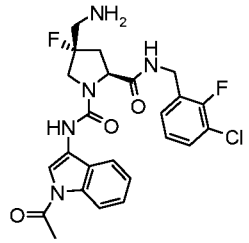
The title compound was obtained from **Example 409** (2S,4S)-4-aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide) as formylation occurred during the concentration of the purified **Example 409** HPLC fractions from the preparative HPLC containing 1% HCOOH. MS (LC-MS): 531 [M-H]-, 533 [M+H]+; t_R (HPLC conditions f): 0.56 min; 19F NMR (100 MHz, DMSO-d_6) δ (ppm): -121, -150.

Example 411: (2S,4S)-4-Aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2,6-difluoro-benzylamide)



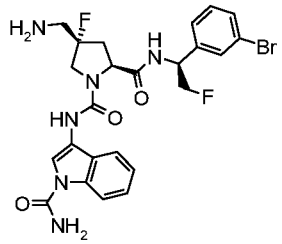
To a solution of (2S,4R)-4-azidomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2,6-difluoro-benzylamide) (100 mg, 0.182 mmol) (prepared according to scheme D5 using (2S,4R)-4-azidomethyl-2-(3-chloro-2,6-difluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester prepared analogously as described in Scheme B15) in THF (5 mL) and water (6.56 µL) under N_2 atmosphere at RT was added 1M PMe_3 in THF (0.219 mL, 0.219 mmol). The reaction mixture was stirred for 16 h then quenched with water and extracted twice with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified preparative HPLC (Waters SunFire C18-ODB, 5 µm, 19x50 mm, 5% CH_3CN/H_2O 2.5 min, 5-100% CH_3CN/H_2O in 10 min, CH_3CN/H_2O containing 0.1 % HCOOH flow: 20 mL/min) to give after lyophilization of the purified fractions the title compound (formic acid salt). MS (UPLC-MS): 523/525 [M+H]+, 521/523 [M-H]-; t_R (HPLC conditions f): 1.42 min; 19F NMR (100 MHz, DMSO-d_6) δ (ppm): -115 (2F), -150.

Example 412: (2S,4S)-4-Aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



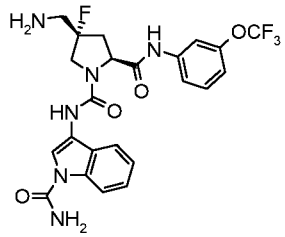
The title compound was prepared analogously as described for **Example 411** using (2S,4R)-4-azidomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide) prepared according to scheme D5 from (2S,4R)-4-azidomethyl-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (described Scheme B15) and 1-(3-isocyanato-indol-1-yl)-ethanone (described in Scheme A1). MS (UPLC-MS): 504/506 [M+H]+, 502/504 [M-H]-; t_R (HPLC conditions f): 1.62 min; 19F NMR (100 MHz, DMSO-d_6) δ (ppm): -121, -153.

Example 413: (2S,4S)-4-Aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-{[(S)-1-(3-bromo-phenyl)-2-fluoro-ethyl]-amide} 1-[(1-carbamoyl-1H-indol-3-yl)-amide]



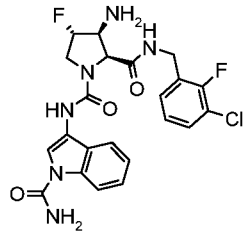
The title compound was prepared analogously as described for **Example 411** from (2S,4R)-4-azidomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-{[(S)-1-(3-bromo-phenyl)-2-fluoro-ethyl]-amide} 1-[(1-carbamoyl-1H-indol-3-yl)-amide] (82 mg, 0.115 mmol) (prepared according to scheme D5 step C using (2S,4R)-4-azidomethyl-2-[(S)-1-(3-bromo-phenyl)-2-fluoro-ethylcarbamoyl]-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester prepared as described in Scheme B16). Purification on preparative HPLC (Waters SunFire C18-ODB, 5 µm, 19x50 mm, 5% CH_3CN/H_2O 2.5 min, 5-100% CH_3CN/H_2O in 10 min, CH_3CN/H_2O containing 0.1 % HCOOH flow: 20 mL/min) to give after lyophilization of the purified fractions the title compound (formic acid salt). MS (UPLC-MS): 561/563 [M+H]+, 561/563 [M-H]-; t_R (HPLC conditions f): 1.42 min.

Example 414: (2S,4S)-4-Aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide]



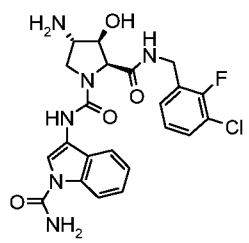
The title compound was prepared analogously as described for **Example 411** from (2S,4R)-4-azidomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide] (43 mg, 0.078 mmol) (prepared according to scheme D5 Step C using (2S,4R)-4-azidomethyl-4-fluoro-2-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester prepared as described Scheme B16 using 2-trifluoromethoxy-phenylamine in step G instead of 3(S)-1-(3-bromo-phenyl)-2-fluoro-ethylamine). Purification by preparative HPLC (Waters SunFire C18-ODB, 5 µm, 19x50 mm, 5% CH_3CN/H_2O 2.5 min, 5-100% CH_3CN/H_2O in 10 min, CH_3CN/H_2O containing 0.1 % HCOOH flow: 20 mL/min) gave after lyophilization of the purified fractions the title compound (formic acid salt). MS (UPLC-MS): 523 [M+H]+, 521 [M-H]-; t_R (HPLC conditions f): 1.59 min; 19F NMR (100 MHz, DMSO-d_6) δ (ppm): -57 (3F), -150.

Example 415: (2S,3S,4S)-3-Amino-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



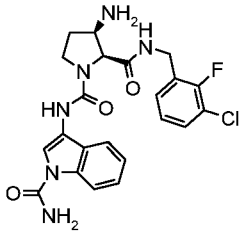
The title compound was prepared according to Scheme D5 from (2S,3S,4S)-3-azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (described in scheme B19) followed by reduction of the azide as described for the preparation of **Example 411**. TLC, R_f (CH_2Cl_2/MeOH 95/5) = 0.2 ; MS (LC-MS): 491 [M+H]+, 489 [M-H]-; t_R (HPLC conditions f): 1.55 min.

Example 416: (2S,3R,4S)-4-Amino-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



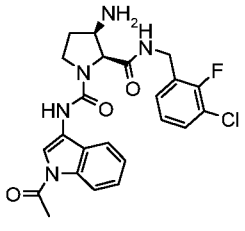
The title compound was prepared according to Scheme D5 from (2S,3S,4S)-4-azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (described in scheme B19) followed by reduction of the azide as described for the preparation of **Example 411**. TLC, R_f (CH_2Cl_2/MeOH 95/5) = 0.2; MS (LC-MS): 489 [M+H]+, 487 [M-H]-; t_R (HPLC conditions f): 1.34 min.

Example 417: (2S,3R)-3-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



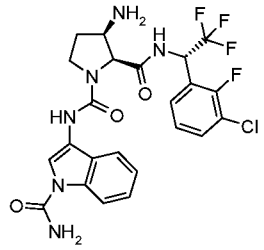
A solution of (2S,3R)-3-azido-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide) (prepared according to scheme D5 step C using (2S,3R)-3-azido-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide trifluoroacetate (prepared as described in Part B) (70 mg, 0.140 mmol) in MeOH (10 mL) was hydrogenated at RT (1 atm) over Pd/C 10% (14 mg, 20% w/w) for 4 h. The reaction mixture was filtered through a 0.45 microns filter and concentrated under reduced pressure. The crude product was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm; flow: 40 mL/min; eluent: 5-60% CH_3CN/H_2O for 20 min, 60% CH_3CN for 2 min, CH_3CN and H_2O containing 0.1% TFA) to afford the title compound as a white solid. MS (LC/MS): 473 [M+H]+; t_R (HPLC conditions b): 2.75 min.

Example 418: (2S,3R)-3-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



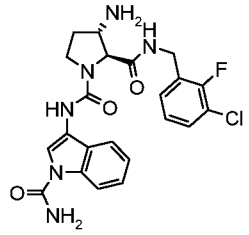
Prepared as described for **Example 417** from (2S,3R)-3-azido-pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide) prepared according to Scheme D5 by using (2S,3R)-3-azido-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide trifluoroacetate (prepared as described in Part B) and 1-(3-isocyanato-indol-1-yl)-ethanone (prepared as described in Scheme A1). White solid. MS (LC/MS): 473 [M+H]+; t_R (HPLC conditions b): 2.91 min.

Example 419: (2S,3R)-3-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2,2,2-trifluoro -ethyl]-amide}



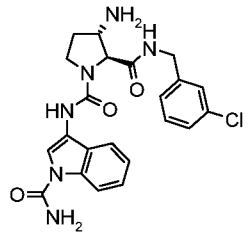
The title compound was prepared as described for **Example 417** starting from (2S,3R)-3-azido-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2,2,2-trifluoro-ethyl]-amide} (prepared according to Scheme D5 (step C) from (2S,3R)-3-azido-pyrrolidine-2-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2,2,2-trifluoro-ethyl]-amide (prepared in a similar manner as described in Part B for (2S,3R)-3-azido-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide trifluoroacetate starting from (S)-1-(3-chloro-2-fluorophenyl)-2,2,2-trifluoroethanamine. White solid. MS (LC/MS): 541.0 [M+H]+; t_R (HPLC conditions c): 4.07 min.

Example 420: (2S,3S)-3-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



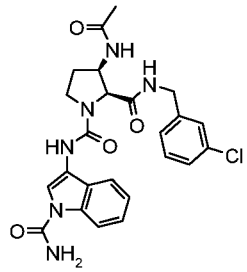
Prepared as described for **Example 417** from (2S,3S)-3-azido-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide) (prepared according to scheme D5 step C by using (2S,3S)-3-azido-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide (prepared as described in Part B). White solid. MS (LC/MS): 473 [M+H]+; t_R (HPLC conditions b): 2.91 min.

Example 421: (2S,3S)-3-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide)



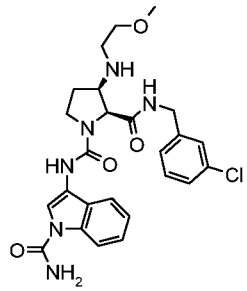
Prepared as described for **Example 417** from (2S,3S)-3-azido-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide) (prepared according to scheme D5 step C by using (2S,3S)-3-azido-pyrrolidine-2-carboxylic acid 3-chloro-benzylamide (prepared using similar protocols as described in Part B for (2S,3S)-3-azido-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide). White solid. MS (LC/MS): 455 [M+H]+; t_R (HPLC conditions b): 2.79 min.

Example 422: (2S,3R)-3-Acetylamino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



To an ice-cooled solution of (2S,3R)-3-amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide) **Example 417** (27.0 mg, 0.057 mmol) in dry CH_2Cl_2 (5 mL) and dry THF (2.5 mL) were added triethylamine (0.024 mL, 0.171 mmol) and acetic anhydride (0.108 mL, 1.14 mmol) under an argon atmosphere. The reaction mixture was stirred at RT for 16 h. Volatiles were removed under reduced pressure, and the residue was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 19x50 mm, eluent: 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 20 mL/min) to give after lyophilization the title compound as a white solid. MS (LC/MS): 515.0 [M+H]+; t_R (HPLC conditions k): 2.96 min.

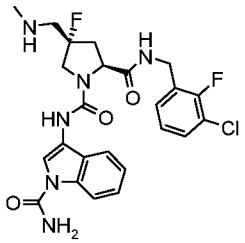
Example 423: (2S,3R)-3-(2-Methoxy-ethylamino)-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



To a solution of (2S,3R)-3-amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide) **Example 417** (36 mg, 0.076 mmol) in dry DMF (1.5 mL) were added triethylamine (0.032 mL, 0.228 mmol) and 1-bromo-2-methoxyethane

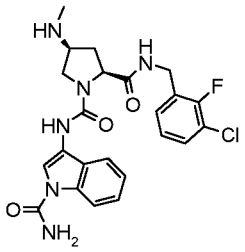
(0.014 mL, 0.144 mmol) under an argon atmosphere, followed by stirring at RT for 60 h. UPLC-MS showed formation of product and the presence of unreacted starting material (2S,3R)-3-amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide). An excess of 1-bromo-2-methoxyethane (10 eq) and triethylamine (10 eq) were added to the reaction mixture, and stirring was continued at RT for 18 h, and then at 50°C for 24 h. The crude material was directly purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 19x50 mm, eluent: 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 20 mL/min) to give after lyophilization the title compound as a solid. MS (LC/MS): 531 [M+H]+; t_R (HPLC conditions k): 2.97 min.

Example 424: (2S,4S)-4-Fluoro-4-methylaminomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



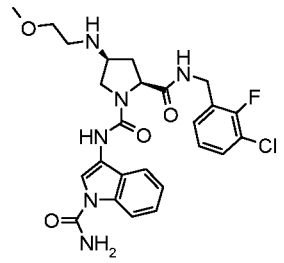
[(3R,5S)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-5-(3-chloro-2-fluoro-benzylcarbamoyl)-3-fluoro-pyrrolidin-3-ylmethyl]-methyl-carbamic acid 2,2,2-trichloro-ethyl ester (prepared according to scheme D5 Steps B and C using (2S,4S)-4-fluoro-4-{[methyl-(2,2,2-trichloro-ethoxycarbonyl)-amino]-methyl}-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-tert-butyl ester (prepared as described in Scheme B17) (56 mg, 0.08 mmol) was dissolved in MeOH (5 mL) under N_2 atmosphere at RT. Zinc dust was added (0.24 mg, 3.7 mmol), the pH was adjusted to pH 5~6 by adding some acetic acid. The reaction mixture was stirred for 1 h then filtered and concentrated. The crude residue was purified by preparative HPLC (Waters SunFire C18-ODB, 5 µm, 19x50 mm, 5% CH_3CN/H_2O 2.5 min, 5-100% CH_3CN/H_2O in 10 min, CH_3CN/H_2O containing 0.1 % HCOOH flow: 20 mL/min) to give after lyophilization of the purified fractions the title compound. MS (UPLC-MS): 519 [M+H]+ ; t_R (HPLC conditions f): 1.32 min; 19F NMR (100 MHz, DMSO-d_6) δ (ppm): -120, -150.

Example 425: (2S,4S)-4-Methylamino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



The title compound was prepared according to Scheme D5 Steps B and C from (2S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-[methyl-(2,2,2-trichloro-ethoxycarbonyl)-amino]-pyrrolidine-1-carboxylic acid tert-butyl ester (37 mg, 0.05 mmol) (prepared as described in Scheme B6) followed by the deprotection of the Troc protecting group as described for **Example 424**. Purification by preparative HPLC (Waters SunFire C18-ODB, 5 µm, 19x50 mm, 5% CH_3CN/H_2O 2.5 min, 5-100% CH_3CN/H_2O in 10 min, CH_3CN/H_2O containing 0.1 % HCOOH flow: 20 mL/min) gave after lyophilization of the purified fractions the title compound (formic acid salt). MS (UPLC/MS): 489 [M+H]+; t_R (HPLC conditions f): 1.48 min; 19F NMR (100 MHz, DMSO-d_6) δ (ppm): -120.

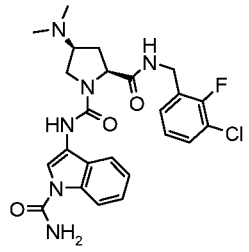
Example 426: (2S,4S[§])-4-(2-Methoxy-ethylamino)-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



To a solution of 2-methoxyethylamine (219 µL, 2.54 mmol) in MeOH (265 µL) was added HCl 1.25 N in MeOH (339 µL, 0.424 mmol) followed by (S)-4-oxo-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide) (100 mg, 0.212 mmol) (prepared as described in scheme D5 from (S)-4-oxo-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester) and $NaBH_3CN$ (16 mg, 0.254 mmol) and the reaction mixture was stirred at 23°C during 1 week. 2-Methoxyethylamine (219 µL, 2.54 mmol) and $NaBH_3CN$ (16 mg, 0.254 mmol) were added again and the reaction mixture was stirred at 23°C for 2 days. The crude mixture was diluted in EtOAc and washed with $NaHCO_3$ saturated aqueous solution. The layers were separated and the aqueous one re-extracted with EtOAc. The combined organic layers were dried, filtered and concenrated to dryness. The crude residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH gradient 100:0 to 9:1) followed by preparative HPLC (Waters SunFire C18ODB, 5 µm, 30x100, eluent: 5% CH_3CN/95% H_2O to 100% CH_3CN in 20 min, CH_3CN and H_2O containing 0.1% of TFA, flow 40 mL/min) to give after lyophlisation of the purified fractions the desired material. MS: 531.1 [M+H]+; t_R (HPLC conditions b): 3.1

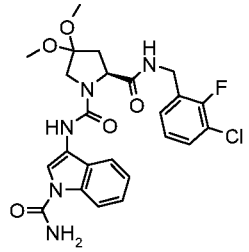
min. The absolute stereochemistry has been assigned tentatively based on the test results for the final compound **Example 426** in the biological assay.

Example 427: (2S,4S)-4-Dimethylamino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



To a solution of (2S,4S)-4-amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide) **Example 26** (20 mg, 0.042 mmol) in MeOH (140 µl) was added formaldehyde (58.3 µl, 0.423 mmol), $NaBH_3CN$ (8.77 mg, 0.140 mmol) and AcOH (4.84 µl, 0.085 mmol), and the reaction mixture was stirred at 23°C under nitrogen for 16 h. After completion, the crude reaction mixture was purified by preparative HPLC (Waters SunFire C18ODB, 5 µm, 19x50, eluent: 5% CH_3CN/95% H_2O to 100% CH_3CN in 17 min, CH_3CN and H_2O containing 0.1% of TFA, flow 20 mL/min) to give after lyophilization of the purified fractions the desired material. MS (LC/MS): 501.1 [M+H]+; t_R (HPLC conditions b): 2.75 min.

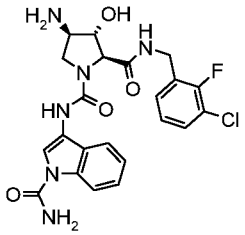
Example 428: (S)-4,4-Dimethoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



To a solution of methylamine hydrochloride (14.3 mg, 0.212 mmol) in MeOH (300 µL) was added HCl 1.25 N in MeOH (400 µl, 0.50 mmol), (S)-4-oxo-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide) (100 mg, 0.212 mmol)(prepared as described in scheme D5 from (S)-4-oxo-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester) and $NaBH_3CN$ (8 mg, 0.127 mmol) and the reaction mixture was stirred at 23°C for 16 h. The crude reaction mixture was diluted with EtOAc and washed with aqueous saturated $NaHCO_3$ solution. The organic layer was dried, filtered and concentrated to dryness, finally purified by preparative HPLC (Waters SunFire C18ODB, 5 µm, 19x50, eluent: 20% CH_3CN/80% H_2O to 100% CH_3CN in 12.5 min, CH_3CN and H_2O containing 0.1% HCOOH, flow

20 mL/min) to give after lyophilization of the purified fractions the desired material. MS: 518 [M+H]+; t_R (HPLC conditions b): 3.79 min.

Example 429: (2S,3S,4R)-4-Amino-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)

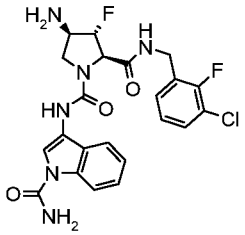


The title compound was prepared as described for **Example 411** using (2S,3R,4R)-4-azido-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide). TLC, R_f (EtOAc)= 0.02; MS (LC-MS): 489 [M+H]+, 487 [M-H]-; t_R (HPLC conditions g): 1.96 min.

(2S,3R,4R)-4-azido-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)

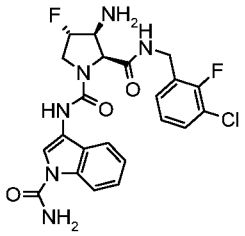
The title compound was prepared according to scheme D5 (steps B and C) from a mixture of (2S,3R,4R)-4-azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester and (2S,3S,4S)-3-azido-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide) in ratio 6:4 (described Scheme B19). The regioisomers were separated by flash column chromatography on silica gel (c-hexane 100% to EtOAc 100%) to give the title compound. TLC, R_f (EtOAc)= 0.23; MS (LC-MS): 515/517 [M+H]+, 513 [M-H]-; t_R (HPLC conditions f): 1.81 min.

Example 430: (2R,3S,4R)-4-Amino-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



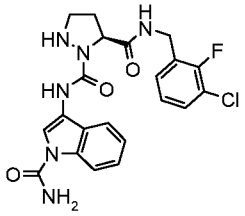
The title compound was prepared according to Scheme D5 (steps B and C) from (2R,3R,4R)-4-azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-3-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (described in scheme B19) followed by reduction of the azide as described for the preparation of **Example 411**. TLC, R_f (EtOAc)= 0.12; MS (LC-MS): 491 [M+H]+, 489 [M-H]-; t_R (HPLC conditions f): 1.45 min.

Example 431: (2S,3S,4S)-3-Amino-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluorobenzylamide)



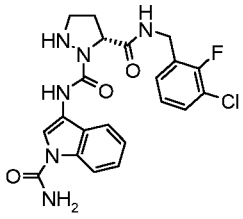
The title compound was prepared according to Scheme D5 (steps B and C) from (2S,3S,4S)-3-azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (described in scheme B19) followed by reduction of the azide as described for the preparation of **Example 411**. (Absolute stereochemistry tentatively assigned by NMR). TLC, R_f (CH_2Cl_2/MeOH 95/5) = 0.2; MS (LC-MS): 491 [M+H]+, 489 [M-H]-; t_R (HPLC conditions f): 1.46 min.

Example 432: 3-{2-[(S)-5-(3-Chloro-2-fluoro-benzylcarbamoyl)-pyrazolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide



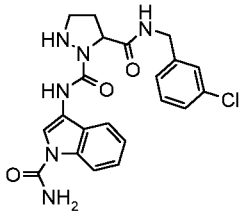
To a solution of (S)-2-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrazolidine-1-carboxylic acid tert-butyl ester (20 mg, 0.036 mmol) in CH_2Cl_2 (200 µL), TFA (27.6 µL, 0.358 mmol) was added, and the reaction mixture was stirred at 23°C for 20 h. The solvents were concentrated and the crude residue was purified by preparative HPLC (Waters SunFire C18ODB, 5 µm, 19x50, eluent: 20% CH_3CN/80% H_2O to 100% CH_3CN in 12.5 min, CH_3CN and H_2O both containing 0.1% of HCOOH, flow 20 mL/min) to give the desired material after lyophilization of the purified fractions. MS (LC-MS): 459 [M+H]+; t_R (HPLC conditions b): 3.72 min. (S)-2-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrazolidine-1-carboxylic acid tert-butyl ester was prepared as described in Scheme D5 step C using (S)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrazolidine-1-carboxylic acid tert-butyl ester (prepared as described in Scheme B5).

Example 433: 3-{2-[(R)-5-(3-Chloro-2-fluoro-benzylcarbamoyl)-pyrazolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide



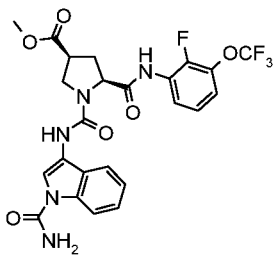
The title compound was prepared from (R)-2-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrazolidine-1-carboxylic acid tert-butyl ester according to the procedure described for the preparation of **Example 432** using 10 equivalents of TFA for the Boc deprotection. MS: 459 [M+H]+; t_R (HPLC conditions b): 3.73 min. (R)-2-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrazolidine-1-carboxylic acid tert-butyl ester was prepared as described in Scheme D5 step C using (R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrazolidine-1-carboxylic acid tert-butyl ester (prepared as described in Scheme B5).

Example 434: Pyrazolidine-1,5-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 5-(3-chloro-benzylamide)



The title compound was prepared from 2-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-3-(3-chloro-benzylcarbamoyl)-pyrazolidine-1-carboxylic acid tert-butyl ester according to the procedure described for the preparation of **Example 432**. MS (LC/MS) 441.1 [M+H]+; t_R (HPLC conditions b): 3.67 min. 2-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-3-(3-chloro-benzylcarbamoyl)-pyrazolidine-1-carboxylic acid tert-butyl ester was prepared as described in Scheme D5 step C using 3-(3-chloro-benzylcarbamoyl)-pyrazolidine-1-carboxylic acid tert-butyl ester (prepared using similar protocols as described Scheme B5).

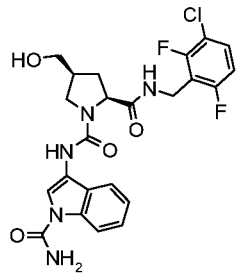
Example 435: (3S,5S)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-5-(2-fluoro-3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-3-carboxylic acid methyl ester



Chlorotrimethylsilane (537 µL, 4.24 mmol) was added dropwise to dry MeOH (700 µL) at 0°C, followed by a solution of (2S,4S)-4-cyano-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-

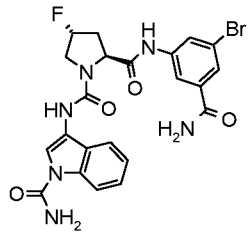
indol-3-yl)-amide] 2-[(2-fluoro-3-trifluoromethoxy-phenyl)-amide] **Example 188** (110 mg, 0.212 mmol) in dry CH_2Cl_2 (600 µL). The reaction mixture was stirred at RT under N_2 overnight. Then cooled to 0°C, water and CH_2Cl_2 were added. The layers were separated and the aqueous one extracted back with CH_2Cl_2. The combined organic extracts were neutralized with an aqueous solution saturated with $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 1:1 to c-hexane/EtOAc 1:3 to EtOAc) to give the desired compound. R_f, TLC (EtOAc) = 0.6; MS (LC-MS): 552.1 [M+H]+, 574.2 [M+Na]+, 550.2 [M-H]-; t_R (HPLC conditions f): 1.98 min.

Example 436: (2S,4S)-4-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2,6-difluoro-benzylamide)



To a solution of (3S,5S)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-5-(3-chloro-2,6-difluoro-benzylcarbamoyl)-pyrrolidine-3-carboxylic acid methyl ester **Example 353** (88 mg, 0.165 mmol) in THF (2 mL) was added Lithium borohydride 2 M in THF (0.18 mL, 0.36 mmol) and the reaction mixture was stirred at RT for 2 h under N_2 atmosphere. After completion, the mixture was quenched with brine and extracted twice with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 19x50 mm, eluent: 20% to 100% CH_3CN in H_2O in 15 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 20 mL/min) to give after lyophilization of the purified fractions the desired material. R_f, TLC (CH_2Cl_2/MeOH 90:10) = 0.65; MS (LC-MS): 506.2 [M+H]+, 1011.4 [2M+H]+, 504.2 [M-H]-; t_R (HPLC conditions f): 1.62 min.

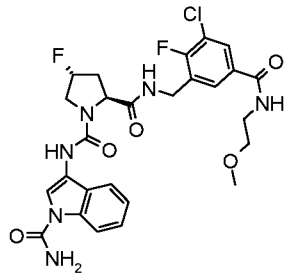
Example 437: (2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-[(3-bromo-5-carbamoyl-phenyl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide]



To a solution of 3-bromo-5-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-benzoic acid **Example 159** (100 mg, 0.188 mmol), ammonium

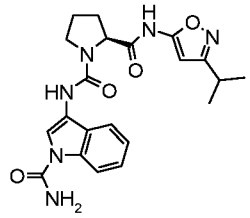
chloride (12 mg, 0.225 mmol) and HBTU (107 mg, 0.282 mmol) in DMF (3 mL) was added DIPEA (64 µl, 0.374 mmol) and the resulting solution was stirred at RT under nitrogen for 7 h. The reaction mixture was poured into water and extracted twice with EtOAc. The combined organic layers were washed water (x2), dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by preparative HPLC (C18-ODB, 5 µm, 19x50 mm, waters, eluent: CH_3CN/H_2O + 0.1 % HCOOH flow: 20 mL/min, standard 20 % method) to give the desired material after lyophilization of the purified fractions. TLC, R_f (EtOAc) = 0.3; MS (LC-MS): 531/533 [M+H]+, 553/555 [M+Na]+, 529/531 [M-H]-; t_R (HPLC conditions a): 2.79 min.

Example 438: (2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(2-methoxy-ethylcarbamoyl)-benzylamide]



To a mixture of 3-({[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-methyl)-5-chloro-4-fluoro-benzoic acid **Example 144** (30 mg, 0.06 mmol), 2-methoxyethylamine (5 mg, 0.07 mmol) and HATU (33 mg, 0.09 mmol) in DMF (1 mL) was added DIPEA (0.04 mL, 0.23 mmol) and the resulting solution was stirred at RT under nitrogen. The crude product was purified without aqueous workup by RP-preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 ml/min) to give the title compound. MS (LC-MS): 577.0 [M]+; t_R (HPLC conditions c): 3.95 min.

Example 439: (S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-isopropyl-isoxazol-5-yl)-amide]

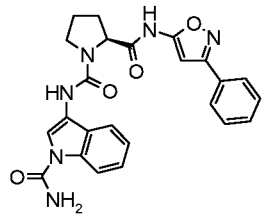


The title compound was obtained as described in steps B and C Scheme D5 using (S)-2-(3-isopropyl-isoxazol-5-ylcarbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester. MS (LC-MS): 425.2 [M+H]+, 447.1 [M+Na]+, 871.3 [2M+Na]+ , 423.1 [M-H]-; t_R (HPLC conditions a): 3.06 min.

(S)-2-(3-Isopropyl-isoxazol-5-ylcarbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

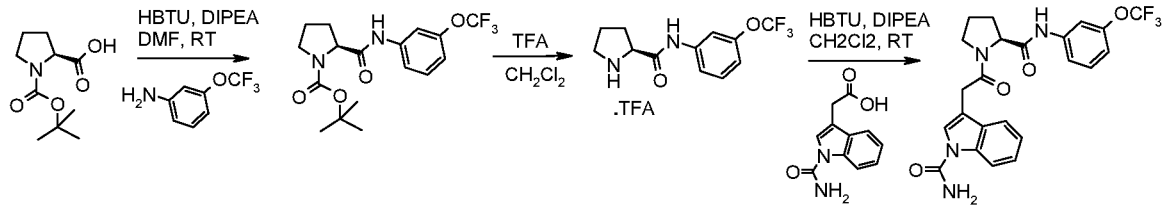
To a mixture of Boc-L-proline (150 mg, 0.697 mmol), 3-isopropylisoxazol-5-amine (88 mg, 0.697 mmol) and HBTU (264 mg, 0.697 mmol) in DMF (7 mL) was added 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) (201 µl, 0.697 mmol) and the reaction mixture was stirred at RT under nitrogen for 48 h. The mixture was poured into HCl 1N and extracted three times with EtOAc. The combined organic layers were washed with an aqueous saturated solution of $NaHCO_3$, with water, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (c-hexane to c-hexane/EtOAc 7-3) to give the title compound. TLC, R_f (c-hexane/EtOAc 1:1) = 0.6; MS (LC-MS): 324.1 [M+H]+, 346.1 [M+Na]+, 669.2 [2M+Na]+, 322.1 [M-H]-; t_R (HPLC conditions a): 3.42 min.

Example 440: (S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-phenyl-isoxazol-5-yl)-amide]



The title compound was prepared in 3 steps as described for the preparation of **Example 439**. MS (LC/MS): 459.1 [M+H]+, 481.1 [M+Na]+, 918.3 [2M+H]+, 940.2 [2M+Na]+, 457.1 [M-H]-; t_R (HPLC conditions a): 3.29 min.

Scheme D6: general protocol described for the preparation of Example 441: 3-{2-[(S)-2-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide



A. (S)-2-(3-Trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound was prepared according to the general procedures described in Scheme D5 Step A. TLC, R_f (c-hexane/EtOAc 1:1) = 0.57; MS (LC/MS): 397.1 [M+Na]+, 275.2 [MH-Boc]+, 373.3 [M-H]-; t_R (HPLC conditions a) 3.81 min.

Dichloromethane can also be used instead of DMF.

B. (S)-Pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide

The title compound as a TFA salt was prepared according to the general procedures described in Scheme D5 Step B. MS (LC/MS): 275.2 [M+H]+, 273.3 [M-H]-; t_R (HPLC conditions a) 2.47 min.

C. Example 441: 3-{2-[(S)-2-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide

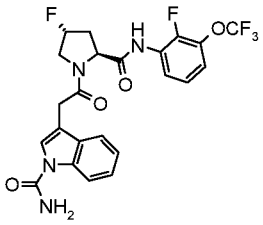
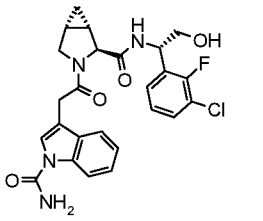
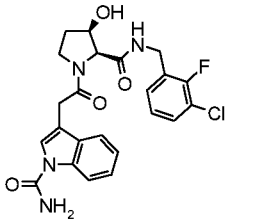
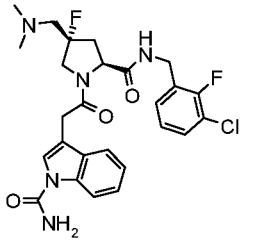
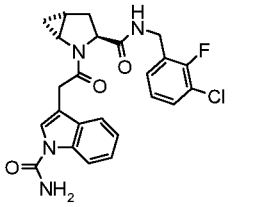
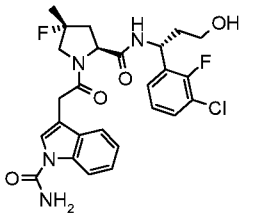
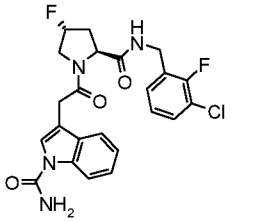
(S)-Pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide TFA salt (59.3 mg, 0.153 mmol, prepared as described in Sheme D5 steps A and B), (1-carbamoyl-1H-indol-3-yl)-acetic acid (40 mg, 0.183 mmol, prepared as described in Scheme A8) and HBTU (86.9 mg, 0.229 mmol) were dissolved in CH_2Cl_2 (4 mL) under nitrogen, DIPEA (52.3 µl, 0.306 mmol) was added and the reaction mixture was stirred at RT for 5 h. After completion of the reaction aqueous 1 N HCl and EtOAc were added, the layers were separated and the aqueous one back-extracted twice with EtOAc. The combined organic extracts were washed with an aqueous saturated solution of $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by preparative HPLC (Waters SunFire C18-ODB, 5 µm, 19x50 mm, 20% CH_3CN/H_2O 2.5 min, 20-100% CH_3CN/H_2O in 10 min, CH_3CN/H_2O containing 0.1 % HCOOH flow: 20 mL/min) to give after extraction of the pure fractions the desired compound. MS (LC/MS): 475 [M+H]+, 497 [M+Na]+; t_R (HPLC conditions a) 3.47 min.

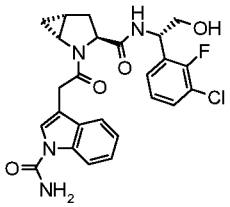
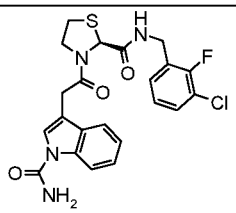
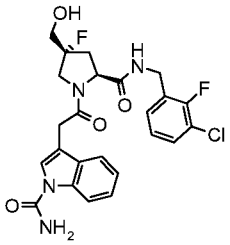
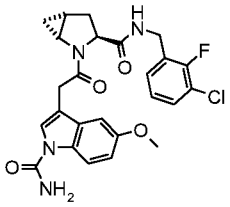
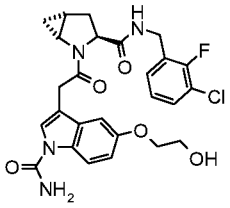
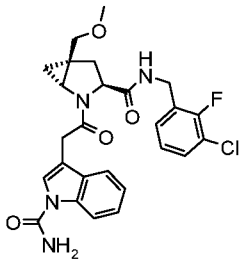
DMF can also be used instead of Dichloromethane.

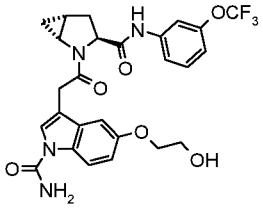
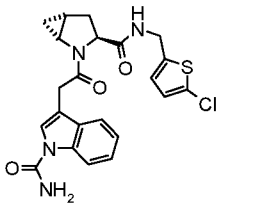
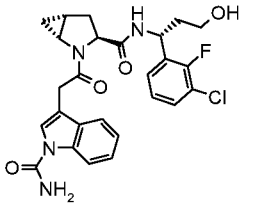
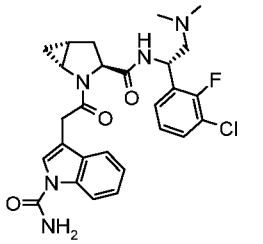
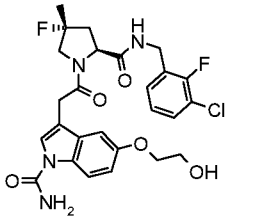
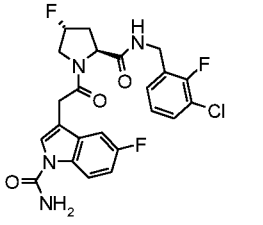
The examples below were prepared according to the general procedures described in Scheme D6 for the preparation of **Example 441***, from commercially available building blocks, if not otherwise stated (see notes at the end of table 5):*

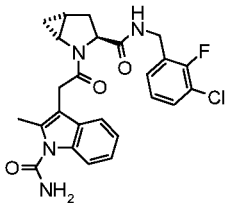
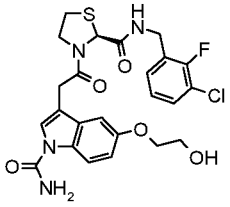
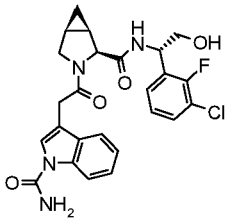
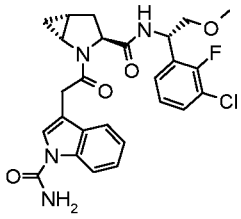
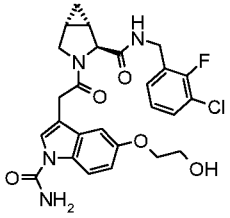
Table 5:

Example	Structure	Name	Characterization (end–table notes), TLC, R_f (eluent); MS (LC/MS); t_R (HPLC conditions); 19F NMR (100 MHz, solvent) δ (ppm)

442		3-{2-[(2S,4R)-4-Fluoro-2-(2-fluoro-3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide	(2,3) 511 [M+H]+, 533 [M+Na]+; t_R (b): 3.88 min.
443		3-(2-{(1S,2S,5R)-2-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-hydroxy-ethylcarbamoyl]-3-azabicyclo[3.1.0]hex-3-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide	(5[B9]) R_f (EtOAc) = 0.15; 499.3/501.3 [M+H]+, 543.3/545.3 [M+HCOO]-; t_R (a): 3.0 min.
444		3-{2-[(2S,3R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-3-hydroxy-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide	(2) 473 [M+H]+; t_R (b): 3.20 min.
445		3-{2-[(2S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-dimethylaminomethyl-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide	(5[B15],6) 532/534 [M+H]+; t_R (f): 1.53 min; 19F NMR (DMSO-d_6): -120, -149.
446		3-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide	White solid. R_f (EtOAc/n-hexane 3:1) = 0.11; 469 [M+H]+; t_R (b): 3.94 min.
447		3-(2-{(2S,4R)-2-[(R)-1-(3-Chloro-2-fluoro-phenyl)-3-hydroxy-propylcarbamoyl]-4-fluoro-4-methyl-pyrrolidin-1-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide	(5[B9]) White solid, R_f (CH_2Cl_2/MeOH 9:1) = 0.6; 519.3/521.3 [M+H]+, 563.3/565.3 [M+HCOO]-; t_R (a): 3.1 min.
448		3-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide	475/477 [M+H]+; t_R (b): 3.76 min.

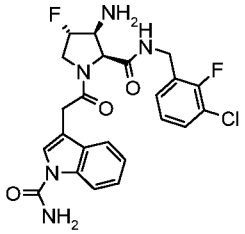
449		3-(2-{(1R,3S,5R)-3-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-hydroxy-ethyl carbamoyl]-2-aza-bicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide	(5[B9]) 499.1 [M+H]+, 520.7/521.4 [M+Na]+, 543.2/545.2 [M+HCOO]-; t_R (f): 1.79 min.
450		3-{2-[(S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-thiazolidin-3-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide	475/477 [M+H]+; t_R (b): 3.95 min.
451		3-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-hydroxymethyl-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide	(5[B12]). R_f (EtOAc) = 0.1; 505.1/507.2 [M+H]+, 527.0/529.2 [M+Na]+, 503/505 [M-H]-, 549.1/551 [M+HCOO]-; t_R (a): 2.96 min.
452		3-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-methoxy-indole-1-carboxylic acid amide	(1[A4],6) R_f (EtOAc) = 0.3; 499.1/501.1 [M+H]+, 543.1/545 [M+HCOO]-, 454/456 [M-$CONH_2$]-; t_R (a): 2.25 min.
453		3-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-(2-hydroxy-ethoxy)-indole-1-carboxylic acid amide	(1[A9]) 529.2/531.1 [M+H]+, 551/553.2 [M+Na]+, 573.1/575 [M+HCOO]-, 484.1/486.1 [M-$CONH_2$]-; t_R (a): 1.64 min.
454		3-{2-[(1R,3S,5S)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-5-methoxymethyl-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide	(4,5) White solid. R_f (EtOAc) = 0.25; 513.3/515.3 [M+H]+, 557.4/559.4 [M+HCOO]-; t_R (a): 3.23 min.

455		5-(2-Hydroxy-ethoxy)-3-{2-oxo-2-[(1R,3S,5R)-3-(3-trifluoromethoxy-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-ethyl}-indole-1-carboxylic acid amide	(1[A9]) 547.2 [M+H]+, 564.3 [M+NH4]+, 545.2 [M-H]-, 591.2 [M+HCOO]-; t_R (f): 1.85 min.
456		3-(2-{(1R,3S,5R)-3-[(5-Chloro-thiophen-2-ylmethyl)-carbamoyl]-2-aza-bicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide	R_f (CH_2Cl_2/MeOH 9:1) = 0.43; 457 [M+H]+; t_R (b): 3.84 min.
457		3-(2-{(1R,3S,5R)-3-[(R)-1-(3-Chloro-2-fluoro-phenyl)-3-hydroxy-propylcarbamoyl]-2-azabicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide	(5[B9]) Rf (EtOAc) = 0.2; 513.3 [M+H]+, 557.3/559.2 [M+HCOO]-; t_R (f): 1.86 min.
458		3-(2-{(1R,3S,5R)-3-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-dimethylamino-ethylcarbamoyl]-2-aza-bicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide	(3 [C4],4) White solid. R_f (CH_2Cl_2/MeOH 9:1) = 0.45; 526.4/528.4 [M+H]+, 570.4/572.2 [M+HCOO]; t_R (a): 2.80 min.
459		3-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidin-1-yl]-2-oxo-ethyl}-5-(2-hydroxy-ethoxy)-indole-1-carboxylic acid amide	(1[A9],5[B13]) R_f (EtOAc) = 0.2; 549.3/551.2 [M+H]+, 593.2/595.3 [M+HCOO]-; t_R (f): 1.70 min.
460		3-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-5-fluoro-indole-1-carboxylic acid amide	(1[A4]) 493 [M+H]+; t_R (b): 3.9 min.

461		3-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-2-methyl-indole-1-carboxylic acid amide	(1) 484 [M+H]+; t_R (b): 3.93 min
462		3-{2-[(S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-thiazolidin-3-yl]-2-oxo-ethyl}-5-(2-hydroxy-ethoxy)-indole-1-carboxylic acid amide	(1[A9]) R_f (EtOAc): 0.15; 535.2/537.3 [M+H]+, 579.3/581.1 [M+HCOO]-; t_R (f): 1.70 min.
463		3-(2-{(1R,2S,5S)-2-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-hydroxy-ethylcarbamoyl]-3-azabicyclo[3.1.0]hex-3-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide	(5[B9]) R_f (CH_2Cl_2/MeOH 9:1) = 0.6; 499.3/501.3 [M+H]+, 543.3/545.3 [M+HCOO]-; t_R (a): 3.02 min.
464		3-(2-{(1R,3S,5R)-3-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-methoxy-ethylcarbamoyl]-2-aza-bicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide	(5[B9]) White solid. R_f (EtOAc) = 0.35; 513.0/515.0 [M+H]+, 557/559 [M+HCOO]-; t_R (a): 3.33 min.
465		3-{2-[(1S*,2S*,5R*)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-3-aza-bicyclo[3.1.0]hex-3-yl]-2-oxo-ethyl}-5-(2-hydroxy-ethoxy)-indole-1-carboxylic acid amide	(1[A9]) R_f (EtOAc) = 0.1, 529.3/531.3 [M+H]+, 573.2/575.4 [M+HCOO]-; t_R (f): 1.61 min.

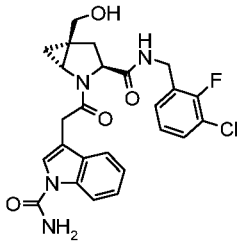
(1) The (1-carbamoyl-1H-indol-3-yl]-acetic acid derivative used in step C was prepared as described in Part A; (2) CH_2Cl_2 was used instead of DMF in step A; (3) The substituted benzylamine or aniline derivative used in step A was prepared as described in Part C [Scheme]; (4) HCl (4 M/dioxane) in dioxane was used instead of TFA in CH_2Cl_2 in step B; (5) The title compound was prepared according to the general procedure described in Scheme D6 steps B and C starting from the substituted proline derivative prepared as described in Part B [Scheme]; (6) DMF was used as solvent in step C.

Example 466: 3-{2-[(2S,3S,4S)-3-Amino-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide



The title compound was prepared according to Scheme D6 from (2S,3S,4S)-3-azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (described in scheme B19) followed by reduction of the azide as described for the preparation of **Example 411** (2S,4S)-4-aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2,6-difluoro-benzylamide). TLC, R_f (CH_2Cl_2/MeOH 95/5) = 0.3; MS (LC-MS): 490 [M+H]+, 488 [M-H]-; t_R (HPLC conditions f): 1.42 min.

Example 467: 3-{2-[(1R,3S,5S)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-5-hydroxymethyl -2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide



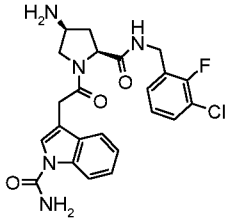
A solution of (1-carbamoyl-1H-indol-3-yl)-acetic acid (1R,3S,5S)-2-[2-(1-carbamoyl-1H-indol-3-yl)-acetyl]-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-5-ylmethyl ester (65 mg, 0.084 mmol) and NaOH 1 N (0.5 mL, 0.5 mmol) in THF (0.4 mL) / water (40 µL) was stirred at RT for 1 h. Water and CH_2Cl_2 were added, the layers were separated and the aqueous one back-extracted with CH_2Cl_2 (x3). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude material was purified by preparative HPLC (Waters Sunfire C18-ODB, 5 µm, 30x100 mm, eluent: 5% to 100% CH_3CN in H_2O in 25 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 mL/min). EtOAc and saturated aqueous $NaHCO_3$ were added to the combined purified fractions, the layers were separated and the aqueous one back-extracted with EtOAc (x3). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to give the desired material.
TLC, R_f (CH_2Cl_2/ MeOH 4-1) = 0.35; MS (UPLC/MS): 499.4/501.4 [M+H]+, 521.3/523.3 [M+Na]+, 543.3/545.2; t_R (HPLC conditions f): 1.75 min.

(1-Carbamoyl-1H-indol-3-yl)-acetic acid (1R,3S,5S)-2-[2-(1-carbamoyl-1H-indol-3-yl)-acetyl]-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-5-ylmethyl ester

The title compound N,O bis-acylated was prepared according to Scheme D6 from (1R,3S,5S)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-5-hydroxymethyl-2-aza-bicyclo[3.1.0] hexane-2-

carboxylic acid tert-butyl ester (prepared as described in Part B Scheme B28) using HCl 4N in dioxane instead of TFA in Step B. (46.2 mg, 0.14 mmol) using (1-carbamoyl-1H-indol-3-yl)-acetic acid (60.2 mg, 0.28 mmol), HBTU (105 mg, 0.28 mmol) and DIPEA (94 µL, 0.55 mmol) in CH_2Cl_2 (1 mL). TLC, R_f (EtOAc) = 0.25; MS (UPLC/MS): 699.4/701.3 [M+H]+, 721.3/723.3 [M+Na]+, 743.4/745.5 [M+HCOO]-; t_R (HPLC conditions f): 2.05 min.

Example 468: 3-{2-[(2S,4S)-4-Amino-2-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide

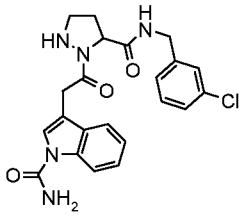


A solution of 3-{2-[(2S,4S)-4-azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide (80 mg, 0.161 mmol) in MeOH (8 mL) was hydrogenated over Pd/C 10% (8 mg, 10% w/w) at RT (1 atm). The reaction mixture was filtered through a 0.45 microns filter and concentrated under reduced pressure to give the title compound as colorless foam. MS (LC/MS): 472 [M+H]+; t_R (HPLC conditions b) 2.94 min.

3-{2-[(2S,4S)-4-Azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide

The title compound was prepared as described in Scheme D6 using (2S,4S)-4-azido-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester. TLC, Rf (EtOAc) = 0.4; MS (UPLC/MS): 583.5/585.4 [M+H]+, 600.5/602.7 [M+NH4]+, 605.5/607.4 [M+Na]+, 627.4/629.4 [M+HCOO]-; t_R (HPLC conditions f) 2.20 min.

Example 469: 3-{2-[5-(3-Chloro-benzylcarbamoyl)-pyrazolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide



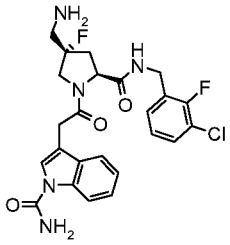
A solution of 2-[2-(1-carbamoyl-1H-indol-3-yl)-acetyl]-3-(3-chloro-benzylcarbamoyl)-pyrazolidine-1-carboxylic acid tert-butyl ester (15 mg, 0.03 mmol) in HCl 4N in dioxane (69.4 µL, 0.278 mmol) was stirred at 23°C for 1 h. The crude material was directly purified by preparative HPLC (waters SunFire C18 ODB 5um, 19x50, 5-100% CH_3CN/H_2O/15min, 100%CH_3CN/2.5min, CH_3CN and H_2O containing 0.1% of TFA, flow : 20 mL/min) to give after

lyophilization of the purified fractions the desired material. MS (LC-MS): 440 [M+H]+; t_R (HPLC conditions b) : 3.49 min.

2-[2-(1-carbamoyl-1H-indol-3-yl)-acetyl]-3-(3-chloro-benzylcarbamoyl)-pyrazolidine-1-carboxylic acid tert-butyl ester

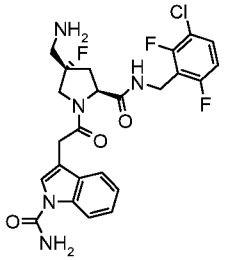
The title compound was prepared as described in Scheme D6 using 3-(3-chloro-benzylcarbamoyl)-pyrazolidine-1-carboxylic acid tert-butyl ester (prepared using a similar procedure as the one described in Scheme B5 for the preparation of 3-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrazolidine-1-carboxylic acid tert-butyl ester).

Example 470: 3-{2-[(2S,4S)-4-Aminomethyl-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide



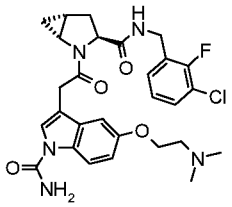
The title compound was prepared according to Scheme D6 from (2S,4R)-4-azidomethyl-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared as described scheme B15) using DMF as solvent followed by azide reduction as described for the preparation of **Example 411**. MS (LC-MS): 504/506 [M+H]+; t_R (HPLC conditions f): 1.42 min; 19F NMR (100 MHz, DMSO-d_6) δ (ppm): -120, -152.

Example 471: 3-{2-[(2S,4S)-4-Aminomethyl-2-(3-chloro-2,6-difluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide



The title compound was prepared according to Scheme D6 from (2S,4R)-4-azidomethyl-2-(3-chloro-2,6-difluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared using similar protocols as described for (2S,4R)-4-azidomethyl-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester scheme B15) using DMF as solvent followed by azide reduction as described for the preparation of **Example 411**. MS (UPLC-MS): 522/524 [M+H]+; t_R (HPLC conditions f): 1.47 min; 19F NMR (100 MHz, DMSO-d_6) δ (ppm): -117 (2F), -150.

Example 472: 3-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo [3.1.0]hex-2-yl]-2-oxo-ethyl}-5-(2-dimethylamino-ethoxy)-indole-1-carboxylic acid amide

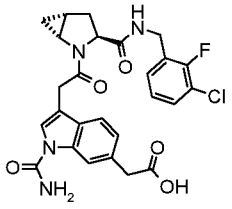


Methanesulfonic acid 2-(1-carbamoyl-3-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indol-5-yloxy)-ethyl ester in a solution of dimethylamine 5.6 M in EtOH (1 mL) was sealed in a microwave vial and heated at 70°C for 2 h (Emrys Optimizer; personal chemistry). The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$, extracted with EtOAc, dried (Na_2SO_4) and evaporated in vacuo. Then crude residue was purified by catch-release (SCX Tosic Acid-1g from Silicycle; eluent MeOH (10 mL) to 2M ammonia in MeOH (10 mL)) to give the desired material which was precipitated in Et_2O. MS (UPLC/MS): 556.5/558.5 [M+H]+, 600.4/602.5 [M+HCOO]-; t_R (HPLC conditions f): 1.46 min.

Methanesulfonic acid 2-(1-carbamoyl-3-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzyl carbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indol-5-yloxy)-ethyl ester

To a solution of **Example 453:** 3-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-(2-hydroxy-ethoxy)-indole-1-carboxylic acid amide (45 mg, 0.08 mmol) and Et_3N (56 µL, 0.41 mmol) in CH_2Cl_2 (1 mL) at 0°C was added methanesulfonyl chloride (31 µL, 0.41 mmol) and the white suspension was stirred at RT under nitrogen overnight. Et3N (56 µL, 0.41 mmol) and methanesulfonyl chloride (31 µL, 0.41 mmol) were added and the mixture was further stirred for 1.5 h to complete the reaction. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried (Na_2SO_4) and evaporated in vacuo. The crude residue was purified by column chromatography on silica gel (eluent: EtOAc to EtOAc/ acetone 1-1). TLC, Rf (EtOAc) = 0.2; MS (UPLC/MS): 607.4/609.3 [M+H]+, 629.2/631.2 [M+Na]+, 562.2/564.1 [M-$CONH_2$]-, 651.3/653.3 [M+HCOO]-; t_R (HPLC conditions f): 1.88 min.

Example 473: (1-Carbamoyl-3-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indol-6-yl)-acetic acid

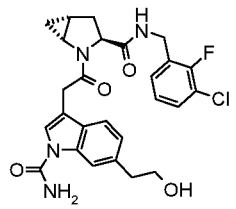


A solution of (1-carbamoyl-3-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indol-6-yl)-acetic acid tert-butyl ester (265 mg, 0.46 mmol) and TFA (1.05 mL, 23.5 mmol) in CH_2Cl_2 (4.8 mL) was stirred at RT for 3 h. The reaction mixture was concentrated taken up in EtOAC, c-hexane was added until a precipitate formed and was filtered. Further purification on trimethylaminopropyl cartridge (Mega Bond Elut-SAX, 1 g 6 mL, from Varian) (eluent: CH_3CN 10 mL then HCl 0.1 N in CH_3CN 10 mL) gave a solid which was precipitated in Et_2O. MS (UPLC): 527.4/529.5 [M+H]+, 544.4/546.3 [M+NH_4]+, 571.3/573.4 [M+HCOO]-; t_R (HPLC conditions f): 1.74 min.

(1-Carbamoyl-3-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indol-6-yl)-acetic acid tert-butyl ester

The title compound was prepared according to the protocol described in Scheme D6 using 6-tert-butoxycarbonylmethyl-1-carbamoyl-1H-indol-3-yl)-acetic acid (prepared as described in Part A) and (2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared as described in Scheme B13). TLC, R_f (EtOAc) = 0.2; MS (UPLC): 549.3/551.2 [M+H]+, 593.2/595.3 [M+HCOO]-; t_R (HPLC conditions f): 1.70 min.

Example 474: 3-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo [3.1.0]hex-2-yl]-2-oxo-ethyl}-6-(2-hydroxy-ethyl)-indole-1-carboxylic acid amide

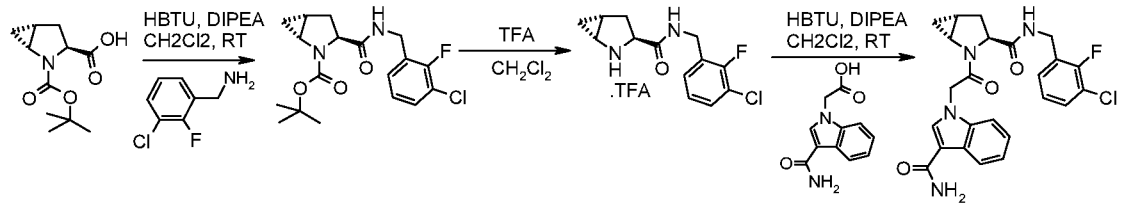


To a solution of (1-carbamoyl-3-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indol-6-yl)-acetic acid methyl ester (35 mg, 0.047 mmol) in THF (0.25 mL) was added $LiBH_4$ (2 M in THF, 47 µL, 0.094 mmol) under nitrogen atmosphere. And the reaction mixture was stirred at RT for 2 h. LiBH4 (2 M in THF, 47 µL, 0.094 mmol) was added again and the mixture was further stirred at RT for 2 h, then poured into aqueous $NaHCO_3$, extracted twice with EtOAc, dried (Na_2SO_4) and the solvent was removed in vacuo. The crude material was purified by prep HPLC (Waters Sunfire, C18-ODB, 5 µm, 19x50 mm, eluent: 20% to 100% (CH_3CN/MeOH 1-4) / H_2O in 15 min, (CH_3CN/MeOH 1-4) and H_2O containing 0.1% HCOOH, flow: 20 mL/min) to give after lyophilization of the purified fraction the desired material as a white powder. TLC, R_f (EtOAc) = 0.25; MS (UPLC/MS): 513.4/515.5 [M+H]+, 530.5/532.7 [M+NH_4]+, 557.4/559.4 [M+HCOO]-; t_R (HPLC conditions f): 1.74 min.

(1-Carbamoyl-3-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indol-6-yl)-acetic acid methyl ester

To a suspension of **Example 473**: (1-carbamoyl-3-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indol-6-yl)-acetic acid (98 mg, 0.18 mmol) in CH_2Cl_2 (1 mL) were added (40 mg, 0.195 mmol), DMAP (2.2 mg, 0.018 mmol) and MeOH (7.17 µL, 0.177 mmol) and the mixture was stirred at RT under nitrogen for 1.5 h. The mixture was poured into water and extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude material was taken up in MeOH and filtered. The filtrate was concentrated and purified by prep HPLC (Waters Sunfire, C18-ODB, 5 µm, 19x50 mm, eluent: 20% to 100% (CH_3CN/MeOH 1-4) / H_2O in 22.5 min, (CH_3CN/MeOH 1-4) and H_2O containing 0.1% HCOOH, flow: 20 mL/min). TLC, R_f (EtOAc) = 0.35; MS (UPLC/MS): 541.4/543.4 [M+H]+, 558.5/560.5 [M+NH_4]+, 563.4/565.0 [M+Na]+, 585.3/587.3 [M+HCOO]-; t_R (HPLC conditions f): 1.92 min.

Scheme D7: preparation of Example 475: 1-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide



A. (1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester

To a mixture of (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester (4 g, 17.6 mmol), 3-chloro-2-fluorobenzylamine (3.09 g, 19.36 mmol) and HBTU (10.01 g, 26.4 mmol) in CH_2Cl_2 (88 mL) was added DIPEA (6.03 mL, 35.2 mmol) and the resulting yellow solution was stirred at RT under nitrogen. The reaction mixture was poured into HCl 1N and extracted twice with CH_2Cl_2. The combined organic layers were neutralized with sat. $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flsh chromatography (c-hexane to c-hexane/ EtOAc 1-9) to give the desired material as a white solid. TLC, R_f (EtOAc) = 0.75; MS (LC/MS): 391.1/393.1 [M+Na]+, 269.0/271.0 [MH-Boc]+, 413.0/415.1 [M+HCOO]-; t_R (HPLC conditions f) 2.1 min.

DMF can also be used instead of Dichloromethane.

B. (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide

To a solution of (1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester (6.35 g, 17.22 mmol) in CH_2Cl_2 (60 mL) was added TFA (13.18 mL, 172 mmol) and the solution was stirred at RT for 3 h. The crude reaction mixture was concentrated under vacuum, Et_2O was added and the white precipitate was filtered off to give the desired compound as a TFA salt. MS (LC/MS): 287.0 [M+H]+, 285.1 [M-H]-; t_R (HPLC conditions f) 1.27 min.

C. Example 475: 1-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide

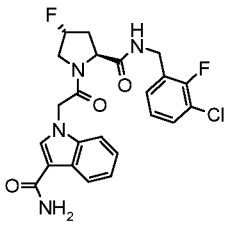
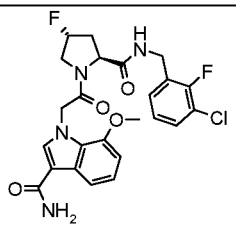
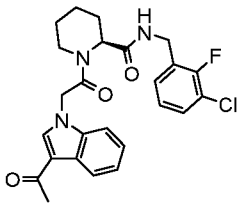
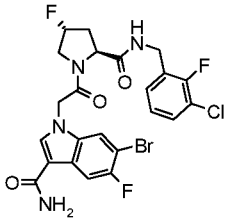
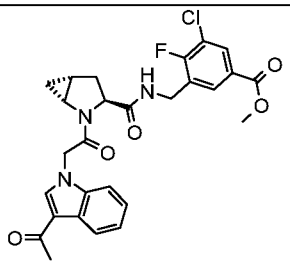
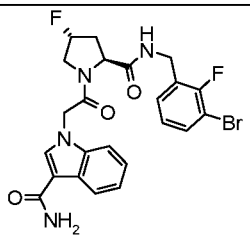
The mixture of (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide trifluoroacetate (70.2 mg, 0.183 mmol), (3-carbamoyl-indol-1-yl)-acetic acid [1016689-54-5] (40.0 mg, 0.183 mmol), HBTU (104 mg, 0.275 mmol) and DIPEA (0.128 mL, 0.733 mmol) in CH_2Cl_2 (8 mL) was stirred at RT over 60 h. The reaction mixture was then diluted with CH_2Cl_2, and the solution was washed twice with 0.1N HCl. The precipitate formed in the aqueous layer was filtered off, washed with CH_2Cl_2 and dried in vacuo to afford the title product as a white solid. MS (LC/MS): 469 [M+H]+, 491 [M+Na]+; t_R (HPLC conditions b): 3.56 min.

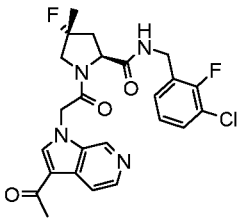
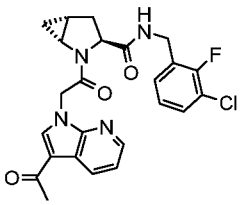
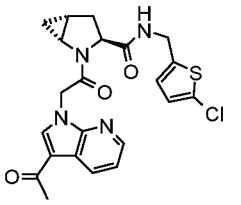
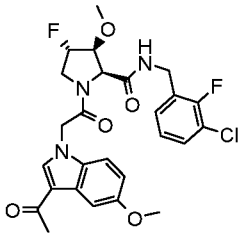
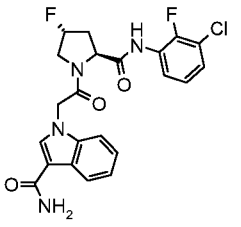
Alternatively, for final compounds containing a basic residue the pure HPLC fractions were neutralized with an aqueous saturated solution of Na_2CO_3, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated to give the desired material as a free base.

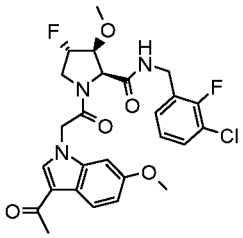
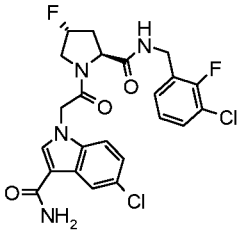
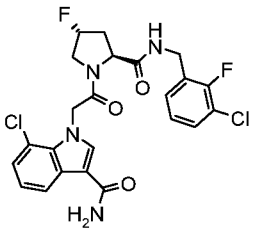
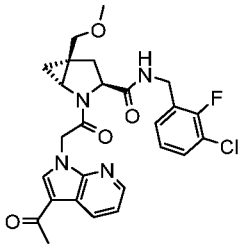
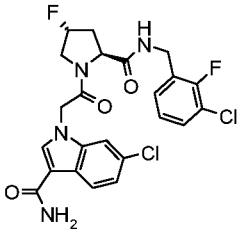
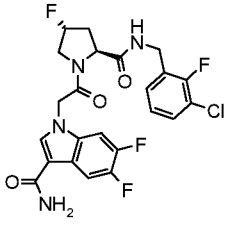
The examples below were prepared according to the general procedure described in Scheme D7 for the preparation of **Example 475** *commercially available building blocks if not otherwise mentioned (see notes at the end of table 6):*

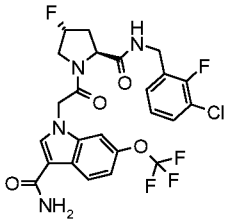
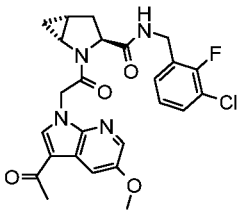
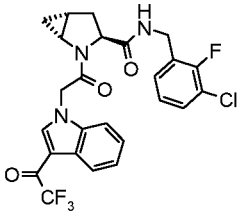
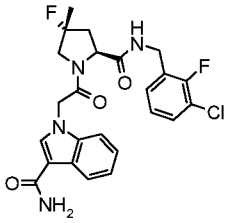
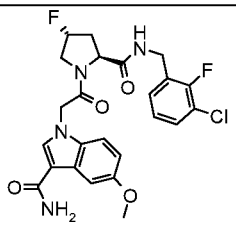
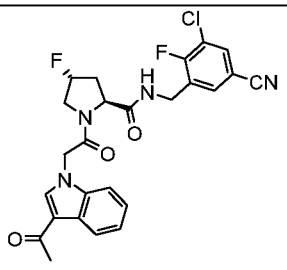
Table 6:

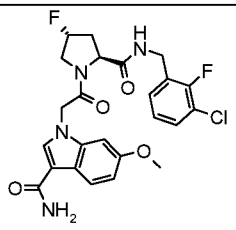
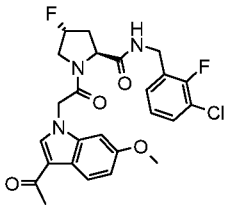
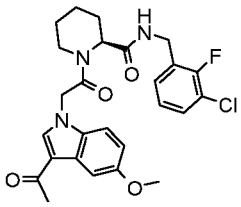
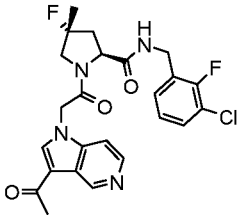
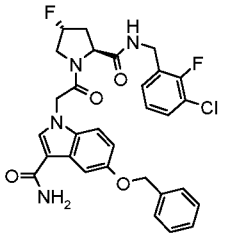
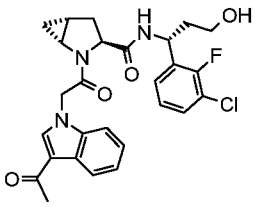
Example	Structure	Name	Characterization (end–table notes), TLC, R_f (eluent); MS (LC/MS); t_R (HPLC conditions)

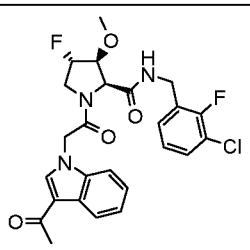
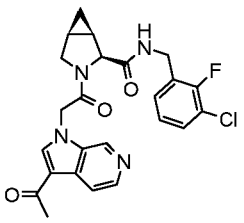
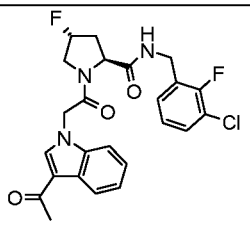
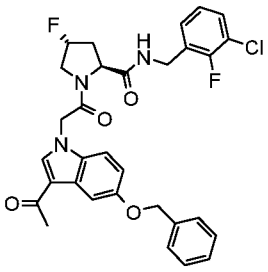
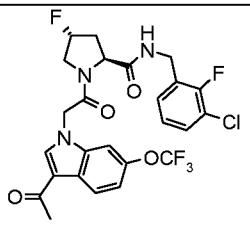
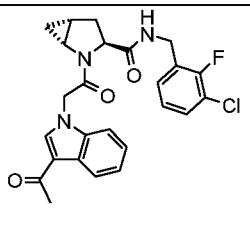
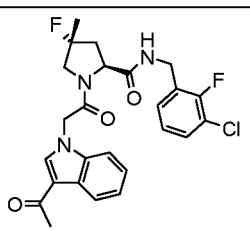
476		1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide	White solid. 475 [M+H]+; t_R (b): 4.19 min.
477		1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-7-methoxy-1H-indole-3-carboxylic acid amide	(4[A11],5) Solid. 505 [M+H]+, 527 [M+Na]+; t_R (c): 4.27 min
478		(S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-piperidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	White solid. 470 [M+H]+, 492 [M+Na]+; t_R (c): 5.01 min.
479		6-Bromo-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-5-fluoro-1H-indole-3-carboxylic acid amide	(4,5) Solid. 573.0 [M+H]+; t_R (k): 3.35 min.
480		3-[({(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carbonyl}-amino)-methyl]-5-chloro-4-fluoro-benzoic acid methyl ester	(1) White solid. R_f (EtOAc 100) = 0.35; 526.0 [M+H]+, 548.0 [M+Na]+; t_R (c): 4.90 min.
481		1-{2-[(2S,4R)-2-(3-Bromo-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide	(1,5) R_f (CH_2Cl_2/MeOH 95:5) = 0.24; 521.0 [M+H]+; t_R (k): 3.10 min.

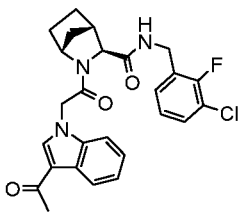
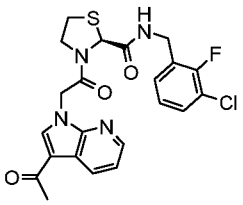
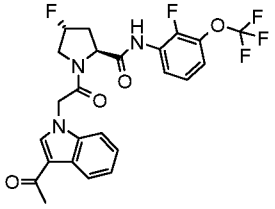
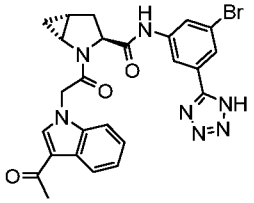
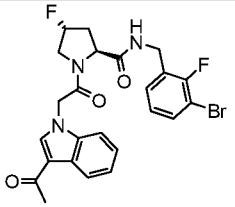
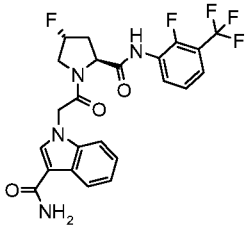
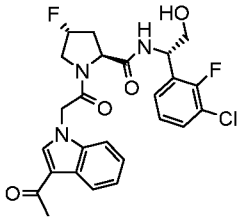
482		(2S,4R)-1-[2-(3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(3[B13],4[A15]) R_f (CH_2Cl_2/MeOH 9:1)= 0.40; 489.2/491.2 [M+H]+, 533.3/535.2 [M+HCOO]-; t_R (f): 1.49 min.
483		(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A13]) R_f (EtOAc) = 0.10; 469.3/471.3 [M+H]+, 937.5/939.5 [2M+H]+, 513.3/515.3 [M+HCOO]-, 981.4/983.5 [2M+HCOO]-; t_R (f): 1.90 min.
484		(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (5-chloro-thiophen-2-ylmethyl)-amide	(4[A13]) R_f (CH_2Cl_2/MeOH 4:1) = 0.45; 457.3/459.2 [M+H]+, 479.2/481,1 [M+Na]+, 501.3/503.2 [M+HCOO]-; t_R (f): 1.86 min.
485		(2S,3S,4S)-1-[2-(3-Acetyl-5-methoxy-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(3[B24],4) 578 [M+HCOO]-, 534 [M+H]+; t_R (f): 1.99 min.
486		1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-phenylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide	461 [M+H]+; t_R (b): 4.25 min.

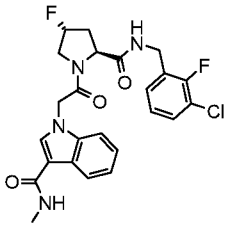
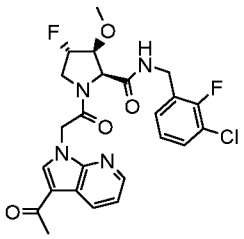
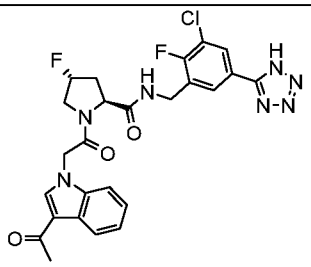
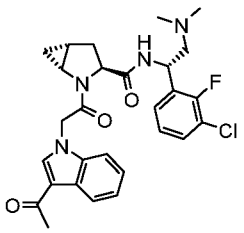
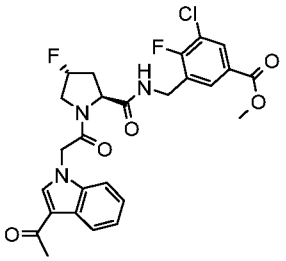
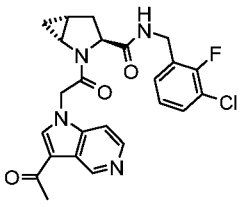
487		(2S,3S,4S)-1-[2-(3-Acetyl-6-methoxy-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(3[B24],4[A13]) and (3-acetyl-6-methoxy-indol-1-yl)-acetic acid (prepared as described in Part A). 578 [M+HCOO]-, 534 [M+H]+; t_R (f): 2.03 min.
488		5-Chloro-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide	(4[A11]) White solid. 509/510 [M+H]+, 532/533 [M+Na]+; t_R (b): 4.50 min.
489		7-Chloro-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide	(4[A11]) White solid. 509/510 [M+H]+, 532/533 [M+Na]+; t_R (b): 4.42 min.
490		(1R,3S,5S)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-5-methoxymethyl-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide	(2,3,4[A13]) White solid. R_f (EtOAc) = 0.25; 513.3/515.3 [M+H]+, 557.4/559.4 [M+HCOO]-; t_R (a): 3.23 min.
491		6-Chloro-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzyl-carbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide	(4) White solid. 509/510 [M+H]+; 532/533 [M+Na]+; t_R (b): 4.52 min.
492		1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-5,6-difluoro-1H-indole-	(4,5) Solid. 511 [M+H]+; t_R (k): 3.28 min.

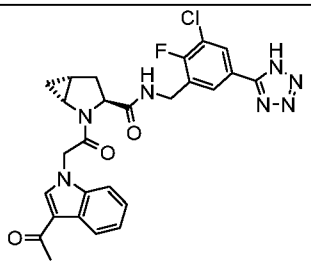
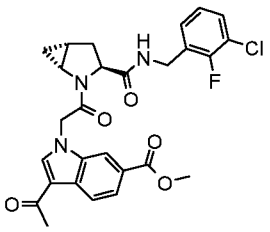
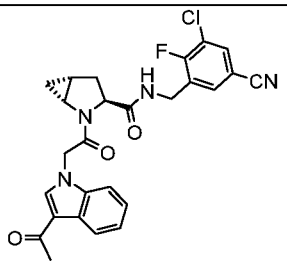
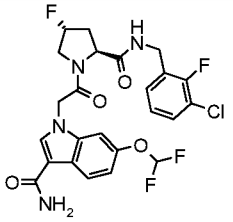
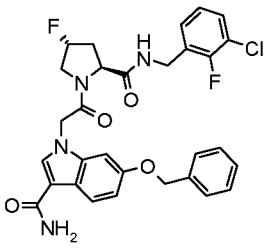
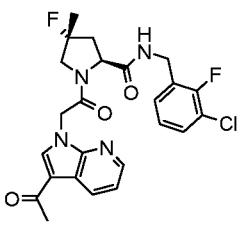
		3-carboxylic acid amide	
493		1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-trifluoromethoxy-1H-indole-3-carboxylic acid amide	(4,5) Solid. 560.0 [M+H]+; t_R (k): 3.45 min.
494		(1R,3S,5R)-2-[2-(3-Acetyl-5-methoxy-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A15]) R_f (CH_2Cl_2/MeOH 9:1) = 0.50; 499.3/501.3 [M+H]+, 543.3/545.3 [M+HCOO]-; t_R (f): 2.08 min.
495		(1R,3S,5R)-2-{2-[3-(2,2,2-Trifluoro-acetyl)-indol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A13],5) White solid. 522.0 [M+H]+; t_R (c): 5.53 min.
496		1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide	(3[B13],5) White solid. 489 [M+H]+; t_R (c): 4.35 min.
497		1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-5-methoxy-1H-indole-3-carboxylic acid amide	(4[A12],5) White solid. 505 [M+H]+; t_R (c): 4.17 min.
498		(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-5-cyano-2-fluoro-benzylamide	(1) White solid. 499.0 [M+H]+, 497.0 [M-H]-; t_R (c): 4.55 min.

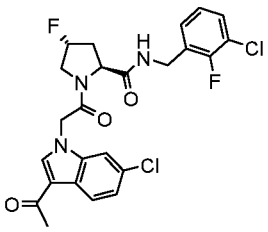
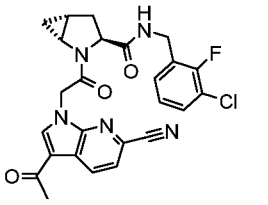
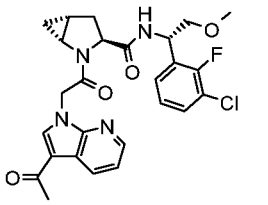
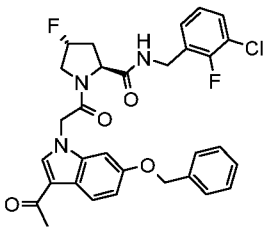
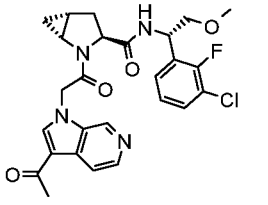
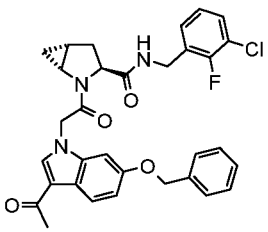
499		1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-methoxy-1H-indole-3-carboxylic acid amide	(4[A10],5) White solid. 505 [M+H]+; t_R (c): 4.19 min.
500		(2S,4R)-1-[2-(3-Acetyl-6-methoxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A13],5) Solid. 504 [M+H]+, 526 [M+Na]+; t_R (k): 3.43 min.
501		(S)-1-[2-(3-Acetyl-5-methoxy-indol-1-yl)-acetyl]-piperidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4) White solid. 500 [M+H]+; t_R (c): 4.96 min.
502		(2S,4R)-1-[2-(3-Acetyl-pyrrolo[3,2-c]pyridin-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(3[B13], 4 [A15]) R_f (CH_2Cl_2/MeOH 9:1) = 0.40; 489.3/491.3 [M+H]+, 533.3/535.3 [M+HCOO]-; t_R (f): 1.50 min.
503		5-Benzyloxy-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide	(4[A11]) White solid. R_f (EtOAc/MeOH 95:5) = 0.27; 581/582 [M+H]+; t_R (b): 4.90 min.
504		(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(R)-1-(3-chloro-2-fluoro-phenyl)-3-hydroxy-propyl]-amide	(3[B9]) R_f (EtOAc)= 0.15; 512.3 [M+H]+, 556.3/558.4 [M+HCOO]-; t_R (a): 3.22 min.

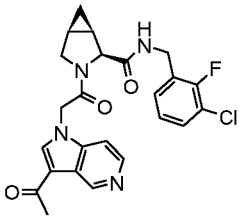
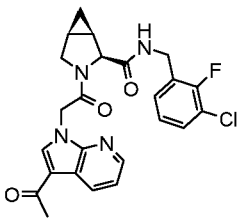
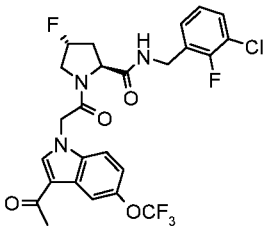
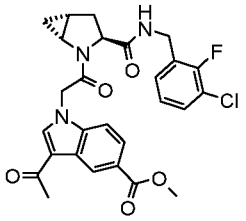
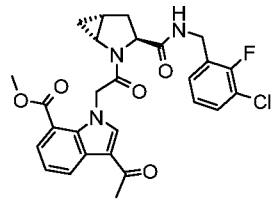
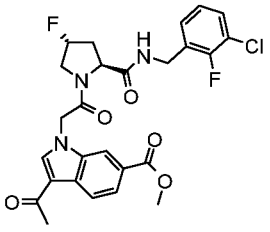
505		(2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(3[B24]) 504 [M+H]+; t_R (f): 2.01 min.
506		(1R,2S,5S)-3-[2-(3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A15]) R_f (CH_2Cl_2/MeOH 9:1)= 0.30; 469.3/471.3 [M+H]+, 513.2/515.2 [M+HCOO]-; t_R (f): 1.48 min.
507		(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	White solid. 474 [M+H]+; t_R (b): 3.90 min.
508		(2S,4R)-1-[2-(3-Acetyl-5-benzyloxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A13],5) White solid. 580/582 [M+H]+; t_R (k): 3.81 min.
509		(2S,4R)-1-[2-(3-Acetyl-6-trifluoromethoxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4,5) White solid. R_f (CH_2Cl_2/MeOH 95:5) = 0.31; 558.0 [M+H]+; t_R (c): 5.26 min.
510		(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide	(5) White solid. 468.0 [M+H]+; t_R (c): 4.77 min.
511		(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(3[B13],5) White solid. R_f (CH_2Cl_2/MeOH 95:5) = 0.31; 488.0 [M+H]+; t_R (c): 4.82 min.

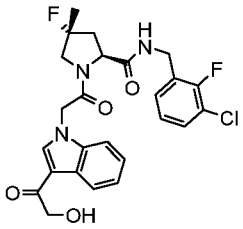
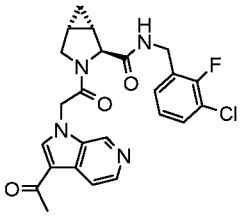
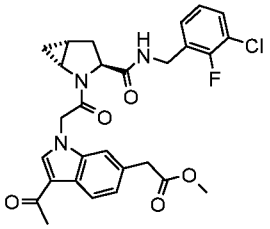
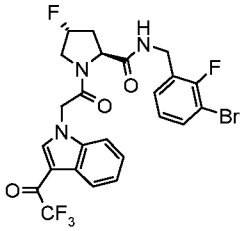
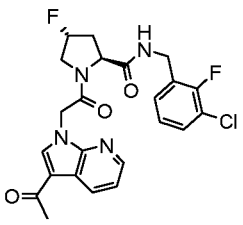
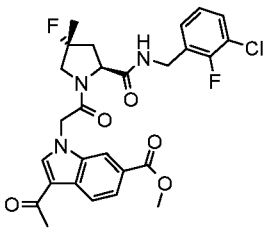
512		(1R,3S,4S)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[2.2.1]heptane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide	482 [M+H]+, 480 [M-H]-; t_R (f): 0.98 min.
513		(S)-3-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-thiazolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A13]) R_f (EtOAc)= 0.80; 475.3/477.2 [M+H]+, 949.4/951.3 [2M+H]+, 519.2/521.2 [M+HCOO]-; t_R (f): 1.91 min.
514		(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid (2-fluoro-3-trifluoromethoxy-phenyl)-amide	(1,5) White solid. 510 [M+H]+, 532 [M+Na]+; t_R (k): 3.62 min
515		(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [3-bromo-5-(2H-tetrazol-5-yl)-phenyl]-amide	(1,2) White solid. 548.0 [M+H]+; t_R (c): 4.51 min.
516		(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-bromo-2-fluoro-benzyl amide	(1,5) White solid. R_f (CH_2Cl_2/MeOH 95:5) = 0.41; 518.0 [M+H]+; t_R (k): 3.45 min
517		1-{2-[(2S,4R)-4-Fluoro-2-(2-fluoro-3-trifluoromethyl-phenylcarbamoyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide	(5,6) White solid. 495 [M+H]+, 989 [2M+1]+; t_R (c): 4.46 min.
518		(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-	(5) White solid. R_f (CH_2Cl_2/MeOH 95:5) = 0.32; 504.0 [M+H]+; t_R (c): 4.21 min.

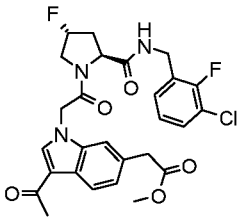
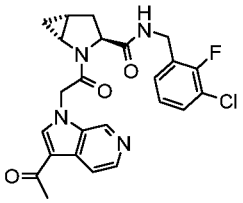
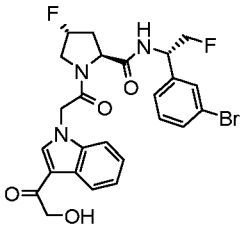
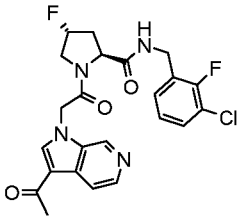
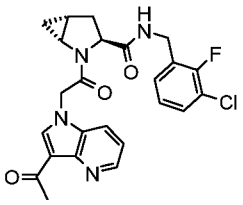
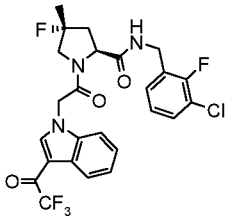
		amide	
519		1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid methylamide	(4) 489 [M+H]+; t_R (b): 3.57 min.
520		(2S,3S,4S)-1-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(3[B24], 4[A13]) 549 [M+HCOO]-, 505 [M+H]+; t_R (f): 1.90 min.
521		(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-5-(1H-tetrazol-5-yl)-benzylamide	(1,2) White solid. 542.3 [M+H]+, 540.3 [M-H]-; t_R (c): 4.27 min
522		(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-dimethylamino-ethyl]-amide	(1[C4],2) R_f (EtOAc) = 0.1; 527/527 [M+H]+; t_R (f): 1.66 min.
523		3-[({(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carbonyl}-amino)-methyl]-5-chloro-4-fluoro-benzoic acid methyl ester	(1,5) White solid. 530.0 [M-H]-; t_R (c): 4.73 min.
524		(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[3,2-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A15]) R_f (CH_2Cl_2/MeOH 4:1)= 0.35, 469.3/471.3 [M+H]+, 513.3/515.3 [M+HCOO]-; t_R (f): 1.46 min.

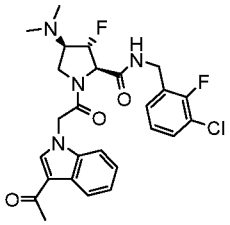
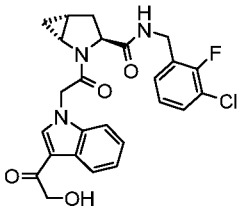
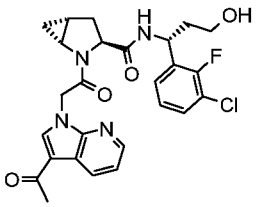
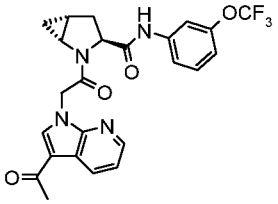
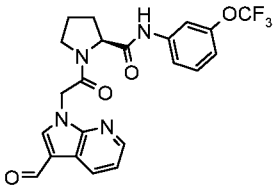
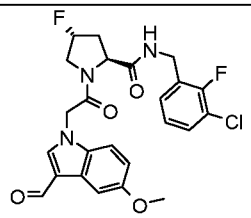
525		(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-5-(1H-tetrazol-5-yl)-benzylamide	(1,2) White solid. 536.3 [M+H]+, 534.3 [M-H]-; t_R (c): 4.41 min.
526		3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-6-carboxylic acid methyl ester	(4[A13],5) Solid. 526 [M+H]+, 1021 [2M+H]+; t_R (k): 3.52 min.
527		(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-5-cyano-2-fluoro-benzylamide	(1) White solid. 493.0 [M+H]+; t_R (c): 4.68 min
528		1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-difluoromethoxy-1H-indole-3-carboxylic acid amide	(4,5) Solid. 541/543 [M+H]+; t_R (k): 3.33 min.
529		6-Benzyloxy-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide	(4[A11]) White solid. 581/582 [M+H]+, 603/604 [M+Na]+; t_R (b): 4.94 min.
530		(2S,4R)-1-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(3[B13], 4[A13]) R_f (EtOAc) = 0.35; 489.3/491.2 [M+H]+, 533.3/535.2 [M+HCOO]-; t_R (f): 1.93 min.

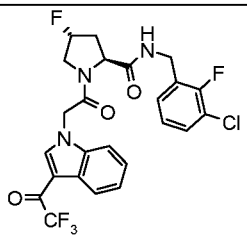
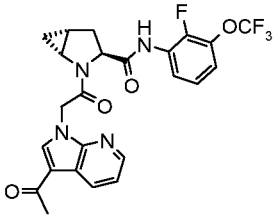
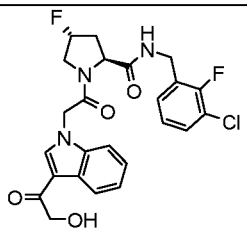
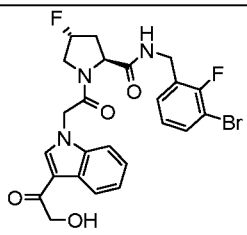
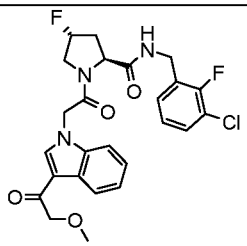
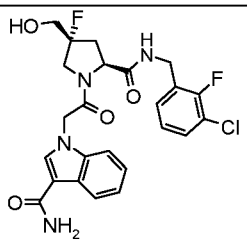
531		(2S,4R)-1-[2-(3-Acetyl-6-chloro-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A13],5) Solid. 508/510 [M+H]+, 530 [M+Na]+; t_R (k): 3.63 min.
532		(1R,3S,5R)-2-[2-(3-Acetyl-6-cyano-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A15]) R_f (EtOAc) = 0.25; 494.3/496.3 [M+H]+, 538.2/540.2 [M+HCOO]-; t_R (f): 2.03 min.
533		(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-methoxy-ethyl]-amide	(2,3[B9],4[A13]) White solid. R_f (EtOAc) = 0.50; 513.2/515.2 [M+H]+, 511.2 [M-H]-, 557.2/559.2 [M+HCOO]-; t_R (a): 3.26 min.
534		(2S,4R)-1-[2-(3-Acetyl-6-benzyloxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A13],5) Solid. 580/581 [M+H]+; t_R (k): 3.83 min.
535		(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-methoxy-ethyl]-amide	(2,3[B9],4[A15]) R_f (CH_2Cl_2/ MeOH 9:1) = 0.45; 513.3/515.3 [M+H]+, 557.2/559.2 [M+HCOO]-; t_R (f): 1.50.
536		(1R,3S,5R)-2-[2-(3-Acetyl-6-benzyloxy-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A13],5) Solid. 574 [M+H]+; t_R (k): 3.89 min.

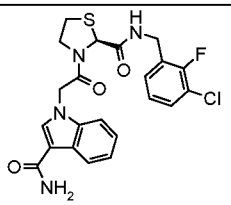
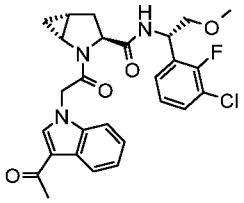
537		(1R,2S,5S)-3-[2-(3-Acetyl-pyrrolo[3,2-c]pyridin-1-yl)-acetyl]-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A15]) R_f (CH_2Cl_2/MeOH 9:1)= 0.40, 469.3/471.3 [M+H]+, 513.3/515.3 [M+HCOO]-; t_R (f): 1.47 min.
538		(1R,2S,5S)-3-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A13]) R_f (CH_2Cl_2/MeOH 4:1)= 0.35; 469.3/471.3 [M+H]+, 513.3/515.2 M+HCOO]-; t_R (a): 3.15 min.
539		(2S,4R)-1-[2-(3-Acetyl-5-trifluoromethoxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A13],5) White solid. 558.0 [M+H]+; t_R (c): 5.25 min.
540		3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-5-carboxylic acid methyl ester	(4[A13],5) Solid. 526/528 [M+H]+, 548/550 [M+Na]+; t_R (k): 3.54 min.
541		3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluorobenzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-7-carboxylic acid methyl ester	(4[A13],5) Solid. MS (LC/MS): 526 [M+H]+, 1051 [2M+H]+; t_R (k): 3.68 min.
542		3-Acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-6-carboxylic acid methyl ester	(4[A13],5) Solid. 532 [M+H]+, 554 [M+Na]+; t_R (k): 3.44 min.

543		(2S,4R)-4-Fluoro-1-{2-[3-(2-hydroxy-acetyl)-indol-1-yl]-acetyl}-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(3[B13],4[A13],5) White solid. 504.0 [M+H]+; t_R (c): 4.56 min.
544		(1S,2S,5R)-3-[2-(3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A15]) R_f (CH_2Cl_2/MeOH 9:1)= 0.45; 469.2/471.2 [M+H]+, 513.2/515.3 [M+HCOO]-; t_R (f): 1.49 min.
545		(3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indol-6-yl)-acetic acid methyl ester	(4,5) Solid. 540 [M+H]+, 562 [M+Na]+; t_R (k): 3.51 min.
546		(2S,4R)-4-Fluoro-1-{2-[3-(2,2,2-trifluoro-acetyl)-indol-1-yl]-acetyl}-pyrrolidine-2-carboxylic acid 3-bromo-2-fluoro-benzylamide	(1,4[A13],5) White solid. R_f (CH_2Cl_2/Acetone 9:1) = 0.41; 573.0 [M+H]+; t_R (k): 3.87 min
547		(2S,4R)-1-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A13]) R_f (CH_2Cl_2/MeOH 4:1)= 0.80; 475.3/477.3 [M+H]+, 519.2/521.2 [M+HCOO]-; t_R (f): 1.84 min.
548		3-Acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-6-carboxylic acid methyl ester	(3[B13],4[A13],5) Solid. 546 [M+H]+, 568 [M+Na]+; t_R (k): 3.58 min.

549		(3-Acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indol-6-yl)-acetic acid methyl ester	(4,5) Solid. 546 [M+H]+, 568 [M+Na]+; t_R (k): 3.46 min.
550		(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluorobenzylamide	(4[A15]) White solid. 469.3/471.3 [M+H]+, 513.2/515.2 [M+HCOO]-; t_R (f): 1.48 min.
551		(2S,4R)-4-Fluoro-1-{2-[3-(2-hydroxy-acetyl)-indol-1-yl]-acetyl}-pyrrolidine-2-carboxylic acid [(S)-1-(3-bromo-phenyl)-2-fluoro-ethyl]-amide	(1,4[A13],5) White solid. 548.0 [M+H]+; t_R (c): 4.47 min.
552		(2S,4R)-1-[2-(3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A15]) R_f (CH_2Cl_2/MeOH 9:1)= 0.40; 475.4/477.3 [M+H]+, 519.3/521.4 [M+HCOO]-; t_R (f): 1.45 min.
553		(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[3,2-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A13]) R_f (CH_2Cl_2/MeOH 4:1)= 0.35, 469.2/471.3 [M+H]+, 513.3/515.3 [M+HCOO]-; t_R (f): 1.45 min.
554		(2S,4R)-4-Fluoro-4-methyl-1-{2-[3-(2,2,2-trifluoro-acetyl)-indol-1-yl]-acetyl}-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(3[B13],4[A13],5) White solid. R_f (CH_2Cl_2/MeOH 95:5) = 0.56; 542.0 [M+H]+; t_R (c): 5.54 min.

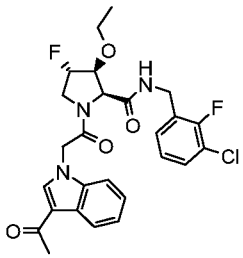
555		(2R,3S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-dimethylamino-3-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(3[B20]) R_f (c-hexane/EtOAc 1/1) = 0.17; 517 [M+H]+, 561 [M-H]-; t_R (f): 1.63 min.
556		(1R,3S,5R)-2-{2-[3-(2-Hydroxy-acetyl)-indol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A13],5) White solid. 484.0 [M+H]+; t_R (c): 4.50 min.
557		(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(R)-1-(3-chloro-2-fluoro-phenyl)-3-hydroxy-propyl]-amide	(3[B9],4 [A13]) R_f (CH_2Cl_2/MeOH 9:1)= 0.7; 513.3/515.3 [M+H]+, 557.2 [M+HCOO]-; t_R (a): 3.02 min.
558		(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (3-trifluoromethoxy-phenyl)-amide	(4[A13]) R_f (EtOAc) = 0.30; 487.3 [M+H]+, 973.5 [2M+H]+, 485.3 [M-H]-, 531.3 [M+HCOO]-, 1017.5 [2M+HCOO]-; t_R (f): 2.08 min.
559		(S)-1-[2-(3-Formyl-indol-1-yl)-acetyl]-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide	R_f (c-hexane/EtOAc 1:2)= 0.04; 460.1 [M+H]+, 482 [M+Na]+, 941.2 [2M+Na]+, 458.2 [M-H]-; t_R (a): 3.58 min.
560		(2S,4R)-4-Fluoro-1-[2-(3-formyl-5-methoxy-indol-1-yl)-acetyl]-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	MS (LC/MS): 490.0 [M+H]+; t_R (l): 1.77 min.

561		(2S,4R)-4-Fluoro-1-{2-[3-(2,2,2-trifluoro-acetyl)-indol-1-yl]-acetyl}-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A13],5) White solid. R_f (c-hexane/EtOAc 1:1) = 0.18; 528.0 [M+H]+; t_R (c): 5.44 min.
562		(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (2-fluoro-3-trifluoromethoxy-phenyl)-amide	(1,4[A13]) R_f (EtOAc) = 0.45; 505.4 [M+H]+, 1009.6 [2M+H]+, 503.3 [M-H]-, 549.3 [M+HCOO]-, 1007.7 [2M+HCOO]-; t_R (f): 2.08 min.
563		(2S,4R)-4-Fluoro-1-{2-[3-(2-hydroxy-acetyl)-indol-1-yl]-acetyl}-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A13],5) White solid. 490.1 [M+H]+, 485.5 [M-H]-; t_R (c): 4.39 min.
564		(2S,4R)-4-Fluoro-1-{2-[3-(2-hydroxy-acetyl)-indol-1-yl]-acetyl}-pyrrolidine-2-carboxylic acid 3-bromo-2-fluoro-benzylamide	(1,4[A13],5) Solid. R_f (CH_2Cl_2/MeOH 9:1) = 0.50; 534.0 [M+H]+; t_R (k): 3.25 min.
565		(2S,4R)-4-Fluoro-1-{2-[3-(2-methoxy-acetyl)-indol-1-yl]-acetyl}-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4[A13],5) White solid. 504.0 [M+H]+; t_R (c): 4.63 min.
566		1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-hydroxymethyl-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide	(3[B12]) 503 [M-H], 505 [M+H]+; t_R (f): 1.66 min.

567		1-{2-[(S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-thiazolidin-3-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide	White solid. 475 [M+H]+ ; t_R (c): 4.32 min.
568		(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-methoxy-ethyl]-amide	(2,3[B9]). White solid. R_f (EtOAc) = 0.35; 511.9 [M+H]+, 510.1 [M-H]-, 556.2 [M+HCOO]-; t_R (a): 3.43 min.

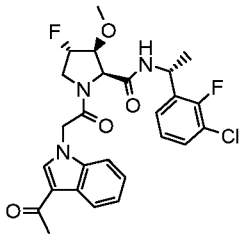
(1) The substituted benzylamine or aniline derivative used in step A was prepared as described in Part C; (2) HCl (4M in dioxane) was used instead of TFA in step B; (3) The title compound was prepared according to the general procedure described in Scheme D6 steps B and C starting from the substituted proline derivative prepared as described in Part B [Scheme]; (4) Compound was prepared as described in Scheme D7 using (3-carbamoyl-indol-1-yl)-acetic acid derivative or (3-acetyl-indol-1-yl)-acetic acid derivative (prepared as described in Part A); (5) DMF was used instead of CH_2Cl_2 in step C; (6) HATU was used as the coupling reagent in step C.

Example 569: (2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-3-ethoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide



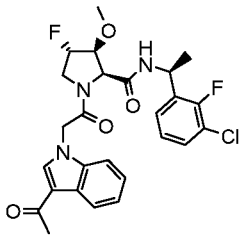
The title compound was prepared according to Scheme D7 from (2S,3S,4S)-4-fluoro-3-ethoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide (prepared as described in Scheme B24 using ethyl iodide instead of methyl iodide in Step B). MS (UPLC-MS): 518 [M+H]+, 562 [M+HCOO]-; t_R (HPLC conditions f): 2.11 min.

Example 570: (2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid [(R)-1-(3-chloro-2-fluoro-phenyl)-ethyl]-amide



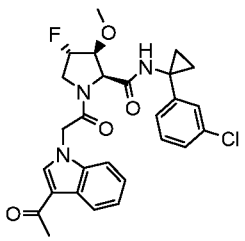
The title compound was prepared according to Scheme D7 from (2S,3S,4S)-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid (R)-1-(3-chloro-2-fluoro-phenyl)-ethyl]-amide prepared as described in Scheme B24 using (R)-1-(3-chloro-2-fluorophenyl)ethanamine in Step D. MS (UPLC-MS): 562 [M+HCOO]-, 518 [M+H]+; t_R (HPLC conditions f): 2.11 min.

Example 571: (2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-ethyl]-amide



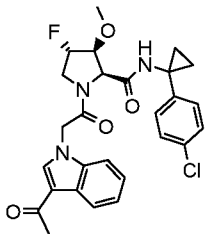
The title compound was prepared according to Scheme D7 from (2S,3S,4S)-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid (S)-1-(3-chloro-2-fluoro-phenyl)-ethyl]-amide prepared as described in Scheme B24 using (S)-1-(3-chloro-2-fluorophenyl)ethanamine in Step D. MS (UPLC-MS): 562 [M+HCOO]-, 518 [M+H]+; t_R (HPLC conditions f): 2.09 min.

Example 572: (2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid [1-(3-chloro-phenyl)-cyclopropyl]-amide



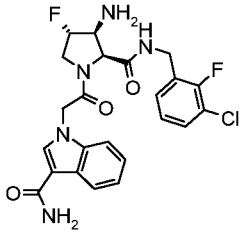
The title compound was prepared according to Scheme D7 from (2S,3S,4S)-2-[1-(3-chloro-phenyl)-cyclopropylcarbamoyl]-4-fluoro-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared using the same protocols as described in Scheme B24 using 1-(3-chloro-phenyl)-cyclopropylamine in Step D). Preparation of 1-(3-chloro-phenyl)-cyclopropylamine was described in Part C. MS (UPLC-MS): 556 [M+HCOO]-, 512 [M+H]+; t_R (HPLC conditions f): 2.05 min.

Example 573: (2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid [1-(4-chloro-phenyl)-cyclopropyl]-amide



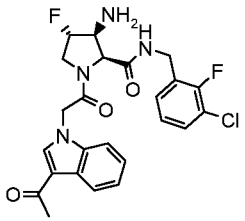
The title compound was prepared according to Scheme D7 from (2S,3S,4S)-2-[1-(3-chloro-phenyl)-cyclopropylcarbamoyl]-4-fluoro-3-methoxy-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared using the same protocols as described in Scheme B24 using 1-(4-chloro-phenyl)-cyclopropylamine in Step D). Preparation of 1-(4-chloro-phenyl)-cyclopropylamine was described in Part C. MS (UPLC-MS): 556 [M+HCOO]-, 512 [M+H]+; t_R (HPLC conditions f): 2.05 min.

Example 574: 1-{2-[(2S,3S,4S)-3-Amino-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide



The title compound was prepared according to Scheme D7 from (2S,3S,4S)-3-azido-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (described in scheme B19) followed by reduction of the azide as described for the preparation of **Example 411** (2S,4S)-4-aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2,6-difluoro-benzylamide). TLC, R_f (CH_2Cl_2/MeOH 95/5) = 0.2 ; MS (LC-MS): 490 [M+H]+, 488 [M-H]-; t_R (HPLC conditions f): 1.46 min.

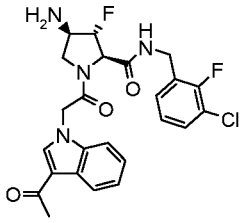
Example 575: (2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-3-amino-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide



The title compound was prepared according to Scheme D7 starting from a mixture of (2R,3S,4R) and (2S,3S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-(9H-fluoren-9-

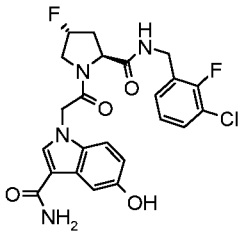
ylmethoxycarbonylamino)-3-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester in a 2:1 ratio (prepared as described in Scheme B22) followed by Fmoc deprotection using the protocol described for the preparation of **Example 396**. The regioisomers were separated by preparative HPLC to give the title compound: MS (UPLC-MS): 489 [M+H]+, 533 [M-H]-; t_R (HPLC conditions f): 1.62 min.

Example 576: (2R,3S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-amino-3-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide



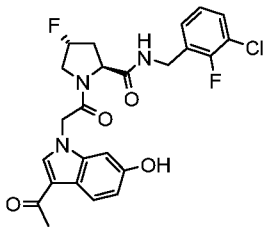
The title compound was prepared according to Scheme D7 starting from a mixture of (2R,3S,4R) and (2S,3S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-(9H-fluoren-9-ylmethoxycarbonylamino)-3-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester in a 2:1 ratio (prepared as described in Scheme B22) followed by Fmoc deprotection using the protocols described for the preparation of **Example 396**. TLC, R_f (CH_2Cl_2/MeOH 95/5) = 0.26 ; MS (UPLC-MS): 489 [M+H]+ , 533 [M+HCOO]-; t_R (HPLC conditions f): 1.63 min.

Example 577: 1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-5-hydroxy-1H-indole-3-carboxylic acid amide



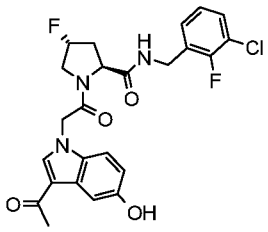
To a suspension of 5-benzyloxy-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide **Example 503** (148 mg, 0.255 mmol) in TFA (2.5 mL), cooled to 0°C, was added thioanisole (0.301 mL, 2.55 mmol), and the reaction mixture was stirred at RT for 3h. Volatiles were evaporated under reduced pressure, and the residue was suspended in a saturated aqueous $NaHCO_3$ solution, followed by freeze-drying in vacuo. The residue was suspended in a small amount of methanol and the solid was filtered off. The filtrate was purified by preparative HPLC (Sunfire, C18-ODB, 5 µm, 30x100 mm, flow: 40 mL/min, 20-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA). The title compound was obtained as a white solid. MS (LC/MS): 491 [M+H]+; 983 [2M+H]+; t_R (HPLC, conditions b): 3.75 min.

Example 578: 1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-hydroxy-1H-indole-3-carboxylic acid amide



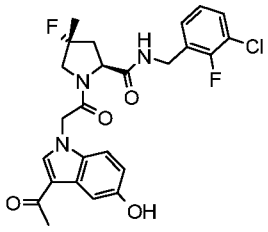
The title compound was prepared in a similar manner as described above for **Example 577** from (6-benzyloxy-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide **Example 529** (220 mg, 0.379 mmol). White solid. MS (LC/MS): 491 [M+H]+; t_R (HPLC conditions b): 3.76 min.

Example 579: (2S,4R)-1-[2-(3-Acetyl-5-hydroxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide



The title compound was prepared in a similar manner as described for **Example 577** from (2S,4R)-1-[2-(3-acetyl-5-benzyloxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide **Example 508** (167 mg, 0.288 mmol). White solid. MS (LC/MS): 490 [M+H]+; t_R (HPLC conditions k): 3.03 min.

Example 580: (2S,4R)-1-[2-(3-Acetyl-5-hydroxy-indol-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide

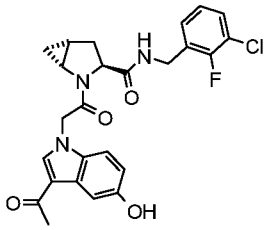


The title compound was prepared in a similar manner as described above for **Example 577** from (2S,4R)-1-[2-(3-acetyl-5-benzyloxy-indol-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide (57.0 mg, 0.096 mmol), TFA (3 mL), and thioanisole (0.114 mL, 0.960 mmol). Solid. MS (LC/MS): 504 [M+H]+; t_R (HPLC, conditions k): 3.22 min.

(2S,4R)-1-[2-(3-acetyl-5-benzyloxy-indol-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide

was prepared as described in Scheme D7 from (3-acetyl-5-benzyloxy-indol-1-yl)-acetic acid (prepared as described in Part A) using DMF instead of CH_2Cl_2 in Step C. White solid. MS (LC/MS): 594 [M+H]+; t_R (HPLC conditions k): 3.89 min.

Example 581: (1R,3S,5R)-2-[2-(3-Acetyl-5-hydroxy-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide

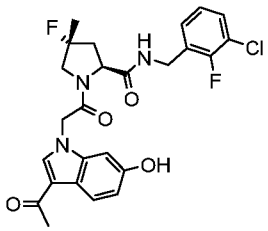


The title compound was prepared in a similar manner as described above for **Example 577** from (1R,3S,5R)-2-[2-(3-acetyl-5-benzyloxy-indol-1-yl)-acetyl]-2-aza-bicyclo [3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide (79.0 mg, 0.138 mmol), TFA (3 mL) and thioanisole (0.163 mL, 1.38 mmol). Solid. MS (LC/MS): 484 [M+H]+; t_R (HPLC, conditions k): 3.18 min.

(1R,3S,5R)-2-[2-(3-acetyl-5-benzyloxy-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide

was prepared as described in Scheme D7 from (3-acetyl-5-benzyloxy-indol-1-yl)-acetic acid (prepared as described in Part A) using DMF instead of CH_2Cl_2 in Step C. White solid. MS (LC/MS): 574 [M+H]+; t_R (HPLC conditions k): 3.88 min.

Example 582: (2S,4R)-1-[2-(3-Acetyl-6-hydroxy-indol-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide

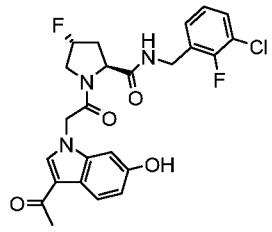


The title compound was prepared in a similar manner as described above for **Example 577** from (2S,4R)-1-[2-(3-acetyl-6-benzyloxy-indol-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide (96.0 mg, 0.137 mmol), TFA (2 mL) and thioanisole (0.162 mL, 1.374 mmol). Solid. MS (LC/MS): 504 [M+H]+; t_R (HPLC, conditions k): 3.26 min.

(2S,4R)-1-[2-(3-acetyl-6-benzyloxy-indol-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide

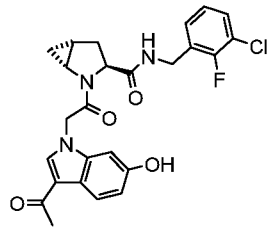
was prepared as described in Scheme D7 from (3-acetyl-6-benzyloxy-indol-1-yl)-acetic acid (prepared as described in Part A) using DMF instead of CH_2Cl_2 in Step C. Solid. MS (LC/MS): 594 [M+H]+; t_R (HPLC conditions k): 3.94 min.

Example 583: (2S,4R)-1-[2-(3-Acetyl-6-hydroxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide



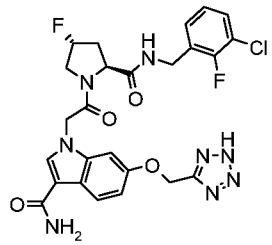
The title compound was prepared in a similar manner as described for **Example 577** from (2S,4R)-1-[2-(3-acetyl-6-benzyloxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide **Example 534** (100 mg, 0.172 mmol). White solid. MS (LC/MS): 490 [M+H]+, 512 [M+Na]+; t_R (HPLC conditions k): 3.15 min.

Example 584: (1R,3S,5R)-2-[2-(3-Acetyl-6-hydroxy-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide



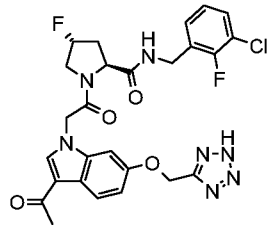
The title compound was prepared in a similar manner as described for **Example 577** from (1R,3S,5R)-2-[2-(3-acetyl-6-benzyloxy-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide **Example 536** (360 mg, 0.527 mmol). Solid. MS (LC/MS): 484 [M+H]+; t_R (HPLC conditions k): 3.21 min.

Example 585: 1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-(1H-tetrazol-5-ylmethoxy)-1H-indole-3-carboxylic acid amide



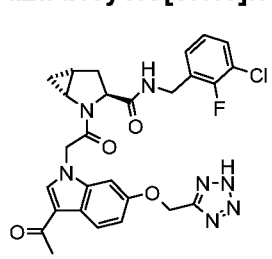
A solution of 1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-hydroxy-1H-indole-3-carboxylic acid amide **Example 578** (148 mg, 0.283 mmol) in DMSO (3 mL) was treated with Cs_2CO_3 (0.28 g, 0.85 mmol). The mixture was stirred at RT for 5 min, followed by addition of 5-(chloromethyl)-1H-tetrazole (35 mg, 0.098 mmol) and stirring at RT for 36 h. The reaction mixture was neutralised by addition of 1N HCl. Water was then added to the mixture to form a precipitate. The solid material was filtered off, washed with water, and dried in vacuo to afford the title compound as a solid. MS (LC/MS): 573 [M+H]+; t_R (HPLC conditions k): 2.92 min.

Example 586: (2S,4R)-1-{2-[3-Acetyl-6-(1H-tetrazol-5-ylmethoxy)-indol-1-yl]-acetyl}-4-fluoro-yrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide



The title compound was prepared in a similar manner as described above for **Example 585** from (2S,4R)-1-[2-(3-acetyl-6-hydroxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide **Example 583** (60.0 mg, 0.122 mmol), cesium carbonate (120 mg, 0.367 mmol) and 5-(chloromethyl)-1H-tetrazole (44.0 mg, 0.366 mmol) in DMSO (2.5 mL). Solid. MS (LC/MS): 572 [M+H]+; t_R (HPLC conditions k): 3.23 min.

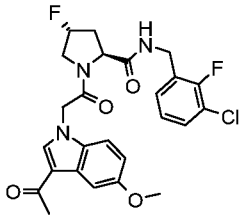
Example 587: (1R,3S,5R)-2-{2-[3-Acetyl-6-(1H-tetrazol-5-ylmethoxy)-indol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide



A solution of (1R,3S,5R)-2-[2-(3-Acetyl-6-hydroxy-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]-hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide **Example 584** (80.0 mg, 0.165 mmol) in DMSO (2 mL) was treated with cesium carbonate (162 mg, 0.496 mmol). After stirring at RT

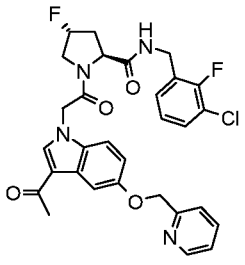
for 5 min, 5-(chloromethyl)-1H-tetrazole (21.0 mg, 0.174 mmol) was added and stirring was continued at RT for 36 h. The mixture was neutralised by addition of 1N HCl, diluted with water extracted with EtOAc (2x). The combined organic layers were washed with water (2x) and brine. The resulting suspension was filtered over phase separator and concentrated. The filtered solid was triturated with methanol, decanted and dried in vacuo to give the title compound. The filtrate was purified by preparative HPLC (Macherey-Nagel Nucleosil 100-10 C18, 5 µm, 40x250 mm, flow: 40 mL/min, eluent: 20-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) to afford after lyophilization of the purified fractions a second batch of the title compound as a white solid. MS (LC/MS): 566 [M+H]+; t_R (HPLC conditions k): 3.22 min.

Example 588: (2S,4R)-1-[2-(3-Acetyl-5-methoxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide



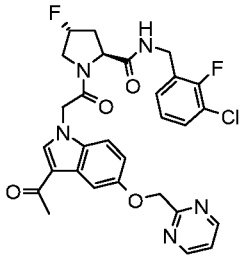
A solution of (2S,4R)-1-[2-(3-acetyl-5-hydroxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide **Example 579** (28.0 mg, 0.057 mmol) in DMSO (2 mL) was treated with potassium hydroxide (15.0 mg, 0.257 mmol). The mixture was stirred at RT for 5 min, followed by addition of iodomethane (0.006 mL, 0.089 mmol) and stirring at RT for 60 h. The reaction mixture was partitioned between water and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organics were washed with brine (3x), dried (phase separator) and concentrated under reduced pressure. The crude product was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 19x50 mm, flow: 20 mL/min, eluent: 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) to afford after lyophilization of the purified fractions the title compound as a solid. MS (LC/MS): 504 [M+H]+, 526 [M+Na]+; t_R (HPLC conditions k): 3.38 min.

Example 589: (2S,4R)-1-{2-[3-Acetyl-5-(pyridin-2-ylmethoxy)-indol-1-yl]-acetyl}-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide



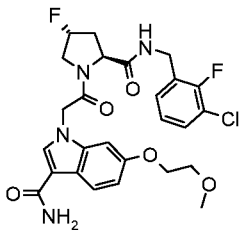
A solution of (2S,4R)-1-[2-(3-acetyl-5-hydroxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide **Example 579** (60.0 mg, 0.122 mmol) in DMSO (2.5 mL) was treated with cesium carbonate (160 mg, 0.490 mmol). After stirring at RT for 5 min, 2-(bromomethyl)pyridine (31.0 mg, 0.122 mmol) was added to the reaction mixture and stirring was continued at RT for 16 h. Water was then added to the mixture to form a solid precipitate which was filtered off, washed with water and dried in vacuo. Purification by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, flow: 40 mL/min, eluent: 20-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) afforded after lyophilization of the purified fractions the title compound as a white solid. MS (LC/MS): 580/581 [M+H]+; t_R (HPLC conditions k): 3.00 min.

Example 590: (2S,4R)-1-{2-[3-Acetyl-5-(pyrimidin-2-ylmethoxy)-indol-1-yl]-acetyl}-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide



The title compound was prepared according to procedure described for the preparation of **Example 589** (2S,4R)-1-{2-[3-acetyl-5-(pyridin-2-ylmethoxy)-indol-1-yl]-acetyl}-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide from (2S,4R)-1-[2-(3-acetyl-5-hydroxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide **Example 579** (23.0 mg, 0.047 mmol), cesium carbonate (61 mg, 0.188 mmol) and 2-(chloromethyl)pyrimidine (0.012 mg, 0.070 mmol) in DMSO (2 mL). White solid. MS (LC/MS): 582/583 [M+H]+; t_R (HPLC conditions k): 3.19 min.

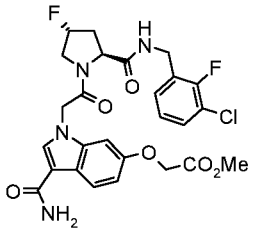
Example 591: 1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-(2-methoxy-ethoxy)-1H-indole-3-carboxylic acid amide



A solution of 1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-hydroxy-1H-indole-3-carboxylic acid amide **Example 578** (50 mg, 0.102 mmol) in DMSO (1 mL) was treated with KOH (26.0 mg, 0.458 mmol). The mixture was stirred at RT for 5 min, followed by addition of (2-bromoethyl)methyl ether (0.015 mL, 0.158 mmol) and stirring

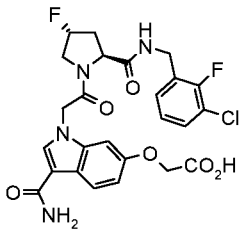
at RT for 2 h. The mixture was partitioned between water and CH_2Cl_2, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organics were washed with brine (3x), dried (phase separator) and concentrated under reduced pressure. Purification by preparative HPLC (SunFire C18-ODB, 5 µm, 30x100 mm, eluent: 20-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 mL/min) afforded after lyophilization of the purified fractions the title compound as a white solid. MS : 549 [M+H]+; t_R (HPLC conditions c): 4.17 min.

Example 592: **(3-Carbamoyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indol-6-yloxy)-acetic acid methyl ester**



A solution of 1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-hydroxy-1H-indole-3-carboxylic acid amide **Example 578** (140 mg, 0.285 mmol) in DMSO (3 mL) was treated with Cs_2CO_3 (0.28 g, 0.85 mmol). The mixture was stirred at RT for 5 min, followed by addition of methyl 2-bromoacetate (0.039 mL, 0.428 mmol) and stirring at RT for 4 h. The mixture was partitioned between water and CH_2Cl_2, and the organic phase was washed twice with brine (the combined aqueous washings were filtered and the solid thus obtained was dried in vacuo to give an aliquot of the title compound), dried (phase separator) and concentrated under reduced pressure. Purification by preparative HPLC (SunFire C18-ODB, 5 µm, 30x100 mm, eluent: 20-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 mL/min) afforded after lyophilization of the purified fractions the title compound as a white solid. MS : 563 [M+H]+; t_R (HPLC conditions c): 4.17 min.

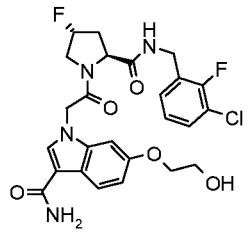
Example 593: (3-Carbamoyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indol-6-yloxy)-acetic acid



To a solution of (3-carbamoyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indol-6-yloxy)-acetic acid methyl ester **Example 592** (18 mg, 0.032 mmol) in a mixture of THF (2 mL) and water (0.2 mL) was added 1N NaOH (0.064 mL),

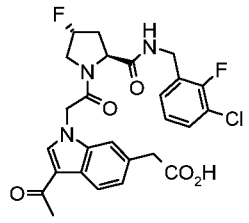
followed by stirring at RT for 4 h. The reaction mixture was partitioned between CH_2Cl_2 and water. The aqueous phase was adjusted to pH = 2 by addition of 1N HCl, followed by extraction with CH_2Cl_2 (3x). The combined organics were dried (phase separator) and concentrated under reduced pressure to afford the title compound as a white solid. MS: 549 [M+H]+; t_R (HPLC conditions c): 3.74 min.

Example 594: **1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-(2-hydroxy-ethoxy)-1H-indole-3-carboxylic acid amide**



To a solution of (3-carbamoyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indol-6-yloxy)-acetic acid methyl ester **Example 592** (30.0 mg, 0.049 mmol) in THF (1 mL) was added $LiBH_4$ (2M in THF; 0.049 mL, 0.098 mmol) and stirring was continued at RT for 2 h. The reaction mixture was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organics were dried (phase separator) and concentrated under reduced pressure. Purification by preparative HPLC (SunFire C18-ODB, 5 µm, 19x50 mm, eluent: 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 20 mL/min) afforded after lyophilization of the purified fractions the desired compound as a white solid. MS: 535 [M+H]+; t_R (HPLC conditions c): 3.72 min.

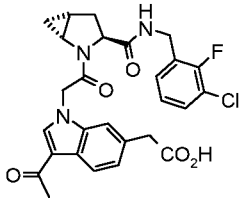
Example 595: (3-Acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indol-6-yl)-acetic acid



To a solution of (3-acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indol-6-yl)-acetic acid methyl ester **Example 549** (200 mg, 0.366 mmol) in THF (5 mL) and water (0.5 mL) was added 1N NaOH (1.46 mL, 1.46 mmol) and the reaction was stirred at RT for 60 h. The mixture was partitioned between diethylether and water. The layers were separated and the aqueous phase was adjusted to pH = 2 by addition of a 1N HCl solution to form a precipitate. The solid was filtered off, washed with water

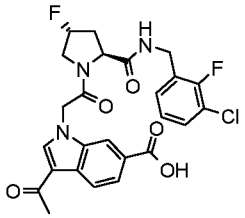
and diethylether and dried in vacuo to afford the title compound as a solid. MS (LC/MS): 532 [M+H]+; t_R (HPLC conditions k): 3.19 min.

Example 596: (3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indol-6-yl)-acetic acid



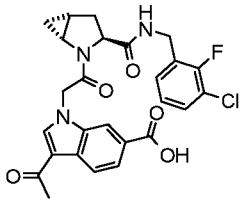
The title compound was prepared in a similar manner as described for **Example 595** from (3-acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indol-6-yl)-acetic acid methyl ester **Example 545** (200 mg, 0.370 mmol). Solid. MS (LC/MS): 526 [M+H]+; t_R (HPLC conditions k): 3.24 min.

Example 597: 3-Acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-6-carboxylic acid

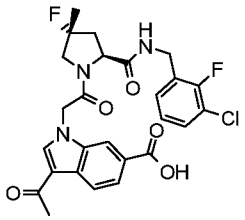


The title compound was prepared in a similar manner as described for **Example 595** from 3-acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-6-carboxylic acid methyl ester **Example 542** (200 mg, 0.370 mmol). Solid. MS (LC/MS): 518 [M+H]+; t_R (HPLC conditions k): 3.14 min.

Example 598: 3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-6-carboxylic acid

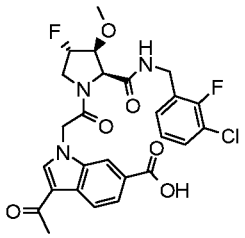


Example 599: 3-Acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-6-carboxylic acid



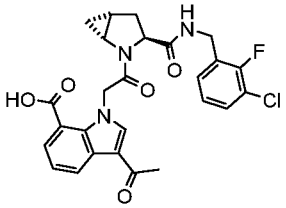
The title compound was prepared in a similar manner as described for **Example 595** from 3-acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-6-carboxylic acid methyl ester **Example 548** (70 mg, 0.128 mmol). Solid. MS (LC/MS): 532 [M+H]+; t_R (HPLC conditions c): 4.34 min.

Example 600: (2S,3S,4S)-4-Fluoro-3-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide)



The title compound was prepared in a similar manner as described for **Example 595** starting from (2S,3S,4S)-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide (prepared as described in Scheme D7 from 3-acetyl-1-carboxymethyl-1H-indole-6-carboxylic acid methyl ester (described in Part C) and (2S,3S,4S)-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide (described Scheme B24). MS (UPLC-MS): 548 [M+H]+, 592 [M+HCOO]-; t_R (HPLC conditions f): 1.84 min.

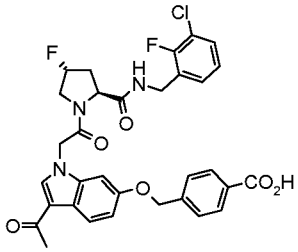
Example 601: 3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-7-carboxylic acid



To a solution of 3-acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-7-carboxylic acid methyl ester **Example 541** (110 mg, 0.209 mmol) in THF (3 mL) and water (0.3 mL) was added 2N LiOH (1.05 mL, 2.09 mmol). Stirring of the reaction mixture was continued at RT for 18 h. A 1N HCl solution was added to adjust to pH=2-3 and the resulting aqueous suspension was filtered. The solid was washed with water then dried in vacuo. The residue was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, flow: 40 mL/min, eluent: 20-100% CH_3CN/H_2O/20 min,

100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) to afford after lyophilization of the purified fractions the title compound as a white solid. MS (LC/MS): 512 [M+H]+; t_R (HPLC conditions k): 3.34 min.

Example 602: 4-(3-Acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indol-6-yloxymethyl)-benzoic acid

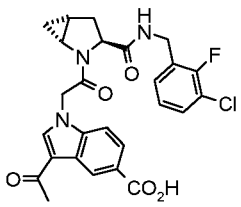


The title compound was prepared in a similar manner as described for **Example 595** from 4-(3-acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indol-6-yloxymethyl)-benzoic acid methyl ester (37.0 mg, 0.058 mmol) and 1N NaOH (0.928 mL, 0.928 mmol) in THF (5 mL) and water (0.5 mL). Solid. MS (LC/MS): 624/626 [M+H]+; t_R (HPLC conditions k): 3.48 min.

4-(3-Acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indol-6-yloxymethyl)-benzoic acid methyl ester

A solution of (2S,4R)-1-[2-(3-acetyl-6-hydroxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide **Example 583** (60.0 mg, 0.122 mmol) in DMSO (2.5 mL) was treated with cesium carbonate (160 mg, 0.490 mmol). After stirring at RT for 5 min, methyl 4-(bromomethyl)benzoate (28.0 mg, 0.122 mmol) was added and the reaction was stirred at RT for 1 h. The mixture was neutralised with 1N HCl and diluted with water to form a precipitate. The solid was filtered off, washed with water and dried in vacuo. The crude product was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, flow: 40 mL/min, eluent: 20-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) to afford after lyophilization the title compound as a white solid. MS (LC/MS): 639 [M+H]+; t_R (HPLC conditions k): 3.82 min.

Example 603: 3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-5-carboxylic acid

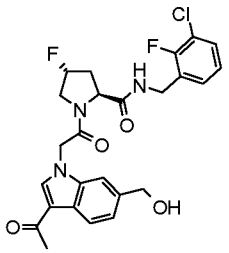


To a solution of 3-acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-5-carboxylic acid methyl ester (141 mg, 0.268 mmol) in THF (3 mL) and water (0.3 mL) was added 2N LiOH (1.07 mL, 2.14 mmol). Stirring of the reaction mixture was continued at 50°C for 60 h. After cooling to RT, a 1N HCl solution was added to adjust to pH= 2-3, and the resulting aqueous suspension was extracted with CH_2Cl_2 (3x). The combined organics were dried (phase separator) and concentrated under reduced pressure. The residue was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, flow: 40 mL/min, eluent: 20-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) to afford after lyophilization of the purified fractions the title compound as a white solid. MS (LC/MS): 512 [M+H]+; t_R (HPLC conditions c): 4.33 min.

3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-5-carboxylic acid methyl ester

The title compound was prepared as described in Scheme D7 from 3-acetyl-1-carboxymethyl-1H-indole-5-carboxylic acid methyl ester (prepared as described in Part A) and by using DMF instead of CH_2Cl_2. Solid. MS (LC/MS): 526 [M+H]+, 548 [M+Na]+; t_R (HPLC conditions k): 3.54 min.

Example 604: (2S,4R)-1-[2-(3-Acetyl-6-hydroxymethyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide

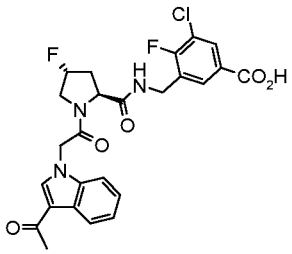


To a solution of (2S,4R)-1-[2-(3-acetyl-6-triisopropylsilanyloxymethyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide (50.0 mg, 0.057 mmol) in THF (5 mL), cooled to at 0°C, was added TBAF (1M in THF, 0.057 mL, 0.057 mmol), and stirring was continued for 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$ followed by addition of EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organics were washed with water (1x) and brine, dried (phase separator) and concentrated in vacuo. Purification by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, flow: 40 mL/min, eluent: 20% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) afforded after lyophilization of the purified fractions the title compound as a white solid. MS (LC/MS): 504 [M+H]+; t_R (HPLC conditions k): 3.10 min.

(2S,4R)-1-[2-(3-Acetyl-6-triisopropylsilanyloxymethyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide

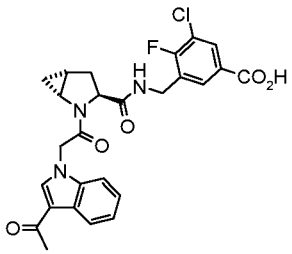
The title compound was prepared as described in Scheme D7 from (3-acetyl-5-triisopropylsilanyloxymethyl-indol-1-yl)-acetic acid (prepared as described in Scheme A14) and by using DMF instead of CH_2Cl_2. Yellow wax. MS (LC/MS): 683 [M+Na]+; t_R (HPLC conditions k): 4.72 min.

Example 605: 3-[({(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carbonyl}-amino)-methyl]-5-chloro-4-fluoro-benzoic acid



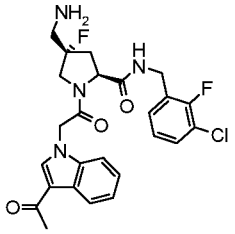
To 3-[({(2S,4R)-1-[2-(3-acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carbonyl}-amino)-methyl]-5-chloro-4-fluoro-benzoic acid methyl ester **Example 523** (35.0 mg, 0.066 mmol) in THF-MeOH-H_2O (ratio 2:1:1; 1 mL) was added LiOH.H_2O (2.76 mg, 0.066 mmol). The reaction mixture was stirred at RT for 4 h. Volatiles were evaporated and the residue was taken up in water, Acidification to pH=1 by addition of a 6M HCl solution formed a precipitate which was filtered and dried at 50°C in vacuo for 1 h to afford the title compound as a solid. MS: 518.0 [M+H]+; t_R (HPLC conditions c): 4.26 min.

Example 606: 3-[({(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carbonyl}-amino)-methyl]-5-chloro-4-fluoro-benzoic acid



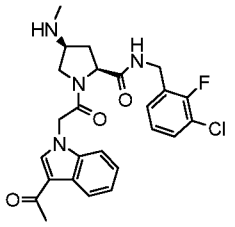
The title compound was prepared according to procedure described for the preparation of 3-[({(2S,4R)-1-[2-(3-acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carbonyl}-amino)-methyl]-5-chloro-4-fluoro-benzoic acid **Example 605** starting from 3-[({(1R,3S,5R)-2-[2-(3-acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carbonyl}-amino)-methyl]-5-chloro-4-fluoro-benzoic acid methyl ester **Example 480**. MS: 512.0 [M+H]+; t_R (HPLC conditions c): 4.41 min.

Example 607: (2S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-aminomethyl-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide



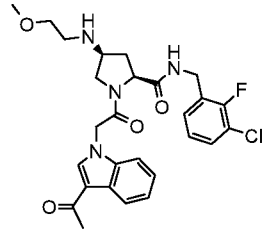
The title compound was prepared according to Scheme D7 from (2S,4R)-4-azidomethyl-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (described in scheme B15) using DMF as solvent in step C, followed by azide reduction as described for the preparation of **Example 411** (2S,4S)-4-aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2,6-difluoro-benzylamide). MS (UPLC-MS): 503 [M+H]+; t_R (HPLC conditions f): 1.60 min; 19F NMR (100 MHz, DMSO-d_6) δ (ppm): -117 , -150.

Example 608: (2S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-methylamino-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide



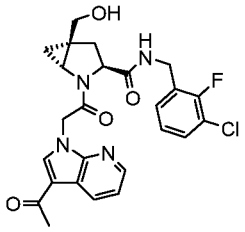
The title compound was prepared according to Scheme D7 from (2S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-[methyl-(2,2,2-trichloro-ethoxycarbonyl)-amino]-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared as described in Scheme B6) followed by the deprotection of the Troc protecting group as described for **Example 424**. Purification by preparative HPLC (Waters SunFire C18-ODB, 5 µm, 19x50 mm, 5% CH_3CN/H_2O 2.5 min, 5-100% CH_3CN/H_2O in 10 min, CH_3CN/H_2O containing 0.1 % HCOOH flow: 20 mL/min) gave after lyophilization of the purified fractions the title compound (formic acid salt). MS (UPLC-MS): 487 [M+H]+; t_R (HPLC conditions f): 1.60 min; 19F NMR (100 MHz, DMSO-d_6) δ (ppm): -120.

Example 609: (2S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-(2-methoxy-ethylamino)-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide



The title compound was prepared according to Scheme D7 from (2S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-[(2-methoxy-ethyl)-(2,2,2-trichloro-ethoxycarbonyl)-amino]-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared as described in Scheme B6 using 1-bromo-2-methoxyethane instead of methyl iodide in step B) followed by deprotection of the Troc protecting group as described for **Example 424**. Purification on preparative HPLC (Waters SunFire C18-ODB, 5 µm, 19x50 mm, 5% CH_3CN/H_2O 2.5 min, 5-100% CH_3CN/H_2O in 10 min, CH_3CN/H_2O containing 0.1 % HCOOH flow: 20 mL/min) gave after lyophilization of the purified fractions the title compound (formic acid salt). MS (UPLC/MS): 531 [M+H]+; t_R (HPLC conditions f): 1.66 min; 19F NMR (100 MHz, DMSO-d_6) δ (ppm): -120.

Example 610: (1R,3S,5S)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-5-hydroxy methyl-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide



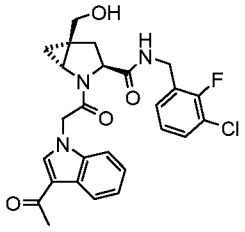
A solution of (3-acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetic acid (1R,3S,5S)-2-[2-(3-acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0] hex-5-ylmethyl ester (90 mg, 0.115 mmol) and NaOH 1 N (0.58 mL, 0.58 mmol) in THF (0.55 mL) / water (55 µL) was stirred at RT for 1 h. Water and CH_2Cl_2 were added, the layers were separated and the aqueous one back-extracted with CH_2Cl_2 (x3). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude material was purified by preparative HPLC (Waters Sunfire C18-ODB, 5 µm, 30x100 mm, eluent: 5% to 100% CH_3CN in H_2O in 25 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 mL/min). EtOAc and saturated aqueous $NaHCO_3$ were added to the combined purified fractions, the layers were separated and the aqueous one back-extracted with EtOAc (x3). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to give the desired material. TLC, R_f (CH_2Cl_2/ MeOH 9-1) = 0.45; MS (UPLC/MS): 499.3/501.3 [M+H]+, 521.1/523.2 [M+Na]+; t_R (HPLC conditions f): 1.73 min.

(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetic acid (1R,3S,5S)-2-[2-(3-acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0] hex-5-ylmethyl ester

The title compound N,O bis-acylated was prepared according to Scheme D7 Steps B and C from (1R,3S,5S)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester (prepared as described in Part B

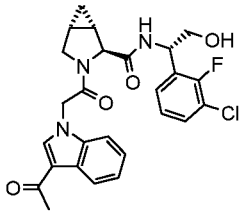
Scheme B28) using HCl 4N in dioxane instead of TFA in Step B and 2 equivalents of (3-acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetic acid (described in Part A) in Step C. Purification by flash column chromatography on silica gel (CH_2Cl_2 to CH_2Cl_2/MeOH 94-6). TLC, R_f (CH_2Cl_2/ MeOH 9-1) = 0.48; MS (UPLC/MS): 699.4/701.3 [M+H]+, 743.4/745.4 [M+HCOO]-; t_R (HPLC conditions f): 2.05 min.

Example 611: (1R,3S,5S)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide



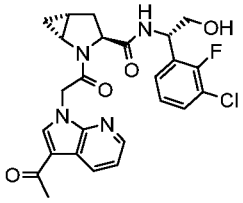
The title compound was prepared in 2 steps according to the procedure described for the preparation of **Example 610** (1R,3S,5S)-2-[2-(3-acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide using (3-acetyl-indol-1-yl)-acetic acid instead of (3-acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetic acid. White powder. TLC, R_f (EtOAc) = 0.05; MS (LC/MS): 498/500 [M+H]+, 520/522 [M+Na]+; t_R (HPLC conditions f): 1.84 min.

Example 612: (1S,2S,5R)-3-[2-(3-Acetyl-indol-1-yl)-acetyl]-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2hydroxy-ethyl]-amide



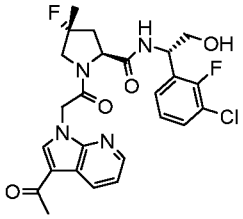
The title compound was prepared in 2 steps according to the procedure described for the preparation of **Example 610** (1R,3S,5S)-2-[2-(3-acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide from (1S,2S,5R)-2-[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethylcarbamoyl]-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester (prepared using similar protocols as described in Scheme B9) and (3-acetyl-indol-1-yl)-acetic acid. White powder. TLC, R_f (EtOAc) = 0.10; MS (UPLC/MS): 498.3/500.4 [M+H]+, 542.4/544.3 [M+HCOO]-; t_R (HPLC conditions a): 3.10 min.

Example 613: (1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo [3.1.0]hexane-3-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide



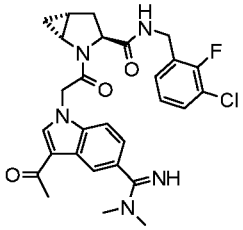
The title compound was prepared in 2 steps according to the procedure described for the preparation of **Example 610** (1R,3S,5S)-2-[2-(3-acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide from (1R,3S,5R)-3-[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethylcarbamoyl]-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester (prepared as described in Scheme B9). White powder. TLC, R_f (CH_2/Cl_2/EtOAc 9:1) = 0.70; MS (UPLC/MS): 499.3/501.3 [M+H]+, 543.2/545.3 [M+HCOO]-; t_R (HPLC conditions a): 3.02 min.

Example 614: (2S,4R)-1-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide



The title compound was prepared in 2 steps according to the procedure described for the preparation of **Example 610** (1R,3S,5S)-2-[2-(3-acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide from (2S,4R)-2-[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethylcarbamoyl]-4-fluoro-4-methyl-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared using similar protocols as described in Scheme B9). White powder. TLC, R_f (CH_2/Cl_2/EtOAc 9:1) = 0.60; MS (UPLC/MS): 519.3/521.3 [M+H]+, 563.3/565.3 [M+HCOO]-; t_R (HPLC conditions a): 2.96 min.

Example 615: (1R,3S,5R)-2-{2-[3-Acetyl-5-(N,N-dimethyl-carbamimidoyl)-indol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide



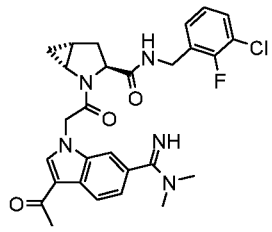
HCl (gaz) was slowly bubbled for 3 h in a suspension of (1R,3S,5R)-2-[2-(3-acetyl-5-cyano-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide (50 mg, 0.1 mmol) in MeOH (3 mL) cooled at 0°C. The reaction mixture was allowed to reach

RT and further stirred for 1 h. After completion argon was bubbled to remove the excess of HCl and the reaction mixture was concentrated. Crude 3-acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-5-carboximidic acid methyl ester (MS (UPLC/MS): 525.3/527.3 [M+H]+) was diluted in MeOH (2 mL), dimethylamine (2 M in MeOH, 0.26 mL, 0.524 mmol) was added and the mixture refluxed overnight. The reaction mixture was concentrated and the crude material was purified by preparative HPLC (Waters Sunfire C18-ODB, 5 µm, 30x100 mm, 5-95% CH_3CN /H_2O, CH_3CN and H_2O containing 0.1% TFA flow: 40 ml/min) to give after lyophilization of the purified fractions the desired material as a TFA salt. TLC, R_f (CH_2Cl_2/MeOH 9:1): 0.65; MS (UPLC/MS): 539.3/541.3 [M+H]+, 583.3/585.4 [M+HCOO]-; t_R (HPLC conditions a): 3.05 min.

(1R,3S,5R)-2-[2-(3-Acetyl-5-cyano-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide

The title compound was prepared according to Scheme D7 from (3-acetyl-5-cyano-indol-1-yl)-acetic acid (prepared as described in Part C). TLC, R_f (CH_2Cl_2/ MeOH 9-1) = 0.40; MS (UPLC/MS): 493.3/495.3 [M+H]+, 537.3/539.3 [M+HCOO]-; t_R (HPLC conditions a): 3.42 min.

Example 616: (1R,3S,5R)-2-{2-[3-Acetyl-6-(N,N-dimethyl-carbamimidoyl)-indol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide

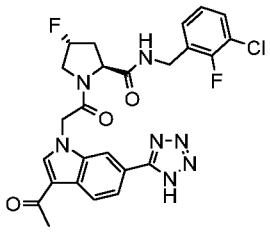


The title compound was prepared in a similar manner as described above for **Example 615** from (3-acetyl-6-cyano-indol-1-yl)-acetic acid (prepared as described in Part C). TLC, R_f (CH_2Cl_2/MeOH 9:1): 0.65; MS (UPLC/MS): 539.3/541.3 [M+H]+ 583.3/585.3 [M+HCOO]-; t_R (HPLC conditions a): 3.13 min.

(2S,4R)-1-[2-(3-acetyl-6-cyano-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide

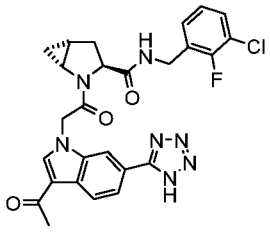
The title compound was prepared according to Scheme D7 from (3-acetyl-6-cyano-indol-1-yl)-acetic acid (prepared as described in Part C). Powder. TLC, R_f (CH_2Cl_2/ MeOH 9-1) = 0.40; MS (UPLC/MS): 493.3/495.3 [M+H]+, 537.3/539.3 [M+HCOO]-; t_R (HPLC conditions a): 3.46 min.

Example 617: (2S,4R)-1-{2-[3-Acetyl-6-(1H-tetrazol-5-yl)-indol-1-yl]-acetyl}-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide



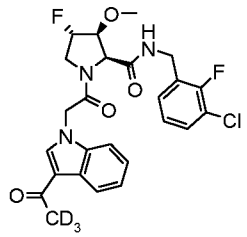
To a suspension of (2S,4R)-1-[2-(3-acetyl-6-cyano-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide (prepared as described in **Example 616** (45.0 mg, 0.09 mmol) in water (2 mL) and isopropanol (1 mL) at RT were added sodium azide (24.0 mg, 0.360 mmol) and zinc bromide (40.0 mg, 0.180 mmol). The mixture was heated to 130°C for 10 h in a microwave apparatus (Personnal Chemistry, Biotage). After cooling to RT, a 6N HCl solution was added to the mixture, followed by extraction with EtOAc (3x). The combined organics were washed with brine, dried (phase separator) and concentrated in vacuo. Purifcation of the residue by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, eluent: 20-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 mL/min) afforded after lyophilization the title compound as solid. MS (LC/MS): 542.0 [M+H]+; t_R (HPLC conditions k): 3.15 min.

Example 618: (1R,3S,5R)-2-{2-[3-Acetyl-6-(1H-tetrazol-5-yl)-indol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide



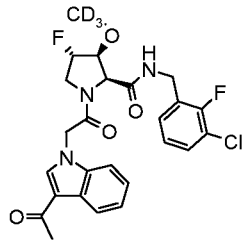
The title compound was prepared in a similar manner as described above for **Example 617** from (1R,3S,5R)-2-[2-(3-acetyl-6-cyano-indol-1-yl)-acetyl]-2-aza-bicyclo [3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide (prepared as described in **Example 616** (100.0 mg, 0.203 mmol), sodium azide (66.0 mg, 1.014 mmol) and zinc bromide (228.0 mg, 1.014 mmol) in water (2 mL) and isopropanol (1 mL). White solid. MS (LC/MS): 536.0 [M+H]+; t_R (HPLC conditions k): 3.21 min.

Example 619: (2S,3S,4S)-1-[2-(3-Acetyl-*d3*-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide



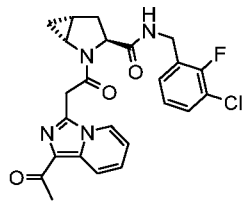
The title compound was prepared according to Scheme D7 from (2S,3S,4S)-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide (prepared as described in Scheme B24) and (3-acetyl-*d3*-indol-1-yl)-acetic acid (prepared in a similar manner as described in Scheme A13 using acetyl-*d3*-chloride in step A) using DMF as solvent in step C. MS (UPLC-MS): 507/509 [M+H]+, 551/553 [M+HCOO]-; t_R (HPLC conditions f): 2.01 min.

Example 620: (2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-*d3*-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide



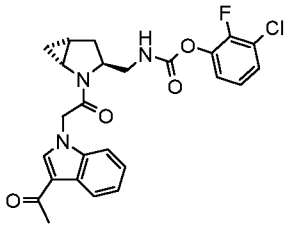
The title compound was prepared according to Scheme D7 from (2S,3S,4S)-4-fluoro-3-methoxy-*d3*-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide (prepared as described in Scheme B24 using methyl-*d3*-iodide instead of methyl iodide in Step B). MS (UPLC-MS): 507/509 [M+H]+, 551/553 [M+HCOO]-; t_R (HPLC conditions f): 2.01 min.

Example 621: (1R,3S,5R)-2-[2-(1-Acetyl-imidazo[1,5-a]pyridin-3-yl)-acetyl]-2-aza-bicyclo [3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide



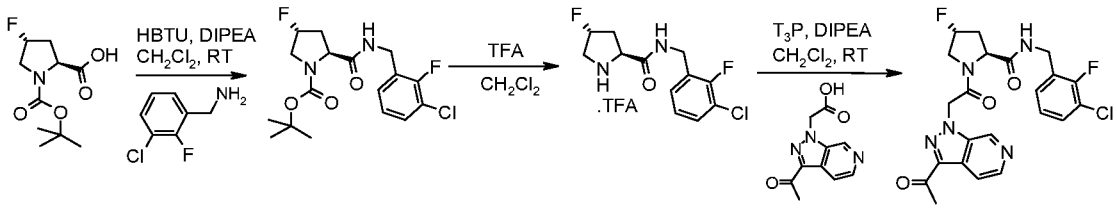
The title compound was prepared according to Scheme D7 using in Step C (1-acetyl-imidazo[1,5-a]pyridin-3-yl)-acetic acid (prepared as described in Scheme A19) and DMF as solvent. MS (UPLC-MS): 469.3/471.4 [M+H]+, 513.4/515.5 [M+HCOO]-; t_R (HPLC conditions a): 3,08 min.

Example 622: {(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hex-3-ylmethyl}-carbamic acid 3-chloro-2-fluoro-phenyl ester



To a solution of [(1R,3S,5R)-1-(2-aza-bicyclo[3.1.0] hex-3-yl)methyl]-carbamic acid 3-chloro-2-fluoro-phenyl ester, trifluoroacetate (prepared as described in **Example 115**) (60.0 mg, 0.211 mmol) in THF (3 mL) was added HBTU (120 mg, 0.316 mmol), DIPEA (0.147 mL, 0.843 mmol) and (3-acetyl-indol-1-yl)-acetic acid (50 mg, 0.232 mmol). The reaction mixture was stirred at RT for 60 h. Volatiles were removed under reduced pressure and the residue was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, eluent: 20-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 mL/min) to give after lyophilization of the purified HPLC fractions the title compound. MS (LC/MS): 484.0 [M+H]+; t_R (HPLC conditions k): 3.69 min.

Scheme D8: preparation of Example 623: (2S,4R)-1-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide formate



A. (2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (2S,4R)-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (3.97 g, 17.02 mmol) in CH_2Cl_2 (34 mL) were successively added 3-chloro-2-fluoro-benzylamine (2.35 mL, 18.72 mmol), HBTU (9.68 g, 25.5 mmol) and DIPEA (8.92 mL, 51.1 mmol). The reaction mixture was stirred at RT for 16 h. Water was added and the phases were separated. The organic layer was washed successively with 0.1N HCl (2x), sat. aq. $NaHCO_3$ (2x) and brine, then dried (phase separator) and concentrated in vacuo. The residual oil was purified via flash column chromatography on silica gel (c-hexane/ EtOAc 9-1 to 1-1). MS (LC/MS): 397 [M+Na]+, 319 [MH-tBu]+; 275 [MH-Boc]+; t_R (HPLC conditions k): 3.52 min.

DMF can also be used instead of Dichloromethane.

B. (2S,4R)-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide trifluoroacetate

To a solution of (2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester (7.94 g, 21.18 mmol) in CH_2Cl_2 (70.5mL) was added TFA (16.32 mL, 212 mmol) and the solution was stirred at RT for 16 h. The crude reaction mixture was concentrated under vacuum and the material this obtained was used without further purification in the next step. MS (LC/MS): 274.9 [M+H]+; t_R (HPLC conditions b): 2.13 min.

C. Example 623: (2S,4R)-1-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide formate

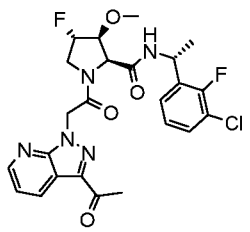
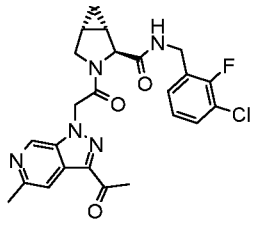
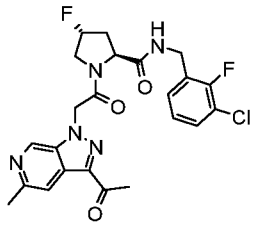
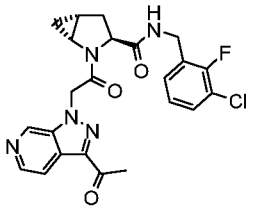
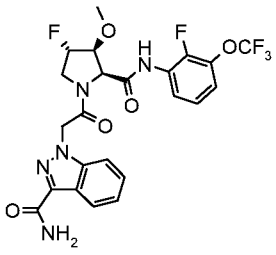
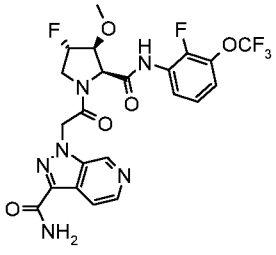
To a solution of (2S,4R)-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide trifluoroacetate (50 mg, 0.13 mmol), propylphosphonic anhydride (50% in EtOAc, 0.057 ml, 0.19 mmol) and (3-acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid trifluoroacetate (prepared as described in Scheme A20, 42.9 mg, 0.13 mmol) in CH_2Cl_2 (5 mL) was added DIPEA (0.067 ml, 0.386 mmol) under nitrogen atmosphere. The reaction mixture was stirred 2 h at RT and quenched by addition of a saturated aqueous solution of $NaHCO_3$. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (x2), the combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by preparative HPLC (Waters Sunfire (C18 ODB, 5µm, 19x50, flow = 20mL/min, 5% CH_3CN in water for 2.5 min, 5 to 100% CH_3CN in water in 10 min to 100% CH_3CN for 2.5 min, both CH_3CN and water containing 0.1% HCOOH) and the pure HPLC fractions were concentrated and lyophilized. MS (LC/MS): 476/478 [M+H]+, t_R (HPLC conditions f): 1.51 min.

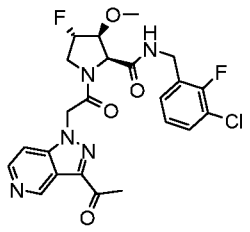
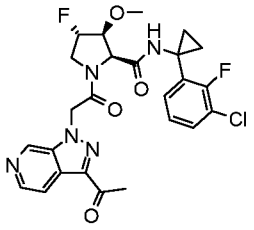
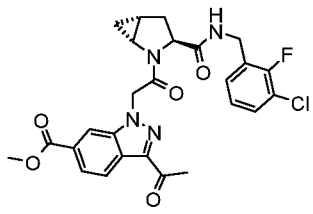
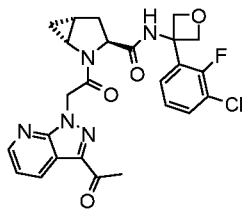
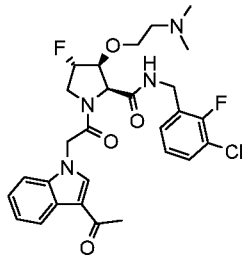
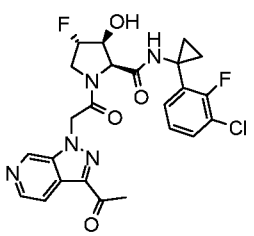
Alternatively, the pure HPLC fractions were neutralized with an aqueous saturated solution of Na_2CO_3, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated to give the desired material as a free base.

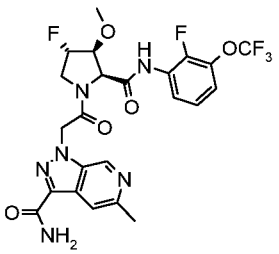
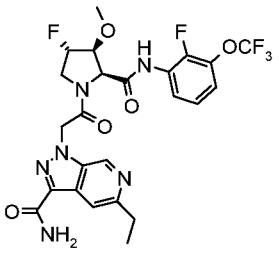
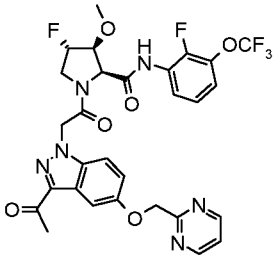
The examples below were prepared according to the general procedures described in Scheme D8 for the preparation of **Example 623** *from commercially available building blocks if not otherwise mentioned (see notes at the end of table 7):*

Table 7:

Example	Structure	Name	Characterization (end–table notes), TLC, R_f (eluent); MS (LC/MS); t_R (HPLC conditions)

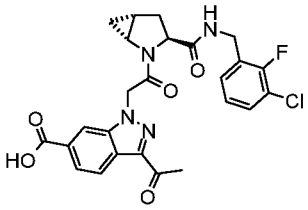
624		(2S,3S,4S)-1-[2-(3-Acetyl-pyrazolo[3,4-b]pyridin-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid [(R)-1-(3-chloro-2-fluoro-phenyl)-ethyl]-amide	(1,2) 520 [M+H]+, 564 [M+HCOO]-; t_R (f): 2.04 min.
625		(1S,2S,5R)-3-[2-(3-Acetyl-5-methyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-3-aza-bicyclo [3.1.0]hexane-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(2) 484 [M+H]+, 528 [M+HCOO]-; t_R (f): 1.59 min.
626		(2S,4R)-1-[2-(3-Acetyl-5-methyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(2) 490 [M+H]+, 534 [M+HCOO]-; t_R (f): 1.54 min.
627		(1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo [3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide	(2) 470/472 [M+H]+; t_R (f): 1.58 min.
628		1-{2-[(2S,3S,4S)-4-Fluoro-2-(2-fluoro-3-trifluoromethoxy-phenylcarbamoyl)-3-methoxy-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide	(1,2) 542.3 [M+H]+, 559.3 [M+NH_4]+, 440.3 [M-H]-; t_R (f): 1.97 min
629		1-{2-[(2S,3S,4S)-4-Fluoro-2-(2-fluoro-3-trifluoromethoxy-phenylcarbamoyl)-3-methoxy-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide trifluoroacetate	(1,2) 543.2 [M+H]+, 541.2 [M-H]-; t_R (f): 1.52 min

630		(2S,3S,4S)-1-[2-(3-Acetyl-pyrazolo[4,3-c]pyridin-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(1,2) 506.2/508.2 [M+H]+, 504.2 [M-H]-, 550.2/552.2 [M+HCOO]-; t_R (f): 1.49 min.
631		(2S,3S,4S)-1-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid [1-(3-chloro-2-fluoro-phenyl)-cyclopropyl]-amide	(1,2) 532.4/534.5 [M+H]+, 576.6/578.5 [M+HCOO]-; t_R (f): 1.64 min.
632		3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzyl carbamoyl)-2-aza-bicyclo [3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-6-carboxylic acid methyl ester	(2) 544.1/546.1 $[M+NH_4]$+, 571.2/573.2 [M+HCOO]-; t_R (m): 1.08 min.
633		(1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo [3.1.0]hexane-3-carboxylic acid [3-(3-chloro-2-fluoro-phenyl)-oxetan-3-yl]-amide	(1,2) 512.1/514.1 [M+H]+, 534.1/536.1 [M+Na]+; t_R (f): 1.89 min.
634		(2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-3-(2-dimethylamino-ethoxy)-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide formate	(1) 561.4/563.4 [M+H]+, 605.5/607.5 [M+HCOO]-; t_R (f): 1.62 min.
635		(2S,3S,4S)-1-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-4-fluoro-3-hydroxy-pyrrolidine-2-carboxylic acid [1-(3-chloro-2-fluoro-phenyl)-cyclopropyl]-amide formate	(1,2) 518.4/520.4 [M+H]+, 562.5 [M+HCOO]-; t_R (f): 1.51 min.

636		1-{2-[(2S,3S,4S)-4-Fluoro-2-(2-fluoro-3-trifluoromethoxy-phenylcarbamoyl)-3-methoxy-pyrrolidin-1-yl]-2-oxo-ethyl}-5-methyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide triflate	(1,2) 557.2 [M+H]+, 555.2 [M-H]-; t_R (f): 1.50 min
637		5-Ethyl-1-{2-[(2S,3S,4S)-4-fluoro-2-(2-fluoro-3-trifluoro methoxy-phenyl carbamoyl)-3-methoxy-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-pyrazolo[3,4-c] pyridine-3-carboxylic acid amide triflate	(1,2) 571.3 [M+H]+, 569.3 [M-H]-; t_R (f): 1.55 min
638		(2S,3S,4S)-1-{2-[3-Acetyl-5-(pyrimidin-2-ylmethoxy)-indazol-1-yl]-acetyl}-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid (2-fluoro-3-trifluoromethoxy-phenyl)-amide	(1,2) 649.3 [M+H]+, 647.3 [M-H]-; t_R (f): 1.99 min

(1) The title compound was prepared according to the general procedure described in Scheme D8 steps B and C starting from the substituted proline derivative prepared as described in Part B; (2) The acid reagent used in step C was prepared as described in Part A.

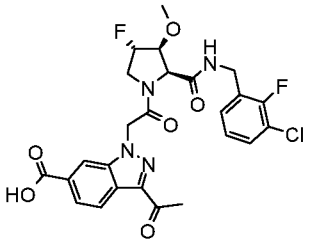
Example 639: 3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-6-carboxylic acid



A solution of **Example 632** (65 mg, 0.123 mmol) in MeOH (5 mL) and sodium hydroxide (d= 1 g/mL, 0.247 mL, 0.617 mmol) was stirred for 16 h at RT. The reaction was quenched by addition of HCl (1N, until pH = 1) and concentrated under reduced pressure. The aqueous residue was extracted with CH_2Cl_2 (x3) and concentrated. The crude material was purified by preparative HPLC (Waters Sunfire C18-ODB, 5 µm, 30x100 mm, eluent: 5% to 100% CH_3CN

in H_2O in 25 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 mL/min). MS (LC/MS): 530.2/532.2 [M+H]+; 511.1/513.1 [M-H]-, 557.2/559.2 [M+HCOO]-; t_R (UPLC conditions m): 0.91 min.

Example 640: 3-Acetyl-1-{2-[(2S,3S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-3-methoxy-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indazole-6-carboxylic acid

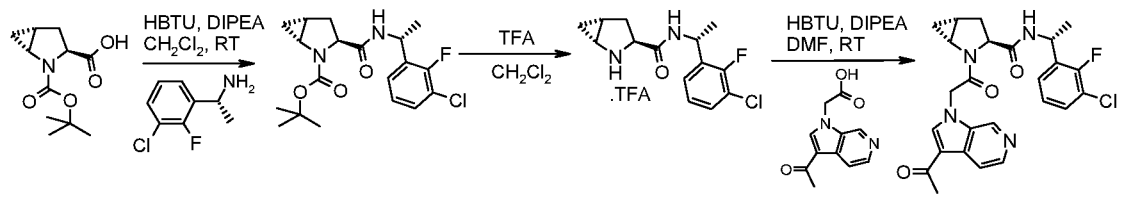


3-Acetyl-1-{2-[(2S,3S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-3-methoxy-pyrroli din-1-yl]-2-oxo-ethyl}-1H-indazole-6-carboxylic acid benzyl ester (47 mg, 0.063 mmol) was dissolved in MeOH (5 mL), Pd/C (10%, 5 mg) was added and the solution was degassed 3 times replacing air by nitrogen and finally nitrogen by hydrogen. The reaction mixture was further stirred under hydrogen atmosphere for 1 h. The catalyst was removed through a pad of Celite and washed with MeOH. The solvent was concentrated under reduced pressure and the crude residue was purified by preparative HPLC (Waters Sunfire C18-ODB, 5 µm, 30x100 mm, eluent: 5% to 100% CH_3CN in H_2O in 25 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 mL/min). MS (LC/MS): 549.5 [M+H]+; 547.5 [M-H]-; t_R (HPLC conditions f): 1.93 min.

3-Acetyl-1-{2-[(2S,3S,4S)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-3-methoxy-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indazole-6-carboxylic acid benzyl ester

was prepared using similar protocols as described in Scheme D8 Step C for the preparation of **Example 623** from 3-acetyl-1-carboxymethyl-1H-indazole-6-carboxylic acid benzyl ester (prepared as described in Part A) and (2S,3S,4S)-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide trifluoroacetate (prepared as described in Scheme B24). White solid. MS (UPLC/MS): 683.6/685.7 [M+HCOO]-; t_R (HPLC conditions f): 2.43 min.

Scheme D9: preparation of Example 641: (1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(R)-1-(3-chloro-2-fluoro-phenyl)-ethyl]-amide



A. (1R,3S,5R)-3-[(R)-1-(3-Chloro-2-fluoro-phenyl)-ethylcarbamoyl]-2-aza-bicyclo [3.1.0]hexane-2-carboxylic acid tert-butyl ester

To a solution of (R)-1-(3-chloro-2-fluoro-phenyl)-ethylamine (1.85 g, 8.80 mmol) in CH_2Cl_2 (44 mL) were successively added (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester (2 g, 8.80 mmol), DIPEA (4.61 mL, 26.4 mmol) and HBTU (4.01 g, 10.56 mmol). The reaction mixture was stirred at RT for 16 h. Water was added and the phases were separated. The organic layer was washed successively with 1N HCl (2x), sat. aq. $NaHCO_3$ (2x) and brine, then dried (phase separator) and concentrated in vacuo. The residual oil was purified via flash column chromatography on silica gel (c-hexane/ EtOAc 9-1 to 9-4). MS (LC/MS): 405 [M+Na]+, 283 [MH-Boc]+; t_R (HPLC conditions c): 4.93 min.

DMF can also be used instead of Dichloromethane.

B. (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(R)-1-(3-chloro-2-fluoro-phenyl)-ethyl]-amide trifluoroacetate

To a solution of (1R,3S,5R)-3-[(R)-1-(3-chloro-2-fluoro-phenyl)-ethylcarbamoyl]-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester (3.2 g, 8.36 mmol) in CH_2Cl_2 (30 mL) was added TFA (15 mL, 195 mmol) and the solution was stirred at RT for 1 h. The crude reaction mixture was concentrated under vacuum, the residue was suspended in MeOH and concentrated again under vacuum. The crude product was used without further purification in the next step. MS (LC/MS): 283.0 [M+H]+; t_R (HPLC conditions c): 3.41 min.

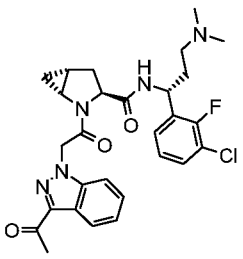
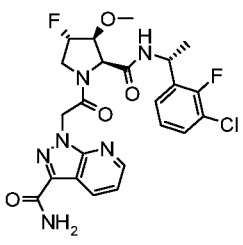
C. Example 641: (1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(R)-1-(3-chloro-2-fluoro-phenyl)-ethyl]-amide

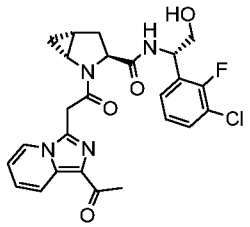
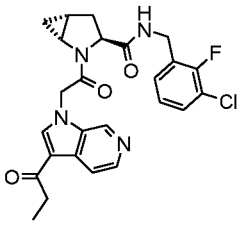
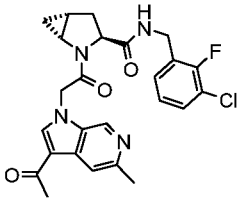
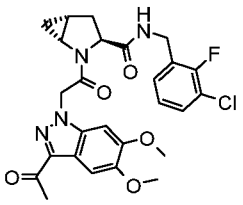
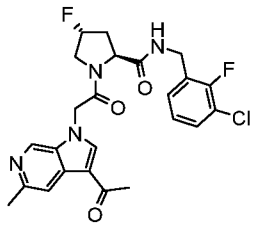
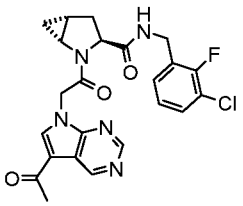
To a solution of (3-acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetic acid trifluoroacetate (prepared as described Scheme [A15], 52 mg, 0.157 mmol) in DMF (1.5 mL) were added successively (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(R)-1-(3-chloro-2-fluoro-phenyl)-ethyl]-amide trifluoroacetate (62.3 mg, 1.57 mmol), HBTU (89 mg, 0.235 mmol) and DIPEA (107 µL, 0.626 mmol). The reaction mixture was stirred at RT for 16 h and poured into water. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (x2). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The residual oil was purified by preparative HPLC (Waters Sunfire C18-ODB, 5 µm, 30x100 mm, eluent: 5% to 100% CH_3CN in H_2O in 25 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 mL/min). The pure fractions were combined, neutralized by filtration through a Varian VariPure HCO_3-MP cartridge and lyophilized to give the desired material as a white powder. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.42; MS (LC/MS): 483.4/485.3 [M+H]+, 527.4/529.4 [M+HCOO]-; t_R (HPLC conditions a): 2.74 min.

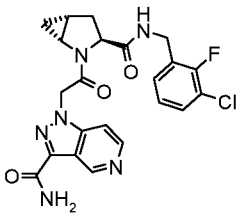
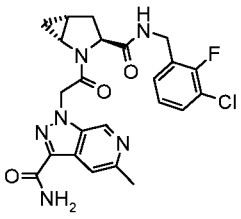
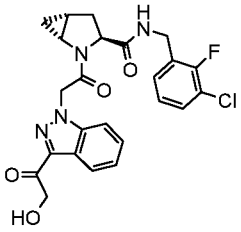
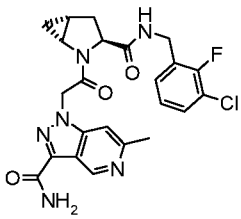
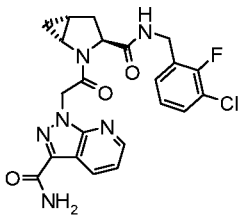
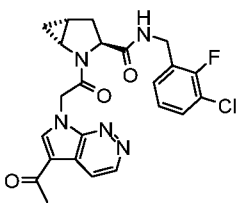
Alternatively, the pure HPLC fractions were neutralized with an aqueous saturated solution of Na_2CO_3, extracted with EtOAc (x2), dried (Na_2SO_4), filtered and concentrated to give the desired material.
Alternatively, the crude residue was purified by preparative HPLC (Waters Sunfire (C18 ODB, 5µm, 19x50, flow = 20mL/min, 5% CH_3CN in H_2O for 2.5 min, 5 to 100% CH_3CN in H_2O in 10 min to 100% CH_3CN for 2.5 min, CH_3CN and H_2O both containing 0.1% HCOOH) and the pure HPLC fractions were concentrated and lyophilized to give the desired compound as a formate salt.

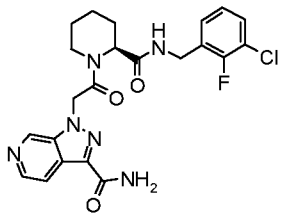
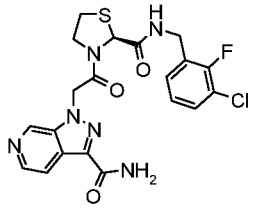
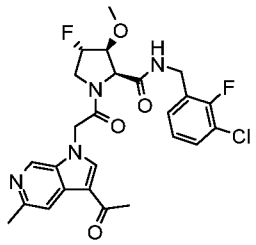
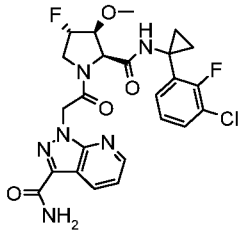
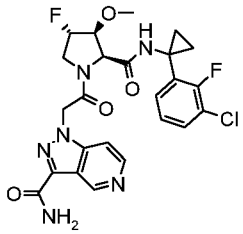
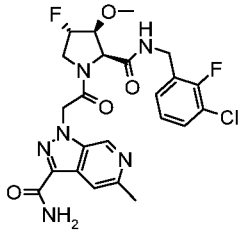
The examples below were prepared according to the general procedures described in Scheme D9 for the preparation of **Example 641** *from commercially available building blocks if not otherwise mentioned (see notes at the end of table 8):*

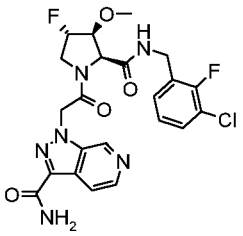
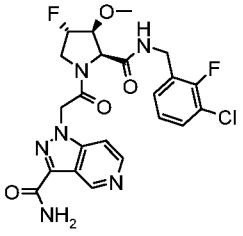
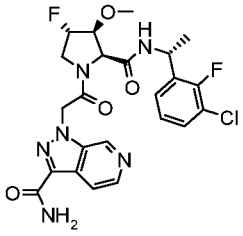
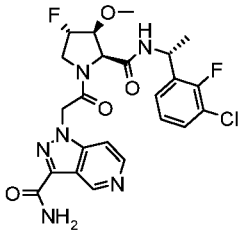
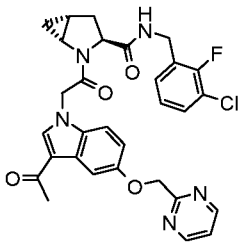
Table 8:

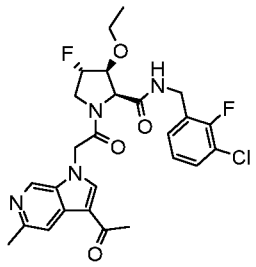
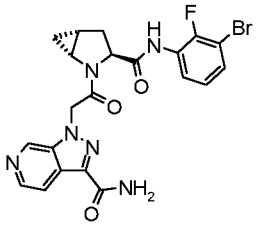
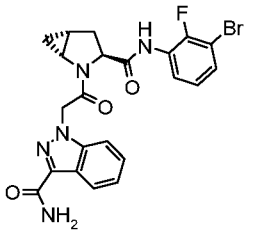
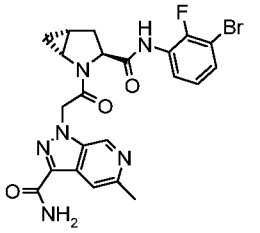
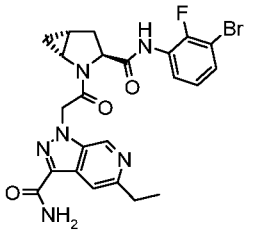
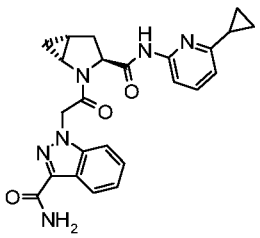
Example	Structure	Name	Characterization (end–table notes), TLC, R_f (eluent); MS (LC/MS); t_R (HPLC conditions)
642		(1R,3S,5R)-2-[2-(3-Acetyl-indazol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(R)-1-(3-chloro-2-fluoro-phenyl)-3-dimethylamino-propyl]-amide	(1,2,4) White solid. R_f (CH_2Cl_2/MeOH 9:1) = 0.55; 540.5/542.5 [M+H]+, 584.5/586.5 [M+HCOO]-; t_R (a): 2.93 min.
643		1-(2-{(2S,3S,4S)-2-[(R)-1-(3-Chloro-2-fluoro-phenyl)-ethylcarbamoyl]-4-fluoro-3-methoxy-pyrrolidin-1-yl}-2-oxo-ethyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxylic acid amide	(3,4) 521 [M+H]+, 543 [M+Na]+; t_R (k): 3.10 min.

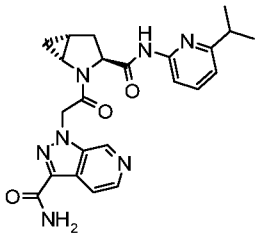
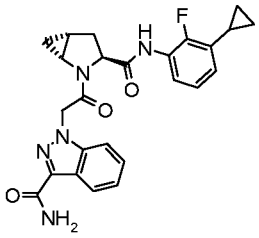
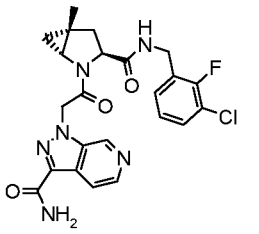
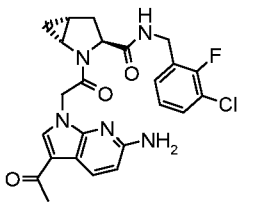
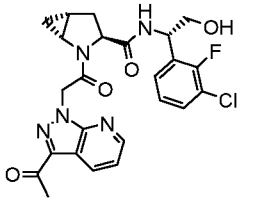
644		(1R,3S,5R)-2-[2-(1-Acetyl-imidazo[1,5-a]pyridin-3-yl)-acetyl]-2-aza-bicyclo [3.1.0]hexane-3-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide	(2,3,4) Rf (CH_2Cl_2/MeOH 9:1) = 0.75; 499.1/501.1 [M+H]+, 543.2/544.3 [M+HCOO]-; t_R (a): 2.74 min.
645		(1R,3S,5R)-2-[2-(3-Propionyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo [3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4) White solid. 483.4/485.4 [M+H]+, 527.3/529.4 [M+HCOO]-; t_R (f): 1.56 min.
646		(1R,3S,5R)-2-[2-(3-Acetyl-5-methyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo [3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4) White solid. R_f (CH_2Cl_2/MeOH 9:1) = 0.4; 483.4/485.4 [M+H]+, 527.5/529.4 [M+HCOO]-; t_R (f): 1.52 min.
647		(1R,3S,5R)-2-[2-(3-Acetyl-5,6-dimethoxy-indazol-1-yl)-acetyl]-2-aza-bicyclo [3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4) 529 [M+H]+; t_R (k): 3.46 min.
648		(2S,4R)-1-[2-(3-Acetyl-5-methyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-4-fluoro - pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4,5) White solid. 587.1 [M-H]-; t_R (c): 3.71 min.
649		(1R,3S,5R)-2-[2-(5-Acetyl-pyrrolo[2,3-d]pyrimidin-7-yl)-acetyl]-2-aza-bicyclo [3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4) White solid. R_f (CH_2Cl_2/MeOH 9:1) = 0.4; 470.4/472.4 [M+H]+, 514.4/516.5 [M+HCOO]-; t_R (f): 1.54 min.

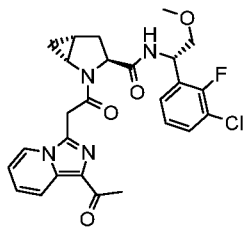
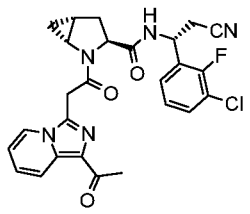
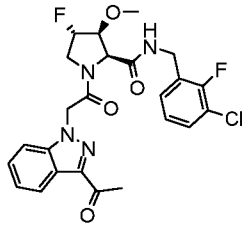
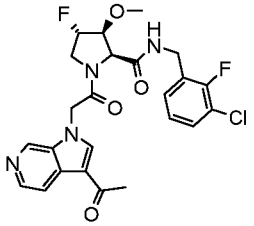
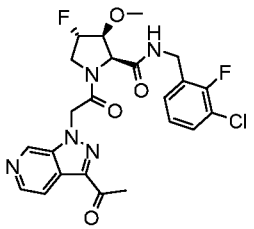
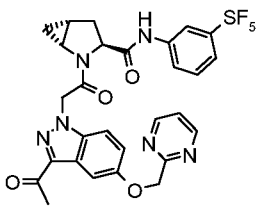
650		1-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrazolo[4,3-c]pyridine-3-carboxylic acid amide	(4) 471 [M+H]+; t_R (k): 2.69 min.
651		1-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-methyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(4) 485 [M+H]+; t_R (k): 2.71 min.
652		(1R,3S,5R)-2-{2-[3-(2-Hydroxy-acetyl)-indazol-1-yl]-acetyl}-2-aza-bicyclo [3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4) 485 [M+H]+, 507 [M+Na]+; t_R (k): 3.24 min.
653		1-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-6-methyl-1H-pyrazolo[4,3-c]pyridine-3-carboxylic acid amide	(4) 485 [M+H]+; t_R (k): 2.73 min.
654		1-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrazolo[3,4-b]pyridine-3-carboxylic acid amide	(4) 471 [M+H]+; t_R (k): 2.99 min.
655		(1R,3S,5R)-2-[2-(5-Acetyl-pyrrolo[2,3-c]pyridazin-7-yl)-acetyl]-2-aza-bicyclo [3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4) R_f (CH_2Cl_2/MeOH 9:1) = 0.4; 470.1/472.2 [M+H]+, 514.2/516.2 [M+HCOO]-; t_R (f): 1.51 min.

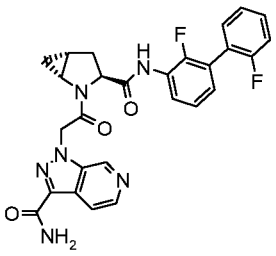
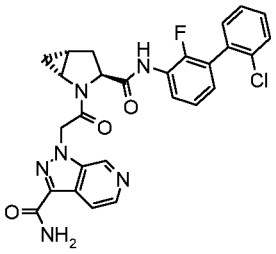
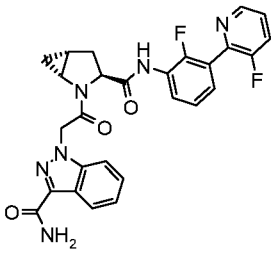
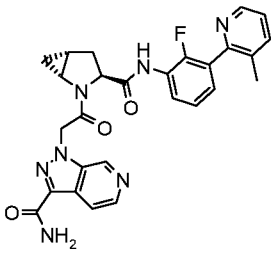
656		1-{2-[(S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-piperidin-1-yl]-2-oxo-ethyl}-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(4) White solid. 473.0 [M+H]+, 495.0 [M+Na]+; t_R (c): 3.63 min.
657		1-{2-[(S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-thiazolidin-3-yl]-2-oxo-ethyl}-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(4) White solid. 477.0 [M+H]+, 498.9 [M+Na]+; t_R (c): 3.50 min.
658		(2S,3S,4S)-1-[2-(3-Acetyl-5-methyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide formate	(3,4) 519/521 [M+H]+; t_R (f): 1.51 min.
659		1-(2-{(2S,3S,4S)-2-[1-(3-Chloro-2-fluoro-phenyl)-cyclopropyl carbamoyl]-4-fluoro-3-methoxy-pyrrolidin-1-yl}-2-oxo-ethyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxylic acid amide	(3,4) 533 [M+H]+; t_R (k): 3.16 min.
660		1-(2-{(2S,3S,4S)-2-[1-(3-Chloro-2-fluoro-phenyl)-cyclopropyl carbamoyl]-4-fluoro-3-methoxy-pyrrolidin-1-yl}-2-oxo-ethyl)-1H-pyrazolo[4,3-c]pyridine-3-carboxylic acid amide	(3,4) 533 [M+H]+; t_R (k): 2.84 min.
661		1-{2-[(2S,3S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-3-methoxy-pyrrolidin-1-yl]-2-oxo-ethyl}-5-methyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(3,4) 521 [M+H]+; t_R (k): 2.73 min.

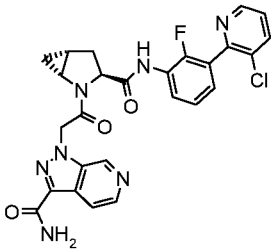
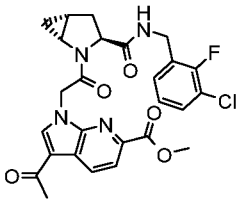
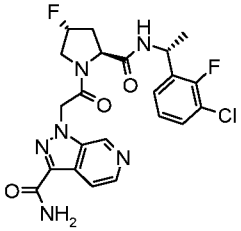
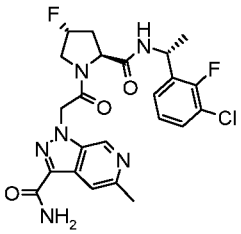
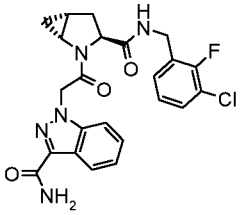
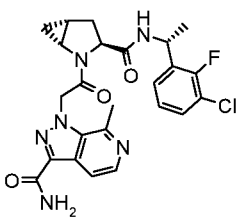
662		1-{2-[(2S,3S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-3-methoxy-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(3,4) 507 [M+H]+; t_R (k): 2.71 min.
663		1-{2-[(2S,3S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-3-methoxy-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-pyrazolo[4,3-c]pyridine-3-carboxylic acid amide	(3,4) 507 [M+H]+; t_R (k): 2.71 min.
664		1-(2-{(2S,3S,4S)-2-[(R)-1-(3-Chloro-2-fluoro-phenyl)-ethylcarbamoyl]-4-fluoro-3-methoxy-pyrrolidin-1-yl}-2-oxo-ethyl)-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(3,4) 521 [M+H]+; t_R (k): 2.78 min.
665		1-(2-{(2S,3S,4S)-2-[(R)-1-(3-Chloro-2-fluoro-phenyl)-ethylcarbamoyl]-4-fluoro-3-methoxy-pyrrolidin-1-yl}-2-oxo-ethyl)-1H-pyrazolo[4,3-c]pyridine-3-carboxylic acid amide	(3,4) 521 [M+H]+; t_R (k): 2.79 min.
666		(1R,3S,5R)-2-{2-[3-Acetyl-5-(pyrimidin-2-ylmethoxy)-indol-1-yl]-acetyl}-2-aza-bicyclo [3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4) 576/578 [M+H]+; t_R (k): 3.48 min.

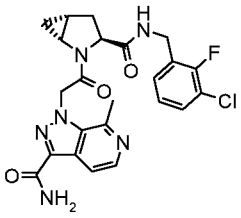
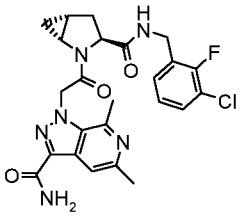
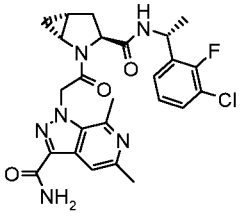
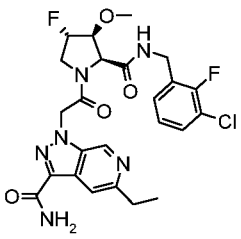
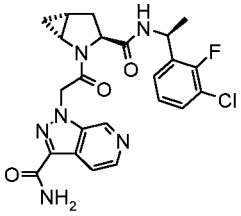
667		(2S,3S,4S)-1-[2-(3-Acetyl-5-methyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-3-ethoxy-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide formate	(3,4) 533/535 [M+H]+; t_R (f): 1.61 min.
668		1-{2-[(1R,3S,5R)-3-(3-Bromo-2-fluoro-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(4) R_f (EtOAc) = 0.1; 501.1/503.0 [M+H]+, 499.0/501.2 [M-H]-, 545.1/548.3 [M+HCOO]-; t_R (a): 2.42 min.
669		1-{2-[(1R,3S,5R)-3-(3-Bromo-2-fluoro-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide	(4) R_f (EtOAc) = 0.6; 517.1/519.1 $[M+NH_4]+$, 498.2/500.1 [M-H]-; t_R (a): 3.18 min.
670		1-{2-[(1R,3S,5R)-3-(3-Bromo-2-fluoro-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-methyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(4) R_f (EtOAc) = 0.1; 515.2/517.1 [M+H]+, 513.2/515.1 [M-H]-, 561.2 [M+HCOO]-; t_R (a): 2.48 min.
671		1-{2-[(1R,3S,5R)-3-(3-Bromo-2-fluoro-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-ethyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(4) R_f (EtOAc) = 0.15; 529.1/531.1 [M+H]+, 527.2/529.1 [M-H]-, 573.2/575.3 [M+HCOO]-; t_R (a): 2.55 min.
672		1-{2-[(1R,3S,5R)-3-(6-Cyclopropyl-pyridin-2-ylcarbamoyl)-2-aza-bicyclo [3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide	(4,5) R_f (EtOAc) = 0.4; 445.3/446.3 [M+H]+, 489.4/491.4 [M+HCOO]-; t_R (a): 2.53 min.

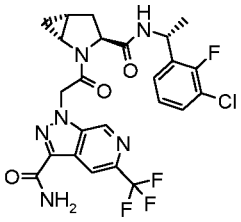
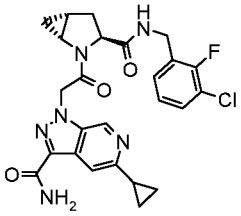
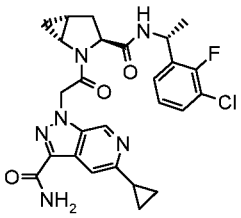
673		1-{2-[(1R,3S,5R)-3-(6-Isopropyl-pyridin-2-ylcarbamoyl)-2-aza-bicyclo [3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(4,5) R_f (EtOAc) = 0.1; 448.3 [M+H]+, 446.0 [M-H]-, 492.3 [M+HCOO]-; t_R (a): 1.31 min.
674		1-{2-[(1R,3S,5R)-3-(3-Cyclopropyl-2-fluoro-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide	(1,4) R_f (c-hexane/EtOAc 2:1) = 0.6; 361.2 [M+H]+, 738.4 [2M+Na]+; t_R (f): 2.29 min.
675		1-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-5-methyl-2-aza-bicyclo [3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(2,3,4) R_f (CH_2Cl_2/MeOH 9:1) = 0.4; 485.3/487.3 [M+H]+, 507.2/509.2 [M+Na]+, 529.3/531.3 [M+HCOO]-; t_R (f): 1.47 min.
676		(1R,3S,5R)-2-[2-(3-Acetyl-6-amino-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo [3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide	(4) R_f (CH_2Cl_2/MeOH 9:1) = 0.5; 503.1/505.1 [M+H]+, 547.1/549.1 [M+HCOO]-; t_R (f): 2.11 min.
677		(1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo [3.1.0]hexane-3-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide	(2,3,4) R_f (CH_2Cl_2/MeOH 9:1) = 0.55; 500.1/502.1 [M+H]+, 1000.3/1001.3 [2M+H]+, 544.1/546.1; t_R (f): 1.81 min.

678		(1R,3S,5R)-2-[2-(1-Acetyl-imidazo[1,5-a]pyridin-3-yl)-acetyl]-2-aza-bicyclo [3.1.0]hexane-3-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-methoxy-ethyl]-amide	(2,3,4) Rf (CH_2Cl_2/MeOH 9:1) = 0.7; 513.2/515.2 [M+H]+, 557.2/558.3 [M+HCOO]-; t_R (a): 3.15 min.
679		(1R,3S,5R)-2-[2-(1-Acetyl-imidazo[1,5-a]pyridin-3-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(R)-1-(3-chloro-2-fluoro-phenyl)-2-cyano-ethyl]-amide	(4) Rf (EtOAc) = 0.2; 508.3 [M+H]+, 506.2 [M-H]-; t_R (a): 3.05 min.
680		(2S,3S,4S)-1-[2-(3-Acetyl-indazol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(3) 505.2/507.2 [M+H]+, 549.3/551.4 [M+HCOO]-; t_R (f): 2.09 min.
681		(2S,3S,4S)-1-[2-(3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(3,4) 505.2/507.2 [M+H]+, 549.2/551.2 [M+HCOO]-; t_R (f): 1.49 min.
682		(2S,3S,4S)-1-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide	(3,4) 506.4/508.4 [M+H]+, 550.5/552.6 [M+HCOO]-; t_R (f): 1.59 min.
683		(1R,3S,5R)-2-{2-[3-Acetyl-5-(pyrimidin-2-ylmethoxy)-indazol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (3- sulfur	(4,7) 451.0 [M+Na]+, 328.9 [M-tBu]+, 427.1 [M-H]-; t_R (c): 5.29 min.

		pentafluoride -phenyl)-amide	
684		1-{2-[(1R,3S,5R)-3-(2,2'-Difluoro-biphenyl-3-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrazolo[3,4-c] pyridine-3-carboxylic acid amide	(1,4,7) 517 [M+H]+; t_R (k): 3.01 min.
685		1-{2-[(1R,3S,5R)-3-(2'-Chloro-2-fluoro-biphenyl-3-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrazolo[3,4-c] pyridine-3-carboxylic acid amide	(1,4,7) 533 [M+H]+; t_R (k): 3.05 min.
686		1-(2-{(1R,3S,5R)-3-[2-Fluoro-3-(3-fluoro-pyridin-2-yl)-phenylcarbamoyl]-2-aza-bicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-1H-indazole-3-carboxylic acid amide	(1,4,7) 517 [M+H]+; t_R (k): 3.10 min.
687		1-(2-{(1R,3S,5R)-3-[2-Fluoro-3-(3-methyl-pyridin-2-yl)-phenylcarbamoyl]-2-aza-bicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-1H-pyrazolo[3,4-c] pyridine-3-carboxylic acid amide	(1,4,7) 514 [M+H]+; t_R (k): 2.32 min.

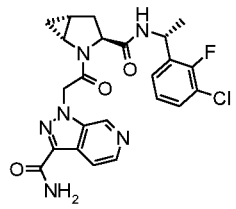
688		1-(2-{(1R,3S,5R)-3-[3-(3-Chloro-pyridin-2-yl)-2-fluoro-phenylcarbamoyl]-2-aza-bicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-1H-pyrazolo[3,4-c] pyridine-3-carboxylic acid amide	(1,4,7) 534 [M+H]+; t_R (k): 2.72 min.
689		3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrrolo[2,3-b] pyridine-6-carboxylic acid methyl ester	(4) 527 [M+H]+, 549 [M+Na]+; t_R (k): 3.43 min.
690		1-(2-{(2S,4R)-2-[(R)-1-(3-Chloro-2-fluoro-phenyl)-ethylcarbamoyl]-4-fluoro-pyrrolidin-1-yl}-2-oxo-ethyl)-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(4) 489/491 [M+H]+, 513 [M+Na]+; t_R (c): 3.43 min.
691		1-(2-{(2S,4R)-2-[(R)-1-(3-Chloro-2-fluoro-phenyl)-ethylcarbamoyl]-4-fluoro-pyrrolidin-1-yl}-2-oxo-ethyl)-5-methyl-1H-pyrazolo[3,4-c] pyridine-3-carboxylic acid amide	(4) 505 [M+H]+; t_R (k): 2.74 min.
692		1-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide	(4) 470 [M+H]+, 492 [M+Na]+; t_R (c): 4.17 min.
693		1-(2-{(1R,3S,5R)-3-[(R)-1-(3-Chloro-2-fluoro-phenyl)-ethylcarbamoyl]-2-aza-bicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-7-methyl-1H-	(4) 499 [M+H]+; t_R (c): 3.51 min.

		pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	
694		1-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-7-methyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(4) 485 [M+H]+; t_R (c): 3.39 min.
695		1-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5,7-dimethyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(4) 499 [M+H]+; t_R (c): 3.46 min.
696		1-(2-{(1R,3S,5R)-3-[(R)-1-(3-Chloro-2-fluoro-phenyl)-ethylcarbamoyl]-2-aza-bicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-5,7-dimethyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(4) 513 [M+H]+, 511 [M-H]-; t_R (c): 3.58 min.
697		1-{2-[(2S,3S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-3-methoxy-pyrrolidin-1-yl]-2-oxo-ethyl}-5-ethyl-1H-pyrazolo[3,4-c]pyridine-3 -carboxylic acid amide	(3,4) 535 [M+H]+; t_R (k): 2.82 min.
698		1-(2-{(1R,3S,5R)-3-[(S)-1-(3-Chloro-2-fluoro-phenyl)-ethylcarbamoyl]-2 -aza-bicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(4) 485 [M+H]+; t_R (c): 3.59 min.

699		1-(2-{(1R,3S,5R)-3-[(R)-1-(3-Chloro-2-fluoro-phenyl)-ethylcarbamoyl]-2-aza-bicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-5-trifluoromethyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(4) 553 [M+H]+; t_R (c): 4.48 min.
700		1-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-cyclopropyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(4) 511 [M+H]+; t_R (c): 3.62 min.
701		1-(2-{(1R,3S,5R)-3-[(R)-1-(3-Chloro-2-fluoro-phenyl)-ethylcarbamoyl]-2-aza-bicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-5-cyclopropyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(4) 525 [M+H]+; t_R (c): 3.75 min.

(1) The amine reagent used in step A was prepared as described in Part C; (2) HCl (4M in dioxane) was used instead of TFA in step B; (3) The title compound was prepared according to the general procedure described in Scheme D9 steps B and C starting from the substituted proline derivative prepared as described in Part B; (4) The acid reagent used in step C was prepared as described in Part A; (5) CH_2Cl_2 was used instead of DMF in step C; (6) T_3P was used instead of HBTU in step C and the reaction was performed in CH_2Cl_2; (7) In step A, DMF was used instead of CH_2Cl_2 and the reaction was performed at 50-70°C.

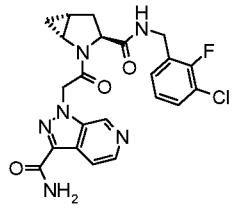
Example 702: 1-(2-{(1R,3S,5R)-3-[(R)-1-(3-Chloro-2-fluoro-phenyl)-ethylcarbamoyl]-2-aza-bicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide



To a solution of (3-carbamoyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid trifluoroacetate salt (2.65 g, 7.94 mmol, prepared as described in Scheme A26) in DMF (30 mL) were added

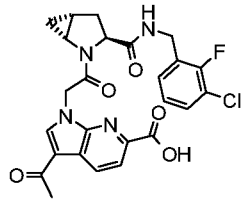
successively (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid, [(R)-1-(3-chloro-2-fluoro-phenyl)-ethyl]-amide trifluoroacetate salt (3.00 g, 7.56 mmol), HBTU (3.44 g, 9.07 mmol) and DIPEA (5.28 mL, 30.2 mmol). The reaction mixture was stirred at RT for 16 h and then was concentrated under vacuum. The residual oil was partitioned between CH_2Cl_2 and a sat. aq. $NaHCO_3$ solution. A solid precipitated from the resulting emulsion and was filtered off, washed with water and dried under vacuum. The solid was suspended in a mixture of water (150 mL) and MeOH (3 mL), stirred for 1 h at RT, filtered, washed with water and finally dried under vacuum to give the title material as a white powder. MS (LC/MS): 485 [M+H]+; t_R (HPLC conditions c): 3.54 min.

Example 703: 1-(2-((1R,3S,5R)-3-((3-Chloro-2-fluorobenzyl)carbamoyl)-2-azabicyclo [3.1.0]hexan-2-yl)-2-oxoethyl)-1H-pyrazolo[3,4-c]pyridine-3-carboxamide



To a solution of (3-carbamoyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid trifluoroacetate salt (2.12 g, 6.35 mmol, prepared as described in Scheme A26) in DMF (32 mL) were successively added (1R,3S,5R)-N-(3-chloro-2-fluorobenzyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide trifluoroacetate salt (2.70 g, 6.35 mmol), HBTU (3.37 g, 8.89 mmol) and DIPEA (4.44 mL, 25.4 mmol). The reaction mixture was stirred at RT for 16 h, and then was concentrated under vacuum. The residual oil was partitioned between CH_2Cl_2 and a sat. aq. $NaHCO_3$ solution. A solid precipitated from the resulting emulsion and was filtered off, washed with water and dried under vacuum. The solid was suspended in a mixture of water (150 mL) and MeOH (3 mL), stirred for 1 h at RT, filtered, washed with water and finally dried under vacuum to give the title material as a white powder. MS (LC/MS): 471 [M+H]+; t_R (HPLC conditions c): 3.41 min.

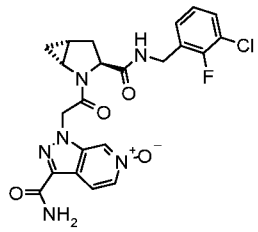
Example 704: 3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrrolo[2,3-b]pyridine-6-carboxylic acid



To a solution of 3-acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrrolo[2,3-b]pyridine-6-carboxylic acid methyl ester (**Example 689,** 70 mg, 0.133 mmol) in THF (3 mL) and water (0.3 mL) was added a 2N

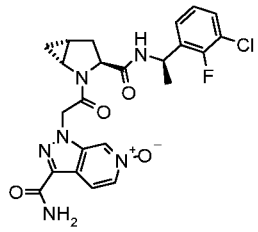
aqueous LiOH solution (0.664 mL, 1.33 mmol). The reaction mixture was stirred at 25°C for 16 h, then a 1N HCl aqueous solution was added to acidify the reaction mixture to pH = 2 to 3. The resulting aqueous suspension was filtered, the solid was washed with water and then dried in vacuo. The crude solid was purified by preparative HPLC (Waters Sunfire C18-OBD, 5 µm, 30x100mm, flow: 40 mL/min, eluent: 20% to 100% CH_3CN in H_2O in 20 min, 100% CH_3CN 2 min, CH_3CN and H_2O containing 0.1% TFA). The pure fractions were combined, CH_3CN was evaporated under reduced pressure and the resulting aqueous solution was lyophilized to give the title compound as a white solid. MS: 513 [M+H]+, 535 [M+Na]+; t_R (HPLC conditions k): 3.14 min.

Example 705: 3-Carbamoyl-1-(2-((1R,3S,5R)-3-(3-chloro-2-fluorobenzylcarbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxoethyl)-1H-pyrazolo[3,4-c]pyridine 6-oxide



To a solution of 1-(2-((1R,3S,5R)-3-(3-chloro-2-fluorobenzylcarbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxoethyl)-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (**Example 703,** 100 mg, 0.21 mmol) in acetic acid (4 mL) was added 3-chlorobenzoperoxoic acid (58 mg, 0.34 mmol) at 55°C. The reaction mixture was stirred at 55°C for 18 h and then cooled to RT. Volatiles were evaporated and the residue was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, flow: 40 mL/min, eluent: 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) to afford the title compound as a white solid. MS: 487 [M+H]+; t_R (HPLC conditions c): 3.44 min.

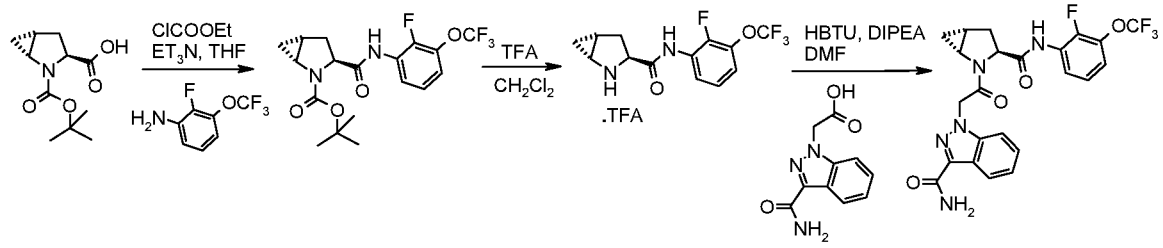
Example 706: 3-Carbamoyl-1-(2-((1R,3S,5R)-3-((R)-1-(3-chloro-2-fluorophenyl)ethylcarbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxoethyl)-1H-pyrazolo[3,4-c]pyridine 6-oxide



To a solution of 1-(2-((1R,3S,5R)-3-((R)-1-(3-chloro-2-fluorophenyl)ethylcarbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxoethyl)-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (**Example 702,** 150 mg, 0.31 mmol) in acetic acid (4 mL) was added 3-chlorobenzoperoxoic acid (85 mg,

0.50 mmol) at 55°C. The reaction mixture was stirred at 55°C for 18 h and then cooled to RT. Volatiles were evaporated and the residue was purified by preparative HPLC (Waters Sunfire, C18-ODB, 5 µm, 30x100 mm, flow: 40 mL/min, eluent: 5-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA) to afford the title compound as a white solid. MS: 501 [M+H]+; t_R (HPLC conditions c): 3.64 min.

Scheme D10: general protocol described for the preparation of Example 707: 1-{2-[(1R,3S,5R)-3-(2-Fluoro-3-trifluoromethoxy-phenylcarbamoyl)-2-aza-bicyclo[3.1.0] hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide



A. (1R,3S,5R)-3-(2-Fluoro-3-trifluoromethoxy-phenylcarbamoyl)-2-aza-bicyclo[3.1.0] hexane-2-carboxylic acid tert-butyl ester

To a solution of (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester (1.83 g, 8.07 mmol) in dry THF (45 mL) at -20°C under nitrogen atmosphere was added triethylamine (3.32 mL, 23.8 mmol) followed by ethylchloroformate (0.775 mL, 8.07 mmol) dropwise. The reaction mixture was stirred at -20°C for 90 min and a solution of 2-fluoro-3-(trifluoromethoxy)aniline (prepared as described in Part C, 1.5 g, 7.69 mmol) in dry THF (5 mL) was added. The reaction mixture was further stirred at -20°C for 1 h, warmed up to RT and stirred at 65°C for 16 h until completion of the reaction. The reaction mixture was diluted with EtOAC, washed with a saturated aqueous solution of $NaHCO_3$ (x3) and brine, dried (phase separator) and concentrated under reduced pressure. The crude residue was purified via flash column chromatography on silica gel (EtOAc/c-hexane 1:1) to give the desired material as a colorless oil. MS: 427 [M+Na]+, 304.9 [MH-Boc]+; t_R (HPLC conditions c): 5.23 min.

B. (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-3-carboxylic acid (2-fluoro-3-trifluoro methoxy-phenyl)-amide trifluoroacetate

To a solution of ((1R,3S,5R)-3-(2-fluoro-3-trifluoromethoxy-phenylcarbamoyl)-2-aza-bicyclo[3.1.0] hexane-2-carboxylic acid tert-butyl ester (2.56 g, 6.33 mmol) in CH_2Cl_2 (20 mL) was added TFA (10 mL, 130 mmol) and the solution was stirred at RT for 16 h. CH_2Cl_2 was concentrated, the residue was supended in MeOH, concentrated again and dried under high vacuum to give the desired material which was used without further purification in the next step. MS: 305 [M+H]+; t_R (HPLC conditions c): 3.55 min.

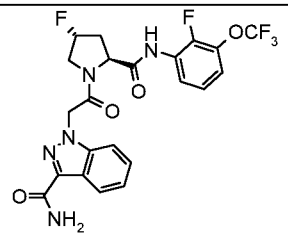
C. Example 707: 1-{2-[(1R,3S,5R)-3-(2-Fluoro-3-trifluoromethoxy-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide

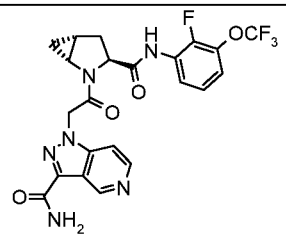
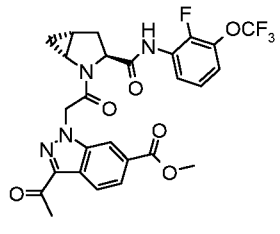
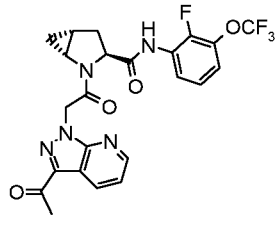
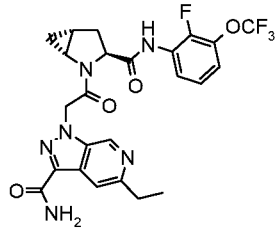
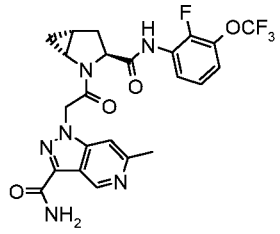
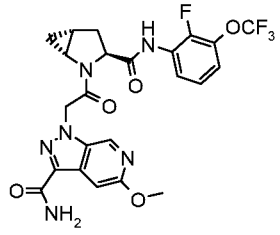
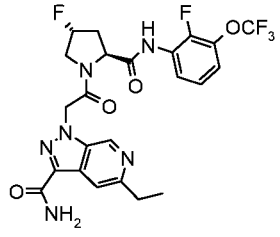
To a solution of (3-carbamoyl-indazol-1-yl)-acetic acid (73.4 mg, 0.335 mmol, prepared as described in Scheme A25) in DMF (2 mL) were successively added (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (2-fluoro-3-trifluoromethoxy-phenyl)-amide trifluoroacetate (140 mg, 0.335 mmol), DIPEA (0.234 mL, 1.34 mmol) and HBTU (152 mg, 0.402 mmol). The reaction mixture was stirred at 25°C for 2 h, concentrated and the residue was purified by preparative HPLC (Waters Sunfire C18-OBD, 5 µm, 30x100mm, flow: 40 mL/min, eluent: 5% to 100% CH_3CN in H_2O in 20 min, 100% CH_3CN 2 min, CH_3CN and H_2O containing 0.1% TFA). The pure fractions were combined, CH_3CN was evaporated under reduced pressure and the resulting aqueous solution was lyophilized. White powder: MS: 506 [M+H]+; t_R (HPLC conditions k): 3.40 min.

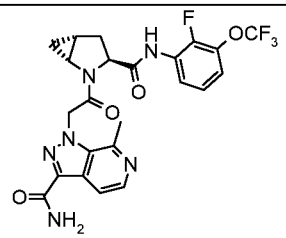
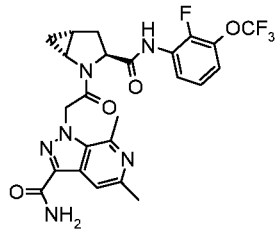
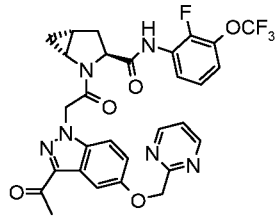
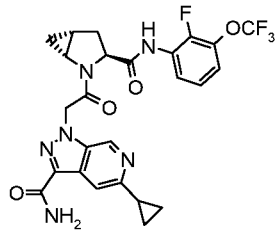
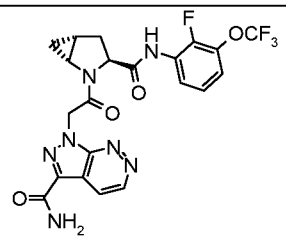
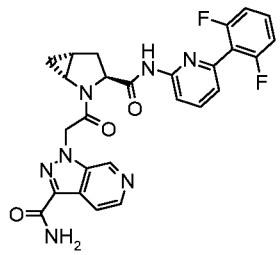
Alternatively, for final compounds containing a basic residue : the pure HPLC fractions were combined, CH_3CN was evaporated under reduced pressure, the resulting aqueous solution was adjusted to pH 8-9 by addition of an aqueous saturated solution of $NaHCO_3$, extracted with CH_2Cl_2 (x3), the combined organic extracts were dried (phase separator) and concentrated under vacuum.

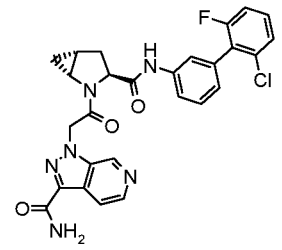
The examples below were prepared according to the general procedures described in Scheme D10 for **Example 707** *using commercially available building blocks if not otherwise stated (see note at the end of table 9):*

Table 9:

Example	Structure	Name	Characterization (end–table notes), TLC, R_f (eluent); MS (LC/MS); t_R (HPLC conditions)
708		1-(2-((2S,4R)-4-fluoro-2-(2-fluoro-3-(trifluoromethoxy)phenylcarbamoyl) pyrrolidin-1-yl)-2-oxoethyl)-1H-indazole-3-carboxamide	(1) 512 [M+H]+; t_R (k): 3.31 min.

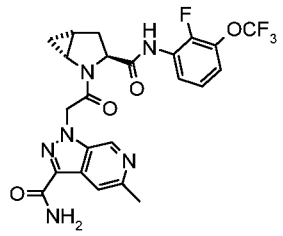
709		1-(2-((1R,3S,5R)-3-(2-fluoro-3-(trifluoromethoxy)phenylcarbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxoethyl)-1H-pyrazolo[4,3-c] pyridine-3-carboxamide	(1) 507 [M+H]+; t_R (k): 2.90 min.
710		Methyl 3-acetyl-1-(2-((1R,3S,5R)-3-(2-fluoro-3-(trifluoromethoxy) phenylcarbamoyl)-2-azabicyclo [3.1.0]hexan-2-yl)-2-oxoethyl)-1H-indazole-6-carboxylate	(1) 563 [M+H]+, 585 [M+Na]+; t_R (k): 3.89 min.
711		(1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (2-fluoro-3-trifluoromethoxy-phenyl)-amide	(1) 506 [M+H]+; t_R (k): 3.67 min.
712		5-Ethyl-1-{2-[(1R,3S,5R)-3-(2-fluoro-3-trifluoromethoxy-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(1) 535 [M+H]+; t_R (k): 2.97 min.
713		1-{2-[(1R,3S,5R)-3-(2-Fluoro-3-trifluoromethoxy-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-6-methyl-1H-pyrazolo[4,3-c]pyridine-3-carboxylic acid amide	(1) 521 [M+H]+; t_R (k): 2.92 min.
714		1-{2-[(1R,3S,5R)-3-(2-Fluoro-3-trifluoromethoxy-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-methoxy-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(1) 537 [M+H]+; t_R (k): 3.24 min.
715		5-Ethyl-1-{2-[(2S,4R)-4-fluoro-2-(2-fluoro-3-trifluoromethoxy-phenyl carbamoyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(1) 541 [M+H]+; t_R (k): 2.95 min.

716		1-{2-[(1R,3S,5R)-3-(2-Fluoro-3-trifluoromethoxy-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-7-methyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(1) 521 [M+H]+; t_R (k): 2.90 min.
717		1-{2-[(1R,3S,5R)-3-(2-Fluoro-3-trifluoromethoxy-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5,7-dimethyl-1H-pyrazolo [3,4-c]pyridine-3-carboxylic acid amide	(1) 535 [M+H]+; t_R (c): 3.84 min.
718		(1R,3S,5R)-2-{2-[3-Acetyl-5-(pyrimidin-2-ylmethoxy)-indazol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (2-fluoro-3-trifluoromethoxy-phenyl)-amide	(1) 613 [M+H]+, 635 [M+Na]+; t_R (c): 4.81 min.
719		5-Cyclopropyl-1-(2-((1R,3S,5R)-3-((2-fluoro-3-(trifluoromethoxy) phenyl)carbamoyl)-2-azabicyclo [3.1.0]hexan-2-yl)-2-oxoethyl)-1H-pyrazolo[3,4-c] pyridine-3-carboxamide	(1) 547 [M+H]+; t_R (c): 3.97 min.
720		1-(2-((1R,3S,5R)-3-((2-Fluoro-3-(trifluoromethoxy)phenyl)carbamoyl) -2-azabicyclo[3.1.0]hexan-2-yl)-2-oxoethyl)-1H-pyrazolo[3,4-c] pyridazine-3-carboxamide	(1) 508.0 [M+H]+, 529.9 [M+Na]+; t_R (c): 4.08 min.
721		1-(2-{(1R,3S,5R)-3-[6-(2,6-Difluoro-phenyl)-pyridin-2-ylcarbamoyl]-2-aza-bicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-1H-pyrazolo[3,4-c]pyridine-3-carboxamide	(1,2) 518 [M+H]+; t_R (k): 2.90 min.

722		1-(2-((1R,3S,5R)-3-(2'-Chloro-6'-fluorobiphenyl-3-ylcarbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxoethyl)-1H-pyrazolo[3,4-c] pyridine-3-carboxamide	(1,2) 533 [M+H]+; t_R (c): 4.12 min.

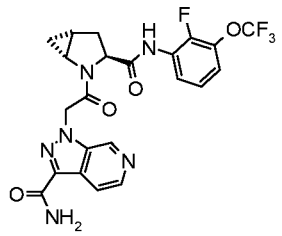
(1) The acid derivative used is step C was prepared as described in Part A; (2) The amine derivative used in step A was prepared as described in Part C.

Example 723: 1-{2-[(1R,3S,5R)-3-(2-Fluoro-3-trifluoromethoxy-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-methyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide



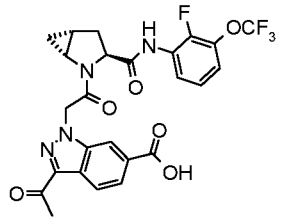
To a solution of (3-carbamoyl-5-methyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid trifluoroacetate salt (3.87 g, 11.1 mmol; prepared as described in Scheme A27) in DMF (45 mL) were successively added (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (2-fluoro-3-trifluoro methoxy-phenyl)-amide trifluoroacetate salt (5.00 g, 11.1 mmol), DIPEA (7.77 mL, 44.5 mmol) and HBTU (5.06 g, 13.3 mmol). The reaction mixture was stirred at 25°C for 2 h and was then concentrated in vacuo. The residue was purified by preparative HPLC (Waters Sunfire C18-OBD, 5 µm, 30x100mm, flow: 50 mL/min, eluent: 5% to 100% CH_3CN in H_2O in 20 min, 100% CH_3CN 2 min, CH_3CN and H_2O containing 0.1% TFA). The pure fractions were combined and volatiles were evaporated under reduced pressure. The resulting aqueous solution was adjusted to pH 8 to 9 by addition of an aqueous saturated solution of $NaHCO_3$, and then was extracted with CH_2Cl_2 (x3). The combined organic extracts were dried (phase separator) and concentrated under vacuum to afford the title compound as a white solid. MS: 521 [M+H]+; t_R (HPLC conditions c): 3.81 min.

Example 724: 1-(2-((1R,3S,5R)-3-((2-Fluoro-3-(trifluoromethoxy)phenyl)carbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxoethyl)-1H-pyrazolo[3,4-c]pyridine-3-carboxamide



To a solution of (3-carbamoyl-pyrazolo[3,4-c]pyridin-1-yl)-acetic acid trifluoroacetate salt (1.60 g, 4.78 mmol; prepared as described in Scheme A26) in DMF (40 mL) were successively added (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (2-fluoro-3-trifluoro methoxy-phenyl)-amide trifluoroacetate salt (2.50 g, 4.78 mmol), DIPEA (3.34 mL, 19.1 mmol) and HBTU (2.17 g, 5.74 mmol). The reaction mixture was stirred at 25°C for 2 h and then was concentrated. The residue was purified by preparative HPLC (Waters Sunfire C18-OBD, 5 µm, 30x100mm, flow: 50 mL/min, eluent: 5% to 100% CH_3CN in H_2O in 20 min, 100% CH_3CN 2 min, CH_3CN and H_2O containing 0.1% TFA). The pure fractions were combined and volatiles were removed under reduced pressure. The resulting aqueous solution was adjusted to pH 8 to 9 by addition of an aqueous saturated solution of $NaHCO_3$ and was then extracted with CH_2Cl_2 (x3). The combined organic extracts were dried (phase separator) and concentrated under vacuum. The residual solid was suspended in Et_2O and stirred at RT for 16 h. The solid was filtered and dried under vacuum to afford the title compound as a white solid. MS: 507 [M+H]+; t_R (HPLC conditions c): 3.77 min.

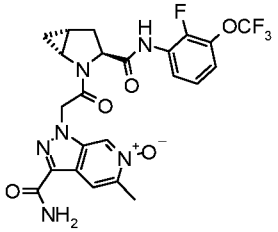
Example 725: 3-Acetyl-1-{2-[(1R,3S,5R)-3-(2-fluoro-3-trifluoromethoxy)phenyl-carbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-6-carboxylic acid



To a solution of methyl 3-acetyl-1-(2-((1R,3S,5R)-3-(2-fluoro-3-trifluoromethoxy)phenyl-carbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxo-ethyl)-1H-indazole-6-carboxylate (**Example 710**, 25 mg, 0.044 mmol) in THF (2 mL) and water (0.2 mL) was added a 2N aqueous LiOH solution (0.089 mL, 0.178 mmol). The reaction mixture was stirred at 25°C for 4 h, then a 1N HCl aqueous solution was added to acidify the reaction mixture to pH = 2 to 3. The resulting aqueous solution was extracted with CH_2Cl_2 (x3), the combined organic extracts were dried (Phase separator) and then concentrated under reduced pressure. The residue was purified by preparative HPLC (Waters Sunfire C18-OBD, 5 µm, 30x100mm, flow: 40 mL/min, eluent: 5% to 100% CH_3CN in H_2O in 20 min, 100% CH_3CN 2 min, CH_3CN and H_2O containing 0.1% TFA). The pure fractions were combined, volatiles were removed under reduced pressure and

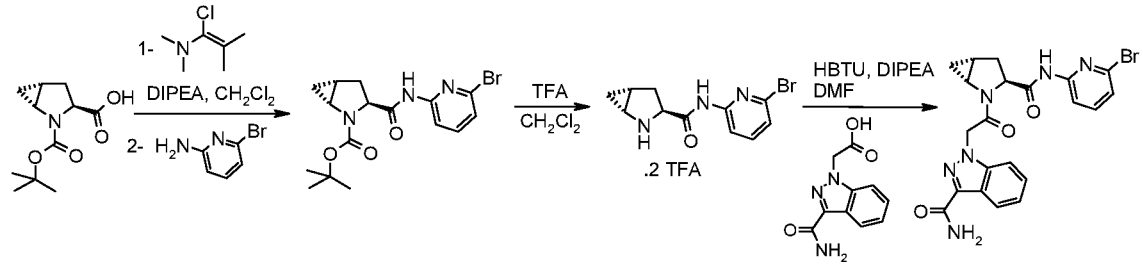
the resulting aqueous solution was lyophilized to afford the title compound as a white solid. MS: 549 [M+H]+; t_R (HPLC conditions c): 4.76 min.

Example 726: 3-Carbamoyl-1-(2-((1R,3S,5R)-3-((2-fluoro-3-hydroxyphenyl)carbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxoethyl)-5-methyl-1H-pyrazolo[3,4-c]pyridine 6-oxide



To a solution of 1-{2-[(1R,3S,5R)-3-(2-fluoro-3-trifluoromethoxy-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-methyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide (**Example 723**, 50 mg, 0.096 mmol) in acetic acid (3 mL) was added 3-chlorobenzoperoxoic acid (38 mg, 0.154 mmol) at 55°C. The reaction mixture was stirred at 55°C for 18 h and then cooled to RT. Volatiles were evaporated, the residue was then dissolved in EtOAc and washed with a sat. aq. $NaHCO_3$ solution (x3) and brine, dried (Phase separator) and concentrated under reduced pressure to afford the title compound as a white solid. MS: 537 [M+H]+; t_R (HPLC conditions k): 3.00 min.

Scheme D11: general protocol described for the preparation of Example 727: 1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide



A. (1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester

To a solution of (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-tert-butyl ester (500 mg, 2.2 mmol) in dry CH_2Cl_2 (2 mL) was added 1-chloro-N,N,2-trimethylpropenylamine (349 µL, 2.64 mmol) at 0°C under nitrogen atmosphere. Formation of the acyl chlorid intermediate was monitored by TLC after quenching of an aliquot with MeOH. After completion (1-1.5 h), 2-amino-6-bromopyridine (457 mg, 2.64 mmol) was added at 0°C, followed by DIPEA (1.13 mL, 6.60 mmol) and the reaction mixture further stirred 2 h at RT. The reaction mixture was poured into water and extracted twice with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. CH_2Cl_2 was added to the crude residue and the

precipitate filtered to give the desired material as a white solid. TLC, R_f (EtOAc) = 0.85; MS: 382.1/384.1 [M+H]+, 380.2/382.3 [M-H]-, 426.7/428.3 [M+HCOO]-; t_R (HPLC conditions h): 2.19 min.

B. (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-3-carboxylic acid (6-bromo-pyridin-2-yl)-amide di(trifluoroacetate) salt

To a solution of (1R,3S,5R)-3-(6-bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carboxylic acid tert-butyl ester (561 mg, 1.47 mmol) in CH_2Cl_2 (11 mL) was added TFA (1.13 mL, 14.7 mmol) and the solution was stirred at RT overnight. CH_2Cl_2 was concentrated and the crude residue was dried under high vacuum to give the desired material which was used without further purification in the next step. MS: 282.1/284.1 [M+H]+, 304.0/306.1 [M+Na]+, 563.1/565.2 [2M+H]+; t_R (HPLC conditions f): 0.96 min.

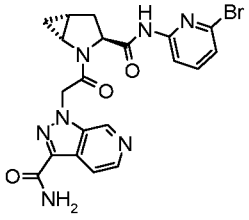
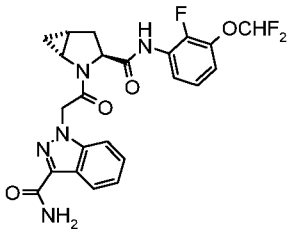
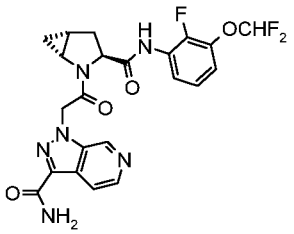
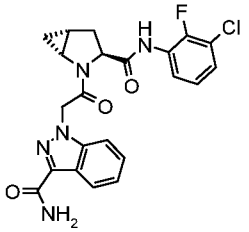
C. Example 727: 1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo [3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide

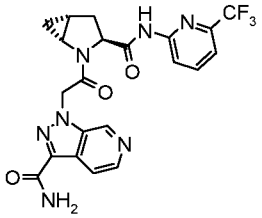
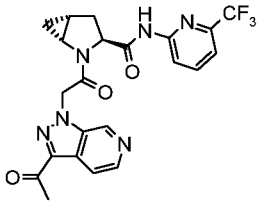
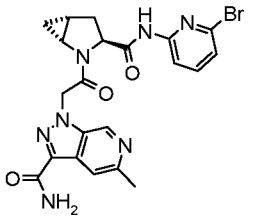
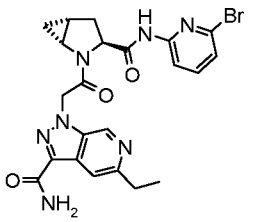
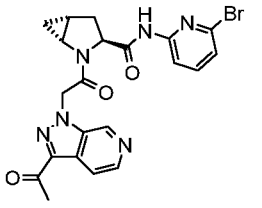
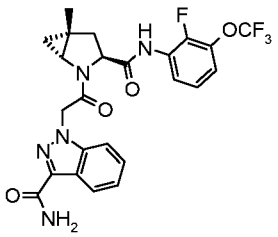
(3-Carbamoyl-indazol-1-yl)-acetic acid (130 mg, 0.59 mmol, prepared as described in Scheme A25), (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (6-bromo-pyridin-2-yl)-amide (2 TFA salt, 303 mg, 0.59 mmol) and HBTU (337 mg, 0.89 mmol) were dissolved in DMF (3 mL). DIPEA (406 µL, 2.37 mmol) was added and the reaction mixture was stirred at 25°C for 1 h. The crude reaction mixture was purified by preparative HPLC (Waters Sunfire C18-OBD, 5 µm, 30x100mm, flow: 40 mL/min, eluent: 20% to 100% CH_3CN in H_2O in 25 min, CH_3CN and H_2O containing 0.1% TFA). The pure fractions were combined, neutralized with an aqueous saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 to give the desired compound. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.55; MS: 483.1/485.1 [M+H]+, 965.4/967.4 [2M+H]+, 982.4/984.3 [2M+NH_4]+, 481.1/483.2 [M-H]-, 527.2/529.1 [M+HCOO]-; t_R (HPLC conditions a): 2.79 min.

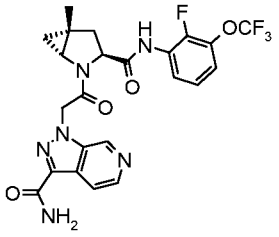
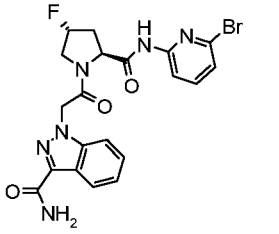
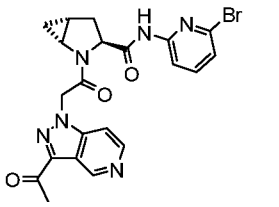
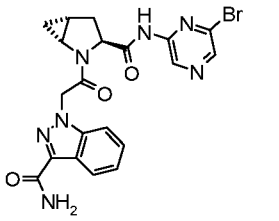
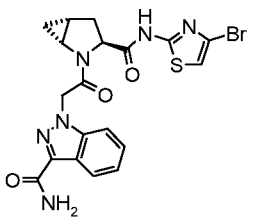
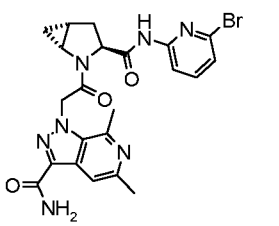
Alternatively, for final compounds containing a basic residue: the pure HPLC fractions were combined, CH_3CN was evaporated under reduced pressure, the resulting aqueous solution was adjusted to pH 8-9 by addition of an aqueous saturated solution of $NaHCO_3$, extracted with CH_2Cl_2 (x3), the combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum.

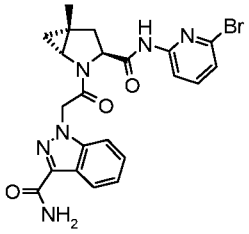
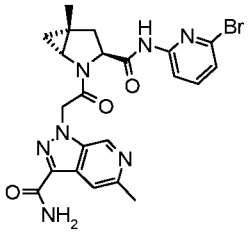
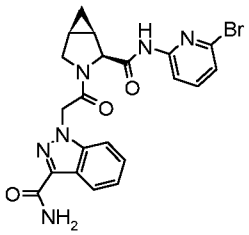
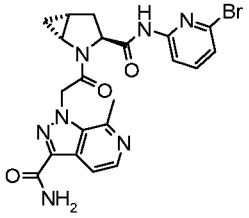
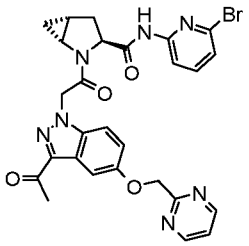
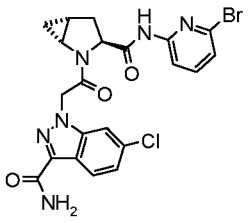
The examples below were prepared according to the general procedures described in Scheme D11 for **Example 727** *using commercially available building blocks if not otherwise stated (see notes at the end of table 10):*

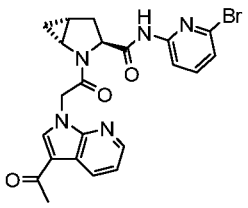
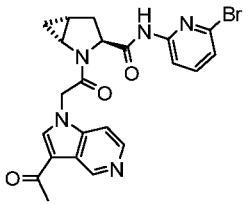
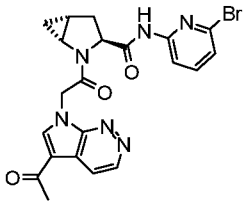
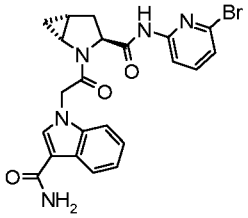
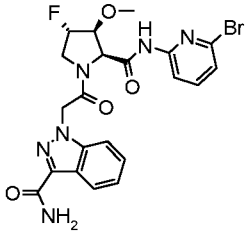
Table 10:

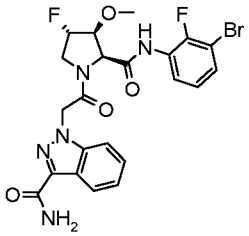
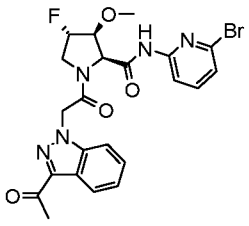
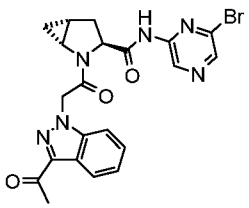
Example	Structure	Name	Characterization (end–table notes), TLC, R_f (eluent); MS (LC/MS); t_R (HPLC conditions)
728		1-{2-[(1R,3S,5R)-3-(6-bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrazolo[3,4-c] pyridine-3-carboxylic acid amide	(1) 484.1/486.1 [M+H]+, 482.0/484.1 [M-H]-, 528.2/530.1 [M+HCOO]-; t_R (a): 2.22 min.
729		1-{2-[(1R,3S,5R)-3-(3-Difluoromethoxy-2-fluoro phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide	(1,2,3) 488.2 [M+H]+, 505.2 [M+NH_4]+, 486.2 [M-H]-; t_R (f): 1.90 min
730		1-{2-[(1R,3S,5R)-3-(3-Difluoromethoxy-2-fluoro-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-pyrazolo[3,4-c] pyridine-3-carboxylic acid amide	(1,2,3) 489.2 [M+H]+, 487.2 [M-H]-, 533.2 [M+HCOO]-; t_R (f): 1.41 min
731		1-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.55; 473.2/475.2 [M+NH_4]+, 478.2/480.2 [M+Na]+, 454.3/456.2 [M-H]-, 500.2/502.2 [M+HCOO]-; t_R (a): 1.86 min.

732		1-{2-Oxo-2-[(1R,3S,5R)-3-(6-trifluoromethyl-pyridin-2-ylcarbamoyl)-2-aza-bicyclo [3.1.0]hex-2-yl]-ethyl}-1 H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(1) R_f (EtOAc) = 0.1; 474.2 [M+H]+, 472.2 [M-H]-, 518.3 [M+HCOO]-; t_R (a): 2.09 min.
733		(1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0] hexane-3-carboxylic acid (6-trifluoromethyl-pyridin-2-yl)-amide	(1) R_f (EtOAc) = 0.25; 473.2 [M+H]+, 471.2 [M-H]-, 517.2 [M+HCOO]-; t_R (a): 2.30 min.
734		1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-methyl-1H-pyrazolo [3,4-c]pyridine-3-carboxylic acid amide	(1) R_f (EtOAc) = 0.1; 498.1/500.1 [M+H]+, 496.2/498.1 [M-H]-, 542.3/544.1 [M+HCOO]-; t_R (a): 2.27 min.
735		1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-ethyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(1) R_f (EtOAc) = 0.26; 12.2/514.2 [M+H]+, 510.2/512.2 [M-H]-, 556.2/558.2 [M+HCOO]-; t_R (a): 2.35 min.
736		(1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0] hexane-3-carboxylic acid (6-bromo-pyridin-2-yl)-amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.5; 483.1/485.1 [M+H]+, 481.1/483.1 [M-H]-; t_R (f): 1.38 min.
737		1-{2-[(1R,3S,5R)-3-(2-Fluoro-3-trifluoromethoxy-phenylcarbamoyl)-5-methyl-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide	(1,4) 419.2 [M+H]+, 436.2 [M+NH_4]+, 417.2 [M-H]-, 463.2 [M+HCOO]-; t_R (f): 2.46 min.

738		1-{2-[(1R,3S,5R)-3-(2-Fluoro-3-trifluoromethoxy-phenyl carbamoyl)-5-methyl-2-aza-bicyclo[3.1.0]hex-2-yl]-2 -oxo-ethyl}-1H-pyrazolo[3,4-c] pyridine-3-carboxylic acid amide	(1,4) R_f (CH_2Cl_2/MeOH 9:1) = 0.5; 521.2 [M+H]+, 1041.5 [2M+H]+, 519.2 [M-H]-, 1039.5 [2M-H]-; t_R (f): 1.49 min.
739		1-{2-[(2S,4R)-2-(6-Bromo-pyridin-2-ylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.5; 489.2/491.1 [M+H]+, 487.1/489.3 [M-H]-; t_R (f): 1.56 min.
740		(1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[4,3-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0] hexane-3-carboxylic acid (6-bromo-pyridin-2-yl)-amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.6; 483.1/485.2 [M+H]+, 965.3/697.3 [2M+H]+, 481.1/483.2 [M-H]-; t_R (f): 1.34 min.
741		1-{2-[(1R,3S,5R)-3-(6-Bromo-pyrazin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.6; 501.2/503.2 [M+NH_4]+, 482.1/484.1 [M-H]-; t_R (f): 1.51 min.
742		1-{2-[(1R,3S,5R)-3-(4-Bromo-thiazol-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.5; 489.1/491.1 [M+H]+, 511.1/513.1 [M+Na]+, 487.1/489.1 [M-H]-; t_R (f): 1.59 min.
743		1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5,7-dimethyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.45; 512.2/514.2 [M+H]+, 510.2/512.2 [M-H]-; t_R (f): 1.25 min.

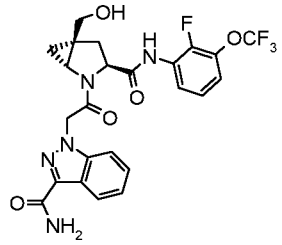
744		1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-5-methyl-2-aza-bicyclo[3.1.0] hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide	(1,4) R_f (CH_2Cl_2/MeOH 9:1) = 0.4; 497.2/499.2 [M+H]+, 495.2/497.2 [M-H]-; t_R (f): 1.82 min.
745		1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-5-methyl-2-aza-bicyclo[3.1.0] hex-2-yl]-2-oxo-ethyl}-5-methyl-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide	(1,4) R_f (CH_2Cl_2/MeOH 9:1) = 0.4; 512.2/514.2 [M+H]+, 510.1/512.2 [M-H]-, 556.3/558.2 [M+HCOO]-; t_R (f): 1.37 min.
746		1-{2-[(1R,2S,5S)-2-(6-Bromo-pyridin-2-ylcarbamoyl)-3-aza-bicyclo[3.1.0]hex-3-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.55; 483.1/485.1 [M+H]+, 481.1/483.1 [M-H]-, 527.3/529.1 [M+HCOO]-; t_R (f): 1.74 min.
747		1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-7-methyl-1H-pyrazolo [3,4-c]pyridine-3-carboxylic acid amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.4; 498.2/500.2 [M+H]+, 496.7/498.4 [M-H]-; t_R (f): 1.26 min.
748		(1R,3S,5R)-2-{2-[3-Acetyl-5-(pyrimidin-2-ylmethoxy)-indazol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (6-bromo-pyridin-2-yl)-amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.75; 590.2/592.2 [M+H]+, 1179.5/1181.4 [2M+H]+, 588.3/590.4 [M-H]-; t_R (f): 1.80 min.
749		1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-6-chloro-1H-indazole-3-carboxylic acid amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.55; 517.1/519.1 [M+H]+, 515.1/517.1 [M-H]-, 561.1/563.2

			[M+HCOO]-; t_R (f): 1.88 min.
750		(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0] hexane-3-carboxylic acid (6-bromo-pyridin-2-yl)-amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.75; 482.1/484.2 [M+H]+, 480.1/482.1 [M-H]-, 526.0/528.1 [M+HCOO]-; t_R (f): 1.75 min.
751		(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[3,2-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0] hexane-3-carboxylic acid (6-bromo-pyridin-2-yl)-amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.5; 482.1/484.2 [M+H]+, 480.0/482.1 [M-H]-, 526.1/528.2 [M+HCOO]-; t_R (f): 1.27 min.
752		(1R,3S,5R)-2-[2-(5-Acetyl-pyrrolo[2,3-c]pyridazin-7-yl)-acetyl]-2-aza-bicyclo[3.1.0] hexane-3-carboxylic acid (6-bromo-pyridin-2-yl)-amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.55; 483.2/485.1 [M+H]+, 481.1/483.1 [M-H]-; t_R (f): 1.29 min.
753		1-{2-[(1R,3S,5R)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.45; 482.1/484.1 [M+H]+, 499.2/501.2 [M+NH_4]+, 480.1/482.1 [M-H]-; t_R (f): 1.64 min.
754		1-{2-[(2S,3S,4S)-2-(6-Bromo-pyridin-2-ylcarbamoyl)-4-fluoro-3-methoxy-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide	(1,5) 519.1/521.1 [M+H]+, 517.1/519.1 [M-H]-; t_R (f): 1.64 min.

755		1-{2-[(2S,3S,4S)-2-(3-Bromo-2-fluoro-phenylcarbamoyl)-4-fluoro-3-methoxy-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide	(1,5) R_f (AcOEt) = 0.5; 553.2/555.2 $[M+NH_4]+$, 534.2/536.1 [M-H]-, 580.1/582.2 [M+HCOO]-; t_R (f): 1.76 min.
756		(2S,3S,4S)-1-[2-(3-Acetyl-indazol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid (6-bromo-pyridin-2-yl)-amide	(1,5) R_f (AcOEt) = 0.9; 518.2/520.1 [M+H]+ 516.1/518.1 [M-H]- 562.2/564.2 [M+HCOO]-; t_R (f): 1.92 min.
757		(1R,3S,5R)-2-[2-(3-Acetyl-indazol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (6-bromo-pyrazin-2-yl)-amide	(1) R_f (CH_2Cl_2/MeOH 9:1) = 0.85; 483.1/485.1 [M+H]+, 500.2/502.2 $[M+NH_4]+$, 481.1/483.1 [M-H]-; t_R (f): 1.91 min.

(1) The acid derivative used is step C was prepared as described in Part A; (2) The amine derivative used in step A was prepared as described in Part C; (3) Step C was performed using T_3P and DIPEA as described in Scheme D8 Step C; (4) The acid derivative used is step A was prepared as described in Part B; (5) The title compound was prepared according to the general procedure described in Scheme D11 steps B and C starting from the substituted proline derivative prepared as described in Part B.

Example 758: 1-{2-[(1R,3S,5S)-3-(2-Fluoro-3-trifluoromethoxy-phenylcarbamoyl)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide



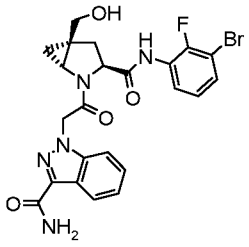
A solution of (3-carbamoyl-indazol-1-yl)-acetic acid (1R,3S,5S)-2-[2-(3-carbamoyl-indazol-1-yl)-acetyl]-3-(2-fluoro-3-trifluoromethoxy-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-5-ylmethyl ester (69.2 mg, 0.085 mmol) and NaOH (1 N, 188 µL, 0.19 mmol) in THF (0.45 mL) and water

(43 µL) was stirred at RT 1 h. Water and EtOAc were added, the layers were separated and the aqueous one extracted with EtOAc (x2). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by preparative HPLC (Waters Sunfire C18-OBD, 5 µm, 30x100 mm, eluent: 20% to 100% CH_3CN in H_2O in 25 min, CH_3CN and H_2O containing 0.1% TFA, flow: 40 mL/min). R_f, TLC (CH_2Cl_2/MeOH 9:1) = 0.45; MS (UPLC/MS): 536.4 [M+H]+, 553.3 [M+NH_4]+, 558.2 [M+Na]+, 534.3 [M-H]-, 580.3 [M+HCOO]-; t_R (HPLC conditions f): 1.82 min.

(3-Carbamoyl-indazol-1-yl)-acetic acid (1R,3S,5S)-2-[2-(3-carbamoyl-indazol-1-yl)-acetyl]-3-(2-fluoro-3-trifluoromethoxy-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-5-ylmethyl ester

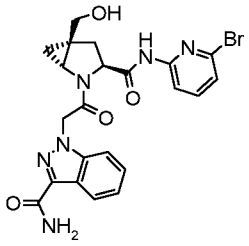
To a mixture of (3-carbamoyl-indazol-1-yl)-acetic acid (prepared as described in Scheme A25, 41 mg, 0.18 mmol, 2 eq.), (1R,3S,5S)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (2-fluoro-3-trifluoromethoxy-phenyl)-amide hydrochloride (prepared as described in Scheme B29, 51 mg, 0.09 mmol, 1 eq.), and HBTU (106 mg, 0.28 mmol) in DMF (0.45 mL) was added DIPEA (64 µL, 0.37 mmol). The reaction mixture was stirred at RT for 30 min, then poured into water and extracted with EtOAc (x2). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. The material thus obtained was used in the next step without further purification. MS (UPLC/MS): 737.3 [M+H]+, 759.3 [M+Na]+, 735.2 [M-H]-; t_R (HPLC conditions f): 2.03 min.

Example 759: 1-{2-[(1R,3S,5S)-3-(3-Bromo-2-fluoro-phenylcarbamoyl)-5-hydroxymethyl -2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide



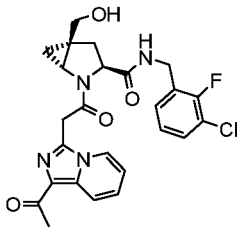
was prepared using the protocols described for the preparation of **Example 758** using 3-bromo-2-fluoro-phenylamine instead of 2-fluoro-3-trifluoromethoxy-phenylamine. R_f, TLC (CH_2Cl_2/MeOH 9:1) = 0.45; MS (UPLC/MS): 547.2/549.2 [M+NH_4]+, 552.2/554.1 [M+Na]+, 1081.3/1083.3 [2M+Na]+, 574.3/576.0 [M+HCOO]-, 1057.3/1059.3 [2M-H]-; t_R (HPLC conditions f): 1.62 min.

Example 760: 1-{2-[(1R,3S,5S)-3-(6-Bromo-pyridin-2-ylcarbamoyl)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide



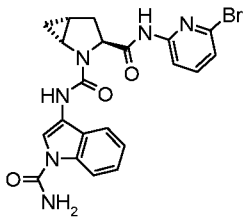
was prepared using the protocols described for the preparation of **Example 758** using 6-bromo-pyridin-2-ylamine instead of 2-fluoro-3-trifluoromethoxy-phenylamine. R_f, TLC (CH_2Cl_2/MeOH 9:1) = 0.4; MS (UPLC/MS): 513.2/515.2 [M+H]+, 530.3/532.2 [M+NH_4]+, 535.3/537.2 [M+Na]+; t_R (HPLC conditions f): 1.47 min.

Example 761: (1R,3S,5S)-2-[2-(1-Acetyl-imidazo[1,5-a]pyridin-3-yl)-acetyl]-5-hydroxy methyl-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide



was prepared using the protocols described for the preparation of **Example 758** from (1R,3S,5S)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]-hexane-2-carboxylic acid tert-butyl ester (prepared as described in Scheme B28) and (1-acetyl-imidazo[1,5-a]pyridin-3-yl)-acetic acid (prepared as described in Scheme A19). R_f, TLC (CH_2Cl_2/MeOH 9:1) = 0.40; MS (UPLC/MS): 499.4/501.4 [M+H]+, 521.4/523.4 [M+Na]+, 543.5/545.5 [M+HCOO]-; t_R (HPLC conditions f): 1.66 min.

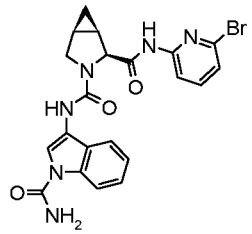
Example 762: (1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(6-bromo -pyridin-2-yl)-amide] 2-[(1-carbamoyl-1H-indol-3-yl)-amide]



To a solution of ((1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (6-bromo-pyridin-2-yl)-amide (2 TFA salt, 40 mg, 0.08 mmol) and Et_3N (44 µl, 0.31 mmol) in THF (0.4 mL) was added a suspension of 3-isocyanato-indole-1-carboxylic acid amide (25 mg, 0.08 mmol, prepared as described in Scheme A1) in THF (0.8 mL). The resulting solution was stirred at RT under nitrogen for 45 min, concentrated and purified by preparative HPLC (Waters SunFire C18-ODB, 5 µm, 19x50 mm, 20-100% CH_3CN/H_2O in 25 min, CH_3CN and H_2O both containing 0.1 % TFA flow: 40 mL/min) to give the desired material after neutralization

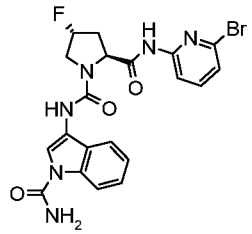
(saturated aqueous solution of $NaHCO_3$) and extraction of the purified fractions (CH_2Cl_2). TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.45; MS (LC/MS): 483.1/485.2 [M+H]+, 965.3/967.3 [2M+H]+, 481.1/483.1 [M-H]-; t_R (HPLC conditions f): 1.83 min.

Example 763: (1R,2S,5S)-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(6-bromo-pyridin-2-yl)-amide] 3-[(1-carbamoyl-1H-indol-3-yl)-amide]



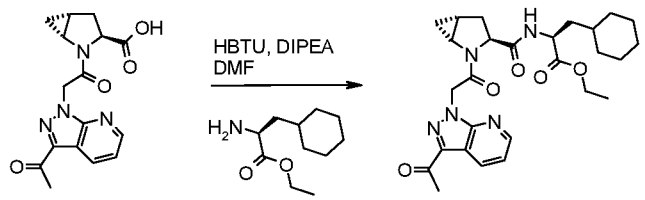
was prepared using the protocol described for the synthesis of **Example 762**; TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.55; 483.1/485.1 [M+H]+, 965.3/967.3 [2M+H]+, 481.1/483.2 [M-H]-; t_R (HPLC conditions f): 1.72 min.

Example 764: (2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-[(6-bromo-pyridin-2-yl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide]



was prepared using the protocol described for the synthesis of **Example 762**; TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.45; 489.1/491.1 [M+H]+, 506.1/508.2 [M+NH_4]+, 487.1/489.1 [M-H]-; t_R (HPLC conditions f): 1.70 min.

<u>Scheme D12: general protocol described for the preparation of Example 765: (S)-2-{{(1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0] hexane-3-carbonyl}-amino)-3-cyclohexyl-propionic acid ethyl ester</u>

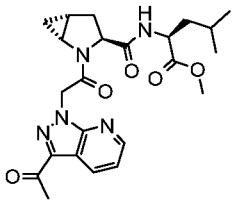
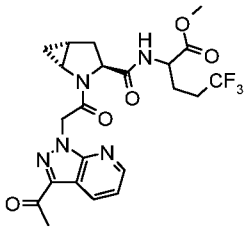
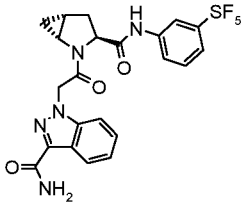


(1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (20 mg, 0.061 mmol, prepared as described in Scheme B30), (S)-2-amino-3-

cyclohexyl-propanoic acid ethyl ester (17.3 mg, 0.073 mmol) and HBTU (34.7 mg, 0.091 mmol) were dissolved in DMF (0.2 mL). DIPEA (32 µl, 0.18 mmol) was added and the reaction mixture was stirred at 25°C for 20 h. The crude material was purified by preparative HPLC (XBridge C18ODB, 5 µm, 30x100, eluent: 20% CH_3CN/ 80% H_2O to 100% CH_3CN in 12 min, CH_3CN and H_2O containing 7.3 mM of NH_3, flow 45 mL/min). The pure fractions were combined and lyophilized to give the desired material as a white powder. MS: 510.1 [M+H]+, 532.0 [M+Na]+; t_R (HPLC conditions l): 3.42 min.

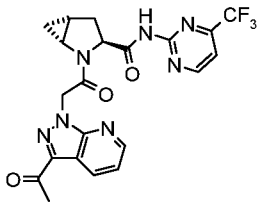
The examples below were prepared according to the general procedures described in Scheme D12 for **Example 765** *using commercially available building blocks, if not otherwise stated:*

Table 11:

Example	Structure	Name	Characterization MS (LC/MS); t_R (HPLC conditions)
766		(S)-2-({(1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0] hexane-3-carbonyl}-amino)-4-methyl-pentanoic acid methyl ester	456.0 [M+H]+, 478.0 [M+Na]+; t_R (l): 2.812 min.
767		2-({(1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0] hexane-3-carbonyl}-amino)-5,5,5-trifluoro-pentanoic acid methyl ester	496.0 [M+H]+, 518.0 [M+Na]+; t_R (l): 2.813 min.
768		1-{2-[(1R,3S,5R)-3-(3-Sulfur pentafluoride -phenyl-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indazole-3-carboxylic acid amide	(1,2) 530 [M+H]+; t_R (k): 3.45 min.

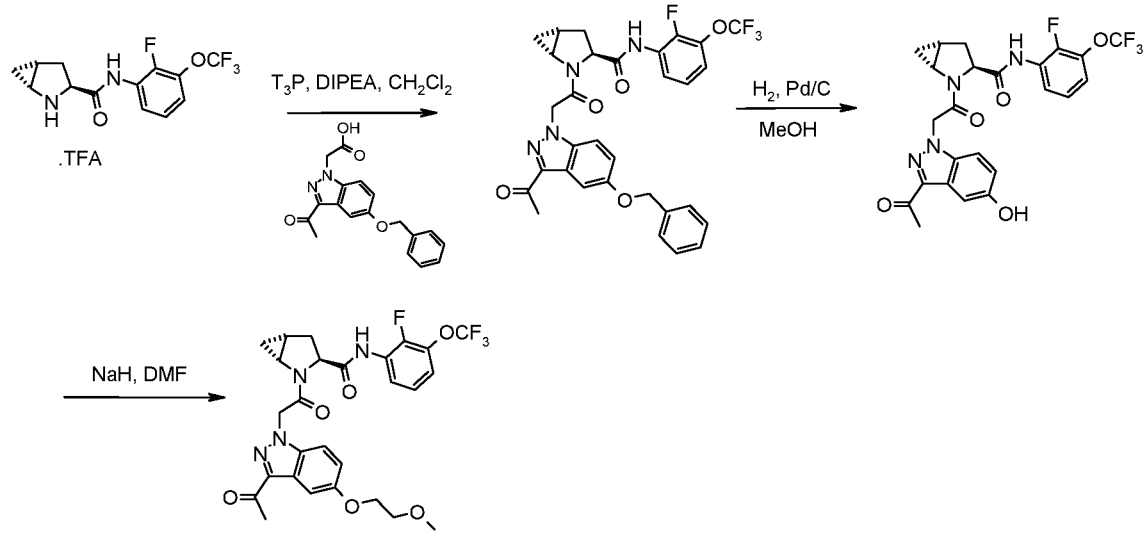
(1) The reaction was performed at 40°C, (2) The acid derivative used as starting material was prepared according to Scheme B31.

Example 769: (1R,3S,5R)-2-[2-(3-Acetyl-pyrazolo[3,4-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (4-trifluoromethyl-pyrimidin-2-yl)-amide



To a solution of (1R,3S,5R)-2-[2-(3-acetyl-pyrazolo[3,4-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (50 mg, 0.15 mmol, prepared as described in part B) in CH_2Cl_2 (3 mL) was added 1-chloro-N,N,2-trimethylprop-1-en-1-amine (81 mg, 0.609 mmol) at 0°C under nitrogen atmosphere. After stirring at 0°C for 1h, 4-(trifluoromethyl)pyrimidin-2-amine (27.3 mg, 0.17 mmol) followed by DIPEA (0.053 ml, 0.305 mmol) were added and the mixture was stirred at RT for 16 h. The mixture was concentrated and the residue was purified by preparative HPLC (Waters Sunfire C18-ODB, 5um, 30x100mm, flow: 40 mL/min, gradient: 0-18.5 min 5% to 100% CH_3CN, 18.5-20 min 100% CH_3CN, H_2O and CH_3CN containing 0.1% TFA). The pure fractions were combined, neutralized with an aqueous saturated solution of Na_2CO_3, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated. MS (UPLC-MS): 474.3 [M+H]+, 472.3 [M-H]-; t_R (HPLC conditions f): 1.81 min.

Scheme D13: general protocol described for the preparation of Example 770: (1R,3S,5R)-2-{2-[3-Acetyl-5-(2-methoxy-ethoxy)-indazol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (2-fluoro-3-trifluoromethoxy-phenyl)-amide



A. (1R,3S,5R)-2-[2-(3-Acetyl-5-benzyloxy-indazol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0] hexane-3-carboxylic acid (2-fluoro-3-trifluoromethoxy-phenyl)-amide

To a solution of (3-acetyl-5-benzyloxy-indazol-1-yl)-acetic acid (1.38 g, 4.30 mmol, prepared as described in Part A), (1R,3S,5R)-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (2-fluoro-3-trifluoro methoxy-phenyl)-amide trifluoroacetate (1.80 g, 4.30 mmol) and propylphosphonic anhydride (50% in EtOAc, 3.80 ml, 6.46 mmol) in CH_2Cl_2 (40 ml) was added DIPEA (2.25 mL, 12.91 mmol) and the resulting mixture was stirred at RT for 2 h. The mixture was concentrated and the crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 1:0 to 0:1). MS (UPLC-MS): 611 [M+H]+; t_R (HPLC conditions f): 2.40 min.

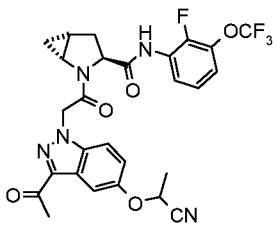
B. (1R,3S,5R)-2-[2-(3-Acetyl-5-hydroxy-indazol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (2-fluoro-3-trifluoromethoxy-phenyl)-amide

A mixture of (1R,3S,5R)-2-[2-(3-acetyl-5-benzyloxy-indazol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (2-fluoro-3-trifluoromethoxy-phenyl)-amide (2.0 g, 3.28 mmol) and Pd/C (10%, 165 mg) in MeOH (40 mL) was stirred under a H_2 atmosphere for 1 h. The mixture was filtered through a celite pad and concentrated. The product was used in the next step without further purification. MS (UPLC-MS): 521 [M+H]+; t_R (HPLC conditions f): 2.02 min.

C. Example 770: (1R,3S,5R)-2-{2-[3-Acetyl-5-(2-methoxy-ethoxy)-indazol-1-yl]-acetyl}-2-aza-bicyclo [3.1.0]hexane-3-carboxylic acid (2-fluoro-3-trifluoromethoxy-phenyl)-amide

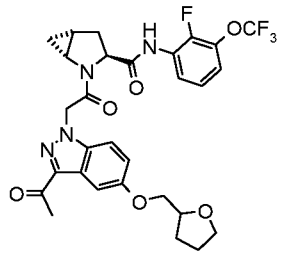
To a suspension of sodium hydride (60% in Mineral oil, 4.8 mg, 0.121 mmol) in DMF (5 mL) at 0°C was added 1R,3S,5R)-2-[2-(3-acetyl-5-hydroxy-indazol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (2-fluoro-3-trifluoromethoxy-phenyl)-amide (60 mg, 0.115 mmol). After stirring for 5 min, 1-bromo-2-methoxyethane (0.016 mL, 0.173 mmol) was added and the reaction mixture was stirred at RT for 16 h. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by preparative HPLC (Waters Sunfire C18-ODB, 5um, 30x100mm, flow: 40 mL/min, gradient: 0-18.5 min 5% to 100% CH_3CN, 18.5-20 min 100% CH_3CN, H_2O and CH_3CN containing 0.1% TFA). Further purification by flash chromatography on silica gel (c-hexane/EtOAc 1:0 to 0:1) afforded the title compound. MS (UPLC-MS): 579.3. t_R (HPLC conditions f): 2.07 min.

Example 771: (1R,3S,5R)-2-{2-[3-Acetyl-5-(cyano-methyl-methoxy)-indazol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (2-fluoro-3-trifluoromethoxy-phenyl)-amide



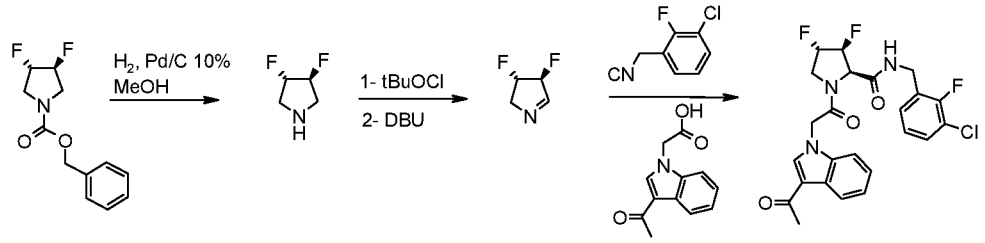
was prepared using the protocol described for the synthesis of **Example 770** in Scheme A13. The crude residue was purified by flash column chromatography on silica gel (c-hexane/EtOAc 1:0 to 0:1). MS (UPLC-MS): 572.2 [M-H]-; t_R (HPLC conditions f): 2.15 min.

Example 772: (1R,3S,5R)-2-{2-[3-Acetyl-5-(tetrahydro-furan-2-ylmethoxy)-indazol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (2-fluoro-3-trifluoromethoxy-phenyl)-amide



was prepared using the protocol described for the synthesis of **Example 770** in Scheme D13 with the following procedure for Step C. To a suspension of sodium hydride (60% in Mineral oil, 4.8 mg, 0.121 mmol) in DMF (5 mL) at 0°C was added 1R,3S,5R)-2-[2-(3-acetyl-5-hydroxy-indazol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (2-fluoro-3-trifluoromethoxy-phenyl)-amide (60 mg, 0.115 mmol). After stirring for 5 min, 2-(bromomethyl)tetrahydrofuran (28.5 mg, 0.173 mmol) was added and the reaction mixture was stirred at RT for 16 h. Additional portions of NaH (60% in Mineral oil, 4.6 mg, 0.115 mmol) and 2-(bromomethyl) tetrahydrofurane (19.0 mg, 0.115 mmol) were added and the resulting mixture was stirred at RT for 16 h. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by preparative HPLC (Waters Sunfire C18-ODB, 5um, 30x100mm, flow: 40 mL/min, gradient: 0-18.5 min 5% to 100% CH_3CN, 18.5-20 min 100% CH_3CN, H_2O and CH_3CN containing 0.1% TFA). MS (UPLC-MS): 605.4. t_R (HPLC conditions f): 2.20 min.

Scheme D14: general protocol described for the preparation of Example 773: (2R,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-3,4-difluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide



A. (3S,4S)-3,4-Difluoro-pyrrolidine

To a solution of (3S,4S)-3,4-Difluoro-pyrrolidine-1-carboxylic acid benzyl ester (ACS Scientific Inc., cat # 6-0511, 3 g, 12.44 mmol) in MeOH (41 mL) was added Pd/C 10 % (500 mg) and the

solution was degassed 3 times replacing air by nitrogen and finally nitrogen by hydrogen. The reaction mixture was further stirred under hydrogen atmosphere for 3 days. After completion, the solution was degassed 3 times replacing hydrogen by nitrogen and the catalyst was removed through a pad of Celite. The resulting solution of volatil (3S,4S)-3,4-difluoro-pyrrolidine in MeOH (approx. 0.209 mol/L) was stored in the fridge and used without further treatment in the next step. R_f (EtOAc): 0.1.

B. (3S,4S)-3,4-difluoro-3,4-dihydro-2H-pyrrole

To a solution of (3S,4S)-3,4-difluoro-pyrrolidine (0.209 M in MeOH, 2.5 mL, 0.52 mmol) in a flask protected with an aluminium sheet at 0°C under argon was added tBuOCl (73 µL, 0.52 mmol). The reaction mixture was stirred at 0°C for 1 h; until TLC (CH_2Cl_2/MeOH 9:1) indicated consumption of the starting material. DBU (79 µL, 0.52 mmol) was then added at 0°C to the resulting solution of (3S,4S)-1-chloro-3,4-difluoro-pyrrolidine and the mixture was allowed to reach RT and further stirred for 3 h. The solution thus obtained was used in the next step.

C. Example 773: (2R,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-3,4-difluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide

To the crude solution of (3S,4S)-3,4-difluoro-3,4-dihydro-2H-pyrrole (0.52 mmol) in MeOH under argon were successively added (3-acetyl-indol-1-yl)-acetic acid (57 mg, 0.26 mmol) and 1-chloro-2-fluoro-3-(isocyanomethyl)benzene (44 mg, 0.26 mmol) in MeOH (0.2 mL). The reaction mixture was stirred at RT for 60 h and poured into a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (x2). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash column chromatography on silica gel (Gold RediSep column, 24 g, CH_2Cl_2 to CH_2Cl_2/ MeOH 95-5), the fractions containing the desired material as a mixture of 2 diastereosiomers were concentrated and the residue was purified again by preparative HPLC (Waters Sunfire C18-OBD, 5 µm, 30x100 mm, eluent: 5% to 100% CH_3CN in H_2O in 25 min, CH_3CN and H_2O containing 0.1 % TFA, flow: 40 mL/min) to give (2S,3S,4S)-1-[2-(3-acetyl-indol-1-yl)-acetyl]-3,4-difluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide: R_f (EtOAc): 0.60; MS (UPLC): 492.2/494.2 [M+H]+, 536.2/538.2 [M+HCOO]- and (2R,3S,4S)-1-[2-(3-acetyl-indol-1-yl)-acetyl]-3,4-difluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide; R_f (EtOAc): 0.50; MS (UPLC): 492.2/494.2 [M+H]+, 536.2/538.2 [M+HCOO]-; t_R (HPLC conditions a): 3.37 min. The absolute stereochemistry has been assigned tentatively based on comparison of ^{1}H-NMR spectra and test results in the biological assay measured for both diastereosiomers.

1H NMR and HRMS data for selected compounds:

^{1}H NMR spectra were recorded using a Bruker Avance DPX 400 and II 600 Spectrometers.

Example 1: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.65 (t, 1H), 8.35 (s, 1H), 8.27 (d, 1H), 8.00 (s, 1H), 7.74 (d, 1H), 7.34 - 7.54 (m, 4H), 7.26 (m, 1H), 7.08 - 7.21 (m, 2H), 5.51-5.38 (m, 1H), 4.55 (t, 1H), 4.27 - 4.46 (m, 2H), 3.92 - 4.07 (m, 1H), 3.89-3.96 (m, 1H), 2.5 (m, 1H), 1.97 - 2.19 (m, 1H).

Example 26: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.28 (m, 2H), 8.20 (s, 1H), 7.98 (s, 1H), 7.72 (d, 1H), 7.34 - 7.57 (m, 4H), 7.26 (t, 1H), 7.06 - 7.23 (m, 2H), 4.24 - 4.52 (m, 3H), 3.82 (dd, 1H), 3.69 (m, 1H), 3.53 (dd, 1H), 2.4 (m, 1H), 1.78 (m, 1H).

Example 73: HRMS: 497.2294 [M+H]+ (calcd 497.2296 for $C_{28}H_{28}N_6O_3$).

Example 107: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.19 - 8.34 (m, 2H), 7.98 (s, 2H), 7.69 - 7.86 (m, 4H), 7.64 (t, 1H), 7.41 (br.s, 2H), 7.26 (t, 1H), 7.18 (t, 1H), 5.44-5.30 (m, 1H), 4.16 (m, 1H), 3.93 (m, 1H), 3.49 - 3.76 (m, 1H), 3.18 (m, 1H), 3.03 (m, 1H), 2.29 (m, 1H), 1.94 - 2.20 (m, 1H).

Example 124: HRMS: 476.1539 [M+H]+ (calcd 476.1540 for $C_{22}H_{20}F_3N_5O_4$), 498.1358 [M+Na]+ (calcd 498.1360 for $C_{22}H_{20}F_3N_5O_4Na$), 493.1805 [M+NH_4]+ (calcd 493.1806 for $C_{22}H_{20}F_3N_5O_4NH_4$); t_R (HPLC conditions a) 3.46 min.

Example 133: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.42 - 8.56 (m, 2H), 8.18 (d, 1H), 8.01 (s, 1H), 7.29 - 7.53 (m, 5H), 7.16 (t, 1H), 6.93 (dd, 1H), 4.75 (dd, 2H), 4.23 - 4.46 (m, 1H), 4.16 (dd, 1H), 3.81 (m, 1H), 3.71 (s, 3H), 2.34 (m, 1H), 2.10 (m, 1H), 1.80 (m, 1H), 0.84 (m, 1H), 0.56 (m, 1H).

Example 134: HRMS: 488.1539 [M+H]+ (calcd 488.1540 for $C_{23}H_{20}F_3N_5O_4$), 510.1358 [M+Na]+ (calcd 510.1360 for $C_{23}H_{20}F_3N_5O_4Na$), 505.1805 [M+NH_4]+ (calcd 505.1806 for $C_{23}H_{20}F_3N_5O_4NH_4$).

Example 136: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.38 - 8.54 (m, 2H), 8.17 (d, 1H), 7.99 (s, 1H), 7.46 (t, 1H), 7.25 - 7.42 (m, 4H), 7.16 (t, 1H), 6.89 (dd, 1H), 4.23 - 4.46 (m, 2H), 4.16 (dd, 1H), 3.83 (m, 1H), 3.78 (s, 3H), 2.33 (dd, 1H), 2.09 (m, 1H), 1.78 (m, 1H), 0.84 (m, 1H), 0.56 (m, 1H).

Example 141: HRMS: 488.1539 [M+H]+ (calcd 488.1540 for $C_{23}H_{20}F_3N_5O_4$), 510.1358 [M+Na]+ (calcd 510.1360 for $C_{23}H_{21}N_4O_4F_3Na$).

Example 148: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.07 (s, 1H), 8.64 (s, 1H), 8.27 (d, 1H), 8.00 (s, 2H), 7.80 (d, 1H), 7.49 - 7.59 (m, 1H), 7.38 (br.s, 2H), 7.11 - 7.30 (m, 4H), 4.18 (t, 1H), 3.88 - 3.97 (m, 1H), 2.29 - 2.41 (m, 1H), 2.08 - 2.21 (m, 1H), 1.74 - 1.88 (m, 1H), 0.77 - 0.89 (m, 1H), 0.50 - 0.65 (m, 1H).

Example 155: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.55 (m, 2H), 8.28 (d, 1H), 8.00 (s, 1H), 7.79 (d, 1H), 7.43 (br.s, 2H), 7.27 (t, 1H), 7.19 (t, 1H), 6.94 (d, 1H), 6.84 (d, 1H), 4.35 (m, 1H), 4.14 (dd, 1H), 3.80 (m, 1H), 2.30 (dd, 1H), 2.09 (m, 1H), 1.77 (m, 1H), 0.84 (m, 1H), 0.54 (m, 1H).

Example 158: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.16 (s, 1H), 8.68 (s, 1H), 8.29 (d, 1H), 8.01 (s, 1H), 7.92 (d, 1H), 7.80 (d, 1H), 7.70 (t, 1H), 7.40 (br.s, 2H), 7.23 - 7.32 (m, 1H), 7.20 (t, 1H), 6.99 (d, 1H), 4.38 (t, 1H), 3.93 (m, 1H), 2.68 (q, 2H), 2.39 (m, 1H), 2.19 (m, 1H), 1.80 (m, 1H), 1.22 (t, 3H), 0.84 (m, 1H), 0.54 (m, 1H).

Example 166: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.57 (s, 1H), 8.46 (t, 1H), 8.29 (d, 1H), 8.01 (s, 1H), 7.79 (d, 1H), 7.39 - 7.55 (m, 3H), 7.35 (t, 1H), 7.27 (m, 1H), 7.18 (m, 2H), 4.25 - 4.48 (m, 2H), 4.17 (dd, 1H), 3.83 (m, 1H), 2.33 (dd, 1H), 2.11 (m, 1H), 1.79 (m, 1H), 0.85 (m, 1H), 0.56 (m, 1H).

Example 170: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.49 (t, 1H), 8.25 (d, 1H), 8.10 (s, 1H), 7.97 (s, 1H), 7.72 (d, 1H), 7.36 - 7.54 (m, 3H), 7.33 (t, 1H), 7.23 (t, 1H), 7.12 (m, 2H), 4.20-4.49 (m, 3H), 3.69 (m, 1H), 3.53 (m, 1H), 2.13 (m, 1H), 1.73-2.02 (m, 3H).

Example 175: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.98 (s, 1H), 8.68 (s, 1H), 8.29 (d, 1H), 7.91 - 8.04 (m, 2H), 7.80 (d, 1H), 7.43 (br.s, 2H), 7.24 - 7.36 (m, 3H), 7.20 (t, 1H), 4.40 (dd, 1H), 3.84 - 3.96 (m, 1H), 2.31 - 2.43 (m, 1H), 2.17 - 2.27 (m, 1H), 1.77 - 1.88 (m, 1H), 0.81 - 0.92 (m, 1H), 0.53 - 0.64 (m, 1H).

Example 176: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.88 (s, 1H), 8.68 (s, 1H), 8.29 (d, 1H), 8.01 (s, 1H), 7.88 (t, 1H), 7.80 (d, 1H), 7.43 (br.s, 2H), 7.16 - 7.37 (m, 4H), 4.35 - 4.44 (m, 1H), 3.87 - 3.95 (m, 1H), 2.32 - 2.43 (m, 1H), 2.16 - 2.27 (m, 1H), 1.78 - 1.87 (m, 1H), 0.82 - 0.91 (m, 1H), 0.55 - 0.63 (m, 1H).

Example 178: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.65 (br.s, 1H), 8.50 (br.s, 1H), 8.26 (d, 1H), 7.97 (br.s, 1H), 7.71 (d, 1H), 6.99 - 7.57 (m, 7H), 5.54 (br.s, 1H), 4.17 - 4.50 (m, 2H), 4.00 (br.s, 2H), 3.20 (br.s, 2H).

Example 181: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.65 (t, 1H), 8.34 (br.s, 1H), 8.27 (d, 1H), 8.00 (s, 1H), 7.76 (d, 1H), 7.41 - 7.55 (m, 3H), 7.37 (t, 1H), 7.26 (t, 1H), 7.04 - 7.21 (m, 2H), 5.36 (t, 1H), 4.59 (t, 1H), 4.37 - 4.49 (m, 1H), 4.21 - 4.37 (m, 1H), 3.81 - 3.94 (m, 1H), 3.53 - 3.81 (m, 3H), 2.34-2.40 (m, 1H), 1.97 - 2.18 (m, 1H).

Example 183: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.56 (s, 1H), 8.45 (t, 1H), 8.28 (d, 1H), 8.02 (s, 1H), 7.80 (d, 1H), 7.44 (m, 2H), 7.22 - 7.38 (m, 5H), 7.18 (t, 1H), 4.30 (m, 1H), 4.17 (dd, 1H), 3.82 (m, 1H), 2.33 (dd, 1H), 2.12 (m, 1H), 1.78 (br.s, 1H), 0.86 (m, 1H), 0.56 (dt, 1H).

Example 184: ^{1}H NMR (400 MHz, DMSO-d_6): 8.54 (s, 1H), 8.47 (m, 1H), 8.28 (d, 1H), 8.01 (s, 1H), 7.81 (d, 1H), 7.47 (t, 1H), 7.44 (m, 2H), 7.36 (t, 1H), 7.27 (t, 1H), 7.18 (t, 2H), 4.36 (m, 2H), 4.23 (m, 1H), 3.77 (m, 1H), 3,45 (d, 1H), 3.36 (d, 1H), 3.29 (s, 3H), 2.39 (dd, 1H), 2.10 (dd, 1H), 0.95 (m, 1H), 0.82 (m, 1H).

Example 186: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.47 (t, 1H), 8.27 (d, 1H), 8.12 (s, 1H), 7.99 (s, 1H), 7.73 (d, 1H), 7.34 - 7.52 (m, 4H), 7.26 (t, 1H), 7.09 - 7.20 (m, 2H), 4.59 (d, 1H), 4.27 - 4.47 (m, 2H), 4.11 - 4.19 (m, 1H), 3.72 - 3.82 (m, 1H), 3.50 - 3.61 (m, 1H), 3.34 (s, 3H), 2.03 - 2.23 (m, 2H).

Example 190: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.56 (t, 1H), 8.37 (s, 1H), 8.28 (d, 1H), 8.02 (s, 1H), 7.80 (d, 1H), 7.33 - 7.52 (m, 4H), 7.26 (t, 1H), 7.10 - 7.20 (m, 2H), 5.32 - 5.58 (m, 1H), 4.59 - 4.71 (m, 1H), 4.30 - 4.48 (m, 2H), 3.81 - 3.91 (m, 1H), 3.69 - 3.79 (m, 1H), 2.15 - 2.32 (m, 2H).

Example 194: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.63 (s, 1H), 8.68 (d, 1H), 8.45 (s, 1H), 8.39 - 8.43 (m, 2H), 8.26 (d, 1H), 7.97 (s, 1H), 7.76 (d, 1H), 7.41 (br.s, 2H), 7.25 (t, 1H), 7.17 (t, 1H), 5.51 (d, 1H), 4.55 - 4.68 (m, 1H), 3.74 - 4.14 (m, 2H), 2.53 - 2.64 (m, 1H), 2.04 - 2.28 (m, 1H).

Example 195: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.56 (s, 1H), 8.45 (t, 1H), 8.29 (d, 1H), 8.01 (s, 1H), 7.79 (d, 1H), 7.44 (br.s, 2H), 7.23 - 7.36 (m, 2H), 7.11 - 7.23 (m, 3H), 4.27 - 4.48 (m, 2H), 4.18 (dd, 1H), 3.81 (m, 1H), 2.33 (dd, 1H), 2.12 (m, 1H), 1.78 (m, 1H), 0.87 (m, 1H), 0.56 (m, 1H).

Example 200: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.52 (m, 1H), 8.23 (m, 2H), 7.97 (s, 1H), 7.75 (d, 1H), 7.28 - 7.51 (m, 4H), 7.22 (t, 1H), 7.04 - 7.18 (m, 2H), 4.32 - 4.50 (m, 2H), 4.18 - 4.32 (m, 1H), 3.96 (t, 1H), 3.80 (t, 1H), 3.61 (s, 3H), 3.31 (m, 2H), 2.08 (m, 1H).

Example 203: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.53 (s, 1H), 8.19 - 8.33 (m, 2H), 7.95 (s, 1H), 7.74 (d, 1H), 7.34 - 7.52 (m, 4H), 7.27 (t, 1H), 6.96 - 7.23 (m, 2H), 5.12 (m, 1H), 5.02 (t, 1H), 4.24 (dd, 1H), 3.79 (m, 1H), 3.58 (m, 2H), 2.21 - 2.31 (m, 1H), 2.07 - 2.17 (m, 1H), 1.77 (m, 1H), 0.85 (m, 1H), 0.53 (m, 1H).

Example 205: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.65 (t, 1H), 8.32 (s, 1H), 8.27 (d, 1H), 8.00 (s, 1H), 7.75 (d, 1H), 7.32 - 7.57 (m, 4H), 7.26 (t, 1H), 7.06 - 7.21 (m, 2H), 4.57 (t, 1H), 4.38 - 4.50 (m, 1H), 4.23 - 4.38 (m, 1H), 3.97 (dd, 1H), 3.61 - 3.80 (m, 1H), 2.4 (m, 1H), 1.86 - 2.14 (m, 1H), 1.57 (d, 3H).

Example 208: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.87 (t, 1H), 8.24 - 8.32 (m, 2H), 7.99 (s, 1H), 7.73 (d, 1H), 7.38 - 7.52 (m, 3H), 7.31 - 7.37 (m, 1H), 7.23 - 7.30 (m, 1H), 7.11 - 7.20 (m, 2H), 5.13 - 5.36 (m, 1H), 4.62 - 4.74 (m, 1H), 4.29 - 4.45 (m, 2H), 3.87 - 3.97 (m, 1H), 3.60 - 3.72 (m, 1H), 2.07 - 2.36 (m, 2H).

Example 210: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.41 (t, 1H), 8.27 (d, 1H), 8.14 (s, 1H), 7.98 (s, 1H), 7.74 (d, 1H), 7.45 (m, 4H), 7.25 (t, 1H), 7.15 (m, 2H), 4.37 - 4.49 (m, 2H), 4.25 - 4.37 (m, 1H), 3.93 (d, 1H), 3.64 (dd, 1H), 1.91 (m, 1H), 1.78 (m, 1H), 0.73 (q, 1H), 0.63 (m, 1H).

Example 213: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.24 - 8.33 (m, 2H), 8.08 (s, 1H), 7.99 (s, 1H), 7.73 (d, 1H), 7.53 (t, 1H), 7.37 - 7.48 (m, 3H), 7.26 (t, 1H), 7.16 (t, 1H), 7.08 (t, 1H), 5.35 (d, 1H), 4.30 - 4.52 (m, 4H), 3.74 - 3.84 (m, 1H), 3.50 - 3.60 (m, 1H), 1.96 - 2.16 (m, 2H).

Example 216: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.53 (s, 1H), 8.46 (t, 1H), 7.88 (m, 2H), 7.68 (d, 1H), 7.27 - 7.57 (m, 4H), 7.18 (t, 1H), 6.83 (dd, 1H), 4.22 - 4.47 (m, 2H), 4.16 (dd, 1H), 3.79 (m, 4H), 2.32 (m, 1H), 2.02 - 2.17 (m, 1H), 1.77 (m, 1H), 0.84 (m, 1H), 0.54 (m, 1H).

Example 218: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.00 (s, 1H), 8.68 (s, 1H), 8.29 (d, 1H), 8.17 - 8.25 (m, 1H), 8.00 (s, 1H), 7.80 (d, 1H), 7.34 - 7.57 (m, 4H), 7.23 - 7.31 (m, 1H), 7.16 - 7.23 (m, 1H), 4.34 - 4.46 (m, 1H), 3.85 - 3.95 (m, 1H), 2.31 - 2.43 (m, 1H), 2.19 - 2.29 (m, 1H), 1.77 - 1.88 (m, 1H), 0.81 - 0.92 (m, 1H), 0.55 - 0.64 (m, 1H).

Example 223: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 8.52 (s, 1H), 8.34 (d, 1H), 8.27 (d, 1H), 7.95 (s, 1H), 7.74 (d, 1H), 7.48 - 7.41 (m, 4H), 7.27 (t, 1H), 7.22 - 7.16 (m, 2H), 5.19 (m, 1H), 4.18 (dd, 1H), 3.79 (m, 1H), 3,40 (2H under H_2O signal), 2.28 (dd, 1H), 2.10 – 2.04 (m, 1H), 1.92 – 1.73 (m, 3H), 0.85 (m, 1H), 0.53 (m, 1H).

Example 237: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.71 (br.s, 1H), 8.48 (s, 2H), 8.35 (s, 1H), 8.26 (d, 1H), 8.02 (s, 1H), 7.88 (br.s, 1H), 7.75 (d, 1H), 7.42 (br.s, 2H), 7.26 (t, 1H), 7.16 (t, 1H), 5.27 - 5.66 (m, 1H), 4.53 (m, 1H), 4.37 (m, 2H), 4.01 (m, 1H), 3.73 - 3.93 (m, 1H), 2.08 - 2.24 (m, 1H), 1.94 - 2.08 (m, 1H).

Example 258: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.53 (s, 1H), 8.37 (t, 1H), 8.29 (d, 1H), 8.01 (s, 1H), 7.79 (d, 1H), 7.44 (br.s, 2H), 7.15 - 7.34 (m, 5H), 4.22 - 4.39 (m, 2H), 4.20 (dd, 1H), 3.81 (m, 1H), 2.31 (m, 1H), 2.13 (m, 1H), 1.77 (m, 1H), 0.85 (m, 1H), 0.54 (td, 1H).

Example 274: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.22 (br.s, 1H), 8.43 (br.s, 1H), 8.27 (d, 1H), 7.94 - 8.06 (m, 2H), 7.77 (d, 1H), 7.41 (br.s, 2H), 7.13 - 7.34 (m, 4H), 5.39 - 5.62 (m, 1H), 4.83 (t, 1H), 3.79 - 4.14 (m, 2H), 2.58 - 2.65 (m, 1H), 2.06 - 2.30 (m, 1H).

Example 285: HRMS: 446.2186 [M+H]+ (calcd 446.2187 for $C_{25}H_{27}N_5O_3F_3$), 468.2005 [M+Na]+ (calcd 468.2006 for $C_{25}H_{27}N_5O_3Na$); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.83 (s, 1H), 8.62 (s, 1H), 8.29 (d, 1H), 8.02 (s, 1H), 7.81 (d, 1H), 7.53 (br. s, 1H), 7.47 (d, 1H), 7.38 (br. s, 2H), 7.12 - 7.31 (m, 3H), 6.93 (d, 1H), 4.23 (t, 1H), 3.93 (br. s, 1H), 2.85 (m, 1H), 2.35 (m, 1H), 2.20 (m, 1H), 1.82 (br. s, 1H), 1.20 (d, 6H), 0.86 (br. s, 1H), 0.58 (br. s, 1H).

Example 294: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.56 (s, 1H), 8.47 (t, 1H), 8.26 - 8.32 (m, 1H), 8.09 (s, 1H), 7.61 - 7.66 (m, 1H), 7.42 - 7.58 (m, 3H), 7.35 (t, 1H), 7.08 - 7.20 (m, 2H), 4.26 - 4.45 (m, 2H), 4.13 - 4.20 (m, 1H), 3.75 - 3.82 (m, 1H), 2.28 - 2.37 (m, 1H), 2.06 - 2.15 (m, 1H), 1.74 - 1.84 (m, 1H), 0.82 - 0.90 (m, 1H), 0.52 - 0.60 (m, 1H).

Example 298: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 10.22 (s, 1H), 8.33 (s, 1H), 8.15 (d, 1H), 7.93 - 8.05 (m, 2H), 7.22 - 7.41 (m, 5H), 6.83 - 6.91 (m, 1H), 5.39 - 5.62 (m, 1H), 4.83 (t, 1H), 3.80 - 4.13 (m, 2H), 3.78 (s, 3H), 2.54 - 2.66 (m, 1H), 2.07 - 2.29 (m, 1H).

Example 300: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.41 - 8.49 (m, 2H), 8.16 (d, 1H), 8.00 (s, 1H), 7.46 (m, 1H), 7.27 - 7.42 (m, 4H), 7.16 (t, 1H), 6.90 (dd, 1H), 4.24 - 4.45 (m, 2H), 4.16 (dd, 1H), 3.98 - 4.13 (m, 2H), 3.84 (m, 1H), 3.67 (t, 2H), 3.32 (s, 3H), 2.35 (m, 1H), 2.05 - 2.17 (m, 1H), 1.71 - 1.86 (m, 1H), 0.86 (m, 1H), 0.55 (m, 1H).

Example 302: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.49 (t, 1H), 8.27 (d, 1H), 7.99 (s, 1H), 7.58 (s, 1H), 7.34 – 7.52 (m, 4H), 7.19 - 7.32 (m, 2H), 7.11 (t, 1H), 6.85 (t, 1H), 4.67 - 4.85 (m,

1H), 4.28 - 4.50 (m, 2H), 2.14 - 2.32 (m, 1H), 1.83 - 1.98 (m, 2H), 1.70 - 1.82 (m, 1H), 1.58 (s, 3H), 1.44 (s, 3H).

Example 306: 1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.56 (s, 1H), 8.45 (t, 1H), 8.21 (d, 1H), 8.01 (s, 1H), 7.69 (s, 1H), 7.40 - 7.54 (m, 3H), 7.34 (t, 1H), 7.11 - 7.21 (m, 2H), 4.27 - 4.45 (m, 2H), 4.18 (dd, 1H), 4.09 (q, 2H), 3.82 (m, 1H), 3.70 (s, 2H), 2.35 (m, 1H), 2.12 (m, 1H), 1.80 (m, 1H), 1.19 (t, 3H), 0.85 (m, 1H), 0.56 (m, 1H).

Example 312: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.50 (t, 1H), 8.27 (d, 1H), 8.18 (s, 1H), 7.99 (s, 1H), 7.77 (d, 1H), 7.31 - 7.53 (m, 4H), 7.25 (t, 1H), 7.14 (m, 2H), 4.76 (t, 1H), 4.35 - 4.49 (m, 2H), 4.30 (dd, 1H), 3.83 (t, 1H), 3.37 - 3.52 (m, 3H), 2.41 (m, 1H), 2.30 (m, 1H), 1.62 (m, 1H).

Example 315: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.55 (s, 1H), 8.46 (t, 1H), 8.22 (s, 1H), 7.98 (s, 1H), 7.72 (d, 1H), 7.41 - 7.55 (m, 3H), 7.35 (m, 1H), 7.17 (t, 1H), 7.08 (dd, 1H), 4.26 - 4.46 (m, 2H), 4.17 (dd, 1H), 4.09 (q, 2H), 3.80 (m, 1H), 3.75 (s, 2H), 2.28 - 2.34 (m, 1H), 2.10 (m, 1H), 1.78 (m, 1H), 1.19 (t, 3H), 0.85 (m, 1H), 0.56 (m, 1H).

Example 331: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.57 (t, 1H), 8.27 (d, 1H), 8.19 (s, 1H), 7.99 (s, 1H), 7.76 (d, 1H), 7.31 - 7.56 (m, 4H), 7.26 (t, 1H), 7.07 - 7.21 (m, 2H), 5.33 (d, 1H), 4.44 (dd, 1H), 4.26 - 4.40 (m, 3H), 3.76 (dd, 1H), 3.57 (dd, 1H), 2.30 - 2.42 (m, 1H), 1.82 - 1.94 (m, 1H).

Example 332: HRMS: 512.1350 [M+H]+ (calcd 512.1352 for $C_{22}H_{18}F_5N_5O_4$), 534.1169 [M+Na]+ (calcd 534.1171 for $C_{22}H_{18}F_5N_5O_4Na$), 529.1617 [M+NH_4]+ (calcd 529.1617 for $C_{22}H_{18}F_5N_5O_4NH_4$).

Example 333: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.31 (s, 1H), 8.59 - 8.69 (m, 1H), 8.43 (s, 1H), 8.26 (d, 1H), 7.98 (s, 1H), 7.90 - 7.96 (m, 1H), 7.76 (d, 1H), 7.30 - 7.51 (m, 2H), 7.25 (t, 1H), 7.17 (t, 1H), 5.50 (d, 1H), 4.83 (t, 1H), 4.31 (q, 2H), 3.77 - 4.12 (m, 2H), 2.53 - 2.66 (m, 1H), 2.09 - 2.30 (m, 1H), 1.30 (t, 3H).

Example 334: HRMS: 488.1539 [M+H]+ (calcd 488.1540 for $C_{23}H_{20}F_3N_5O_4$), 510.1358 [M+Na]+ (calcd 510.1360 for $C_{23}H_{20}F_3N_5O_4Na$). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.22 (s, 1H), 8.66 (s, 1H), 8.27 (d, 1H), 8.00 (s, 1H), 7.83 (s, 1H), 7.80 (d, 1H), 7.54 (d, 1H), 7.43 (t, 1H), 7.40 (m, 2H), 7.26 (t, 1H), 7.19 (t, 1H), 7.03 (d, 1H), 4.18 (t, 1H), 3.95 (m, 1H), 2.30 (m, 1H), 2.10 (m, 1H), 1.80 (m, 1H), 0.83 (m, 1H), 0.59 (m, 1H).

Example 340: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.27 (s, 1H), 8.68 (s, 1H), 8.29 (d, 1H), 8.15 - 8.24 (m, 2H), 8.01 (s, 1H), 7.82 (d, 1H), 7.71 (s, 1H), 7.39 (br.s, 2H), 7.28 (t, 1H), 7.21 (t, 1H), 4.18 (t, 1H), 3.86 - 4.00 (m, 1H), 2.30 - 2.44 (m, 2H), 2.10 - 2.24 (m, 1H), 1.74 - 1.89 (m, 1H), 0.77 - 0.92 (m, 1H), 0.54 - 0.68 (m, 1H).

Example 343: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.32 - 10.48 (m, 1H), 8.51 - 8.59 (m, 1H), 8.48 (s, 1H), 8.25 (d, 1H), 7.97 (s, 1H), 7.86 - 7.92 (m, 1H), 7.77 (d, 2H), 7.40 (br.s, 2H),

7.23 (t, 1H), 7.15 (t, 1H), 5.48 (d, 1H), 4.87 (t, 1H), 3.76 - 4.12 (m, 2H), 2.54 - 2.65 (m, 1H), 2.03 - 2.29 (m, 1H).

Example 344: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.37 (s, 1H), 8.69 (s, 1H), 8.40 (s, 1H), 8.28 (d, 1H), 8.15 (s, 1H), 8.01 (s, 1H), 7.88 (s, 1H), 7.82 (d, 1H), 7.40 (br. s, 2H), 7.27 (t, 1H), 7.20 (t, 1H), 4.21 (t, 1H), 3.90 - 4.01 (m, 1H), 2.41 (dd, 1H), 2.19 (dt, 1H), 1.78 - 1.91 (m, 1H), 0.86 (dt, 1H), 0.58 - 0.68 (m, 1H).

Example 350: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.45 (t, 1H), 8.27 (d, 1H), 8.01 (s, 1H), 7.97 (s, 1H), 7.68 (d, 1H), 7.37 - 7.48 (m, 3H), 7.21 - 7.33 (m, 2H), 7.14 (t, 1H), 6.99 (br.s, 1H), 4.27 - 4.57 (m, 4H), 2.26 - 2.42 (m, 1H), 2.08 - 2.23 (m, 1H), 1.77 - 1.89 (m, 1H), 1.55 - 1.66 (m, 1H), 1.22 (d, 2H).

Example 358: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.53 (s, 1H), 8.39 - 8.45 (m, 1H), 8.28 (d, 1H), 8.00 (s, 1H), 7.81 (d, 1H), 7.31 - 7.54 (m, 4H), 7.27 (t, 1H), 7.17 (t, 2H), 4.29 - 4.44 (m, 2H), 4.17 - 4.26 (m, 1H), 3.69 (m, 1H), 3.49 – 3.44 (m, 2H under DMSO signal), 2.30 - 2.37 (m, 1H), 2.04 - 2.16 (m, 1H), 0.97 (m, 1H), 0.75 (m, 1H).

Example 359: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.6 (t, 1H), 8.26 (m, 2H), 7.97 (s, 1H), 7.75 (d, 1H), 7.45-7.34 (m, 4H), 7.24 (t, 1H), 7.14 (m, 2H), 6.28 - 6.05 (tt, 1H), 4.46 - 4.27 (m, 3H), 3.89 (m, 1H), 3.65 (m,1H), 2.88 (m, 1H), 2.39 (m, 1H), 1.8 (m, 1H).

Example 362: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.80 (s, 1H), 8.75 (m, 1H), 8.27 (d, 1H), 7.98 (s, 1H), 7.66 (d, 1H), 7.41 - 7.56 (m, 3H), 7.37 (t, 1H), 7.25 (t, 1H), 7.03 - 7.22 (m, 3H), 4.72 (dd, 1H), 4.21 - 4.47 (m, 2H), 3.30 (m, 1H), 2.88 (dd, 1H).

Example 371: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.09 (br.s, 1H), 8.44 (m, 2H), 8.06 (d, 1H), 7.92 (s, 1H), 7.46 (t, 1H), 7.24 - 7.40 (m, 3H), 7.19 (t, 1H), 7.11 (d, 1H), 6.75 (dd, 1H), 4.24 - 4.47 (m, 2H), 4.16 (dd, 1H), 3.80 (m, 1H), 2.31 (dd, 1H), 2.00 - 2.20 (m, 1H), 1.77 (m, 1H), 0.85 (m, 1H), 0.54 (m, 1H).

Example 374: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.95 (br.s, 1H), 8.46 (m, 2H), 8.17 (d, 1H), 8.01 (s, 1H), 7.25 - 7.55 (m, 5H), 7.17 (t, 1H), 6.92 (dd, 1H), 4.66 (m, 2H), 4.27 - 4.43 (m, 2H), 4.17 (dd, 1H), 3.82 (m, 1H), 2.33 (dd, 1H), 2.10 (m, 1H), 1.78 (m, 1H), 0.86 (m, 1H), 0.55 (d, 1H).

Example 377: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.56 (s, 1H), 8.45 (t, 1H), 8.21 (d, 1H), 8.01 (s, 1H), 7.69 (s, 1H), 7.27 - 7.57 (m, 4H), 7.17 (m, 2H), 4.26 - 4.45 (m, 2H), 4.18 (dd, 1H), 3.83 (m, 1H), 3.62 (s, 2H), 2.31 - 2.37 (m, 1H), 2.04 - 2.17 (m, 1H), 1.78 (m, 1H), 0.85 (m, 1H), 0.55 (m, 1H).

Example 378: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.28 (br.s, 1H), 8.54 (s, 1H), 8.45 (t, 1H), 8.21 (s, 1H), 7.98 (s, 1H), 7.71 (d, 1H), 7.41 - 7.54 (m, 3H), 7.35 (t, 1H), 7.17 (t, 1H), 7.08 (dd, 1H), 4.27 - 4.45 (m, 2H), 4.17 (dd, 1H), 3.81 (m, 1H), 3.66 (s, 2H), 2.24 - 2.33 (m, 1H), 2.12 (m, 1H), 1.77 (m, 1H), 0.84 (m, 1H), 0.55 (m, 1H).

Example 379: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.48 (m, 2H), 8.16 (d, 1H), 8.00 (s, 1H), 7.46 (m, 1H), 7.24 - 7.42 (m, 4H), 7.17 (t, 1H), 6.90 (dd, 1H), 4.89 (t, 1H), 4.22 - 4.46 (m, 2H), 4.16 (dd, 1H), 3.99 (m, 2H), 3.84 (m, 1H), 3.74 (q, 2H), 2.34 (m, 1H), 2.10 (m, 1H), 1.73 (m, 1H), 0.85 (m, 1H), 0.55 (m, 1H).

Example 384: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.51 (s, 1H), 8.45 (t, 1H), 8.14 (s, 1H), 7.93 (s, 1H), 7.68 (d, 1H), 7.27 - 7.55 (m, 4H), 7.18 (t, 1H), 7.05 (dd, 1H), 4.65 (t, 1H), 4.25 - 4.46 (m, 2H), 4.17 (dd, 1H), 3.81 (m, 1H), 3.63 (m, 2H), 2.83 (t, 2H), 2.26 - 2.33 (m, 1H), 2.10 (m, 1H), 1.77 (m, 1H), 0.84 (m, 1H), 0.54 (m, 1H).

Example 385: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.39 - 8.53 (m, 2H), 8.17 (d, 1H), 7.98 (s, 1H), 7.63 (s, 1H), 7.46 (t, 1H), 7.27 - 7.40 (m, 3H), 7.09 - 7.21 (m, 2H), 4.65 (t, 1H), 4.26 - 4.45 (m, 2H), 4.17 (dd, 1H), 3.83 (m, 1H), 3.64 (m, 2H), 2.81 (t, 2H), 2.27 - 2.34 (m, 1H), 2.12 (m, 1H), 1.77 (m, 1H), 0.87 (m, 1H), 0.55 (m, 1H).

Example 387: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.46 (m, 2H), 8.16 (m, 2H), 7.99 (s, 1H), 7.46 (m, 1H), 7.25 - 7.41 (m, 3H), 7.15 (t, 1H), 6.89 (dd, 1H), 4.25 - 4.45 (m, 2H), 4.16 (dd, 1H), 3.96 - 4.12 (m, 2H), 3.84 (m, 1H), 2.59 - 2.72 (m, 2H), 2.34 (m, 1H), 2.24 (s, 6H), 2.11 (m, 1H), 1.71 - 1.83 (m, 1H), 0.84 (m, 1H), 0.55 (m, 1H).

Example 388: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.47 (m, 2H), 8.17 (s, 2H), 7.98 (s, 1H), 7.45 (t, 1H), 7.34 (m, 4H), 7.14 (t, 1H), 6.90 (dd, 1H), 4,36 (m, 3H), 4,16 (m, 1H), 4.24 (dd, 1H), 4,06 (m, 3H), 3.82 (m, 1H), 2,82 (m, 2H), 2,34 (m, 1H), 2,10 (m, 1H), 1,78 (m, 1H), 1,70 (m, 4H), 0,85 (m, 1H), 0,56 (m, 1H).

Example 392: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.28 (s, 1H), 8.43 (m, 2H), 7.78 (m, 2H), 7.56 (d, 1H), 7.47 (t, 1H), 7.35 (t, 1H), 7.30 (br.s, 2H), 7.18 (t, 1H), 6.66 (dd, 1H), 4.25 - 4.48 (m, 2H), 4.16 (m, 1H), 3.79 (m, 1H), 2.31 (dd, 1H), 2.03 - 2.13 (m, 1H), 1.70 - 1.83 (m, 1H), 0.85 (m, 1H), 0.52 (m, 1H).

Example 394: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.53 (s, 1H), 8.44 (t, 1H), 7.88 (s, 1H), 7.82 (d, 1H), 7.68 (d, 1H), 7.27 - 7.49 (m, 4H), 7.16 (t, 1H), 6.85 (dd, 1H), 4.79 (s, 2H), 4.22 - 4.45 (m, 2H), 4.14 (dd, 1H), 3.78 (m, 1H), 3.70 (s, 3H), 2.32 (m, 1H), 1.98 - 2.15 (m, 1H), 1.77 (m, 1H), 0.83 (m, 1H), 0.54 (m, 1H).

Example 395: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.52 (s, 1H), 8.45 (t, 1H), 7.88 (m, 2H), 7.68 (d, 1H), 7.26 - 7.55 (m, 4H), 7.18 (t, 1H), 6.84 (dd, 1H), 4.88 (br.s, 1H), 4.26 - 4.46 (m, 2H), 4.16 (dd, 1H), 4.00 (t, 2H), 3.70 - 3.85 (m, 3H), 2.32 (dd, 1H), 2.02 - 2.18 (m, 1H), 1.77 (m, 1H), 0.85 (m, 1H), 0.55 (m, 1H).

Example 396: HRMS: 494.1648 [M+H]+ (calcd 491.1649 for C22H21F3N6O4).

Example 409: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.57 (t, 1H), 8.28 (m, 3H), 8.02 (s, 1H), 7.8 (d, 1H), 7.4 (t, 2H), 7.3 (t, 1H), 7.2 (t, 1H), 7.15 (m, 2H), 4.7 (d, 1H), 4.4 (d, 2H), 3.94 (m, 2H), 3.0 (d, 2H), 2.4 (t, 1H), 2.3 (t, 1H).

Example 412: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.7 (t, 1H), 8.53 (s, 1H), 8.35 (d, 1H), 7.87 (m, 2H), 7.47 (t, 1H), 7.41 (t, 1H), 7.36 (t, 1H), 7.28 (t, 1H), 7.12 (t, 1H), 4.60 (t, 1H), 4.37 (m, 2H), 3.97 (dd, 1H), 3.80 (dd, 1H), 3.0 (dd, 2H), 2.61 (s, 3H), 2.45 (m, 1H), 2.07 (m, 1H).

Example 415: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.81 - 7.92 (m, 3H), 7.41 - 7.57 (m, 2H), 7.33 - 7.41 (m, 1H), 7.23 - 7.33 (m, 1H), 7.04 - 7.17 (m, 1H), 4.54 - 4.64 (m, 2H), 4.40 (dd, 2H), 4.09 - 4.17 (m, 1H), 3.94 - 3.66 (m, 2H), 2.61 (s, 3H).

Example 417: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.80 (t, 1H), 8.26 - 8.32 (m, 2H), 8.16 (br.s, 2H), 7.95 (s, 1H), 7.72 (d, 1H), 7.41 - 7.51 (m, 4H), 7.22 - 7.30 (m, 1H), 7.10 - 7.17 (m, 2H), 4.49 - 4.62 (m, 2H), 4.31 - 4.42 (m, 1H), 3.84 - 3.99 (m, 2H), 3.56 - 3.67 (m, 1H), 2.28 - 2.37 (m, 1H), 2.01 - 2.14 (m, 1H).

Example 430: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.88 (br. s, 1H), 8.23 - 8.32 (m, 1H), 8.15 (s, 1H), 7.97 (s, 1H), 7.73 (d, 1H), 7.37 - 7.51 (m, 2H), 7.24 (t, 1H), 7.09 - 7.18 (m, 2H), 4.90 (d, 1H), 4.57 (d, 1H), 4.29 - 4.47 (m, 2H), 3.81 - 3.88 (m, 1H), 3.51 - 3.64 (m, 1H).

Example 431: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.78 (br. s, 1H), 8.42 (s, 1H), 8.25 (d, 1H), 7.93 (s, 1H), 7.67 (d, 1H), 7.38 - 7.56 (m, 2H), 7.25 (t, 1H), 7.06 - 7.19 (m, 2H), 5.18 - 5.40 (m, 1H), 4.69 (d, 1H), 4.25 - 4.48 (m, 2H), 4.02 - 4.25 (m, 2H), 3.77 - 3.92 (m, 1H).

Example 432: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.80 (s, 1H), 8.54 (t, 1H), 8.27 (d, 1H), 8.03 (s, 1H), 7.60 (d, 1H), 7.37 - 7.54 (m, 3H), 7.34 (t, 1H), 7.27 (t, 1H), 7.06 - 7.23 (m, 2H), 5.43 (dd, 1H), 4.48 (t, 1H), 4.24 - 4.44 (m, 2H), 3.22 (m, 1H), 2.63 - 2.80 (m, 1H), 1.95 (m, 1H).

Example 446: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.44 (t, 1H), 8.22 - 8.28 (m, 1H), 7.77 (s, 1H), 7.55 - 7.60 (m, 1H), 7.42 - 7.54 (m, 3H), 7.21 - 7.31 (m, 2H), 7.09 - 7.20 (m, 2H), 4.28 - 4.47 (m, 2H), 4.22 - 4.28 (m, 1H), 3.94 (s, 2H), 3.64 - 3.72 (m, 1H), 2.08 - 2.29 (m, 2H), 1.75 - 1.85 (m, 1H), 0.75 - 0.92 (m, 1H), 0.51 - 0.57 (m, 1H).

Example 452: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.46 (t, 1H), 8.13 (d, 1H), 7.74 (s, 1H), 7.33 - 7.54 (m, 3H), 7.28 (t, 1H), 7.03 - 7.19 (m, 2H), 6.87 (dd, 1H), 4.29 - 4.42 (m, 2H), 4.25 (dd, 1H), 3.90 (s, 2H), 3.75 (s, 3H), 3.68 (m, 1H), 2.19 - 2.31 (m, 1H), 2.04 - 2.19 (m, 1H), 1.78 (m, 1H), 0.94 (m, 1H), 0.54 (m, 1H).

Example 466: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.40 - 8.82 (m, 1H), 8.11 - 8.37 (dd, 1H), 7.73 (s, 1H), 7.54-7.55 (dd, 1H), 7.07-7.46 (m, 8H), 4.90-5.04 (m, 1H), 4.34-4.47 (m, 3H), 4.08-4.16 (m, 1H), 3.61-3.87 (m, 4H)

Example 476: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4:1 mixture of rotamers δ (ppm): 9.02 (t, 0.2H), 8.63 (t, 0.8H), 8.11 - 8.21 (m, 1H), 7.89 - 7.96 (m, 1H), 7.36 - 7.51 (m, 2H), 6.96 - 7.29 (m, 4H), 5.41 - 5.61 (m, 1H), 5.08 - 5.40 (m, 2H), 4.88 (t, 0.2H), 4.13 - 4.56 (m, 3.8H), 3.81 - 4.11 (m, 1H), 2.43 - 2.49 (m, 1H), 1.97 - 2.18 (m, 1H).

Example 483: ^{1}H NMR (400 MHz, DMSO-d_6): 8.51-8.46 (m, 3H), 8.35 (m, 1H), 7.46 (m, 1H), 7,31 (dd, 1H), 7.21 (m, 1H), 7.09 (t, 1H), 5,53 (d, 1H), 5,37 (d, 1H), 4.41-4.27 (m, 3H), 3.72 (m, 1H), 2.47 (s, 3H), 2,26 (m, 1H), 2.19-2.13 (m, 1H), 1.89 (m, 1H), 1.08 (m, 1H), 0.75 (m, 1H).

Example 491: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4:1 mixture of rotamers δ (ppm): 9.03 (t, 0.2H), 8.64 (t, 0.8H), 8.11 - 8.19 (m, 1H), 7.91 - 7.99 (m, 1H), 7.61 (m, 0.8H), 7.48 - 7.58 (br s, 1H), 7.34 - 7.48 (m, 1.2H), 7.11 - 7.28 (m, 2H), 6.97 (t, 1H), 5.43 - 5.63 (m, 1H), 5.09 - 5.43 (m, 2H), 4.89 (t, 0.2H), 4.10 - 4.59 (m, 3.8H), 3.83 - 4.05 (m, 0.8H), 3.42 - 3.59 (m, 0.2H), 2.71 - 2.85 (m, 0.2H), 2.42 - 2.47 (m, 0.8H), 1.98 - 2.27 (m, 1H).

Example 496: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 9.01 (t, 0.2H), 8.63 (t, 0.8H), 8.12 - 8.19 (m, 1H), 7.89 - 7.94 (m, 1H), 7.36 - 7.49 (m, 2H), 7.20 - 7.27 (m, 0.8H), 7.09 - 7.19 (m, 3H), 6.90 - 7.04 (m, 0.8H), 6.74 - 6.81 (m, 0.2H), 6.54 - 6.61 (m, 0.2H), 5.33 (d, 0.8H), 5.22 (d, 0.2H), 5.07 (d, 0.8H), 4.88 (t, 0.2H), 4.56 (d, 0.2H), 4.33 - 4.52 (m, 2H), 4.11 - 4.31 (m, 1.8H), 3.90 - 4.03 (m, 0.2H), 3.70 - 3.87 (m, 0.8H), 2.46 - 2.54 (m, 1H, overlapped by DMSO residual signal) 1.90 - 2.27 (m, 1H), 1.47 - 1.66 (m, 3H).

Example 497: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 9.02 (t, 0.2H), 8.82 (br. s, NH2) 8.63 (t, 0.8H), 7.83 - 7.90 (m, 1H), 7.66 (s, 1H), 7.12 - 7.51 (m, 3H), 7.02 (t, 1H), 6.72 - 6.80 (m, 1H), 5.39 - 5.58 (m, 0.8H), 5.00 - 5.37 (m, 2H), 4.86 (t, 0.2H), 4.23 - 4.62 (m, 3.4H), 4.09 - 4.22 (m, 0.8H), 3.81 - 4.05 (m, 0.8H), 3.78 (s, 3H), 2.71 - 2.85 (m, 0.2H), 1.97 - 2.26 (m, 0.8H), (NH_2 protons partially exchanged with deuterium).

Example 499: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 9.03 (t, 0.2H), 8.65 (t, 0.8H), 8.00 (d, 1H), 7.72 - 7.84 (m, 1H), 7.33 - 7.48 (m, 1H), 7.24 (t, 0.8H), 7.14 (t, 0.2H), 6.88 - 7.01 (m, 1.6H), 6.69 - 6.82 (m, 1.4H), 5.40 - 5.61 (m, 1H), 5.30 (d, 0.8H), 5.14 - 5.22 (m, 0.2H), 5.05 (d, 0.8H), 4.88 (t, 0.2H), 4.23 - 4.57 (m, 3.2H), 4.09 - 4.23 (m, 0.8H), 3.80 - 4.06 (m, 1H), 3.68 - 3.77 (m, 3H), 3.42 - 3.61 (m, 1H), 2.71 - 2.84 (m, 0.2H), 1.98 - 2.28 (m, 0.8H), (NH_2 protons exchanged with deuterium).

Example 500: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 9.05 (t, 0.2H), 8.65 (t, 0.8H), 8.06 - 8.12 (m, 1H), 8.01 - 8.05 (m, 1H), 7.35 - 7.47 (m, 1.2H), 7.11 - 7.27 (m, 1H), 6.98 (d, 0.8H), 6.92 (t, 0.8H), 6.80 - 6.88 (m, 1.2H), 5.40 - 5.61 (m, 1H), 5.28 - 5.39 (m, 0.8H), 5.08 - 5.24 (m, 1H), 4.88 (t, 0.2H), 4.59 (d, 0.2H), 4.24 - 4.53 (m, 2.8H), 4.08 - 4.20 (m, 1H), 3.83 - 4.05 (m, 1H), 3.68 - 3.77 (m, 3H), 2.70 - 2.84 (m, 0.2H), 2.40 (s, 3H), 1.99 - 2.27 (m, 0.8H).

Example 505: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.72 (t, 1H), 8.23 (s, 1H), 8.20 (m, 1H), 7.45 (m, 2H), 7.27 (t, 1H), 7.21 (m, 2H), 7.03 (t, 1H), 5.37 (d, 1H), 5.2 (m, 2H), 4.65 (d, 1H), 4.4 (dd, 1H), 4.3 (m, 3H), 4.1 (m, 2H), 3.4 (s, 3H), 2.42 (s, 3H).

Example 507: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4:1 mixture of rotamers δ (ppm): 9.03 (t, 0.2H), 8.63 (t, 0.8H), 8.15 - 8.29 (m, 2H), 7.38 - 7.51 (m, 2H), 7.13 - 7.31 (m, 3.2H), 6.97 (t, 0.8H), 5.43 - 5.61 (m, 1H), 5.14 - 5.43 (m, 1.8H), 4.87 (t, 0.2H), 4.64 (d, 0.2H), 4.10 - 4.54 (m, 3.8H), 3.84 - 4.05 (m, 0.8H), 3.43 - 3.61 (m, 0.2H), 2.44 (s, 3H and m, 1H), 1.96 - 2.30 (m, 1H).

Example 508: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 9.02 (t, 0.2H), 8.62 (t, 0.8H), 8.12 - 8.22 (m, 1H), 7.75 - 7.83 (m, 1H), 7.30 - 7.53 (m, 7H), 7.24 (t, 0.8H), 7.16

(t, 0.2H), 7.10 (d, 0.2H), 6.96 - 7.03 (m, 0.8H), 6.88 - 6.96 (m, 1H), 5.41 - 5.61 (m, 0.8H), 5.27 - 5.41 (m, 1H), 5.19 - 5.26 (m, 0.2H), 5.09 - 5.19 (m, 2.8H), 4.85 (t, 0.2H), 4.59 (d, 0.2H), 4.22 - 4.51 (m, 2.8H), 4.07 - 4.21 (m, 0.8H), 3.80 - 4.05 (m, 1H), 3.43 - 3.60 (m, 0.2H), 3.35 (m, 1H, overlapping with H_2O residual signal) 2.68 - 2.84 (m, 0.2H), 2.41 (s, 3H), 1.98 - 2.19 (m, 0.8H).

Example 510: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.49 (t, 1H), 8.31 (s, 1H), 8.16 - 8.24 (m, 1H), 7.41 - 7.55 (m, 2H), 7.15 - 7.28 (m, 3H), 7.04 (t, 1H), 5.39 (dd, 2H), 4.37 - 4.46 (m, 1H), 4.21 - 4.35 (m, 2H), 3.68 - 3.80 (m, 1H), 2.45 (s, 3H), 2.23 - 2.33 (m, 1H), 2.11 - 2.22 (m, 1H), 1.80 - 1.95 (m, 1H), 1.00 - 1.13 (m, 1H), 0.70 - 0.82 (m, 1H).

Example 514: 1H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 10.54 (s, 0.2H), 10.20 (s, 0.8H), 8.23 - 8.31 (m, 1H), 8.15 - 8.21 (m, 1H), 7.84 - 8.00 (m, 1H), 7.39 - 7.49 (m, 1H), 7.18 - 7.39 (m, 4H), 5.33 - 5.66 (m, 2H), 5.13 - 5.28 (m, 1H), 4.69 - 4.89 (m, 1H), 4.15 - 4.28 (m, 1H), 3.89 - 4.14 (m, 1H), 2.56 - 2.66 (m, 1H), 2.44 (s, 3H), 2.08 - 2.30 (m, 1H).

Example 515: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.31 (s, 1H), 8.27 - 8.41 (m, 2H), 8.18 (d, 1H), 8.04 - 8.11 (m, 1H), 7.88 (s, 1H), 7.52 (d, 1H), 7.10 - 7.32 (m, 2H), 5.45 (dd, 2H), 4.31 (dd, 1H), 3.86 (t, 1H), 2.44 (s, 3H), 2.32 - 2.40 (m, 1H), 2.21 - 2.32 (m, 1H), 1.83 - 2.02 (m, 1H), 0.98 - 1.13 (m, 1H), 0.73 - 0.89 (m, 1H).

Example 521: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3:1 mixture of rotamers 9.23 (t, 0.25H), 8.75 (t, 0.75H), 8.24 (s, 0.75H), 8.05 - 8.18 (m, 2.25H), 7.97 (m, 1H), 7.41 (m, 0.75H), 7.01 - 7.21 (m, 2.25H), 5.13 - 5.63 (m, 2.75H), 4.91 (t, 0.25H), 3.83 - 4.64 (m, 5H), 2.37 - 2.46 (m, 3H), 1.96 - 2.20 (m, 1H).

Example 524: ^{1}H NMR (400 MHz, DMSO-d_6): 9.35 (s, 1H), 8.50 (t, 1H), 8.40 (s, 1H), 8.32 (d, 1H), 7.54 (d, 1H), 7.46 (m, 1H), 7.19 (t, 1H), 7.03 (t, 1H), 5.53 (d, 1H), 5.33 (d, 1H), 4.43 (dd, 1H), 4.31-4.26 (m, 2H), 3.71 (m, 1H), 2.49 (s, 3H), 2.34-2.26 (m, 1H), 2.20-2.14 (m, 1H), 1.90 (m, 1H), 1.06 (m, 1H), 0.78 (m, 1H).

Example 525: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.61 (t, 1H), 8.30 (s, 1H), 8.14 - 8.20 (m, 1H), 8.11 (dd, 1H), 7.97 - 8.02 (m, 1H), 7.41 - 7.51 (m, 1H), 7.18 (dd, 2H), 5.39 (dd, 2H), 4.39 - 4.46 (m, 2H), 4.33 (dd, 1H), 3.71 - 3.79 (m, 1H), 2.44 (s, 3H), 2.13 - 2.37 (m, 2H), 1.86 - 1.98 (m, 1H), 1.02 - 1.15 (m, 1H), 0.74 - 0.84 (m, 1H).

Example 526: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 8.51 - 8.61 (m, 2H), 8.26 - 8.33 (m, 1H), 8.22 (s, 1H), 7.85 (dd, 1H), 7.37 - 7.44 (m, 1H), 7.16 (t, 1H), 6.91 (t, 1H), 5.63 (d, 1H), 5.40 (d, 1H), 4.38 - 4.47 (m, 1H), 4.24 - 4.33 (m, 2H), 3.67 - 3.91 (m, 4H), 2.47 (s, 3H), 2.26 - 2.35 (m, 1H), 2.13 - 2.22 (m, 1H), 1.85 - 1.96 (m, 1H), 1.04 - 1.13 (m, 1H), 0.73 - 0.80 (m, 1H).

Example 534: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 9.05 (t, 0.2H), 8.67 (t, 0.8H), 8.13 (s, 0.8H), 8.05 (m, 1.2H), 7.29 - 7.50 (m, 6.2H), 7.22 (t, 0.8H), 7.08 - 7.15 (m, 1H), 6.83 - 6.98 (m, 2H), 5.41 - 5.63 (m, 0.8H), 5.28 - 5.40 (m, 1H), 4.87 - 5.25 (m, 3.2H), 4.23 - 4.67 (m, 3H), 3.83 - 4.21 (m, 1.8H), 3.43 - 3.61 (m, 0.2H), 2.54 - 2.60 (m, 1H), 2.41 (s, 3H), 1.99 - 2.21 (m, 1H).

Example 536: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 8.53 (t, 1H), 8.21 (s, 1H), 8.00 - 8.09 (m, 1H), 7.30 - 7.42 (m, 6H), 7.14 - 7.21 (m, 2H), 6.88 - 6.97 (m, 2H), 5.20 - 5.48 (m, 2H), 4.89 - 5.07 (m, 2H), 4.38 - 4.50 (m, 1H), 4.23 - 4.33 (m, 2H), 3.70 - 3.78 (m, 1H), 2.42 (s, 3H), 2.26 - 2.36 (m, 1H), 2.12 - 2.22 (m, 1H), 1.84 - 1.94 (m, 1H), 1.01 - 1.09 (m, 1H), 0.70 - 0.79 (m, 1H).

Example 542: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 9.05 (t, 0.2H), 8.66 (t, 0.8H), 8.38 - 8.46 (m, 1H), 8.28 (d, 1H), 7.95 - 8.20 (m, 1H), 7.84 (dd, 1H), 7.34 - 7.48 (m, 1.2H), 7.10 - 7.22 (m, 1H), 6.85 (t, 0.8H), 5.28 - 5.63 (m, 2.8H), 4.92 (t, 0.2H), 4.72 (d, 0.2H), 4.11 - 4.55 (m, 3.8H), 3.88 - 4.06 (m, 1H), 3.78 - 3.88 (m, 3H), 3.35 (m, 1H, overlapping with H_2O residual signal) 2.56 - 2.61 (m, 0.2H), 2.46 (s, 3H), 2.02 - 2.23 (m, 0.8H).

Example 545: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 8.51 (t, 1H), 8.27 - 8.33 (m, 1H), 8.12 (d, 1H), 7.40 - 7.50 (m, 2H), 7.10 - 7.23 (m, 2H), 6.96 - 7.09 (m, 1H), 5.46 (d, 1H), 5.29 (s, 1H), 4.36 - 4.50 (m, 1H), 4.22 - 4.36 (m, 2H), 3.56 - 3.78 (m, 5H), 2.44 (s, 3H), 2.24 - 2.37 (m, 1H), 2.12 - 2.22 (m, 1H), 1.84 - 1.95 (m, 1H), 1.26 (d, 1H), 1.02 - 1.10 (m, 1H), 0.73 - 0.80 (m, 1H).

Example 548: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 9.04 (t, 0.2H), 8.67 (t, 0.8H), 8.38 - 8.46 (m, 1H), 8.25 - 8.31 (m, 1H), 8.16 (s, 0.8H), 7.95 (s, 0.2H), 7.84 (d, 1H), 7.34 - 7.46 (m, 1.2H), 7.11 - 7.22 (m, 1H), 6.84 (t, 0.8H), 5.47 - 5.58 (m, 0.8H), 5.35 - 5.44 (m, 0.2H), 5.28 (d, 0.8H), 4.89 - 4.99 (m, 0.2H), 4.70 (d, 0.2H), 4.35 - 4.58 (m, 2H), 4.09 - 4.29 (m, 1.6H), 3.92 - 4.04 (m, 0.2H), 3.84 - 3.91 (m, 1H), 3.72 - 3.84 (m, 3H), 3.35 (m, 1H, overlapping with H_2O residual signal) 2.55 - 2.60 (m, 0.2H), 2.46 (s, 3H), 1.93 - 2.18 (m, 0.8H), 1.47 - 1.69 (m, 3H).

Example 549: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 8.99 - 9.09 (m, 0.2H), 8.64 (t, 0.8H), 8.15 - 8.24 (m, 1H), 8.12 (d, 1H), 7.35 - 7.50 (m, 2H), 7.22 (t, 0.8H), 7.04 - 7.19 (m, 1.4H), 6.95 (t, 0.8H), 5.28 - 5.61 (m, 1.8H), 5.11 - 5.28 (m, 1H), 4.88 (t, 0.2H), 4.62 (d, 0.2H), 4.23 - 4.54 (m, 3H), 4.09 - 4.23 (m, 0.8H), 3.81 - 4.05 (m, 1H), 3.56 - 3.75 (m, 6H), 2.54 - 2.60 (m, 0.2H), 2.39 - 2.45 (m, 3H), 1.97 - 2.29 (m, 0.8H).

Example 550: ^{1}H NMR (400 MHz, DMSO-d_6): 8.90 (m, 1H), 8.51 (t, 1H), 8.49 (s, 1H), 8.33 (d, 1H), 8.06 (m, 1H), 7.45 (m, 1H), 7.20 (m, 1H), 7.06 (t, 1H), 5.63 (d, 1H), 5.42 (d, 1H), 4.42 (dd, 1H), 4.32-4.28 (m, 2H), 3.72 (m, 1H), 2.48 (s, 3H), 2.34-2.26 (m, 1H), 2.21-2.14 (m, 1H), 1.90 (m, 1H), 1.08 (m, 1H), 0.81 (m, 1H).

Example 551: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3:1 mixture of rotamers 9.24 (d, 0.25H), 8.78 (d, 0.75H), 8.31 (s, 0.75H), 8.23 (s, 0.25H), 8.13 - 8.21 (m, 1H), 7.69 (s, 0.25H), 7.62 (s, 0.75H), 7.32 - 7.50 (m, 3H), 7.10 - 7.27 (m, 3.25H), 7.04 (d, 0.25H), 5.43 - 5.63 (m, 1H), 5.06 - 5.43 (m, 3H), 4.94 (t, 0.25H), 4.74 (d, 0.25H), 4.40 - 4.67 (m, 5H), 4.09 - 4.24 (m, 0.75H), 3.81 - 4.06 (m, 1.25H), 2.00 - 2.21 (m, 1H).

Example 556: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.49 (t, 1H), 8.39 (s, 1H), 8.15 - 8.26 (m, 1H), 7.40 - 7.55 (m, 2H), 7.13 - 7.30 (m, 3H), 7.05 (t, 1H), 5.40 (dd, 2H), 4.55 (s, 2H), 4.36 -

4.45 (m, 1H), 4.20 - 4.35 (m, 2H), 3.67 - 3.78 (m, 1H), 2.23 - 2.32 (m, 1H), 2.12 - 2.21 (m, 1H), 1.81 - 1.95 (m, 1H), 1.06 (ddd, 1H), 0.71 - 0.82 (m, 1H).

Example 561: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 4:1 mixture of rotamers 9.04 (t, 0.2H), 8.63 (t, 0.8H), 8.42 - 8.57 (m, 1H), 8.11 - 8.29 (m, 1H), 7.59 (d, 0.8H), 7.29 - 7.50 (m, 3.4H), 7.09 - 7.27 (m, 1H), 6.94 (t, 0.8H), 5.23 - 5.68 (m, 2.8H), 4.86 (t, 0.2H), 4.78 (d, 0.2H), 3.82 - 4.57 (m, 4.4H), 3.43 - 3.63 (m, 0.2H), 2.57 (d, 0.2H), 1.97 - 2.24 (m, 1H).

Example 563: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4:1 mixture of rotamers 9.03 (t, 0.2H), 8.63 (t, 0.8H), 8.34 (s, 0.8H), 8.29 (s, 0.2H), 8.20 (d, 1H), 7.34 - 7.51 (m, 2H), 7.11 - 7.30 (m, 3.2H), 6.98 (t, 0.8H), 5.14 - 5.63 (m, 2.8H), 4.87 (t, 0.2H), 4.64 (d, 0.2H), 4.54 (s, 2H), 3.79 - 4.52 (m, 4.8H), 1.97 - 2.20 (m, 1H).

Example 564: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4:1 mixture of rotamers 9.02 (t, 0.2H), 8.62 (t, 0.8H), 8.34 (s, 0.8H), 8.29 (s, 0.2H), 8.14 - 8.25 (m, 1H), 7.51 - 7.62 (m, 1H), 7.38 - 7.50 (m, 1H), 7.17 - 7.31 (m, 3H), 7.10 (t, 0.2H), 6.91 (t, 0.8H), 5.11 - 5.65 (m, 2.8H), 4.87 (t, 0.2H), 4.63 (d, 0.2H), 4.54 (s, 2H), 3.82 - 4.51 (m, 4.8H), 1.97 - 2.21 (m, 1H).

Example 565: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4:1 mixture of rotamers 9.04 (t, 0.2H), 8.63 (t, 0.8H), 8.33 (s, 0.8H), 8.29 (s, 0.2H), 8.15 - 8.25 (m, 1H), 7.37 - 7.50 (m, 2H), 7.19 - 7.28 (m, 3H), 7.16 (t, 0.2H), 6.97 (t, 0.8H), 5.15 - 5.63 (m, 2.8H), 4.87 (t, 0.2H), 4.64 (d, 0.2H), 3.78 - 4.54 (m, 6.8H), 3.39 (s, 3H), 1.98 - 2.20 (m, 1H).

Example 568: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 8.41 (d, 1H), 8.29 (s, 1H), 8.19 (m, 1H), 7.48 - 7.42 (m, 2H), 7.30 (t, 1H), 7.26 - 7.20 (m, 2H), 7.10 (t, 1H), 5.47 (d, 1H), 5.28 - 4.21 (m, 2H), 4.33 (dd, 1H), 3.72 (m, 1H), 3.48 (d, 1H), 3.33 (d, 1H), 3.22 (s, 3H), 2.43 (s, 3H), 2.27 - 2.22 (m, 1H), 2.18 - 2.12 (m, 1H), 1.87 (m, 1H), 1.05 (m, 1H), 0.73 (m, 1H).

Example 577: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4:1 mixture of rotamers δ (ppm): 8.99 (t, 0.2H), 8.62 (t, 0.8H), 7.78 - 7.85 (m, 1H), 7.56 (m, 1H), 7.35 - 7.51 (m, 1.2H), 7.25 (t, 0.8H), 7.14 - 7.20 (m, 1H), 7.04 (t, 0.8H), 6.93 (d, 0.2H), 6.59 - 6.66 (m, 1H), 5.38 - 5.59 (m, 1H), 4.96 - 5.31 (m, 1.8H), 4.85 (t, 0.2H), 4.09 - 4.52 (m, 4H), 3.96 - 4.04 (m, 0.2H), 3.78 - 3.95 (m, 0.8H), 2.40 - 2.49 (m, 1H, under DMSO residual peak), 1.96 - 2.25 (m, 1H).

Example 578: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4:1 mixture of rotamers δ (ppm): 8.93 - 9.19 (m, 1H), 8.63 (t, 1H), 7.90 (d, 1H), 7.67 - 7.74 (m, 1H), 7.22 - 7.53 (m, 2H), 7.01 - 7.22 (m, 1H), 6.55 - 6.75 (m, 2H), 5.27 - 5.62 (m, 1H), 4.79 - 5.26 (m, 2H), 4.10 - 4.54 (m, 3.8H), 3.96 - 4.05 (m, 0.2H), 3.78 - 3.95 (m, 0.8H), 3.42 - 3.58 (m, 0.2H), 2.70 - 2.84 (m, 0.2H), 2.40 - 2.49 (m, 0.8H), 1.97 - 2.31 (m, 1H).

Example 579: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 8.96 - 9.10 (m, 1.2H), 8.63 (t, 0.8H), 8.05 - 8.14 (m, 1H), 7.57 - 7.64 (m, 1H), 7.36 - 7.51 (m, 1.2H), 7.11 - 7.29 (m, 1.8H), 6.95 - 7.05 (m, 1H), 6.67 (dd, 1H), 5.40 - 5.60 (m, 0.8H), 5.04 - 5.35 (m, 2H), 4.84 (t, 0.2H), 4.23 - 4.62 (m, 3H), 3.96 - 4.22 (m, 1H), 3.79 - 3.96 (m, 0.8H), 3.42 - 3.59 (m, 0.2H),

3.35 (m, 1H, overlapping with H_2O residual signal) 2.70 - 2.83 (m, 0.2H), 2.38 (s, 3H), 1.97 - 2.17 (m, 0.8H).

Example 580: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 8.59 - 9.06 (m, 1H), 8.06 - 8.15 (m, 1H), 7.57 - 7.64 (m, 1H), 7.33 - 7.51 (m, 1.2H), 7.13 - 7.30 (m, 1.8H), 6.94 - 7.07 (m, 1H), 6.67 (dd, 1H), 4.95 - 5.31 (m, 2H), 4.85 (t, 0.2H), 4.39 - 4.58 (m, 1.8H), 4.06 - 4.39 (m, 2H), 3.90 - 4.03 (m, 0.2H), 3.68 - 3.84 (m, 0.8H), 3.35 (m, 1H, overlapping with H_2O residual signal) 2.70 - 2.84 (m, 0.2H), 2.38 (s, 3H), 1.90 - 2.27 (m, 0.8H), 1.48 - 1.65 (m, 3H), (OH proton exchanged with deuterium).

Example 581: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 8.48 (t, 1H), 8.18 (s, 1H), 7.61 (d, 1H), 7.43 - 7.51 (m, 1H), 7.17 - 7.30 (m, 2H), 7.07 (t, 1H), 6.69 (dd, 1H), 5.15 - 5.44 (m, 2H), 4.23 - 4.50 (m, 3H), 3.65 - 3.74 (m, 1H), 2.39 (s, 3H), 2.21 - 2.32 (m, 1H), 2.10 - 2.21 (m, 1H), 1.81 - 1.94 (m, 1H), 0.99 - 1.10 (m, 1H), 0.70 - 0.79 (m, 1H), (OH proton exchanged with deuterium).

Example 582: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 8.60 - 9.04 (m, 1H), 7.98 - 8.07 (m, 0.8H), 7.90 - 7.98 (m, 1H), 7.84 - 7.90 (m, 0.2H), 7.37 - 7.52 (m, 1.2H), 7.14 - 7.29 (m, 1H), 7.03 (t, 0.8H), 6.70 - 6.79 (m, 1.8H), 6.59 (d, 0.2H), 4.93 - 5.30 (m, 1.8H), 4.85 (t, 0.2H), 4.40 - 4.57 (m, 1.8H), 4.09 - 4.40 (m, 2H), 3.91 - 4.05 (m, 0.2H), 3.66 - 3.85 (m, 1H), 3.35 (m, 1H, overlapping with H_2O residual signal) 2.71 - 2.85 (m, 0.2H), 2.32 - 2.42 (m, 3H), 1.88 - 2.25 (m, 0.8H), 1.47 - 1.66 (m, 3H), (OH proton exchanged with deuterium).

Example 583: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 9.18 - 9.36 (m, 1H), 9.00 (t, 0.2H), 8.63 (t, 0.8H), 7.89 - 8.17 (m, 2H), 7.37 - 7.53 (m, 1.2H), 7.22 - 7.31 (m, 0.8H), 6.99 - 7.21 (m, 1H), 6.58 - 6.82 (m, 2H), 5.40 - 5.61 (m, 0.8H), 5.27 (d, 1H), 4.98 - 5.20 (m, 1H), 4.85 (t, 0.2H), 4.23 - 4.58 (m, 3.2H), 4.09 - 4.23 (m, 0.8H), 3.78 - 4.07 (m, 1H), 3.35 (m, 1H, overlapping with H_2O residual signal) 2.69 - 2.83 (m, 0.2H), 2.38 (s, 3H), 1.95 - 2.25 (m, 0.8H).

Example 584: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 8.51 (t, 1H), 8.10 (s, 1H), 7.87 - 8.00 (m, 1H), 7.45 (t, 1H), 7.23 (t, 1H), 7.10 (t, 1H), 6.69 - 6.85 (m, 2H), 5.08 - 5.42 (m, 2H), 4.23 - 4.53 (m, 3H), 3.64 - 3.78 (m, 1H), 2.39 (s, 3H), 2.21 - 2.31 (m, 1H), 2.11 - 2.21 (m, 1H), 1.83 - 1.94 (m, 1H), 1.01 - 1.11 (m, 1H), 0.69 - 0.77 (m, 1H), (OH proton exchanged with deuterium).

Example 585: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 9.04 (t, 0.2H), 8.66 (t, 0.8H), 8.03 - 8.11 (m, 1H), 7.80 - 7.88 (m, 1H), 7.34 - 7.49 (m, 1.2H), 7.23 (t, 0.8H), 7.11 - 7.19 (m, 1H), 6.88 - 7.04 (m, 2H), 5.27 - 5.60 (m, 3.8H), 5.21 (d, 0.2H), 5.08 (d, 0.8H), 4.88 (t, 0.2H), 4.23 - 4.60 (m, 3.2H), 4.09 - 4.23 (m, 0.8H), 3.82 - 4.06 (m, 1H), 3.51 - 3.60 (m, 1H), 2.70 - 2.87 (m, 0.2H), 1.95 - 2.31 (m, 0.8H), (NH_2 protons exchanged with deuterium).

Example 586: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 9.22 - 9.34 (m, 1H), 8.95 - 9.10 (m, 0.2H), 8.59 - 8.79 (m, 0.8H), 7.90 - 8.24 (m, 2H), 7.34 - 7.51 (m, 1.2H), 7.14 - 7.29 (m, 1.6H), 6.95 - 7.14 (m, 1.2H), 6.70 - 6.95 (m, 1H), 5.28 - 5.62 (m, 3H), 5.01 - 5.27 (m, 1H), 4.82 - 4.92 (m, 0.2H), 4.53 - 4.65 (m, 0.2H), 4.23 - 4.53 (m, 2.8H), 4.07 - 4.23 (m,

0.8H), 3.76 - 4.07 (m, 1H), 3.35 (m, 1H, overlapping with H_2O residual signal) 2.37 - 2.44 (m, 3H), 1.94 - 2.28 (m, 1H).

Example 587: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 8.51 (t, 1H), 8.23 (s, 1H), 8.02 - 8.14 (m, 1H), 7.33 - 7.46 (m, 1H), 7.10 - 7.25 (m, 2H), 6.89 - 7.05 (m, 2H), 5.37 - 5.53 (m, 2H), 5.20 - 5.35 (m, 2H), 4.34 - 4.54 (m, 1H), 4.21 - 4.34 (m, 2H), 3.67 - 3.78 (m, 1H), 2.40 - 2.45 (m, 3H), 2.26 - 2.37 (m, 1H), 2.11 - 2.23 (m, 1H), 1.90 (d, 1H), 1.00 - 1.15 (m, 1H), 0.73 - 0.86 (m, 1H).

Example 588: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 9.02 (t, 0.2H), 8.63 (t, 0.8H), 8.11 - 8.22 (m, 1H), 7.67 - 7.73 (m, 1H), 7.30 - 7.53 (m, 2H), 7.12 - 7.28 (m, 1H), 6.96 - 7.11 (m, 1H), 6.80 - 6.87 (m, 1H), 5.40 - 5.61 (m, 0.8H), 5.08 - 5.39 (m, 2H), 4.85 (t, 0.2H), 4.59 (d, 0.2H), 4.22 - 4.52 (m, 2.8H), 4.08 - 4.21 (m, 0.8H), 3.81 - 4.05 (m, 1H), 3.79 (s, 3H), 3.53 - 3.62 (m, 0.2H), 3.35 (m, 1H, overlapping with H_2O residual signal) 2.70 - 2.85 (m, 0.2H), 2.41 (s, 3H), 1.98 - 2.19 (m, 0.8H).

Example 589: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 8.58 - 9.07 (m, 2H), 8.14 - 8.24 (m, 1H), 7.98 (t, 1H), 7.76 - 7.82 (m, 1H), 7.66 (d, 1H), 7.35 - 7.51 (m, 3H), 7.09 - 7.28 (m, 1.2H), 6.92 - 7.03 (m, 1.8H), 5.41 - 5.63 (m, 1H), 5.10 - 5.40 (m, 3.8H), 4.85 (t, 0.2H), 4.59 (d, 0.2H), 4.22 - 4.52 (m, 2.8H), 4.08 - 4.20 (m, 1H), 3.80 - 4.05 (m, 1H), 2.40 (s, 3H), 1.96 - 2.27 (m, 1H).

Example 590: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 8.58 - 9.05 (m, 3H), 8.11 - 8.19 (m, 1H), 7.68 - 7.72 (m, 1H), 7.41 - 7.49 (m, 2H), 7.32 - 7.40 (m, 1H), 7.13 - 7.27 (m, 1H), 6.95 - 7.11 (m, 1H), 6.91 (dd, 1H), 5.40 - 5.59 (m, 1H), 5.27 - 5.39 (m, 3H), 5.09 - 5.25 (m, 1H), 4.85 (t, 0.2H), 4.58 (d, 0.2H), 4.42 - 4.51 (m, 1H), 4.23 - 4.42 (m, 1.8H), 4.07 - 4.20 (m, 0.8H), 3.80 - 4.04 (m, 1H), 3.35 (m, 1H, overlapping with H_2O residual signal) 2.38 (s, 3H), 1.97 - 2.19 (m, 1H).

Example 592: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 9.02 (t, 0.2H), 8.65 (t, 0.8H), 8.02 (d, 1H), 7.78 - 7.84 (m, 1H), 7.34 - 7.49 (m, 1H), 7.11 - 7.27 (m, 1H), 6.91 - 7.02 (m, 1.8H), 6.81 (m, 1.2H), 5.25 - 5.60 (m, 1.8H), 5.18 (d, 0.2H), 5.04 (d, 0.8H), 4.87 (t, 0.2H), 4.53 - 4.76 (m, 2H), 4.24 - 4.52 (m, 3H), 4.08 - 4.23 (m, 0.8H), 3.81 - 4.06 (m, 1H), 3.69 (s, 3H), 3.42 - 3.59 (m, 0.2H), 2.71 - 2.85 (m, 0.2H), 1.97 - 2.18 (m, 0.8H). (NH_2 protons partially exchanged with deuterium).

Example 593: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 12.90 (br. s, 1H), 9.01 (t, 0.2H), 8.64 (t, 0.8H), 8.02 (d, 1H), 7.77 - 7.85 (m, 1H), 7.36 - 7.50 (m, 1H), 7.24 (t, 0.8H), 7.16 (t, 0.2H), 6.94 - 7.04 (m, 1.6H), 6.76 - 6.90 (m, 1.4H), 5.39 - 5.61 (m, 0.8H), 5.24 - 5.35 (m, 1H), 5.19 (d, 0.2H), 5.05 (d, 0.8H), 4.87 (t, 0.2H), 4.24 - 4.68 (m, 5H), 4.09 - 4.22 (m, 1H), 3.81 - 4.05 (m, 1H), 3.43 - 3.64 (m, 0.8H), 3.35 (m, 0.2 H, overlapping with H_2O residual signal) 2.71 - 2.85 (m, 0.2H), 1.98 - 2.17 (m, 0.8H). (NH_2 protons exchanged with deuterium).

Example 595: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 12.29 (br. s, 1H), 9.05 (t, 0.2H), 8.64 (t, 0.8H), 8.15 - 8.22 (m, 1H), 8.11 (d, 1H), 7.35 - 7.49 (m, 2H), 7.23 (t, 0.8H), 7.09 - 7.19 (m, 1.4H), 6.95 (t, 0.8H), 5.41 - 5.63 (m, 1H), 5.38 (d, 0.8H), 5.22 - 5.33 (m, 0.2H), 5.16 (d, 0.8H), 4.88 (t, 0.2H), 4.61 (d, 0.2H), 4.23 - 4.53 (m, 3H), 4.10 - 4.22 (m, 0.8H), 3.81 - 4.06 (m, 1H), 3.48 - 3.64 (m, 2H), 3.35 (m, 1H, overlapping with H_2O residual signal) 2.70 - 2.84 (m, 0.2H), 2.42 (s, 3H), 1.98 - 2.27 (m, 0.8H).

Example 596: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 12.29 (br. s, 1H), 8.52 (t, 1H), 8.28 (s, 1H), 8.11 (d, 1H), 7.36 - 7.50 (m, 2H), 7.10 - 7.23 (m, 2H), 7.01 (t, 1H), 5.45 (d, 1H), 5.27 (d, 1H), 4.35 - 4.51 (m, 1H), 4.23 - 4.35 (m, 2H), 3.70 - 3.79 (m, 1H), 3.50 - 3.67 (m, 2H), 2.44 (s, 3H), 2.24 - 2.36 (m, 1H), 2.11 - 2.22 (m, 1H), 1.90 (q, 1H), 1.01 - 1.13 (m, 1H), 0.73 - 0.81 (m, 1H).

Example 597: ^{1}H NMR (400 MHz, DMSO-d_6): 85:15 mixture of rotamers δ (ppm): 12.77 (br. s, 1H), 9.06 (t, 0.15H), 8.68 (t, 0.85H), 8.36 - 8.46 (m, 1H), 8.26 (d, 1H), 8.18 (s, 0.85H), 7.98 (s, 0.15H), 7.83 (d, 1H), 7.36 - 7.49 (m, 1.15H), 7.10 - 7.27 (m, 1H), 6.92 (t, 0.85H), 5.24 - 5.64 (m, 2.85H), 4.92 (t, 0.15H), 4.72 (d, 0.15H), 4.11 - 4.55 (m, 3.85H), 3.86 - 4.06 (m, 1H), 3.35 (m, 1H, overlapping with H_2O residual signal) 2.55 - 2.60 (m, 0.15H), 2.46 (s, 3H), 2.00 - 2.20 (m, 0.85H).

Example 598: 1H NMR (400 MHz, DMSO-d_6): δ (ppm): 8.46 - 8.60 (m, 2H), 8.18 - 8.31 (m, 2H), 7.84 (dd, 1H), 7.42 (t, 1H), 7.19 (t, 1H), 6.98 (t, 1H), 5.61 (d, 1H), 5.38 (d, 1H), 4.35 - 4.45 (m, 1H), 4.23 - 4.35 (m, 2H), 3.74 - 3.82 (m, 1H), 2.47 (s, 3H), 2.24 - 2.35 (m, 1H), 2.11 - 2.22 (m, 1H), 1.85 - 1.94 (m, 1H), 1.04 - 1.13 (m, 1H), 0.73 - 0.81 (m, 1H).

Example 599: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 9.03 (t, 0.2H), 8.66 (t, 0.8H), 8.35 - 8.44 (m, 1H), 8.21 - 8.29 (m, 1H), 8.16 (s, 0.8H), 7.96 (s, 0.2H), 7.83 (d, 1H), 7.36 - 7.49 (m, 1.2H), 7.13 - 7.25 (m, 1H), 6.92 (t, 0.8H), 5.46 - 5.57 (m, 0.8H), 5.34 - 5.43 (m, 0.2H), 5.27 (d, 0.8H), 4.88 - 5.00 (m, 0.2H), 4.71 (d, 0.2H), 4.34 - 4.57 (m, 2H), 4.09 - 4.29 (m, 1.8H), 3.98 (dd, 1H), 3.73 - 3.91 (m, 0.8H), 3.40 - 3.48 (m, 0.2H), 2.55 - 2.60 (m, 0.2H), 2.46 (s, 3H), 1.93 - 2.27 (m, 0.8H), 1.47 - 1.67 (m, 3H), (COOH proton exchanged with deuterium).

Example 604: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 9.04 (t, 0.2H), 8.65 (t, 0.8H), 8.14 - 8.21 (m, 1H), 8.10 - 8.14 (m, 1H), 7.38 - 7.47 (m, 2H), 7.14 - 7.26 (m, 2.2H), 6.97 (t, 0.8H), 5.43 - 5.61 (m, 0.8H), 5.39 (d, 0.8H), 5.12 - 5.32 (m, 1H), 4.88 (t, 0.2H), 4.63 (d, 0.2H), 4.52 - 4.59 (m, 2H), 4.34 - 4.52 (m, 2H), 4.11 - 4.32 (m, 2H), 3.83 - 4.06 (m, 1H), 3.35 (m, 1H, overlapping with H_2O residual signal) 2.42 (s, 3H), 1.98 - 2.27 (m, 1H).

Example 605: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3:1 mixture of rotamers 9.14 (t, 0.25H), 8.69 (t, 0.75H), 8.24 (s, 1H), 8.18 (d, 1.75H), 7.92 - 8.02 (m, 1.25H), 7.87 (m, 1H), 7.44 (m, 1H), 7.08 - 7.27 (m, 3H), 5.17 - 5.60 (m, 3.75H), 4.85 - 4.95 (t, 0.25H), 4.59 (d, 0.25H), 3.78 - 4.55 (m, 5.75H), 2.70 - 2.85 (m, 0.25H), 1.90 - 2.16 (m, 0.75H).

Example 615: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.27 (s, 1H), 8.86 (s, 1H), 8.52 (d, 1H), 8.50 (m, 1H), 8.41 (d, 1H), 7.74 (d, 1H), 7.47 - 7.40 (m, 2H), 7.20 (t, 1H), 7.05 (t, 1H), 5.60 (d, 1H), 5.37 (d, 1H), 4.40 (dd, 1H), 3.32 - 4.26 (m, 2H), 3,73 (m, 1H), 3.25 (s, 3H), 3.02 (s, 3H), 2.49 (s, 3H), 2.34 – 2.26 (m, 1H), 2.20 – 2.14 (m, 1H), 1.90 (m, 1H), 1.08 (m, 1H), 0.78 (m, 1H).

Example 617: ^{1}H NMR (400 MHz, DMSO-d_6): 85:15 mixture of rotamers δ (ppm): 9.06 (t, 0.15H), 8.70 (t, 0.85H), 8.33 - 8.44 (m, 2H), 8.25 (s, 0.85H), 8.09 (s, 0.15H), 7.85 (d, 1H), 7.38 - 7.49 (m, 0.15H), 7.28 - 7.35 (m, 0.85H), 7.11 - 7.22 (m, 1H), 6.81 (t, 1H), 5.42 - 5.65 (m, 1.85H), 5.27 - 5.42 (m, 1H), 4.93 (t, 0.15H), 4.75 (d, 0.15H), 4.11 - 4.58 (m, 3.85H), 3.89 - 4.09 (m, 1H), 2.54 - 2.62 (m, 0.15H), 2.48 (s, 3H), 2.00 - 2.29 (m, 0.85H).

Example 621: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 8.51 (t, 1H), 8.34 (d, 1H), 8.18 (br. d, 1H), 7,46 (m, 1H), 7.35 (m, 1H), 7,22 (m, 1H), 7.08 (t, 1H), 6,95 (dt, 1H), 4,63 (d, 1H), 4.24 - 4.45 (m, 4H), 3,69 (m, 1H), 2,51 (s, 3H), 2,29 (m, 1H), 2,18 (m, 1H), 1,84 (m, 1H), 1,02 (m, 1H), 0,79 (m, 1H).

Example 628: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 10.51 (s, 0.2H), 10.16 (s, 0.8H), 8.18 (m, 1H), 7.91 (m, 0.2H), 7.83 (m, 0.8H), 7.65 (m, 1H), 7.62 (d, 0.8H), 7.56 (d, 0.2H), 7.46-7.22 (m, 5H), 5.66-5.24 (m, 3H), 5.08 (d, 0.2H), 4.95 (d, 0.8 H), 4.56 (m, 0.2H), 4.33 (ddd, 0.8H), 4.24-4.00 (m, 1.6H), 3.87-3.60 (m, 0.4H), 3.47 (s, 0.6H), 3.43 (s, 2.4H).

Example 652: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 8.48 (br. s, 1H), 8.22 (d, 1H), 7.71 (d, 1H), 7.36 - 7.52 (m, 4H), 7.20 (t, 1H), 7.05 (t, 1H), 5.84 (d, 1H), 5.55 (d, 1H), 4.85 (s, 2H), 4.37 - 4.47 (m, 2H), 4.25 - 4.33 (m, 2H), 3.68 - 3.76 (m, 1H), 2.24 - 2.36 (m, 1H), 2.10 - 2.21 (m, 1H), 1.83 - 1.94 (m, 1H), 0.99 - 1.08 (m, 1H), 0.83 (m, 1H).

Example 657: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.17 (br. s, 1H), 8.65 (br. s, 1H), 8.38 (t, 1H), 8.07 (d, 1H), 7.85 (br. s, 1H), 7.56 (br. s, 1H), 7.46 (t, 1H), 7.22 (t, 1H), 6.99 - 7.15 (m, 1H), 5.76 (br. s, 2H), 5.45 (d, 1H), 4.38 (d, 1H), 4.28 (d, 1H), 4.15 - 4.24 (m, 1H), 4.02 - 4.12 (m, 1H).

Example 661: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 8.99 (d, 0.8H), 8.92 (s, 0.2H), 8.63 (t, 1H), 7.90 (s, 1H), 7.77 (br. s, 1H), 7.48 - 7.55 (m, 1H), 7.40 - 7.48 (m, 1H), 7.17 - 7.29 (m, 1H), 7.04 (t, 1H), 5.53 - 5.80 (m, 1.8H), 5.43 - 5.50 (m, 0.2H), 5.30 - 5.41 (m, 0.4H), 5.19 - 5.27 (m, 0.2H), 5.01 - 5.13 (m, 0.4H), 4.66 (d, 0.8H), 4.51 - 4.60 (m, 0.2H), 4.34 - 4.49 (m, 1.2H), 4.09 - 4.32 (m, 2.6H), 3.95 - 4.09 (m, 0.8H), 3.56 - 3.86 (m, 0.4H), 3.39 (s, 3H), 2.61 (s, 3H).

Example 662: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 9.12 (d, 0.8H), 8.97 - 9.07 (m, 0.4H), 8.64 (br. s, 0.8H), 8.37 (d, 1H), 8.07 (dd, 1H), 7.84 (br. s, 1H), 7.56 (br. s, 1H), 7.40 - 7.52 (m, 1.2H), 7.18 - 7.30 (m, 1H), 7.05 (t, 0.8H), 5.57 - 5.81 (m, 1.6H), 5.47 (m, 0.4H), 5.34 (m, 0.4H), 5.17 - 5.28 (m, 0.2H), 5.05 - 5.17 (m, 0.4H), 4.67 (d, 0.8H), 4.50 - 4.62

(m, 0.2H), 4.35 - 4.49 (m, 1.2H), 4.11 - 4.32 (m, 2.8H), 3.99 - 4.10 (m, 0.8H), 3.64 - 3.83 (m, 0.2H), 3.40 (s, 3H).

Example 663: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 9.43 (d, 0.8H), 8.99 (m, 0.2H), 8.62 (m, 1H), 8.39 - 8.48 (m, 1H), 7.89 (br. s, 1H), 7.63 (m, 1.8H), 7.40 - 7.55 (m, 1.2H), 7.17 - 7.30 (m, 1.2H), 7.04 (t, 0.8H), 5.55 - 5.71 (m, 1H), 5.43 - 5.54 (m, 1H), 5.20 - 5.41 (m, 0.6H), 4.90 - 5.13 (m, 0.4H), 4.65 (d, 0.8H), 4.50 - 4.60 (m, 0.2H), 4.35 - 4.48 (m, 1.2H), 4.08 - 4.32 (m, 2.8H), 3.96 - 4.08 (m, 0.8H), 3.61 - 3.85 (m, 0.2H), 3.39 (s, 3H).

Example 664: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 9.12 (s, 0.8H), 8.96 - 9.03 (m, 0.2H), 8.93 (s, 0.2H), 8.55 - 8.66 (m, 0.8H), 8.34 - 8.41 (m, 1H), 8.05 - 8.11 (m, 1H), 7.84 (br. s, 0.8H), 7.78 (br. s, 0.2H), 7.50 - 7.60 (m, 1H), 7.35 - 7.50 (m, 1.2H), 7.30 (t, 0.8H), 7.04 - 7.19 (m, 1H), 5.55 - 5.79 (m, 1.8H), 5.47 (m, 0.2H), 5.20 - 5.39 (m, 0.8H), 5.00 - 5.13 (m, 1.2H), 4.95 (d, 0.2H), 4.67 (d, 0.8H), 4.12 - 4.30 (m, 1.8H), 3.93 - 4.08 (m, 0.8H), 3.57 - 3.85 (m, 0.4H), 3.41 - 3.48 (m, 3H), 1.48 (d, 0.6H), 1.34 (d, 2.4H).

Example 668: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.86 (s, 1H), 9.18 (s, 1H), 8.37 (d, 1H), 8.07 (d, 1H), 7,84 (m, 1H), 7.76 (t, 1H), 7.55 (m, 1H), 7.46 (t, 1H), 7.12 (t, 1H), 5.97 (d, 1H), 5.67 (d, 1H), 4.52 (m, 1H), 3.80 (m, 1H), 2.40-2.20 (m, 2H), 1.93 (m, 1H), 1.05 (m, 1H), 0.83 (m, 1H).

Example 675: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.14 (s, 1H), 8.50 (m, 1H), 8.38 (d, 1H), 8.08 (d, 1H), 7.84 (m, 1H), 7.55 (m, 1H), 7.45 (t, 1H), 7.21 (t, 1H), 7.07 (t, 1H), 5.88 (d, 1H), 5.57 (d, 1H), 4.41 - 4.24 (m, 3H), 3,48 (m, 1H), 2,44 (dd, 3H), 1.93 (dd, 1H), 1.28 (s, 3H), 1.01-0.96 (m, 2H).

Example 684: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.79 (br. s, 1H), 9.19 (s, 1H), 8.37 (d, 1H), 8.08 (dd, 1H), 7.81 - 8.01 (m, 2H), 7.37 - 7.66 (m, 3H), 7.11 - 7.37 (m, 4H), 5.98 (d, 1H), 5.67 (d, 1H), 4.55 (dd, 1H), 3.75 - 3.89 (m, 1H), 2.21 - 2.41 (m, 2H), 1.87 - 2.01 (m, 1H), 0.98 - 1.13 (m, 1H), 0.82 (m, 1H).

Example 685: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.79 (br. s, 1H), 9.28 (s, 1H), 8.40 (d, 1H), 8.15 (d, 1H), 7.91 (t, 2H), 7.53 - 7.70 (m, 2H), 7.32 - 7.53 (m, 3H), 7.24 (t, 1H), 6.97 - 7.14 (m, 1H), 6.00 (d, 1H), 5.69 (d, 1H), 4.56 (dd, 1H), 3.75 - 3.86 (m, 1H), 2.23 - 2.40 (m, 2H), 1.85 - 2.01 (m, 1H), 0.94 - 1.13 (m, 1H), 0.82 (td, 1H).

Example 686: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.81 (br. s, 1H), 8.58 (m, 1H), 8.19 (d, 1H), 7.81 - 8.03 (m, 2H), 7.48 - 7.73 (m, 3H), 7.23 - 7.47 (m, 4H), 5.82 (d, 1H), 5.51 (d, 1H), 4.54 (dd, 1H), 3.76 - 3.84 (m, 1H), 2.32 (m, 2H), 1.86 - 1.98 (m, 1H), 1.00 - 1.10 (m, 1H), 0.71 - 0.81 (m, 1H).

Example 688: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.81 (br. s, 1H), 9.22 (s, 1H), 8.64 (dd, 1H), 8.38 (d, 1H), 8.02 - 8.19 (m, 2H), 7.82 - 8.02 (m, 2H), 7.46 - 7.63 (m, 2H), 7.27 (t, 1H), 7.18 - 7.23 (m, 1H), 5.99 (d, 1H), 5.68 (d, 1H), 4.55 (dd, 1H), 3.75 - 3.91 (m, 1H), 2.19 - 2.41 (m, 2H), 1.84 - 2.03 (m, 1H), 0.96 - 1.17 (m, 1H), 0.75 - 0.90 (m, 1H).

Example 690: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 8.42 - 8.51 (m, 1H), 7.52 (br. s, 2H), 7.46 (t, 1H), 7.28 (br. s, 1H), 7.20 (t, 1H), 7.11 (s, 1H), 7.06 (t, 1H), 5.62 (d, 1H), 5.35 (d, 1H), 4.37 - 4.47 (m, 1H), 4.22 - 4.35 (m, 3H), 3.63 - 3.71 (m, 1H), 2.21 - 2.32 (m, 1H), 2.09 - 2.20 (m, 1H), 1.81 - 1.92 (m, 1H), 0.97 - 1.06 (m, 1H), 0.67 - 0.76 (m, 1H).

Example 693: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 8.40 - 8.48 (m, 1H), 8.24 (d, 1H), 8.08 (d, 1H), 7.89 - 7.98 (m, 1H), 7.58 (br. s, 1H), 7.37 - 7.44 (m, 1H), 7.27 (t, 1H), 6.98 (t, 1H), 6.00 (d, 1H), 5.72 (d, 1H), 5.04 (m, 1H), 4.29 (dd, 1H), 3.74 - 3.81 (m, 1H), 2.78 (s, 3H), 2.29 (dd, 1H), 2.09 - 2.20 (m, 1H), 1.84 - 1.97 (m, 1H), 1.33 (d, 3H), 1.01 - 1.11 (m, 1H), 0.68 (m, 1H).

Example 694: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 8.48 (t, 1H), 8.24 (d, 1H), 8.08 (d, 1H), 7.90 (br. s, 1H), 7.61 (br. s, 1H), 7.45 (t, 1H), 7.21 (t, 1H), 7.06 (t, 1H), 6.02 (d, 1H), 5.75 (d, 1H), 4.20 - 4.40 (m, 3H), 3.71 - 3.85 (m, 1H), 2.84 (s, 3H), 2.31 (dd, 1H), 2.14 (m, 1H), 1.83 - 2.01 (m, 1H), 0.99 - 1.16 (m, 1H), 0.62 - 0.80 (m, 1H).

Example 695: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 8.47 (br. s, 1H), 8.00 (br. s, 1H), 7.88 (br. s, 1H), 7.61 (br. s, 1H), 7.45 (t, 1H), 7.21 (t, 1H), 7.02 - 7.12 (m, 1H), 6.01 (d, 1H), 5.73 (d, 1H), 4.22 - 4.40 (m, 3H), 3.73 - 3.82 (m, 1H), 2.85 (s, 3H), 2.62 (s, 3H), 2.31 (dd, 1H), 2.07 - 2.19 (m, 1H), 1.85 - 1.96 (m, 1H), 1.00 - 1.12 (m, 1H), 0.64 - 0.76 (m, 1H).

Example 696: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 8.36 - 8.50 (m, 1H), 7.96 (m, 1H), 7.63 (br. s, 1H), 7.40 (t, 1H), 7.27 (t, 1H), 6.98 (t, 1H), 6.02 (d, 1H), 5.71 (d, 1H), 4.97 - 5.13 (m, 1H), 4.28 (dd, 1H), 3.72 - 3.83 (m, 1H), 2.82 (s, 3H), 2.60 - 2.72 (m, 3H), 2.21 - 2.39 (m, 1H), 2.07 - 2.19 (m, 1H), 1.83 - 1.97 (m, 1H), 1.33 (d, 3H), 1.01 - 1.13 (m, 1H), 0.62 - 0.76 (m, 1H).

Example 697: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 9.09 (s, 0.8H), 9.01 (br. s, 0.2H), 8.59 - 8.69 (m, 1H), 7.89 - 8.00 (m, 1H), 7.81 (br. s, 1H), 7.48 - 7.59 (m, 1.2H), 7.38 - 7.48 (m, 1H), 7.18 - 7.30 (m, 1H), 7.04 (t, 0.8H), 5.56 - 5.80 (m, 1.8H), 5.20 - 5.52 (m, 0.8H), 5.10 (m, 0.4H), 4.66 (d, 0.8H), 4.50 - 4.61 (m, 0.2H), 4.33 - 4.49 (m, 1.4H), 3.97 - 4.33 (m, 3.4H), 3.60 - 3.86 (m, 0.2H), 3.39 (s, 3H), 2.92 (m, 2H), 1.20 - 1.40 (m, 3H).

Example 702: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.14 (s, 1H), 8.30 - 8.47 (m, 2H), 8.07 (m, 1H), 7.88 (br. s, 1H), 7.53 (br. s, 1H), 7.35 - 7.46 (m, 1H), 7.28 (t, 1H), 6.94 - 7.16 (m, 1H), 5.90 (d, 1H), 5.62 (d, 1H), 5.06 (quin, 1H), 4.30 (dd, 1H), 3.57 - 3.78 (m, 1H), 2.20 - 2.36 (m, 1H), 2.06 - 2.20 (m, 1H), 1.76 - 1.99 (m, 1H), 1.33 (d, 3H), 0.94 - 1.10 (m, 1H), 0.70 - 0.84 (m, 1H).

Example 703: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.16 (s, 1H), 8.45 - 8.54 (m, 1H), 8.38 (d, 1H), 8.08 (dd, 1H), 7.85 (br. s, 1H), 7.55 (br. s, 1H), 7.45 (t, 1H), 7.20 (t, 1H), 7.07 (t, 1H), 5.92 (d, 1H), 5.63 (d, 1H), 4.36 - 4.51 (m, 1H), 4.25 - 4.33 (m, 2H), 3.68 - 3.75 (m, 1H), 2.24 - 2.37 (m, 1H), 2.10 - 2.22 (m, 1H), 1.84 - 1.95 (m, 1H), 1.00 - 1.10 (m, 1H), 0.80 (m, 1H).

Example 705: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 8.99 (br. s, 1H), 8.40 - 8.54 (m, 1H), 8.02 (s, 2H), 7.88 (br. s, 1H), 7.61 (br. s, 1H), 7.36 - 7.53 (m, 1H), 7.17 - 7.28 (m, 1H), 7.04 -

7.17 (m, 1H), 5.75 (d, 1H), 5.45 (d, 1H), 4.24 - 4.48 (m, 3H), 3.58 - 3.71 (m, 1H), 2.21 - 2.32 (m, 1H), 2.10 - 2.21 (m, 1H), 1.82 - 1.93 (m, 1H), 0.97 - 1.07 (m, 1H), 0.82 (m, 1H).

Example 706: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 8.98 (s, 1H), 8.39 (m, 1H), 8.01 (d, 2H), 7.90 (br. s, 1H), 7.58 (br. s, 1H), 7.36 - 7.49 (m, 1H), 7.29 (t, 1H), 7.06 - 7.19 (m, 1H), 5.73 (d, 1H), 5.43 (d, 1H), 5.06 (quin, 1H), 4.28 (dd, 1H), 3.60 - 3.69 (m, 1H), 2.24 (m, 1H), 2.12 (m, 1H), 1.80 - 1.92 (m, 1H), 1.34 (d, 3H), 0.95 - 1.05 (m, 1H), 0.76 - 0.86 (m, 1H).

Example 707: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.96 (br. s, 1H), 8.19 (d, 1H), 7.78 - 7.88 (m, 1H), 7.65 (d, 2H), 7.21 - 7.49 (m, 5H), 5.81 (d, 1H), 5.51 (d, 1H), 4.50 (dd, 1H), 3.78 - 3.85 (m, 1H), 2.22 - 2.39 (m, 2H), 1.92 (m, 1H), 1.04 (dt, 1H), 0.77 (m, 1H).

Example 708: ^{1}H NMR (400 MHz, DMSO-d_6): 9:1 mixture of rotamers δ (ppm): 10.52 (s, 0.1H), 10.19 (s, 0.9H), 8.12 - 8.25 (m, 1H), 7.84 - 7.98 (m, 1H), 7.63 (d, 2H), 7.34 - 7.47 (m, 2H), 7.20 - 7.34 (m, 3H), 5.54 - 5.75 (m, 2H), 5.38 - 5.54 (m, 0.9H), 4.96 - 5.27 (m, 0.2H), 4.73 (t, 0.9H), 4.16 - 4.33 (m, 1H), 4.00 (dd, 1H), 3.91 (m, 1H), 2.56 - 2.65 (m, 1H), 2.04 - 2.31 (m, 1H).

Example 709: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.97 (d, 1H), 9.49 (s, 1H), 8.50 (d, 1 H), 7.99 (br. s, 1H), 7.79 - 7.86 (m, 2H), 7.69 (br. s, 1H), 7.22 - 7.37 (m, 2H), 5.90 (d, 1H), 5.59 (d, 1H), 4.51 (dd, 1H), 3.76 - 3.83 (m, 1H), 2.21 - 2.39 (m, 2H), 1.89 - 1.98 (m, 1H), 0.99 - 1.09 (m, 1H), 0.79 (m, 1H).

Example 712: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.97 (br. s, 1H), 9.17 (br. s, 1H), 7.99 (s, 1H), 7.79 - 7.89 (m, 2H), 7.57 (br. s, 1H), 7.23 - 7.38 (m, 2H), 5.97 (d, 1H), 5.65 (d, 1H), 4.51 (dd, 1H), 3.76 - 3.86 (m, 1H), 2.93 (q, 2H), 2.23 - 2.41 (m, 2H), 1.87 - 1.99 (m, 1H), 1.30 (t, 3H), 1.01 - 1.11 (m, 1H), 0.82 (td, 1H).

Example 716: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 10.01 (br. s, 1H), 8.24 (d, 1H), 8.09 (d, 1H), 7.80 - 7.99 (m, 2H), 7.61 (br. s, 1H), 7.21 - 7.36 (m, 2H), 6.11 (d, 1H), 5.76 (d, 1 H), 4.52 (dd, 1H), 3.81 - 3.93 (m, 1H), 2.90 (s, 3H), 2.39 (m, 1H), 2.21 - 2.33 (m, 1H), 1.90 - 2.03

Example 717: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 10.01 (br. s, 1H), 7.96 (m, 1H), 7.69 - 7.91 (m, 2H), 7.59 (br. s, 1H), 7.16 - 7.39 (m, 2H), 6.09 (d, 1H), 5.72 (d, 1H), 4.51 (dd, 1H), 3.73 - 3.98 (m, 1H), 2.88 (s, 3H), 2.59 (s, 3H), 2.31 - 2.45 (m, 1H), 2.20 - 2.31 (m, 1H), 1.95 (dt, 1H), 1.02 - 1.13 (m, 1H), 0.68 - 0.78 (m, 1H).

Example 718: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.95 (br. s, 1H), 8.85 (d, 2H), 7.78 - 7.87 (m, 1H), 7.64 (d, 1H), 7.57 (s, 1H), 7.47 (t, 1H), 7.17 - 7.37 (m, 3H), 5.88 (d, 1H), 5.55 (d, 1H), 5.36 (s, 2H), 4.51 (dd, 1H), 3.77 - 3.86 (m, 1H), 2.58 (s, 3H), 2.23 - 2.37 (m, 2H), 1.84 - 1.97 (m, 1H), 0.95 - 1.09 (m, 1H), 0.74 - 0.89 (m, 1H).

Example 719: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.96 (br. s, 1H), 8.93 - 9.08 (m, 1H), 7.92 (d, 1H), 7.70 - 7.86 (m, 2H), 7.49 (br. s, 1H), 7.19 - 7.39 (m, 2H), 5.90 (d, 1H), 5.60 (d, 1H), 4.50 (dd, 1H), 3.74 - 3.85 (m, 1H), 2.15 - 2.42 (m, 3H), 1.84 - 2.03 (m, 1H), 0.99 - 1.09 (m, 1H), 0.89 - 0.99 (m, 4H), 0.76 - 0.84 (m, 1H).

Example 721: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 10.63 (br. s, 1H), 9.29 (s, 1H), 8.40 (d, 1H), 8.05 - 8.23 (m, 2H), 7.82 - 8.02 (m, 2H), 7.44 - 7.71 (m, 2H), 7.15 - 7.33 (m, 3H), 6.02 (d, 1H), 5.69 (d, 1H), 4.43 - 4.60 (m, 1H), 3.72 - 3.93 (m, 1H), 2.20 - 2.38 (m, 2H), 1.87 - 1.97 (m, 1H), 1.00 - 1.08 (m, 1H), 0.75 - 0.84 (m, 1H).

Example 723: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.98 (br. s, 1H), 9.25 (br. s, 1H), 8.09 (br. s, 1H), 7.90 (br. s, 1H), 7.78 - 7.87 (m, 1H), 7.61 (br. s, 1H), 7.22 - 7.39 (m, 2 H), 5.99 (d, 1H), 5.67 (d, 1H), 4.51 (dd, 1H), 3.76 - 3.86 (m, 1H), 2.67 (s, 3H), 2.21 - 2.41 (m, 2H), 1.88 - 1.99 (m, 1H), 1.05 (dt, 1H), 0.82 (m, 1H).

Example 724: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.98 (br. s, 1H), 9.22 (s, 1H), 8.39 (d, 1H), 8.11 (d, 1H), 7.77 - 7.93 (m, 2H), 7.47 - 7.67 (m, 1H), 7.22 - 7.36 (m, 2H), 5.99 (d, 1H), 5.68 (d, 1H), 4.52 (dd, 1H), 3.76 - 3.86 (m, 1H), 2.21 - 2.40 (m, 2H), 1.87 - 1.99 (m, 1H), 1.01 - 1.10 (m, 1H), 0.83 (m, 1H).

Example 726: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.98 (br. s, 1H), 9.08 (s, 1H), 8.10 (s, 1H), 7.78 - 7.90 (m, 2H), 7.57 (br. s, 1H), 7.22 - 7.36 (m, 2H), 5.79 (d, 1H), 5.47 (d, 1H), 4.50 (m, 1H), 3.60 - 3.83 (m, 1H), 2.44 (s, 3H), 2.21 - 2.38 (m, 2H), 1.91 (m, 1H), 0.97 - 1.07 (m, 1H), 0.80 - 0.90 (m, 1H).

Example 727: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 10.77 (m, 1H), 8.18 (d, 1H), 8.03 (d, 1H), 7.72 (t, 1H), 7,70 (m, 1H), 7.65 (d, 1H), 7.43 (t, 1H), 7.40 (m, 1H), 7.33 (d, 1H), 7.27 (t, 1H), 5.82 (d, 1H), 5.50 (d, 1H), 4.45 (m, 1H), 3.80 (m, 1H), 2.32 (m, 1H), 2.21 (m, 1H), 1.90 (m, 1H), 1.01 (m, 1H), 0.75 (m, 1H).

Example 731: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.86 (m, 1H), 8.19 (d, 1H), 7.74 (br. t, 1H), 7.67 (m, 1H), 7.66 (d, 1H), 7.45 (br. t, 1H), 7.39 (m, 1H), 7.34 (br. t, 1H), 7.28 (td, 1H), 5.81 (d, 1H), 5.51 (d, 1H), 4.50 (dd, 1H), 3.80 (m, 1H), 2.30 (m, 2H), 1.92 (m, 1H), 1.04 (m, 1H), 0.77 (m, 1H).

Example 741: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 11.14 (br.s, 1H), 9.27 (s, 1H), 8.55 (s, 1H), 8.18 (d, 1H), 7.68 (m, 1H), 7.66 (d, 1H), 7.45 (t, 1H), 7.38 (m, 1H), 7.27 (t, 1H), 5.83 (d, 1H), 5.51 (d, 1H), 4.47 (m, 1H), 3.83 (m, 1H), 2.32-2.37 (m, 1H), 2.22-2.28 (m, 1H), 1.91 (m, 1H), 1.01 (m, 1H), 0.77 (m, 1H).

Example 744: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 10.77 (m, 1H), 8.18 (d, 1H), 8.04 (d, 1H), 7.72 (t, 1H), 7.67 (m, 1H), 7.64 (d, 1H), 7.44 (t, 1H), 7.37 (m, 1H), 7.33 (d, 1H), 7.26 (t, 1H), 5.78 (d, 1H), 5.44 (d, 1H), 4.40 (m, 1H), 3.59 (m, 1H), 2.46 (dd, 1H), 1.98 (dd, 1H), 1.90 (m, 1H), 1.30 (s, 3H), 0.96 (br. t, 1H), 0.90 (dd, 1H).

Example 746: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 90:10 mixture of rotamers, only the major rotamer is described: δ (ppm): 10.85 (s, 1H), 8.16 (d, 1H), 8.01 (d, 1H), 7.70 (t, 1H), 7.64 (d, 1H), 7.62 (m, 1H), 7.43 (t, 1H), 7.37 (m, 1H), 7.31 (d, 1H), 7.25 (t, 1H), 5.44 (s, 2H), 4.62 (br. d, 1H), 4.00 (dd, 1H), 3.87 (d, 1H), 1.99 (m, 1H), 1.87 (m, 1H), 0.78 (m, 1H), 0.73 (m, 1H).

Example 754: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 85:15 mixture of rotamers, only the major rotamer is described: δ (ppm): 10.98 (m, 1H), 8.17 (d, 1H), 8.03 (d, 1H), 7.72 (t, 1H), 7.64 (d, 1H), 7.63 (m, 1H), 7.44 (t, 1H), 7.38 (m, 1H), 7.34 (d, 1H), 7.26 (t, 1H), 5.63 (d, 1H), 5.51 (d, 1H), 5.50-5.34 (m, 1H), 4.90 (m, 1H), 4.33 (m, 1H), 4.23 -4.03 (m, 2H), 3.41 (s, 3H).

Example 762: ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm): 10.68 (m, 1H), 8.65 (m, 1H), 8.28 (d, 1H), 8.10 (d, 1H), 8.00 (s, 1H), 7.80 (d, 1H), 7.75 (t, 1H), 7.38 (m, 2H), 7.35 (d, 1H), 7.27 (t, 1H), 7.20 (t, 1H), 4.35 (t, 1H), 3.93 (m, 1H), 2.38 (dd, 1H), 2.17 (m, 1H), 1.80 (m, 1H), 0.85 (m, 1H), 0.55 (m, 1H).

Example 770: ^{1}H NMR (400 MHz, DMSO-d_6): 4:1 mixture of rotamers δ (ppm): 9.95 (s, 1H), 7.81 (m, 1H), 7.63 (d, 1H), 7.56 (d, 1H), 7.30 (m, 1H), 7.27 (m, 1H), 7.14 (dd, 1H), 5.89-5.52 (AB system, 2H), 4.50 (dd, 1H), 4.14 (m, 2H), 3.80 (m, 1H), 3.70 (m, 2H), 3.32 (s, 3H), 2.59 (s, 3H), 2.29 (m, 2H), 1.91 (m, 1H), 1.02 (m, 1H), 0.81 (m, 1H).

Example 773: ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 85:15 mixture of rotamers δ (ppm): 9.15 (t, 0.15H), 8.72 (t, 0.85H), 8.32 (s, 0.15H), 8.23 (s, 0.85H), 8.19 - 8.20 (m, 1H), 7.48 - 7.49 (m, 1H), 7.44 (m, 0.85H), 7.41 (m, 0.15H), 7.20 - 7.23 (m, 2H), 7.18 (t, 0.15H), 7.01 (t, 0.85H), 5.75 (m, 0.15H), 5.67 (m, 0.15H), 5.61 (m, 0.85H), 5.52 (m, 1H), 5.45 (d, 0.85H), 5.28 (d, 0.15H), 5.22 (d, 0.85H), 4.72 (m, 1H), 4.54 (m, 0.3H), 4.43 (dd, 0.85H), 4.31 (dd, 0.85H), 4.08-4.25 (m, 1.70H), 4.01 (m, 0.15H), 3.70 (m, 0.15H), 2.43 (s, 3H).

Factor D inhibition data using Method 1 to determine the IC_{50} s.

Example	IC_{50} (nM)	Example	IC_{50} (nM)	Example	IC_{50} (nM)
1	7	**31**	12150	**61**	7100
2	25	**32**	3350	**62**	85
3	450	**33**	24050	**63**	11400
4	3980	**34**	90	**64**	22450
5	30	**35**	2850	**65**	13100
6	2100	**36**	3250	**66**	65
7	32	**37**	22000	**67**	22200
8	9	**38**	6300	**68**	15100
9	250	**39**	1050	**69**	1050
10	604	**40**	11150	**70**	2575
11	7	**41**	3200	**71**	2900
12	11135	**42**	2850	**72**	7000
13	139	**43**	7750	**73**	325
14	55	**44**	2600	**74**	3650
15	1100	**45**	22500	**75**	12550
16	94	**46**	22800	**76**	15650
17	4048	**47**	8950	**77**	14550
18	815	**48**	7500	**78**	10400
19	10	**49**	900	**79**	6000
20	1126	**50**	21600	**80**	14950
21	31	**51**	8500	**81**	4750
22	191	**52**	400	**82**	24750
23	1850	**53**	1750	**83**	2250
24	1700	**54**	1850	**84**	6000
25	6750	**55**	125	**85**	11350
26	25	**56**	1950	**86**	14300
27	8300	**57**	1350	**87**	4650
28	2525	**58**	350	**88**	6800
29	588	**59**	6400	**89**	7700
30	2700	**60**	800	**90**	1150
91	2950	**124**	500	**157**	850
92	8650	**125**	5100	**158**	80
93	4000	**126**	100	**159**	55

94	10950	**127**	3	**160**	1400
95	1350	**128**	2000	**161**	987
96	8050	**129**	4	**162**	5
97	900	**130**	54	**163**	100
98	1850	**131**	4600	**164**	400
99	23250	**132**	18	**165**	140
100	17550	**133**	6	**166**	3
101	15200	**134**	500	**167**	108
102	567	**135**	59	**168**	250
103	550	**136**	17900	**169**	268
104	1487	**137**	300	**170**	30
105	800	**138**	9	**171**	200
106	700	**139**	1500	**172**	1050
107	75	**140**	18300	**173**	111
108	55	**141**	650	**174**	35
109	2700	**142**	19	**175**	10
110	20	**143**	350	**176**	30
111	60	**144**	15	**177**	85
112	550	**145**	300	**178**	6
113	1150	**146**	9	**179**	400
114	500	**147**	120	**180**	650
115	1536	**148**	45	**181**	20
116	1150	**149**	10800	**182**	63
117	11850	**150**	25	**183**	20
118	17500	**151**	9323	**184**	9
119	4800	**152**	4400	**185**	550
120	3200	**153**	55	**186**	20
121	1250	**154**	1367	**187**	22200
122	150	**155**	20	**188**	1067
123	2930	**156**	150	**189**	942
190	20	**223**	12	**256**	4000
191	48	**224**	700	**257**	3950
192	17750	**225**	350	**258**	78
193	160	**226**	417	**259**	25
194	93	**227**	800	**260**	200
195	14	**228**	100	**261**	75

196	700	**229**	29	**262**	200
197	100	**230**	2550	**263**	400
198	357	**231**	103	**264**	10
199	8650	**232**	989	**265**	83
200	25	**233**	850	**266**	1625
201	20	**234**	150	**267**	83
202	450	**235**	80	**268**	8
203	6	**236**	8	**269**	1600
204	7	**237**	70	**270**	54
205	14	**238**	650	**271**	629
206	187	**239**	52	**272**	271
207	321	**240**	141	**273**	2263
208	29	**241**	250	**274**	14
209	1900	**242**	200	**275**	30
210	22	**243**	200	**276**	1310
211	1319	**244**	17	**277**	627
212	10	**245**	1046	**278**	350
213	12	**246**	2000	**279**	2900
214	1572	**247**	400	**280**	250
215	386	**248**	119	**281**	18
216	65	**249**	1425	**282**	3675
217	41	**250**	549	**283**	900
218	24	**251**	325	**284**	286
219	1850	**252**	114	**285**	55
220	233	**253**	1068	**286**	2650
221	23	**254**	150	**287**	112
222	137	**255**	434	**288**	1100
289	555	**322**	348	**355**	104
290	15783	**323**	902	**356**	480
291	3250	**324**	4250	**357**	389
292	3	**325**	2250	**358**	8
293	35	**326**	7151	**359**	250
294	5	**327**	1700	**360**	1000
295	150	**328**	102	**361**	25
296	218	**329**	181	**362**	5
297	350	**330**	250	**363**	9250

298	7	**331**	35	**364**	900
299	1800	**332**	450	**365**	45
300	4	**333**	47	**366**	3250
301	95	**334**	53	**367**	7950
302	75	**335**	550	**368**	66
303	8	**336**	750	**369**	850
304	653	**337**	250	**370**	95
305	1354	**338**	18900	**371**	3
306	4	**339**	65	**372**	45
307	13300	**340**	29	**373**	1
308	127	**341**	95	**374**	3
309	550	**342**	55	**375**	2
310	475	**343**	30	**376**	247
311	70	**344**	68	**377**	20
312	115	**345**	800	**378**	24
313	1300	**346**	69	**379**	5
314	20	**347**	677	**380**	17
315	13	**348**	200	**381**	57
316	3100	**349**	150	**382**	184
317	2800	**350**	85	**383**	4
318	3	**351**	600	**384**	32
319	548	**352**	200	**385**	7
320	7	**353**	252	**386**	8
321	85	**354**	1664	**387**	57
388	28	**421**	9300	**454**	103
389	30	**422**	888	**455**	767
390	38	**423**	780	**456**	85
391	30	**424**	68	**457**	107
392	7	**425**	1232	**458**	169
393	7	**426**	436	**459**	211
394	70	**427**	665	**460**	20
395	25	**428**	478	**461**	6250
396	667	**429**	1036	**462**	75
397	3161	**430**	58	**463**	3114
398	3050	**431**	31	**464**	254
399	1600	**432**	7	**465**	1589

400	3950	**433**	1789	**466**	43
401	1050	**434**	35	**467**	47
402	300	**435**	250	**468**	350
403	1000	**436**	150	**469**	3350
404	1000	**437**	107	**470**	250
405	295	**438**	924	**471**	89
406	150	**439**	1250	**472**	255
407	1050	**440**	1050	**473**	463
408	1400	**441**	5625	**474**	95
409	25	**442**	850	**475**	350
410	15	**443**	4468	**476**	33
411	26	**444**	243	**477**	628
412	14	**445**	580	**478**	258
413	101	**446**	16	**479**	89
414	311	**447**	739	**480**	33
415	48	**448**	26	**481**	22
416	315	**449**	51	**482**	188
417	40	**450**	25	**483**	60
418	168	**451**	90	**484**	358
419	476	**452**	15	**485**	15
420	1150	**453**	13	**486**	2450
487	13	**520**	22	**553**	5297
488	250	**521**	37	**554**	44
489	124	**522**	415	**555**	2272
490	214	**523**	51	**556**	25
491	28	**524**	64	**557**	134
492	237	**525**	36	**558**	1986
493	108	**526**	54	**559**	15700
494	50	**527**	483	**560**	141
495	19	**528**	75	**561**	14
496	176	**529**	186	**562**	804
497	128	**530**	72	**563**	42
498	692	**531**	11	**564**	13
499	36	**532**	223	**565**	369
500	36	**533**	34	**566**	436
501	471	**534**	51	**567**	293

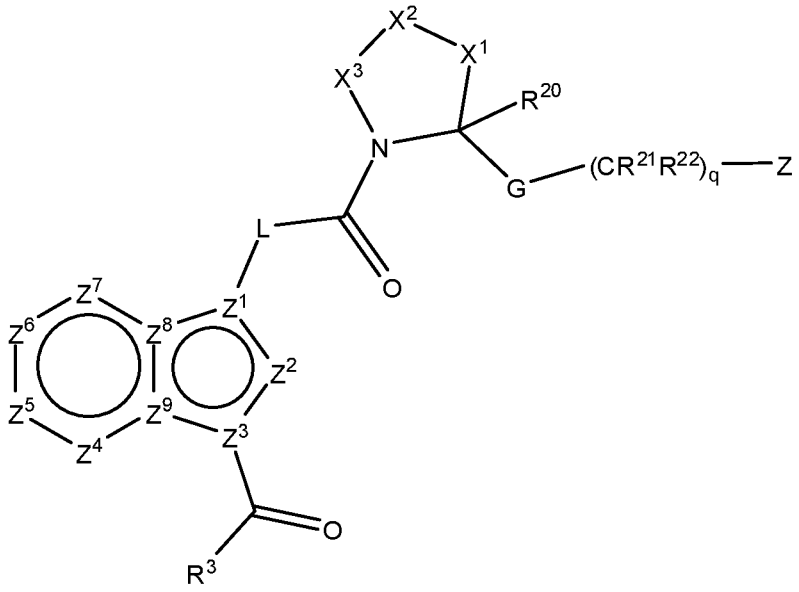
502	449	**535**	62	**568**	121
503	115	**536**	121	**569**	13
504	57	**537**	609	**570**	27
505	14	**538**	911	**571**	99
506	331	**539**	31	**572**	284
507	16	**540**	236	**573**	865
508	12	**541**	91	**574**	217
509	58	**542**	19	**575**	843
510	16	**543**	245	**576**	400
511	71	**544**	1110	**577**	71
512	411	**545**	113	**578**	50
513	193	**546**	10	**579**	39
514	95	**547**	38	**580**	252
515	268	**548**	363	**581**	60
516	8	**549**	69	**582**	134
517	1456	**550**	33	**583**	25
518	41	**551**	899	**584**	38
519	722	**552**	40	**585**	17
586	132	**619**	14	**652**	19
587	79	**620**	17	**653**	47
588	31	**621**	19	**654**	18
589	237	**622**	5595	**655**	91
590	10	**623**	24	**656**	358
591	109	**624**	26	**657**	78
592	115	**625**	19	**658**	24
593	56	**626**	36	**659**	25
594	85	**627**	16	**660**	16
595	41	**628**	38	**661**	10
596	95	**629**	17	**662**	13
597	14	**630**	36	**663**	36
598	14	**631**	11	**664**	24
599	46	**632**	18	**665**	58
600	14	**633**	55	**666**	6
601	110	**634**	53	**667**	16
602	227	**635**	18	**668**	19
603	1613	**636**	13	**669**	10

604	37	**637**	9	**670**	90
605	54	**638**	5	**671**	77
606	14	**639**	62	**672**	178
607	28	**640**	8	**673**	157
608	1835	**641**	32	**674**	75
609	1559	**642**	15	**675**	23
610	45	**643**	25	**676**	11
611	141	**644**	79	**677**	10
612	3433	**645**	132	**678**	40
613	215	**646**	12	**679**	134
614	245	**647**	16	**680**	16
615	42	**648**	17	**681**	19
616	123	**649**	441	**682**	12
617	28	**650**	22	**683**	48
618	39	**651**	21	**684**	27
685	5	**715**	27	**745**	5
686	30	**716**	46	**746**	7
687	98	**717**	31	**747**	13
688	10	**718**	24	**748**	4
689	156	**719**	13	**749**	4
690	34	**720**	140	**750**	34
691	68	**721**	98	**751**	81
692	3	**722**	20	**752**	95
693	6	**723**	90	**753**	66
694	17	**724**	61	**754**	5
695	15	**725**	18	**755**	17
696	101	**726**	169	**756**	7
697	3	**727**	9	**757**	3
698	29	**728**	8	**758**	64
699	118	**729**	62	**759**	9
700	6	**730**	143	**760**	12
701	15	**731**	53	**761**	70
702	10	**732**	44	**762**	5
703	10	**733**	25	**763**	14
704	23	**734**	4	**764**	4
705	21	**735**	3	**765**	211

706	45	**736**	18	**766**	216
707	88	**737**	36	**767**	346
708	54	**738**	93	**768**	146
709	144	**739**	23	**769**	378
710	52	**740**	13	**770**	9
711	71	**741**	5	**771**	8
712	38	**742**	37	**772**	7
713	260	**743**	5	**773**	28
714	300	**744**	4		

What is claimed is

1. A compound of formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein

Z^1 is C and L is a divalent residue selected from the group consisting of –N(H)– and –C(H)(R^1)–, or

Z^1 is N and L is CH_2;

R^1 is hydrogen, hydroxy, or amino;

Z^2 is C(R^2) or N;

Z^3 is C or N,

Z^4 is C(R^4) or N;

Z^5 is C(R^5) or N, or an N-oxide thereof;

Z^6 is C(R^6) or N, or an N-oxide thereof;

Z^7 is C(R^7) or N, or an N-oxide thereof;

Z^8 is C or N;

Z^9 is C or N;

wherein one of Z^1, Z^3, Z^8 and Z^9 is N and three of Z^1, Z^3, Z^8 and Z^9 are C;

wherein 0, 1, or 2 or 3 of Z^2, Z^4, Z^5, Z^6 and Z^7 are N;

R^2 is hydrogen or C_1-C_6alkyl;

R^3 is selected from the group consisting of hydrogen, C_1-C_4alkyl, hydroxyC_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl, haloC_1-C_4alkyl, amino or methylamino;

R^4 is selected from the group consisting of hydrogen, halogen, and C_1-C_6alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, halogen, hydroxy, NR^8R^9, cyano, CO_2H, $CONR^{10}R^{11}$ SO_2C_1-C_6alkyl, SO_2NH_2, $SO_2NR^{10}R^{11}$, C_1-C_6alkoxycarbonyl, -$C(NR^{10})NR^8R^9$, C_1-C_6alkyl, haloC_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy,

haloC$_1$-C$_6$alkoxy, and C$_2$-C$_6$alkenyloxy, wherein each alkyl, alkenyl, alkoxy and alkenyloxy is unsubstituted or substituted with up to 4 substitutents independently selected from halogen, hydroxy, cyano, tetrazole, C$_1$-C$_4$alkoxy, C$_1$-C$_4$haloalkoxy, CO_2H, C$_1$-C$_6$alkoxycarbonyl, $C(O)NR^{10}R^{11}$, NR^8R^9, optionally substituted phenyl, optionally substituted heterocycle having 4 to 7 ring atoms and 1, 2, or 3 ring heteroatoms selected from N, O or S, optionally substituted heteroaryl having 5 or 6 ring atoms and 1, 2 or 3 ring heteroatoms selected from N, O or S, and wherein optional phenyl, heterocycle or heteroaryl substituents are selected from halogen, hydroxy, C$_1$-C$_4$alkyl, C$_1$-C$_4$alkoxy and CO_2H;

R^5 and $R^{6,}$ taken in combination with the atoms to which they are attached, form a cycle having 4 to 7 ring atoms and 0, 1 or 2 additional ring N, O or S atoms;

R^7 is selected from the group consisting of hydrogen, halogen, C$_1$-C$_6$alkyl, C$_1$-C$_6$alkoxy, haloC$_1$-C$_6$alkyl, haloC$_1$-C$_6$alkoxy C$_1$-C$_6$alkoxycarbonyl, CO_2H and $C(O)NR^{10}R^{11}$;

R^8 and R^9 are independently selected from the group consisting of hydrogen, and C$_1$-C$_6$alkyl, haloC$_1$-C$_6$alkyl, C$_1$-C$_6$alkoxyC$_1$-C$_6$alkyl, hydroxyC$_1$-C$_6$alkyl, or NR^8R^9, taken in combination, form a heterocycle having 4 to 7 ring atoms and 0 or 1 additional ring N, O or S atoms, which heterocycle is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C$_1$-C$_4$alkyl, halogen, hydroxy, C$_1$-C$_4$alkoxy;

R^{10} and R^{11}, are each independently selected from the group consisting of hydrogen and C$_1$-C$_6$alkyl, haloC$_1$-C$_6$alkyl, C$_1$-C$_6$alkoxyC$_1$-C$_6$alkyl, or hydroxyC$_1$-C$_6$alkyl;

X^1 is $CR^{14}R^{15}$ or sulfur;

X^2 is $CR^{16}R^{17}$, oxygen, sulfur, N(H) or N(C$_1$-C$_6$alkyl), wherein at least one of X^1 and X^2 is carbon; or

X^1 and X^2, in combination, forms an olefin of the formula $–C(R^{16})=C(H)-$ or $–C(R^{16})=C(C_1\text{-}C_4\text{alkyl})-$, wherein the $C(R^{16})$ is attached to X^3;

X^3 is $(CR^{18}R^{19})_m$ or N(H) wherein m is 0,1 or 2, wherein X^3 is $CR^{18}R^{19}$ or $(CR^{18}R^{19})_2$ when either X^1 or X^2 is sulfur or X^2 is oxygen; or

X^2 and X^3, taken in combination, are $–N=C(H)–$ or $–N=C(C_1\text{-}C_4\text{alkyl})–$ in which the C(H) or $C(C_1\text{-}C_4\text{alkyl})$ is attached to X^1;

R^{14} is selected from the group consisting of hydrogen, halogen, hydroxy, amino and C$_1$-C$_6$alkyl;

R^{15} is selected from the group consisting of hydrogen, hydroxy, halogen, C$_1$-C$_6$alkyl, haloC$_1$-C$_6$alkyl, C$_2$-C$_6$alkenyl, C$_2$-C$_6$alkynyl, C$_1$-C$_6$alkoxy, haloC$_1$-C$_6$alkoxy, NR^8R^9, N(H)C(O)C$_1$-C$_6$alkyl, N(H)C(O)OC$_1$-C$_6$alkyl and $OC(O)NR^{10}R^{11}$ each of alkyl, alkoxy, alkenyl, and alkynyl substituents may be substituted with 0, 1, or 2 groups independently selected at each occurrence from the group consisting of halogen, hydroxy, C$_1$-C$_6$alkyl, C$_1$-C$_6$alkoxy, and NR^8R^9;

R^{16} is hydrogen, halogen, hydroxy, azide, cyano, COOH, C_1-C_6alkoxycarbonyl, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, NR^8R^9, $N(H)C(O)C_1$-C_6alkyl, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, or C_1-C_6alkyl substituted with NR^8R^9, N(H)C(O)H or N(H)C(O)(C_1-C_4alkyl);

R^{17} is hydrogen, halogen, hydroxy, cyano, C_1-C_6alkyl, C_1-C_6alkoxy, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, haloC_1-C_6alkyl, or C_1-C_6haloalkoxy;

R^{18} is selected from the group consisting of hydrogen, phenyl and C_1-C_6alkyl, which alkyl group is unsubstituted or substituted with hydroxy, amino, azide, and $NHC(O)C_1$-C_6alkyl;

R^{19} and R^{20} are each independently selected from hydrogen and C_1-C_6alkyl; or

$CR^{16}R^{17}$, taken in combination forms a spirocyclic 3 to 6 membered carbocycle which is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen and methyl; or

R^{16} and R^{17}, taken in combination, form an exocyclic methylidene (=CH_2);

R^{15} and R^{16} taken in combination form an epoxide ring or a 3 to 6 membered carbocyclic ring system which carbocyclic ring is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen, methyl, ethyl, hydroxyC_1-C_4alkyl, C_1-C_6alkoxyC_1-C_4alkyl, C_1-C_4alkoxycarbonyl, CO_2H, and C_1-C_4alkyl substituted with NR^8R^9;

R^{16} and R^{18} or R^{17} and R^{19}, taken in combination, form a fused 3 membered carbocyclic ring system which is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen, methyl, ethyl, hydroxyC_1-C_4alkyl, C_1-C_6alkoxyC_1-C_4alkyl, C_1-C_4alkoxycarbonyl, CO_2H, and C_1-C_4alkyl substituted with NR^8R^9; or

R^{14} and R^{20} taken in combination form a fused 3 carbocyclic ring system;

R^{14} and R^{19} taken in combination form a form 1 to 3 carbon alkylene linker;

R^{17} and R^{20} taken in combination form 1 to 3 carbon alkylene linker;

G is a divalent residue selected from C(O)-N(H), CH_2-N(H)–$S(O)_2$–, CH_2–N(H)–C(O), CH_2-N(H)-C(O)-O, CH_2N(H), CH_2-N(H)-C(O)-N(H), CH_2-N(H)-C(O)-N(Me), CH_2N(H)-$S(O)_2$-N(H)-, and CH_2N(H)-$S(O)_2$-N(Me)-, wherein the right most residue is attached to –$(CR^{21}R^{22})_q$;

q is 0, 1, 2, 3 or 4;

R^{21} is independently selected at each occurrence from the group consisting of hydrogen, hydroxy, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, cyanoC_1-C_4alkyl, phenyl, CO_2H, C_1-C_6alkoxy carbonyl, $C(O)NH_2$, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, C_1-C_6alkyl substituted with NR^8R^9, imidazoylC_1-C_6alkyl, heterocycleC_1-C_6alkyl, where the heterocycle is selected from azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, 1-oxa-6-aza-spiro[3.3]heptane, 2-oxa-6-aza-spiro[3.3]heptane, piperazinyl, 1,6-diaza-spiro[3.3]heptane, and 2,6-diaza-spiro[3.3]heptane each of which is optionally substituted by 1 or 2 substituent selected from fluoro, hydroxy, C_1-C_4alkyl or C_1-C_4alkoxy;

R^{22} is independently selected at each occurrence from hydrogen or C_1-C_6alkyl; or

When q is 1, 2, 3 or 4, R^{21} and a R^{22} substituent, taken in combination with the carbon atoms to which they are attached, form a 3 to 6 membered carbocycle or 4 to 6 membered heterocyle having a ring oxygen or nitrogen; or

when q is 2, 3 or 4, two R^{21} or R^{22} residues, located on adjacent carbon atoms, form, together with the carbon atoms to which they are attached, a 3 to 6 membered carbocycle; and

Z is C_1-C_6alkyl, C_1-C_6haloalkyl, phenyl, phenoxy, naphthyl, naphthyloxy, C_3-C_7cycloalkyl, indanyl, a 5, 6, 9 or 10 membered saturated or partially unsaturated, monocyclic or bicyclic heterocycle having 1, 2, or 3 ring heteroatoms selected from N, O, or S, or a 5 or 6 membered heteroaryl or heteroaryloxy, which heteroaryl has 1 or 2 ring heteroatoms selected from N, O or S provided that the ring does not have 2 O or S atoms, each residue is unsubstituted or substituted with 1, 2, 3, or 4 substituents which are independently selected from the group consisting of substituted or unsubstituted C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6haloalkyl, halogen, SF_5, CN, hydroxy, CO_2H, tetrazolyl, $C(O)R^{25}$, $S(O)_2R^{26}$, substituted or unsubstituted C_1-C_6alkoxy, haloC_1-C_6alkoxy, phenoxy, $NR^{23}R^{24}$, $CH_2NR^{23}R^{24}$, unsubstituted or substituted 5 or 6 membered heteroaryl and unsubstituted or substituted phenyl, which substituted phenyl and heteroaryl has 1 or 2 substituents independently selected from the group consisting of cyano, halo, C_1-C_6alkyl or C_1-C_6haloalkyl, OH, COOH, COR^{25}, $S(O)_2R^{26}$, amino, and CH_2NH_2, and which substituted alkyl or alkoxy has a substituent selected from hydroxy, C_1-C_4alkoxy, cyano, CO_2H, tetrazole or $NR^{23}R^{24}$;

R^{23} is hydrogen or C_1-C_6alkyl;

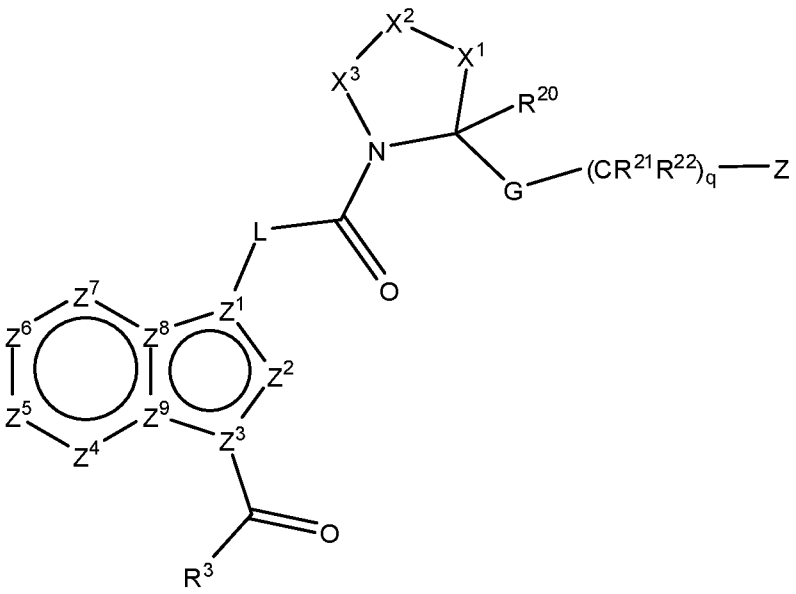
R^{24} is hydrogen, C_1-C_6alkyl, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, aminoC_1-C_6alkyl, mono- and di-C_1-C_6alkylaminoC_1-C_6alkyl; or

$NR^{23}R^{24}$, taken in combination form a 4, 5 or 6 membered heterocycle having 0 or 1 additional ring heteroatoms selected from the group consisting of N, O or S, and which is substituted with 0, 1 or 2 substituents independently selected from fluoro, hydroxy, C_1-C_4alkyl or C_1-C_4alkoxy;

R^{25} is independently selected at each occurrence from the group consisting of C_1-C_6alkoxy and $NR^{23}R^{24}$; and

R^{26} is selected from the group consisting of amino, hydroxy, C_1-C_6alkyl, and, mono- and di-C_1-C_6alkylamino.

2. A compound of formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein

Z^1 is C and L is a divalent residue selected from the group consisting of –N(H)– and –C(H)(R^1)–, or

Z^1 is N and L is CH_2;

R^1 is hydrogen, hydroxy, or amino;

Z^2 is C(R^2) or N;

Z^3 is C or N,

Z^4 is C(R^4) or N;

Z^5 is C(R^5) or N, or an N-oxide thereof;

Z^6 is C(R^6) or N, or an N-oxide thereof;

Z^7 is C(R^7) or N, or an N-oxide thereof;

Z^8 is C or N;

Z^9 is C or N;

wherein one of Z^1, Z^3, Z^8 and Z^9 is N and three of Z^1, Z^3, Z^8 and Z^9 are C;

wherein 0, 1, or 2 or 3 of Z^2, Z^4, Z^5, Z^6 and Z^7 are N;

R^2 is hydrogen or C_1-C_6alkyl;

R^3 is selected from the group consisting of hydrogen, C_1-C_4alkyl, hydroxyC_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl, haloC_1-C_4alkyl, amino or methylamino;

R^4 is selected from the group consisting of hydrogen, halogen, and C_1-C_6alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, halogen, hydroxy, NR^8R^9, cyano, CO_2H, $CONR^{10}R^{11}$ SO_2C_1-C_6alkyl, SO_2NH_2, $SO_2NR^{10}R^{11}$, C_1-C_6alkoxycarbonyl, -$C(NR^{10})NR^8R^9$, C_1-C_6alkyl, haloC_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, and C_2-C_6alkenyloxy, wherein each alkyl, alkenyl, alkoxy and alkenyloxy is unsubstituted or substituted with up to 4 substitutents independently selected from halogen, hydroxy, tetrazole, C_1-C_4alkoxy, C_1-C_4haloalkoxy, CO_2H, C_1-C_6alkoxycarbonyl, $C(O)NR^{10}R^{11}$,

NR^8R^9, optionally substituted phenyl, heterocycle having 4 to 7 ring atoms and 1, 2, or 3 ring heteroatoms selected from N, O or S, heteroaryl having 5 or 6 ring atoms and 1 or 2 ring heteroatoms selected from N, O or S, and wherein optional phenyl substituents are selected from halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy and CO_2H;

R^5 and $R^{6,}$ taken in combination with the atoms to which they are attached, form a cycle having 4 to 7 ring atoms and 0, 1 or 2 additional ring N, O or S atoms;

R^7 is selected from the group consisting of hydrogen, halogen, C_1-C_6alkyl, C_1-C_6alkoxy, haloC-C_6alkyl, haloC-C_6alkoxy C_1-C_6alkoxycarbonyl, CO_2H and $C(O)NR^{10}R^{11}$;

R^8 and R^9 are independently selected from the group consisting of hydrogen, and C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, hydroxyC_1-C_6alkyl, or NR^8R^9, taken in combination, form a heterocycle having 4 to 7 ring atoms and 0 or 1 additional ring N, O or S atoms, which heterocycle is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_1-C_4alkyl, halogen, hydroxy, C_1-C_4alkoxy;

R^{10} and R^{11}, are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, or hydroxyC_1-C_6alkyl;

X^1 is $CR^{14}R^{15}$ or sulfur;

X^2 is $CR^{16}R^{17}$, oxygen, sulfur, N(H) or N(C_1-C_6alkyl), wherein at least one of X^1 and X^2 is carbon; or

X^1 and X^2, in combination, forms an olefin of the formula $–C(R^{16})=C(H)-$ or $–C(R^{16})=C(C_1$-C_4alkyl)-, wherein the $C(R^{16})$ is attached to X^3;

X^3 is $(CR^{18}R^{19})_m$ or N(H) wherein m is 0,1 or 2, wherein X^3 is $CR^{18}R^{19}$ or $(CR^{18}R^{19})_2$ when either X^1 or X^2 is sulfur or X^2 is oxygen; or

X^2 and X^3, taken in combination, are $–N=C(H)–$ or $–N=C(C_1$-C_4alkyl)– in which the C(H) or $C(C_1$-C_4alkyl) is attached to X^1;

R^{14} is selected from the group consisting of hydrogen, halogen, hydroxy, amino and C_1-C_6alkyl;

R^{15} is selected from the group consisting of hydrogen, hydroxy, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, NR^8R^9, N(H)C(O)C_1-C_6alkyl, N(H)C(O)OC_1-C_6alkyl and $OC(O)NR^{10}R^{11}$ each of alkyl, alkoxy, alkenyl, and alkynyl substituents may be substituted with 0, 1, or 2 groups independently selected at each occurrence from the group consisting of halogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, and NR^8R^9;

R^{16} is hydrogen, halogen, hydroxy, azide, cyano, COOH, C_1-C_6alkoxycarbonyl, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, NR^8R^9, N(H)C(O)C_1-C_6alkyl, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, or C_1-C_6alkyl substituted with NR^8R^9, N(H)C(O)H or N(H)C(O)(C_1-C_4alkyl);

R^{17} is hydrogen, halogen, hydroxy, cyano, C_1-C_6alkyl, C_1-C_6alkoxy, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, haloC_1-C_6alkyl, or C_1-C_6haloalkoxy;

R^{18} is selected from the group consisting of hydrogen, phenyl and C_1-C_6alkyl, which alkyl group is unsubstituted or substituted with hydroxy, amino, azide, and NHC(O)C_1-C_6alkyl;

R^{19} and R^{20} are each independently selected from hydrogen and C_1-C_6alkyl; or

$CR^{16}R^{17}$, taken in combination forms a spirocyclic 3 to 6 membered carbocycle which is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen and methyl; or

R^{16} and R^{17}, taken in combination, form an exocyclic methylidene (=CH_2);

R^{15} and R^{16} taken in combination form an epoxide ring or a 3 to 6 membered carbocyclic ring system which carbocyclic ring is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen, methyl, ethyl, hydroxyC_1-C_4alkyl, C_1-C_6alkoxyC_1-C_4alkyl, C_1-C_4alkoxycarbonyl, CO_2H, and C_1-C_4alkyl substituted with NR^8R^9; or

R^{16} and R^{18} or R^{17} and R^{19}, taken in combination, form a fused 3 membered carbocyclic ring system which is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen, methyl, ethyl, hydroxyC_1-C_4alkyl, C_1-C_6alkoxyC_1-C_4alkyl, C_1-C_4alkoxycarbonyl, CO_2H, and C_1-C_4alkyl substituted with NR^8R^9; or

R^{14} and R^{20} taken in combination form a fused 3 carbocyclic ring system;

R^{14} and R^{19} taken in combination form a form 1 to 3 carbon alkylene linker;

R^{17} and R^{20} taken in combination form 1 to 3 carbon alkylene linker;

G is a divalent residue selected from C(O)-N(H), CH_2-N(H)–$S(O)_2$–, CH_2–N(H)–C(O), CH_2-N(H)-C(O)-O, CH_2N(H), CH_2-N(H)-C(O)-N(H), CH_2-N(H)-C(O)-N(Me), CH_2N(H)-$S(O)_2$-N(H)-, and CH_2N(H)-$S(O)_2$-N(Me)-, wherein the right most residue is attached to –$(CR^{21}R^{22})_q$;

q is 0, 1, 2, 3 or 4;

R^{21} is independently selected at each occurrence from the group consisting of hydrogen, hydroxy, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, phenyl, CO_2H, C_1-C_6alkoxy carbonyl, $C(O)NH_2$, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, C_1-C_6alkyl substituted with NR^8R^9, imidazoylC_1-C_6alkyl heterocycleC_1-C_6alkyl, where the heterocycle is selected from azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, 1-oxa-6-aza-spiro[3.3]heptane, 2-oxa-6-aza-spiro[3.3]heptane, piperazinyl, 1,6-diaza-spiro[3.3]heptane, and 2,6-diaza-spiro[3.3]heptane each of which is optionally sustituted by 1 or 2 substituent selected from fluoro, hydroxy, C_1-C_4alkyl or C_1-C_4alkoxy;

R^{22} is independently selected at each occurrence from hydrogen or C_1-C_6alkyl; or

When q is 1, 2, 3 or 4, R^{21} and a R^{22} substituent, taken in combination with the carbon atoms to which they are attached, form a 3 to 6 membered carbocycle or 4 to 6 membered heterocyle having a ring oxygen or nitrogen; or

when q is 2, 3 or 4, two R^{21} or R^{22} residues, located on adjacent carbon atoms, form, together with the carbon atoms to which they are attached, a 3 to 6 membered carbocycle; and

Z is C_1-C_6alkyl, C_1-C_6haloalkyl, phenyl, phenoxy, naphthyl, naphthyloxy, C_3-C_7cycloalkyl, indanyl, a 5, 6, 9 or 10 membered saturated or partially unsaturated, monocyclic or bicyclic heterocycle having 1, 2, or 3 ring heteroatoms selected from N, O, or S, or a 5 or 6 membered heteroaryl or heteroaryloxy, which heteroaryl has 1 or 2 ring heteroatoms selected from N, O or S provided that the ring does not have 2 O or S atoms, each residue is unsubstituted or substituted with 1, 2, 3, or 4 substituents which are independently selected from the group consisting of substituted or unsubstituted C_1-C_6alkyl, C_1-C_6haloalkyl, halogen, CN, hydroxy, CO_2H, tetrazolyl, $C(O)R^{25}$, $S(O)_2R^{26}$, substituted or unsubstituted C_1-C_6alkoxy, haloC_1-C_6alkoxy, phenoxy, $NR^{23}R^{24}$, $CH_2NR^{23}R^{24}$, 5 or 6 membered heteroaryl and unsubstituted or substituted phenyl, which substituted phenyl has 1 or 2 substituents independently selected from the group consisting of cyano, halo, C_1-C_6alkyl or C_1-C_6haloalkyl, OH, COOH, COR^{25}, $S(O)_2R^{26}$, amino, and CH_2NH_2, and which substituted alkyl or alkoxy has a substituent selected from hydroxy, C_1-C_4alkoxy, cyano, CO_2H, tetrazole or $NR^{23}R^{24}$;

R^{23} is hydrogen or C_1-C_6alkyl;

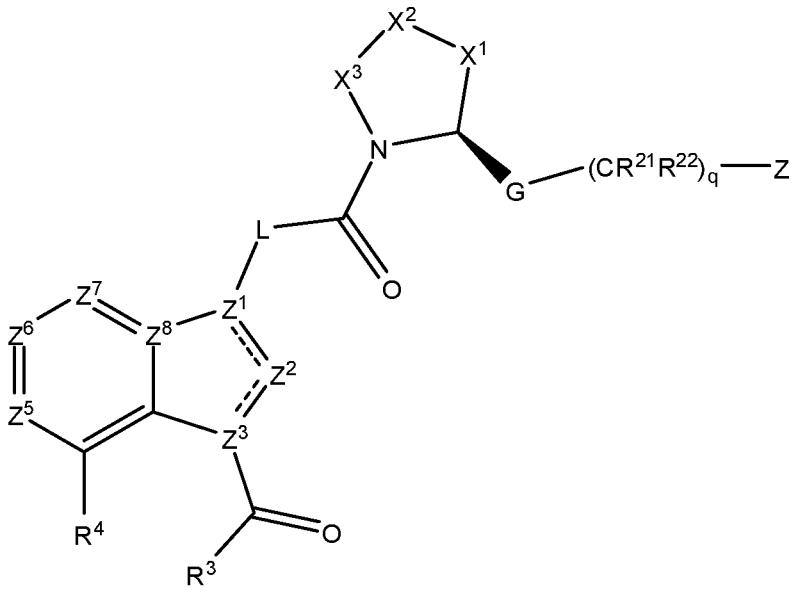
R^{24} is hydrogen, C_1-C_6alkyl, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, aminoC_1-C_6alkyl, mono- and di-C_1-C_6alkylaminoC_1-C_6alkyl; or

$NR^{23}R^{24}$, taken in combination form a 4, 5 or 6 membered heterocycle having 0 or 1 additional ring heteroatoms selected from the group consisting of N, O or S, and which is substituted with 0, 1 or 2 substituents independently selected from fluoro, hydroxy, C_1-C_4alkyl or C_1-C_4alkoxy;

R^{25} is independently selected at each occurrence from the group consisting of C_1-C_6alkoxy and $NR^{23}R^{24}$; and

R^{26} is selected from the group consisting of amino, hydroxy, C_1-C_6alkyl, and, mono- and di-C_1-C_6alkylamino.

3. The compound of claim 1 or claim 2, or a salt thereof, which is represented by formula (II)



(II)

wherein:

Z^2 is CH or N;

X^1 is CHR^{15} or S;

X^2 is $CR^{16}R^{17}$ or S, wherein at least one of X^1 and X^2 is not sulfur;

X^3 is $CR^{18}R^{19}$ or N(H);

R^{15} is selected from the group consisting of hydrogen, hydroxy, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, NR^8R^9, N(H)C(O)C_1-C_4alkyl, N(H)C(O)OC_1-C_4alkyl and OC(O)$NR^{10}R^{11}$, each alkyl and alkoxy may be substituted with 0, 1, or 2 groups independently selected at each occurrence from the group consisting of hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, and NR^8R^9;

R^{16} is hydrogen, halogen, hydroxy, amino, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, heterocycleC_0-C_4alkyl, NR^8R^9, N(H)C(O)C_1-C_4 alkyl, hydroxyC_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl or C_1-C_4alkyl substituted with NR^8R^9;

R^{17} is hydrogen, halogen, hydroxy, C_1-C_4alkyl, hydroxyC_1-C_4alkyl or C_1-C_2alkoxyC_1-C_4alkyl;

R^{18} is selected from the group consisting of hydrogen, phenyl and C_1-C_6alkyl, which alkyl group is unsubstituted or substituted with hydroxy, amino, NHC(O)C_1-C_6alkyl, amide or mono- or di-C_1-C_4alkyl-amide;

R^{19} is hydrogen; or

$CR^{16}R^{17}$, taken in combination, forms a spirocyclic 3 to 6 membered carbocycle; or

R^{15} and R^{16}, taken in combination, form a cyclopropyl ring which is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen, methyl, ethyl, hydroxymethyl, hydroxyethyl, methoxymethyl; or

R^{17} and R^{19} taken in combination form a cyclopropyl ring.

4. The compound of any one of claims 1-3, in which X^1 is CHR^{15}; and R^{15} is hydrogen, fluoro, hydroxy, amino, C_1-C_4alkyl, C_1-C_6alkoxy, OCH_2CH_2OMe, or C_2-C_4alkoxy substituted with NR^8R^9;

X^2 is $CR^{16}R^{17}$;

R^{16} is hydrogen, halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, NR^8R^9, hydroxyC_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl, C_1-C_4alkyl substituted with NR^8R^9 or C_2-C_4alkoxy substituted with NR^8R^9;

R^{17} is hydrogen, halogen, hydroxy or C_1-C_4alkyl; or

R^{15} and R^{16} taken in combination form a cyclopropyl ring; or

R^{17} and R^{19} taken in combination form a cyclopropyl ring.

5. The compound of any one of claims 1-3, in which

X^1 is S; and X^2 and X^3 are CH_2; or

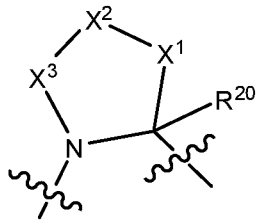
X^1 is CHR^{15}, wherein R^{15} is hydrogen, fluoro, methyl, hydroxy, methoxy, ethoxy, methoxyethoxy, C_2-C_4alkoxy substituted with NR^8R^9 or amino; X^3 is CH_2; and X^2 is $CR^{16}R^{17}$, wherein R^{16} is fluoro, amino, hydroxymethyl, methoxymethyl, aminomethyl or methyl and R^{17} is hydrogen or fluoro; or

X^1 is CHR^{15}, X^2 is $CR^{16}R^{17}$, and X^3 is CHR^{19}, wherein R^{17} and R^{19}, taken in combination form a cyclopropyl ring, and R^{16} is hydrogen, hydroxymethyl, or methoxymethyl, and R^{15} is hydrogen; or

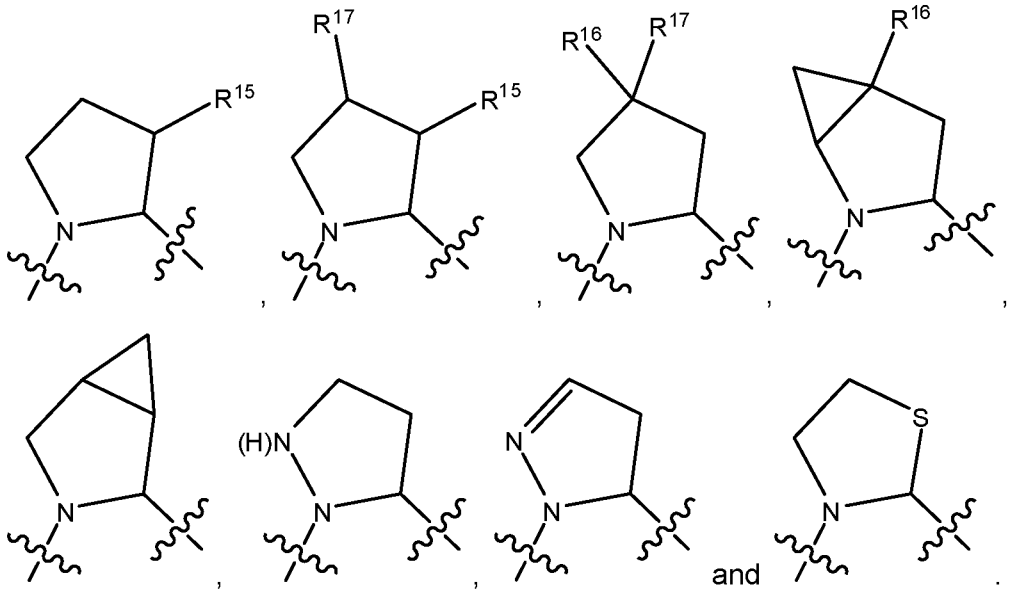
X^1 is CHR^{15}, X^2 is $CR^{16}R^{17}$, and X^3 is CHR^{19}, wherein R^{15} and R^{16}, taken in combination form a cyclopropyl ring, R^{17} and R^{19} are hydrogen; or

X^1 and X^2 are CH_2, and X^3 is N(H).

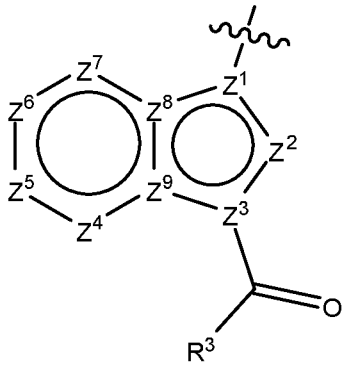
6. The compound of any one of claims 1-3, wherein the heterocyclic ring of the formula:



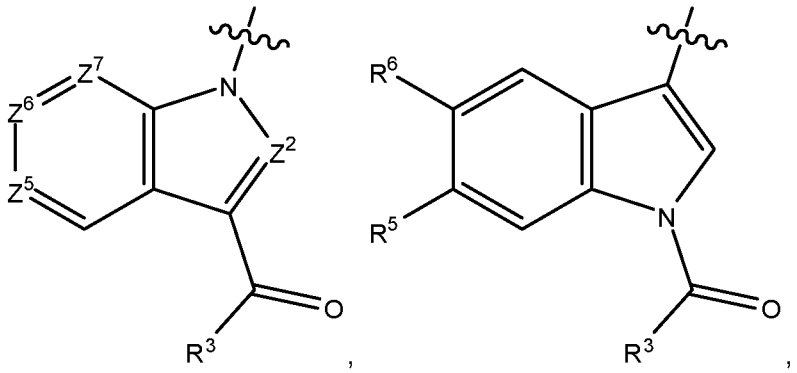
Is selected from the group consisting of:

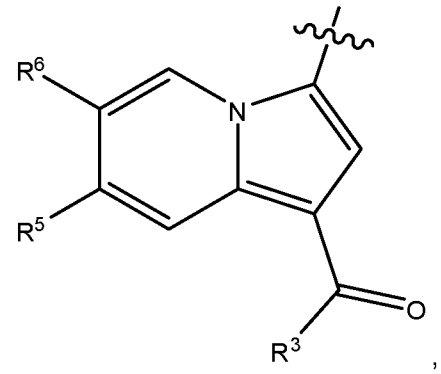


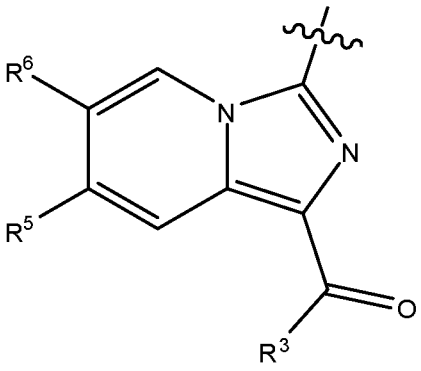
7. The compound of claim 1 or claim 2, wherein the bicyclic ring of the formula:

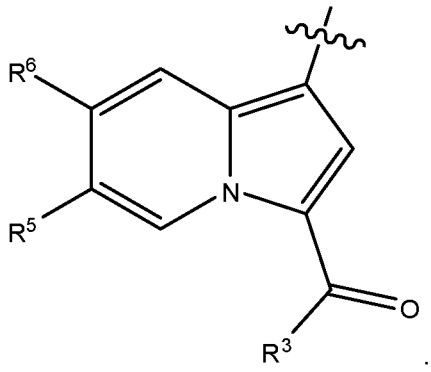


is selected from the group consisting of:





,


and


.

8. The compound of any of the preceding claims in which L is –N(H)– or –CH_2–.

9. The compound of any one of the preceding claims in which G is –C(O)-N(H)–.

10. The compound of any one of the preceding claims in which q is 0 or 1;

R^{21} is selected from the group consisting of hydrogen, C_1-C_6alkyl, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl and C_1-C_6alkyl substituted with NR^8R^9;

R^{22} is hydrogen; or

$CR^{21}R^{22}$, taken in combination, form a cyclopropyl ring;

Z is phenyl, pyridyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, thienyl, each of which is unsubstituted or substituted with 1, 2 or 3 substituents, each of which is independently selected from the group consisting of:

halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy, haloC_1-C_4alkyl, haloC_1-C_4alkoxy, $NR^{23}R^{24}$, CO_2H, $C(O)NR^{23}R^{24}$, $CO_2(C_1$-C_4alkyl), tetrazole, piperidinyl, piperazinyl, morpholino, and alkyl substituted with C_1-C_4alkoxy or $NR^{23}R^{24}$.

11. The compound of any one of the preceding claims in which q is 0 or 1;

R^{21} is selected from the group consisting of hydrogen, C_1-C_6alkyl, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, aminoC_1-C_6alkyl, and mono- and di-C_1-C_4alkylaminoC_1-C_6alkyl, wherein the alkyl residue is substituted with 0 or 1 heterocycles having 4, 5 or 6 ring atoms,

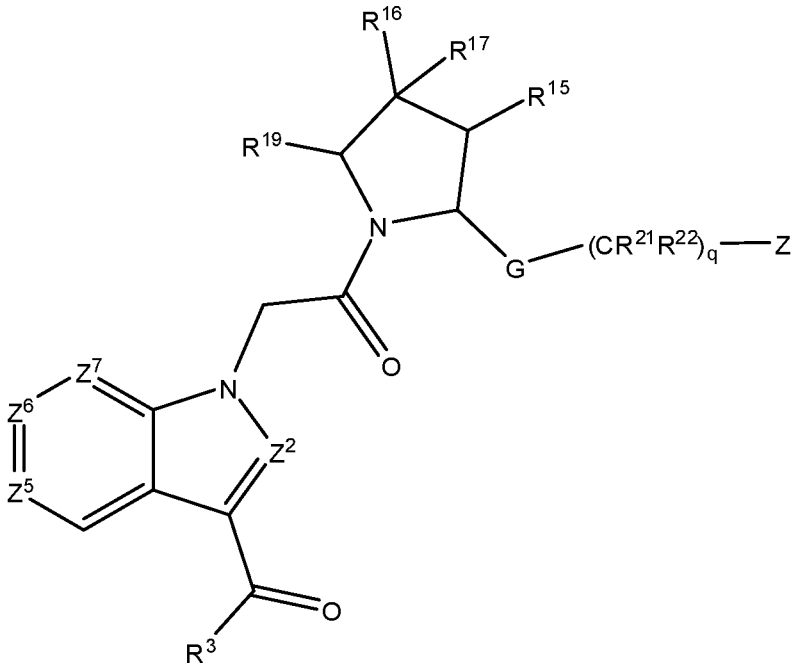
one ring nitrogen atom and 0 or 1 additional ring heteroatoms selected from N, O or S, which heterocyle is substituted with 0 or 1 substituents selected from fluorine or methoxy;

R^{22} is hydrogen; or

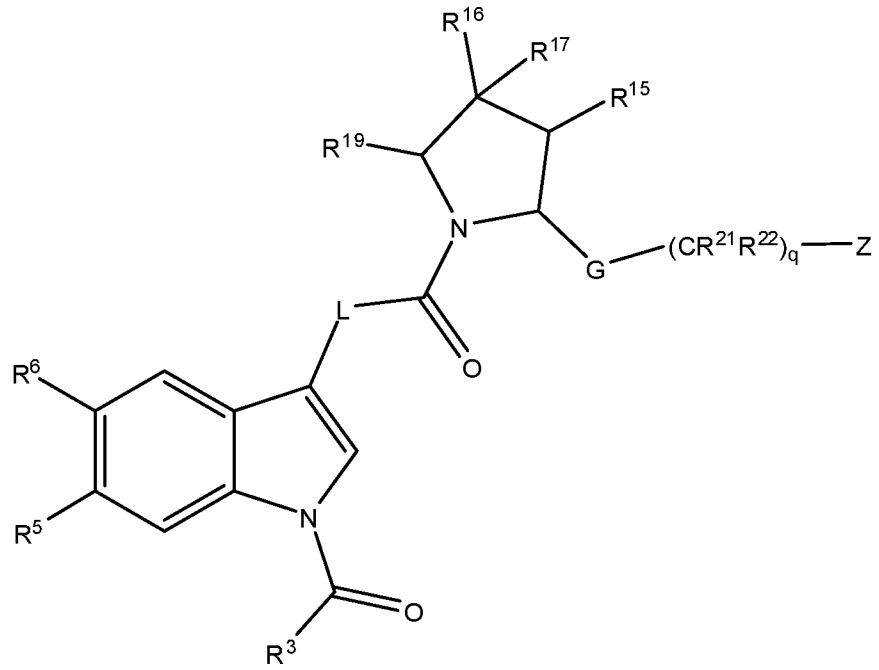
$CR^{21}R^{22}$, taken in combination, form a cyclopropyl ring; and

Z is phenyl which is unsubstituted or substituted with 1, 2, or 3 substituents, each of which is independently selected from the group consisting of halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy, haloC_1-C_4alkyl, haloC_1-C_4alkoxy, CO_2H, tetrazole, heterocycle, $C(O)NH_2$, CO_2(C_1-C_4alkyl), amino, and mono- and di-C_1-C_4alkylamino, wherein each N-alkyl residue is substituted with 0 or 1 residues selected from the group consisting of hydroxy, C_1-C_4alkoxy, C_1-C_4alkoxy, amino, or mono- or di-C_1-C_2alkylamino and each heterocycle is selected from 5 or 6 member heterocycles having 1 or 2 ring heteroatoms selected from N, O or S and which heterocycle is substituted with 0 or 1 substituents selected from halogen, C_1-C_4alkyl or C_1-C_4alkoxy.

12. The compound of any one of claims 1-3, in which the compound is represented by one of the formulae (III), (IV) or (V):

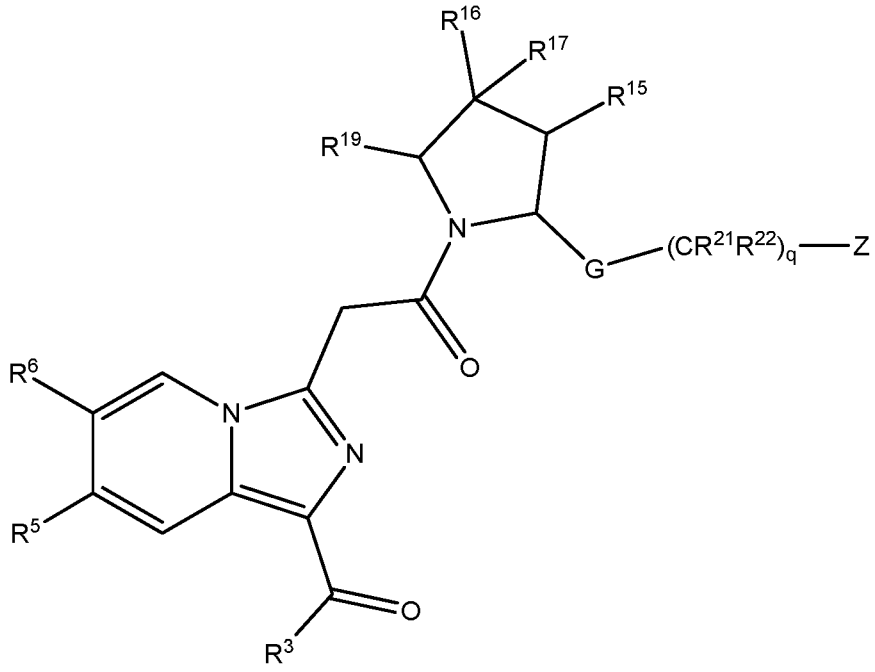


(III)



(IV)

or



(V)

wherein

Z^2 is CH or N;

Z^5 is CR^5 or N;

Z^6 is CR^6 or N;

Z^7 is CH, $C(CH_3)$ or N, wherein 0 or 1 or 2 of Z^5, Z^6 and Z^7 is N;

R^3 is hydrogen, methyl, ethyl, iPr, amino, hydroxymethyl, CH2OMe, or mono-, di- and tri-fluoromethyl, NHMe;

R^5 is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkenyl, C_2-C_4alkenyloxy, hydroxy, CO_2H, tetrazole , C_1-C_4alkoxycarbonyl, cyano, wherein each alkyl or alkoxy group is unsubstituted or substituted with up to 5 halogen atoms and with 0 or 1 additional substituents selected from the group consisting of hydroxy, tetrazole,C_1-C_4alkoxy, CO_2H, C_1-C_4alkoxycarbonyl, optionally substituted phenyl, pyridyl and pyrimidinyl, and wherein the phenyl is unsubstituted or substituted with 1 or 2 substituents independently selected from halogen, hydroxy, methyl, methoxy and CO_2H;

R^6 is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkenyl, C_2-C_4alkenyloxy, hydroxy, CO_2H, C_1-C_4alkoxycarbonyl, cyano, wherein each alkyl or alkoxy group is unsubstituted or substituted with up to 5 halogen atoms and with 0 or 1 additional substituents selected from the group consisting of hydroxy, $NR^{10}R^{11}$, tetrazole, cyano, imidazolyl, C_1-C_4alkoxy, CO_2H, C_1-C_4alkoxycarbonyl, optionally substituted phenyl, pyrrolyl, morpholino, piperidino, piperazino, and pyridyl, and wherein the phenyl is unsubstituted or substituted with 1 or 2 substituents independently selected from halogen, hydroxy, methyl, methoxy, mono- and dimethyl amino, and CO_2H;

L is CH_2 or NH ;

R^{15} is hydrogen, fluoro, methyl, hydroxy, methoxy, ethoxy and OCH_2CH_2OMe, $OCH_2CH_2N(CH_3)_2$, amino or OCH_2CH_2pyrrolyl;

R^{16} is hydrogen, fluoro, methyl, amino, hydroxymethyl, methoxymethyl, or aminomethyl;

R^{17} is hydrogen, fluoro or methyl;

R^{19} is hydrogen or R^{19} and R^{17}, taken in combination, form a cyclopropyl ring; or

R^{15} and R^{16}, taken in combination, form a cyclopropyl ring;

G is -C(O)N(H)-; and

q is 0, 1, or 2;

R^{21} is hydrogen, methyl, or ethyl, which methyl and ethyl are unsubstituted or substituted with hydroxy, methoxy, amino, mono- or di-methyl amino, morpholinomethyl, optionally substituted azetidinomethyl, which azetidino ring is subsituted with 0 or 1 fluoro or methoxy; or

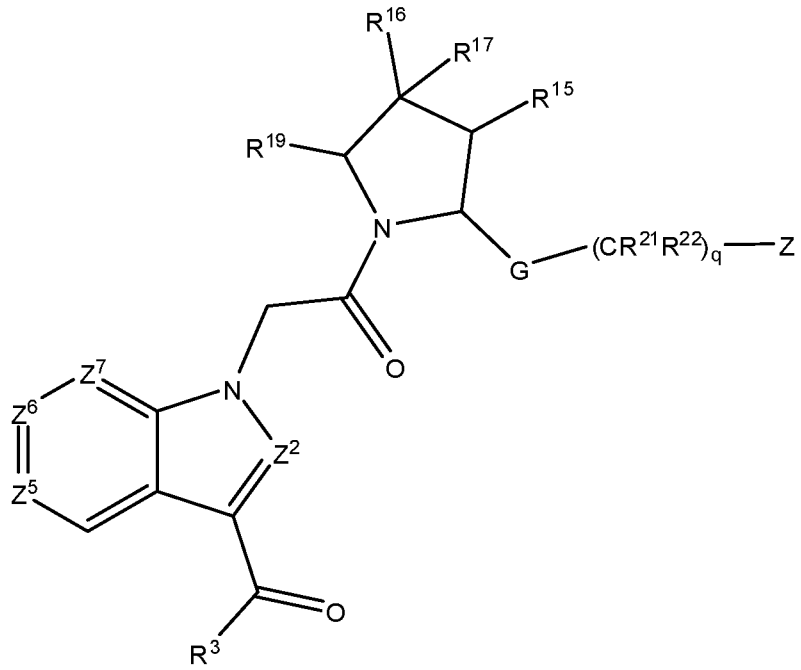
R^{22} is hydrogen;

$CR^{21}R^{22}$, taken in combination, form a cyclopropane ring; or

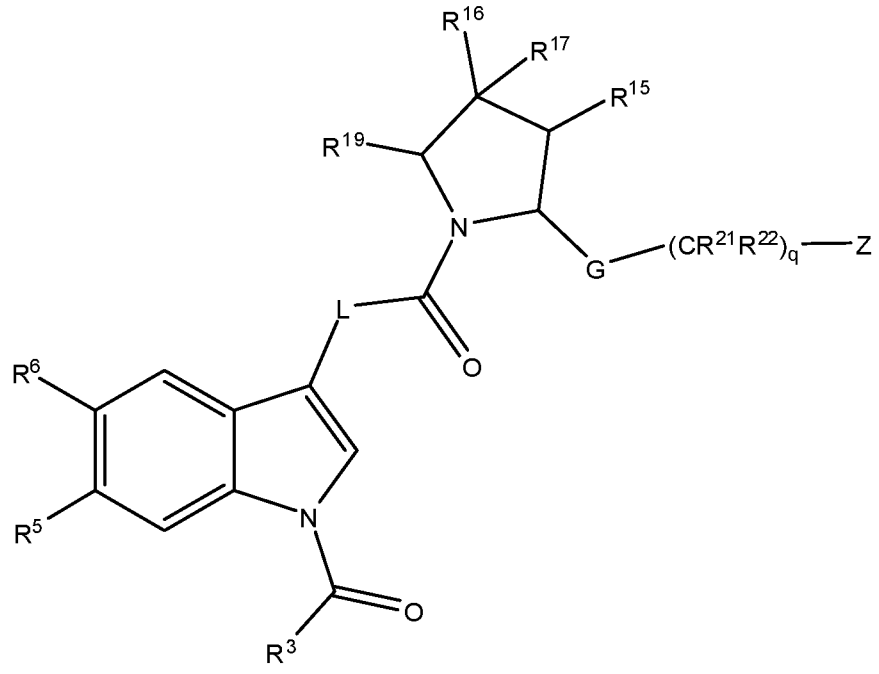
when q is 2, $CR^{21}R^{22}CR^{21}R^{22}$, taken in combination form a cis- or trans- cyclopropane ring;

Z is phenyl, pyridyl, or thienyl , each of which is unsubstituted or substituted with 1, 2, or 3 residues independently selected at each occurrence from the group consisting of halogen, methyl, methoxy, hydroxy, trifluoromethyl, trifluoromethoxy, CO_2H, tetrazole, and $NR^{23}R^{24}$.

13. The compound of claim 1, in which the compound is represented by one of the formulae (IIIb) or (IVb):



(IIIb)



(IVb)

wherein

Z^2 is CH or N;

Z^5 is CR^5 or N;

Z^6 is CR^6 or N; or an N-oxide thereof

Z^7 is CH, $C(CH_3)$ or N, wherein 0 or 1 or 2 of Z^5, Z^6 and Z^7 is N;

R^3 is hydrogen, methyl, ethyl, iPr, amino, hydroxymethyl, CH2OMe, or mono-, di- and tri-fluoromethyl, NHMe;

R^5 is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkenyl, C_2-C_4alkenyloxy, hydroxy, CO_2H, tetrazole , C_1-C_4alkoxycarbonyl, cyano, wherein each alkyl or alkoxy group is unsubstituted or substituted with up to 5 halogen atoms and with 0 or 1 additional substituents selected from the group consisting of hydroxy, cyano, tetrazole,C_1-C_4alkoxy, CO_2H, C_1-C_4alkoxycarbonyl, tetrahydrofuranyl, optionally substituted phenyl, pyridyl and pyrimidinyl, and wherein the phenyl is unsubstituted or substituted with 1 or 2 substituents independently selected from halogen, hydroxy, methyl, methoxy and CO_2H;

R^6 is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkenyl, C_2-C_4alkenyloxy, hydroxy, CO_2H, C_1-C_4alkoxycarbonyl, cyano, wherein each alkyl or alkoxy group is unsubstituted or substituted with up to 5 halogen atoms and with 0 or 1 additional substituents selected from the group consisting of hydroxy, $NR^{10}R^{11}$, tetrazole, cyano, imidazolyl, C_1-C_4alkoxy, CO_2H, C_1-C_4alkoxycarbonyl, optionally substituted phenyl, pyrrolyl, morpholino, piperidino, piperazino, and pyridyl, and wherein the phenyl is unsubstituted or substituted with 1 or 2 substituents independently selected from halogen, hydroxy, methyl, methoxy, mono- and dimethyl amino, and CO_2H;

L is CH_2 or NH ;

R^{15} is hydrogen, fluoro, methyl, hydroxy, methoxy, ethoxy and OCH_2CH_2OMe, $OCH_2CH_2N(CH_3)_2$, amino or OCH_2CH_2pyrrolyl;

R^{16} is hydrogen, fluoro, methyl, amino, hydroxymethyl, methoxymethyl, or aminomethyl;

R^{17} is hydrogen, fluoro or methyl;

R^{19} is hydrogen or R^{19} and R^{17}, taken in combination, form a cyclopropyl ring; or

R^{15} and R^{16}, taken in combination, form a cyclopropyl ring;

G is -C(O)N(H)-; and

q is 0 or 1;

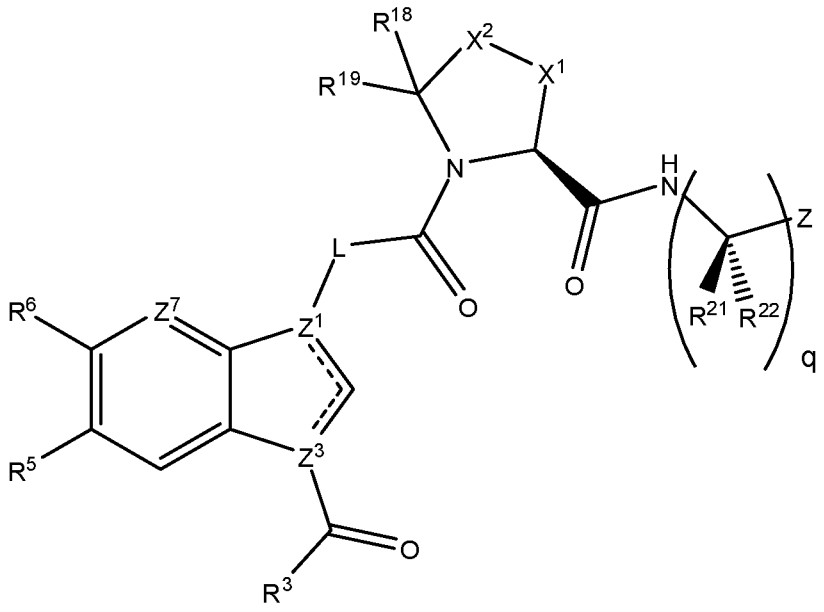
R^{21} is hydrogen, methyl, or ethyl, which methyl and ethyl are unsubstituted or substituted with hydroxy, methoxy, cyano, amino, mono- or di-methyl amino, morpholinomethyl, optionally substituted azetidinomethyl, which azetidino ring is subsituted with 0 or 1 fluoro or methoxy; or

R^{22} is hydrogen;

$CR^{21}R^{22}$, taken in combination, form a cyclopropane ring;

Z is phenyl, pyridyl, pyrazinyl or thienyl , each of which is unsubstituted or substituted with 1, 2, or 3 residues independently selected at each occurrence from the group consisting of halogen, methyl, ethyl, isopropyl, cyclopropyl, methoxy, hydroxy, trifluoromethyl, di or trifluoromethoxy, SF_5, CO_2H, tetrazole, and $NR^{23}R^{24}$, unsubstituted or substituted phenyl and unsubstituted or substituted pyridinyl, which substituted phenyl and pyridinyl has 1 or 2 substituents independently selected from the group consisting of halogen and methyl.

14. The compound of any one of claims 1-3, or a salt thereof, which is represented by formula (VI):



(VI)

wherein

q is 0, 1 or 2;

R^{21} is hydrogen;

R^{22} is hydrogen, methyl, or ethyl, which methyl and ethyl are unsubstituted or substituted with hydroxy, methoxy, amino, or mono- or di-methyl amino; or

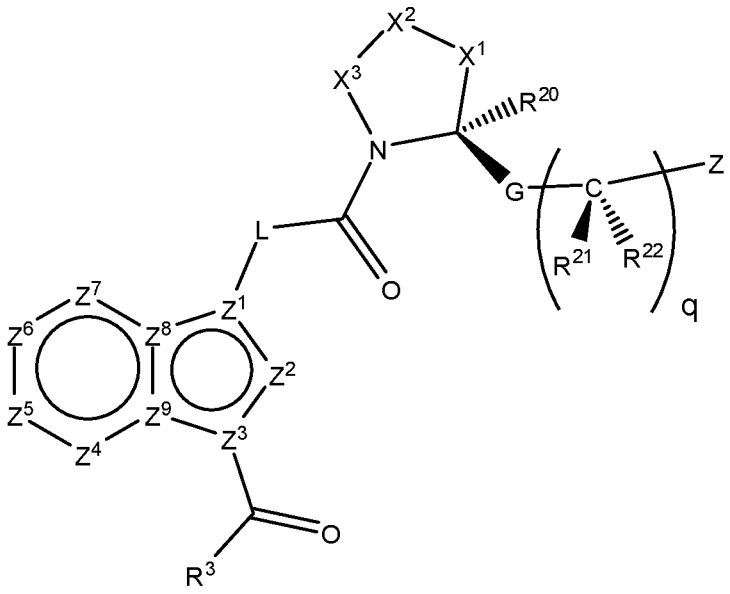
$CR^{21}R^{22}$, taken in combination, form a cyclopropane ring;

when q is 2, $CR^{21}R^{22}CR^{21}R^{22}$, taken in combination form a cis- or trans- cyclopropane ring;

Z is phenyl which is unsubstituted or substituted with 1, 2, or 3 residues selected from the group consisting of fluoro, chloro, bromo, methyl, trifluoromethyl, methoxy, trifluoromethoxy, $NR^{23}R^{24}$, tetrazole or CO_2H; or

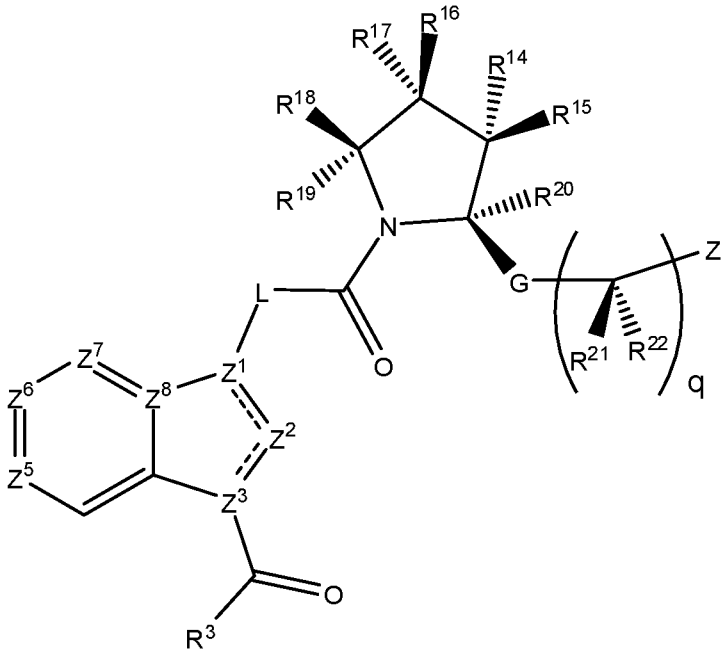
Z is pyridyl or thienyl, each of which is unsubstituted or substituted with 1 or 2 substitutents selected from the group consisting of fluoro, chloro, bromo, methyl, trifluoromethyl, methoxy, or trifluoromethoxy.

15. The compound of claim 1 or claim 2, or a salt thereof, which is represented by formula (VI):



(VI).

16. A compound which is represented by formula (VII):



(VII),

or a pharmaceutically acceptable salt thereof, wherein

L is a divalent residue selected from the group consisting of –N(H)– and –C(H)(R^1)–,

R^1 is hydrogen, hydroxy, or amino;

Z^1 is C or N;

Z^2 is C(H) or N;

Z^3 is C or N,

Z^5 is $C(R^5)$, N or an N oxide thereof;

Z^6 is $C(R^6)$, N or an N oxide thereof;

Z^7 is $C(R^7)$, N or an N oxide thereof;

Z^8 is C or N

wherein one of Z^1 and Z^3 is N and the other is C;

wherein 0, 1, 2 or 3 of Z^2, Z^5, Z^6, Z^7 and Z^8 are N;

R^3 is selected from the group consisting of hydrogen, C_1-C_4alkyl, hydroxyC_1-C_4alkyl, C_1-C_4alkoxyC_1-C_4alkyl, haloC_1-C_4alkyl, amino or methylamino;

R^5 and R^6 are independently selected from the group consisting of hydrogen, halogen, hydroxy, NR^8R^9, cyano, CO_2H, $CONR^{10}R^{11}$ SO_2C_1-C_6alkyl, and $SO_2NR^{10}R^{11}$, C_1-C_6alkoxycarbonyl, $C(NR^8)NR^8R^9$, C_1-C_6alkyl, haloC_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, C_2-C_6alkenyloxy, wherein each alkyl, alkenyl, alkoxy and alkenyloxy is unsubstituted or substituted with up to 4 substitutents independently selected from halogen, hydroxy, tetrazole, C_1-C_4alkoxy, C_1-C_4haloalkoxy, CO_2H, C_1-C_6alkoxycarbonyl, $C(O)NR^{10}R^{11}$, NR^8R^9 optionally substituted phenyl, heterocycle having 4 to 7 ring atoms and 1, 2, or 3 ring heteroatoms selected from N, O or S, heteroaryl having 5 or 6 ring atoms and 1 or 2 ring heteroatoms selected from N, O or S, and wherein optional phenyl substituents are selected from halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy and CO_2H;

R^5 and $R^{6,}$ taken in combination with the atoms to which they are attached, form a cycle having 4 to 7 ring atoms and 0 or 1 additional ring N, O or S atoms;

R^7 is selected from the group consisting of hydrogen, halogen, C_1-C_6alkyl, C_1-C_6alkoxy, haloC-C_6alkyl, haloC-C_6alkoxy C_1-C_6alkoxycarbonyl, CO_2H and $C(O)NR^{10}R^{11}$;R^8 and R^9 are independently selected from the group consisting of hydrogen, and C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, hydroxyC_1-C_6alkyl, or NR^8R^9, taken in combination, form a heterocycle having 4 to 7 ring atoms and 0 or 1 additional ring N, O or S atoms, which heterocycle is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_1-C_4alkyl, halogen, hydroxy, C_1-C_4alkoxy;

R^8 and R^9 are independently selected from the group consisting of hydrogen, and C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, hydroxyC_1-C_6alkyl, or NR^8R^9, taken in combination, form a heterocycle having 4 to 7 ring atoms and 0 or 1 additional ring N, O or S atoms,which heterocycle is substituted with 0, 1, or 2 substituents independently selected from the group consisting of C_1-C_4alkyl, halogen, hydroxy, C_1-C_4alkoxy;

R^{10} and R^{11}, are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, or hydroxyC_1-C_6alkyl;

R^{14} is selected from the group consisting of hydrogen, halogen, hydroxy, amino and C_1-C_6alkyl;

R^{15} is selected from the group consisting of hydrogen, hydroxy, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, NR^8R^9, N(H)C(O)C_1-C_6alkyl, N(H)C(O)OC_1-C_6alkyl and OC(O)$NR^{10}R^{11}$ each of alkyl, alkoxy, alkenyl, and alkynyl substituents may be substituted with 0, 1, or 2) groups independently selected at each occurrence from the group consisting of halogen, hydroxy, C_1-C_6alkyl, C_1-C_6alkoxy, and $NR^{10}R^{11}$;

R^{16} is hydrogen, halogen, hydroxy, azide, cyano, COOH, C_1-C_6alkoxycarbonyl, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, NR^8R^9, N(H)C(O)C_1-C_6alkyl, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, or C_1-C_6alkyl substituted with NR^8R^9, N(H)C(O)H or N(H)C(O)(C_1-C_4alkyl);

R^{17} is hydrogen, halogen, hydroxy, C_1-C_6alkyl, C_1-C_4alkoxy, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, or C_1-C_6haloalkoxy;

R^{18} is selected from the group consisting of hydrogen, phenyl and C_1-C_6alkyl, which alkyl group is unsubstituted or substituted with hydroxy, amino, azide, and NHC(O)C_1-C_6alkyl;

R^{19} and R^{20} are each independently selected from hydrogen and C_1-C_6alkyl; or

$CR^{16}R^{17}$, taken in combination, form a spirocyclic 3 to 6 membered carbocycle which is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen and methyl; or

R^{16} and R^{17}, taken in combination, form an exocyclic methylidene (=CH_2);

R^{15} and R^{16} or R^{14} and R^{17} taken in combination form an epoxide ring or a 3 to 6 membered carbocyclic ring system which carbocyclic ring is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen, methyl, ethyl, hydroxyC_1-C_4alkyl, C_1-C_6alkoxyC_1-C_4alkyl, C_1-C_4alkoxycarbonyl, CO_2H, and C_1-C_4alkyl substituted with NR^8R^9; or

R^{17} and R^{19} or R^{16} and R^{18}, taken in combination, form a fused 3 membered carbocyclic ring system which is substituted with 0, 1, or 2 substituents independently selected from the group consisting of halogen, methyl, ethyl, hydroxyC_1-C_4alkyl, C_1-C_4alkoxycarbonyl, CO_2H, and C_1-C_4alkyl substituted with NH^8R^9; or

R^{14} and R^{20} taken in combination form a fused 3 carbocyclic ring system;

R^{14} and R^{19}, taken in combination, form a 1 to 3 carbon alkylene linker; or

R^{17} and R^{20}, taken in combination, form a 1 to 3 carbon alkylene linker;

G is a divalent residue selected from C(O)-N(H), CH_2-N(H)–$S(O)_2$–, CH_2–N(H)–C(O), CH_2-N(H)-C(O)-O, CH_2N(H), CH_2-N(H)-C(O)-N(H), CH_2-N(H)-C(O)-N(Me), CH_2N(H)-$S(O)_2$-N(H)-, and CH_2N(H)-$S(O)_2$-N(Me)-, wherein the right most residue is attached to –$(CR^{21}R^{22})_q$;

q is 0, 1, 2, 3 or 4;

R^{21} is independently selected at each occurrence from the group consisting of hydrogen, hydroxy, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, phenyl, CO_2H, C_1-C_6alkoxy carbonyl,

$C(O)NH_2$, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, C_1-C_6alkyl substituted with NR^8R^9, imidazoylC_1-C_6alkyl heterocycleC_1-C_6alkyl, where the heterocycle is selected from azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, 1-oxa-6-aza-spiro[3.3]heptane, 2-oxa-6-aza-spiro[3.3]heptane, piperazinyl, 1,6-diaza-spiro[3.3]heptane, and 2,6-diaza-spiro[3.3]heptane each of which is optionally sustituted by 1 or 2 substituent selected from fluoro, hydroxy, C_1-C_4alkyl or C_1-C_4alkoxy;

R^{22} is independently selected at each occurrence from hydrogen or C_1-C_6alkyl; or

when q is 1, 2, 3 or 4, R^{21} and a R^{22} substituent, taken in combination with the carbon atoms to which they are attached, form a 3 to 6 membered carbocycle or 4 to 6 membered heterocyle having a ring oxygen or nitrogen; or

when q is 2, 3 or 4, two R^{21} or R^{22} residues, located on adjacent carbon atoms, form, together with the carbon atoms to which they are attached, a 3 to 6 membered carbocycle; and

Z is C_1-C_6alkyl, C_1-C_6haloalkyl, phenyl, phenoxy, naphthyl, naphthyloxy, C_3-C_7cycloalkyl, indanyl, a 5, 6, 9 or 10 membered saturated or partially unsaturated, monocyclic or bicyclic heterocycle having 1, 2, or 3 ring heteroatoms selected from N, O, or S, or a 5 or 6 membered heteroaryl or heteroaryloxy, which heteroaryl has 1 or 2 ring heteroatoms selected from N, O or S provided that the ring does not have 2 O or S atoms, each residue is unsubstituted or substituted with 1, 2, 3, or 4 substituents which are independently selected from the group consisting of substituted or unsubstituted C_1-C_6alkyl, C_1-C_6haloalkyl, halogen, CN, hydroxy, CO_2H, tetrazolyl, $C(O)R^{25}$, $S(O)_2R^{26}$, substituted or unsubstituted C_1-C_6alkoxy, haloC_1-C_6alkoxy, phenoxy, $NR^{23}R^{24}$, $CH_2NR^{23}R^{24}$, 5 or 6 membered heteroaryl and unsubstituted or substituted phenyl, which substituted phenyl has 1 or 2 substituents independently selected from the group consisting of cyano, halo, C_1-C_6alkyl or C_1-C_6haloalkyl, OH, COOH, COR^{25}, $S(O)_2R^{26}$, amino, and CH_2NH_2, and which substituted alkyl or alkoxy has a substituent selected from hydroxy, C_1-C_4alkoxy, cyano, CO_2H, tetrazole or $NR^{23}R^{24}$;

R^{23} is hydrogen or C_1-C_6alkyl;

R^{24} is hydrogen, C_1-C_6alkyl, hydroxyC_1-C_6alkyl, C_1-C_6alkoxyC_1-C_6alkyl, aminoC_1-C_6alkyl, mono- and di-C_1-C_6alkylaminoC_1-C_6alkyl; or

$NR^{23}R^{24}$, taken in combination form a 4, 5 or 6 membered heterocycle having 0 or 1 additional ring heteroatoms selected from the group consisting of N, O or S, and which is substituted with 0, 1 or 2 substituents independently selected from fluoro, hydroxy, C_1-C_4alkyl or C_1-C_4alkoxy;

R^{25} is independently selected at each occurrence from the group consisting of C_1-C_6alkoxy and $NR^{23}R^{24}$; and

R^{26} is selected from the group consisting of amino, hydroxy, C_1-C_6alkyl, and, mono- and di-C_1-C_6alkylamino.

17. A compound of claim 1 or claim 2, which compound is selected from the group consisting of:

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-benzylamide 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(pyridin-3-ylmethyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-5-{[(2-methoxy-ethyl)-methyl-amino]-methyl}-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide};

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(pyridin-4-ylmethyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(4-methyl-piperazin-1-yl)-benzylamide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-hydroxy-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(4-methyl-piperazin-1-ylmethyl)-benzylamide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-chloro-thiophen-2-ylmethyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-5-diethylamino-methyl-2-fluoro-benzyl-amide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((S)-2-hydroxy-1-phenyl-ethyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2,3-difluoro-benzylamide);

(2S,3S)-2-{[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-3-methyl-pentanoic acid tert-butyl ester;

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(4-methoxy-piperidin-1-yl)-benzylamide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-5-{[(2-dimethylamino-ethyl)-methyl-amino]-methyl}-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-5-morpholin-4-ylmethyl-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-5-morpholin-4-yl-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(4-methoxy-piperidin-1-ylmethyl)-benzylamide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{3-chloro-2-fluoro-5-[(2-methoxy-ethyl)-methyl-amino]-benzylamide};

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{3-chloro-5-[(2-dimethylamino-ethylamino)-methyl]-2-fluoro-benzylamide};

2-({[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-methyl)-benzoic acid;

2-({[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-3-carbonyl]-amino}-methyl)-benzoic acid;

(2S,3S)-2-{[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-3-methyl-pentanoic acid;

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-phenylamide;

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 2-benzylamide 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide) as a formate salt;

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-methyl-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-trifluoromethyl-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-fluoro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-cyano-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 2-(3-bromo-benzylamide) 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-hydroxy-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-methoxy-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-trifluoromethoxy-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-phenoxy-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 2-[(biphenyl-3-ylmethyl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide] as a formate salt;

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-pyrrol-1-yl-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-(5-chloro-thiophen-2-yl)-benzylamide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(4-methyl-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(4-chloro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(4-trifluoromethyl-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(4-trifluoromethoxy-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(4-hydroxy-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2-hydroxy-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2-fluoro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2-chloro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 2-[(biphenyl-2-ylmethyl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2,3-difluoro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(5-chloro-2-methoxy-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-4-methoxy-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(5-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-4-fluoro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-methyl-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(5-chloro-2-methyl-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-4-methyl-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3,5-dichloro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3,4-dichloro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2,6-difluoro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(naphthalen-2-ylmethyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(naphthalen-1-ylmethyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-methyl-thiazol-2-ylmethyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-chloro-thiophen-2-ylmethyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(4-methyl-pyridin-2-ylmethyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-phenyl)-ethyl]-amide} as a formate salt;

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(R)-1-(3-chloro-phenyl)-ethyl]-amide} as a formate salt;

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[1-(3,5-dichloro-phenyl)-2-hydroxy-ethyl]-amide};

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[1-(3-chloro-phenyl)-3-hydroxy-propyl]-amide};

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(1-phenyl-cyclopropyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 2-benzhydryl-amide 1-[(1-carbamoyl-1H-indol-3-yl)-amide] as a formate salt;

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-cyclohexylmethyl-amide;

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((1R,2S)-2-hydroxy-cyclohexylmethyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((1S,2S)-2-hydroxy-cyclohexylmethyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-cyclohexylamide;

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3-yl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(6-chloro-indan-1-yl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(6-chloro-chroman-4-yl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(phenethyl-amide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-hydroxy-2-phenyl-ethyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((1R,2S)-2-phenyl-cyclopropyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((R)-2-phenyl-propyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((S)-2-phenyl-propyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[2-(3-chloro-phenyl)-ethyl]-amide};

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1Hindol-3-yl)-amide] 2-{[2-(2-chloro-phenyl)-ethyl]-amide};

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1Hindol-3-yl)-amide] 2-{[2-(2-fluoro-phenyl)-ethyl]-amide};

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1Hindol-3-yl)-amide] 2-{[2-(3-fluoro-phenyl)-ethyl]-amide};

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[2-(3-chloro-5-fluoro-phenyl)-ethyl]-amide};

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-phenoxy-ethyl)-amide];

(2S,3S)-2-{[(2S,4S)-4-Amino-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-3-methyl-pentanoic acid methyl ester;

(S)-2-{[(2S,4S)-4-Amino-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-pentanoic acid methyl ester;

(R)-2-{[(2S,4S)-4-Amino-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-3-methyl-butyric acid methyl ester;

(S)-2-{[(2S,4S)-4-Amino-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-4-methyl-pentanoic acid methyl ester;

(S)-2-{[(2S,4S)-4-Amino-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-3-tert-butoxy-propionic acid methyl ester;

(S)-2-{[(2S,4S)-4-Amino-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-3-phenyl-propionic acid methyl ester;

(S)-{[(2S,4S)-4-Amino-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-phenyl-acetic acid methyl ester;

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((1S,2S)-1-carbamoyl-2-methyl-butyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-ethyl-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[((1S,2S)-1-hydroxymethyl-2-methyl-butyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-isopropyl-phenyl)-amide];

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 2-biphenyl-3-ylamide 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

3-{[(2S,4R)-2-(Benzenesulfonylamino-methyl)-4-fluoro-pyrrolidine-1-carbonyl]-amino}-indole-1-carboxylic acid amide;

3-({(2S,4R)-4-Fluoro-2-[(3-fluoro-benzenesulfonylamino)-methyl]-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide;

3-({(2S,4R)-4-Fluoro-2-[(3-chloro-benzenesulfonylamino)-methyl]-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide;

3-({(2S,4R)-4-Fluoro-2-[(3-bromo-benzenesulfonylamino)-methyl]-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide;

3-({(2S,4R)-4-Fluoro-2-[(3-trifluoromethoxy-benzenesulfonylamino)-methyl]-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide;

3-({(2S,4R)-2-[(3-Chloro-2-fluoro-benzenesulfonylamino)-methyl]-4-fluoro-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide;

3-({(2S,4R)-2-[(5-Chloro-thiophene-2-sulfonylamino)-methyl]-4-fluoro-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide;

3-({(S)-2-[(3-Chloro-benzenesulfonylamino)-methyl]-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide;

3-{[(2S,4R)-4-Fluoro-2-(phenylacetylamino-methyl)-pyrrolidine-1-carbonyl]-amino}-indole-1-carboxylic acid amide;

[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidin-2-ylmethyl]-carbamic acid phenyl ester;

[(1R,3S,5R)-2-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-3-ylmethyl]-carbamic acid 3-chloro-2-fluoro-phenyl ester;

3-({(2S,4R)-2-[(3-Chloro-2-fluoro-benzylamino)-methyl]-4-fluoro-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide;

3-({(S)-2-[(3-Trifluoromethoxy-phenylamino)-methyl]-pyrrolidine-1-carbonyl}-amino)-indole-1-carboxylic acid amide;

1-{2-Oxo-2-[(S)-2-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidin-1-yl]-ethyl}-1H-indole-3-carboxylic acid amide;

(S)-1-[2-(1-Acetyl-1H-indol-3-yl)-acetyl]-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide;

(2S,4R)-1-[2-(1-Acetyl-1H-indol-3-yl)-2-amino-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(3-carbamoyl-indolizin-1-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(3-carbamoyl-indolizin-1-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-indolizin-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(S)-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4S)-4-Cyano-pyrrolidine-1,2 dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,3R)-3-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-6-yl)-acetic acid tert-butyl ester;

(2S,4S)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-acetyl-1H-indol-3-yl)-amide] 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2hydroxy-ethyl]-amide};

(1R,3S,5R)-2-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-(3-chloro-2-fluoro-benzylamide) 2-[(1-methylcarbamoyl-1H-indol-3-yl)-amide];

(2S,4R)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-{[1-carbamoyl-5-(2-methoxy-ethoxy)-1H-indol-3-yl]-amide} 2-(3-chloro-2-fluoro-benzylamide);

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid methyl ester;

(1S,3S,5S)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-trifluoromethoxy-phenyl)-amide];

(1S,2S,5R)-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

2-Aza-bicyclo[2.1.1]hexane-1,2-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 1-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-(3-bromo-2-fluoro-benzylamide) 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,5R)-5-(Acetylamino-methyl)-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(R)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(1S,2S,5R)-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-fluoro-3-trifluoromethoxy-phenyl)-amide];

3-Chloro-5-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-benzoic acid methyl ester;

3-({[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-methyl)-5-chloro-4-fluoro-benzoic acid;

(S)-2,5-Dihydro-pyrrole-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(1R,2S,5S)-6-Oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Trifluoromethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(3-bromo-phenyl)-amide] 2-[(1-carbamoyl-1H-indol-3-yl)-amide];

(1S,5R)-2-Aza-bicyclo[3.1.0]hexane-1,2-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 1-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-[(3-bromo-phenyl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide] ;

(R)-2,2-Dimethyl-thiazolidine-3,4-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 4-[(3-trifluoromethoxy-phenyl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(4'-cyano-biphenyl-3-yl)-amide];

3-Bromo-5-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-benzoic acid methyl ester;

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-5-(2-dimethylamino-ethylcarba-moyl)-2-fluoro-benzylamide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(5-chloro-thiophen-2-ylmethyl)-amide];

2-Bromo-4-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-benzoic acid methyl ester;

(2S,4R)-4-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(6-ethyl-pyridin-2-yl)-amide];

3-Bromo-5-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-benzoic acid;

(S)-Pyrrolidine-1,2-dicarboxylic acid 2-[(4-tert-butyl-thiazol-2-yl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(R)-Thiazolidine-3,4-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 4-[(3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-methoxy-ethoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(6-ethyl-pyridin-2-yl)-amide];

(2S,4S)-4-Hydroxy-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-bromo-4-methyl-pyridin-3-yl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(1R,2S,5S)-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-[(5-bromo-2-methyl-pyridin-3-yl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2,3-difluoro-benzylamide);

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(5-bromo-pyridin-3-yl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-fluoro-pyridin-2-yl)-amide];

(1R,3S,5R)-2-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(2-fluoro-benzylamide);

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(2-fluoro-3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-chloro-2-fluoro-phenyl)-amide] ;

(2S,3R)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide) ;

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,5R)-5-Azidomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(S)-5-Aza-spiro[2.4]heptane-5,6-dicarboxylic acid 5-[(1-carbamoyl-1H-indol-3-yl)-amide] 6-(3-chloro-benzylamide);

(2S,4R)-4-Fluoro-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-benzylamide) ;

(1R,3S,5S)-5-Methoxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-fluoro-pyridin-4-yl)-amide];

(2S,3R)-3-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(S)-Piperidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4S)-4-Cyano-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-fluoro-3-trifluoromethoxy-phenyl)-amide];

(2R,3S,4R)-4-Dimethylamino-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2R,3R)-3-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(S)-2-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-chloro-pyridin-3-yl)-amide] ;

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-bromo-pyridin-3-yl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(2,3-difluoro-benzylamide);

(2S,4R)-4-Hydroxy-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1S,2S,5R)-6-Oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

3-Bromo-5-{[(S)-3-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-thiazolidine-2-carbonyl]-amino}-benzoic acid methyl ester;

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-methyl-5-phenyl-2H-pyrazol-3-yl)-amide];

(3S,5S)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-5-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrrolidine-3-carboxylic acid methyl ester;

4,5-Dihydro-pyrazole-1,5-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 5-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Hydroxy-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide};

(2S,3S,4S)-4-Fluoro-3-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,3S,4S)-3-Acetylamino-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1S,2S,5R)-3-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide};

(2R,3S)-3-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-4-morpholin-4-ylmethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1R,2S,5S)-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2R,3S,4R)-4-Acetylamino-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1R,2S,5S)-3-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide};

(2S,3R)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1S,3S,5R)-5-Methoxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-fluoro-pyridin-3-ylmethyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-6-methoxy-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[(S)-1-(3-bromo-phenyl)-2-hydroxy-ethyl]-amide} 2-[(1-carbamoyl-1H-indol-3-yl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(2-fluoro-3-trifluoromethyl-phenyl)-amide];

3-{[(S)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-benzoic acid methyl ester;

(S)-Piperidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-(Acetylamino-methyl)-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2-fluoro-3-trifluoromethyl-benzylamide);

(1R,3S,5R)-2-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-{[(R)-1-(3-chloro-2-fluoro-phenyl)-3-hydroxy-propyl]-amide};

(2S,4S)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2,3-difluoro-4-methoxy-benzylamide);

(1R,3S,5R)-2Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)amide] 3-[(pyridin-3-ylmethyl)-amide];

(2S,3S)-3-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(5-chloro-pyridin-3-ylmethyl)-amide];

(2S,4R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(R)-1-(3-chloro-2-fluoro-phenyl)-3-hydroxy-propyl]-amide};

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-fluoro-pyridin-4-ylmethyl)-amide];

(1R,2S,5S)-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-methoxy-ethyl]-amide};

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-fluoro-2-trifluoromethyl-pyridin-4-ylmethyl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-sulfamoyl-phenyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-difluoromethoxy-phenyl)-amide];

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2,3-difluoro-5-methoxy-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-methoxy-ethyl]-amide};

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-chloro-pyridin-3-ylmethyl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(6-ethyl-pyridin-2-yl)-amide];

(2S,4R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide};

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-5-methylcarbamoyl-benzylamide);

(2S,4S)-4-Fluoro-4-fluoromethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-fluoro-pyridin-2-ylmethyl)-amide];

(2S,4S)-4-Fluoro-4-morpholin-4-ylmethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

3-({[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-methyl)-5-chloro-4-fluoro-benzoic acid methyl ester;

(1S,2S,5R)-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-methoxy-ethyl]-amide};

{[(2S,4R)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-(3-chloro-phenyl)-acetic acid;

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(5-chloro-pyridin-3-yl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-dimethylamino-ethyl]-amide};

(2S,4S)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(morpholine-4-carbonyl)-benzylamide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-methoxy-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-5-diethylamino-2-fluoro-benzylamide);

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide};

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-chloro-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(3-methoxy-azetidine-1-carbonyl)-benzylamide];

(2S,4R)-4-Cyano-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,3S)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-benzylamide 2-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,3R)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-chloro-thiophen-2-ylmethyl)-amide];

(2S,4S)-4-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(2-fluoro-3-trifluoromethyl-benzylamide);

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(2,3-difluoro-6-methoxy-benzylamide);

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-chloro-thiazol-5-ylmethyl)-amide];

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-5-fluoro-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5S)-5-Hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-(3-chloro-2-fluoro-benzylamide) 2-[(1-methylcarbamoyl-1H-indol-3-yl)-amide];

(S)-4-Methylene-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(5-allyloxy-1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-6-methyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-methoxy-ethyl]-amide} 2-[(1-methylcarbamoyl-1H-indol-3-yl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

3-Bromo-5-{[(1R,3S,5R)-2-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-3-carbonyl]-amino}-benzoic acid methyl ester;

(2S,5R)-5-Phenyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide;

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-fluoro-3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5S)-5-Hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-acetyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-trifluoromethoxy-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-6-yloxy)-acetic acid methyl ester;

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-5-dimethylcarbamoyl-2-fluoro-benzylamide);

2-Bromo-4-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-benzoic acid;

(S)-Pyrrolidine-1,2-dicarboxylic acid 2-[(5-tert-butyl-2-methyl-2H-pyrazol-3-yl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(6-allyloxy-1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-acetyl-1H-indol-3-yl)-amide] 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-dimethylamino-ethyl]-amide};

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-methylcarbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,3R)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-chloro-thiazol-5-ylmethyl)-amide];

(1R,3S,5S)-5-Methoxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-(3-chloro-2-fluoro-benzylamide) 2-[(1-methylcarbamoyl-1H-indol-3-yl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-isopropyl-phenyl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(6-bromo-1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide}2-[(1-methylcarbamoyl-1H-indol-3-yl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-6-ethyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-dimethylamino-ethyl]-amide} 2-[(1-methylcarbamoyl-1H-indol-3-yl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-6-trifluoromethyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-6-chloro-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-5-methoxy-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-chloro-thiophen-2-ylmethyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-5-fluoro-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(2-chloro-thiazol-5-ylmethyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-phenyl)-2,2,2-trifluoro-ethyl]-amide};

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-6-fluoro-1H-indol-3-yl)-amide] 3-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-5-methoxy-1H-indol-3-yl)-amide] 2-[(2-fluoro-3-trifluoromethoxy-phenyl)-amide];

(S)-Azetidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-5-methoxy-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(S)-4,4-Difluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(S)-5,5-Dimethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-{[1-carbamoyl-5-(2-methoxy-ethoxy)-1H-indol-3-yl]-amide} 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-fluoro-4-methyl-pyridin-2-ylmethyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-trifluoromethyl-pyridin-3-ylmethyl)-amide];

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yl)-acetic acid ethyl ester;

(1S,5R)-2-Aza-bicyclo[3.1.0]hexane-1,2-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 1-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-6-difluoromethoxy-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(2-methoxy-pyridin-4-yl)-amide];

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-chloro-pyridin-3-yl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(6-allyloxy-1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(6-benzyloxy-1-carbamoyl-1H-indol-3-yl)-amide]2-[(3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2-dimethylamino-ethyl]-amide};

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-6-yl)-acetic acid ethyl ester;

(2S,4R)-4-Methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-[(2-tert-butyl-pyridin-4-yl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(1-Carbamoyl-3-{[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidine-1-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid methyl ester;

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(R)-1-(3-chloro-phenyl)-2,2,2-trifluoro-ethyl]-amide};

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-{[(S)-1-(3-chloro-phenyl)-2-hydroxy-ethyl]-amide};

(S)-Thiazolidine-2,3-dicarboxylic acid 3-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(5-bromo-pyridin-3-yl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(4-methyl-piperazine-1-carbonyl)-benzylamide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-fluoro-pyridin-4-yl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-carbamoyl-phenyl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-methanesulfonyl-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(6-chloro-chroman-4-yl)-amide] (mixture of 2 diastereoisomers);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-fluoro-pyridin-2-yl)-amide];

(2S,4S)-4-Dimethylaminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{3-chloro-5-[(2-dimethylamino-ethyl)-methyl-amino]-2-fluoro-benzylamide};

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-[(3-tert-butyl-phenyl)-amide] 2-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,4S)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(S)-4,4-Difluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

3-Bromo-5-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-4-fluoro-benzoic acid ethyl ester ;

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-[(3-trifluoromethoxy-phenyl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(5-allyloxy-1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,5R)-5-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,5S)-5-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,5R)-5-Ethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromthoxy-phenyl)-amide];

3-Chloro-5-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-benzoic acid;

3-Bromo-5-{[(1R,3S,5R)-2-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-3-carbonyl]-amino}-benzoic acid;

3-Bromo-5-{[(S)-3-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-thiazolidine-2-carbonyl]-amino}-benzoic acid;

3-Bromo-5-{[(1R,3S,5R)-2-(1-carbamoyl-5-methoxy-1H-indol-3-ylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-3-carbonyl]-amino}-benzoic acid;

3-Bromo-5-{[(2S,4R)-1-(1-carbamoyl-1H-indol-3-ylcarbamoyl)-4-fluoro-pyrrolidine-2-carbonyl]-amino}-4-fluoro-benzoic acid;

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[3-bromo-5-(1H-tetrazol-5-yl)-phenyl]-amide} 2-[(1-carbamoyl-1H-indol-3-yl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[3-bromo-5-(1-tert-butyl-1H-tetrazol-5-yl)-phenyl]-amide} 2-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(1H-tetrazol-5-yl)-benzylamide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-[5-(1-tert-butyl-1H-tetrazol-5-yl)-3-chloro-2-fluoro-benzylamide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2R,3S)-3-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide);

(2R,3R)-3-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide);

(2S,5R)-5-Methyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,5R)-5-Ethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(3S,5S)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-5-(3-chloro-2,6-difluoro-benzylcarbamoyl)-pyrrolidine-3-carboxylic acid methyl ester;

(3S,5S)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-5-(3-chloro-2,6-difluoro-benzylcarbamoyl)-pyrrolidine-3-carboxylic acid;

(2S,4S)-4-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 2-(3-bromo-2-fluoro-benzylamide) 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,4S)-4-Fluoro-4-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1S,3S,5R)-5-Hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5S)-5-Hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Difluoromethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,5R)-5-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

4,5-Dihydro-pyrazole-1,5-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 5-(3-chloro-benzylamide);

(S)-4,5-Dihydro-pyrazole-1,5-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 5-(3-chloro-2-fluoro-benzylamide);

(R)-4,5-Dihydro-pyrazole-1,5-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 5-(3-chloro-2-fluoro-benzylamide);

(2S,3R)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(R)-1-(3-chloro-2-fluoro-phenyl)-ethyl]-amide};

(2S,3R)-3-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-ethyl]-amide};

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-{[1-(2-hydroxy-acetyl)-1H-indol-3-yl]-amide} 2-[(3-trifluoromethoxy-phenyl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-6-cyano-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-6-difluoromethoxy-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-6-hydroxy-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-5-hydroxy-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-5-hydroxy-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-5-hydroxy-1H-indol-3-yl)-amide] 3-(2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-5-cyanomethoxy-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid;

(1-Carbamoyl-3-{[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidine-1-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid;

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-6-yloxy)-acetic acid;

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yl)-acetic acid;

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-6-yl)-acetic acid;

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-hydroxy-ethoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide);

(S)-Thiazolidine-2,3-dicarboxylic acid 3-{[1-carbamoyl-5-(2-hydroxy-ethoxy)-1H-indol-3-yl]-amide} 2-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-hydroxy-ethoxy)-1H-indol-3-yl]-amide} 3-[(3-trifluoromethoxy-phenyl)-amide];

(1S,2S,5R)-3-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-{[1-carbamoyl-5-(2-hydroxy-ethoxy)-1H-indol-3-yl]-amide} 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-4-methyl-pyrrolidine-1,2-dicarboxylic acid 1-{[1-carbamoyl-5-(2-hydroxy-ethoxy)-1H-indol-3-yl]-amide} 2-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-6-(2-hydroxy-ethyl)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-hydroxy-ethyl)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-hydroxy-2-methyl-propoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-dimethylamino-ethoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-pyrrolidin-1-yl-ethoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide);

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-5-(2-imidazol-1-yl-ethoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide);

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid tert-butyl ester;

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-5-yloxy)-acetic acid;

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-[(1-carbamoyl-6-hydroxy-1H-indol-3-yl)-amide] 3-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-6-hydroxy-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(1-Carbamoyl-3-{[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hexane-2-carbonyl]-amino}-1H-indol-6-yloxy)-acetic acid methyl ester;

(1R,3S,5R)-2-Aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-{[1-carbamoyl-6-(2-hydroxy-ethoxy)-1H-indol-3-yl]-amide} 3-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,3S,4R)-4-Amino-3-methoxy-pyrrolidine-1,2-dicarboxylicacid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(6-benzyloxy-1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(S)-Piperazine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide);

(S)-Pyrrolidine-1,2-dicarboxylic acid 2-[(4'-aminomethyl-biphenyl-3-yl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 2-[(4'-aminomethyl-2'-fluoro-biphenyl-3-yl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,5R)-5-Aminomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Aminomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4S)-4-Aminomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,4R)-4-Aminomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Dimethylaminomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Aminomethyl-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4R)-4-Aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Fluoro-4-formylaminomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2,6-difluoro-benzylamide);

(2S,4S)-4-Aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 2-{[(S)-1-(3-bromo-phenyl)-2-fluoro-ethyl]-amide} 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,4S)-4-Aminomethyl-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-trifluoromethoxy-phenyl)-amide];

(2S,3S,4S)-3-Amino-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,3R,4S)-4-Amino-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,3R)-3-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,3R)-3-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-acetyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,3R)-3-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-{[(S)-1-(3-chloro-2-fluoro-phenyl)-2,2,2-trifluoro-ethyl]-amide};

(2S,3S)-3-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,3S)-3-Amino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-benzylamide);

(2S,3R)-3-Acetylamino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,3R)-3-(2-Methoxy-ethylamino)-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Fluoro-4-methylaminomethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Methylamino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-(2-Methoxy-ethylamino)-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,4S)-4-Dimethylamino-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(S)-4,4-Dimethoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,3S,4R)-4-Amino-3-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2R,3S,4R)-4-Amino-3-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

(2S,3S,4S)-3-Amino-4-fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluorobenzylamide);

3-{2-[(S)-5-(3-Chloro-2-fluoro-benzylcarbamoyl)-pyrazolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[(R)-5-(3-Chloro-2-fluoro-benzylcarbamoyl)-pyrazolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

Pyrazolidine-1,5-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 5-(3-chloro-benzylamide);

(3S,5S)-1-(1-Carbamoyl-1H-indol-3-ylcarbamoyl)-5-(2-fluoro-3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidine-3-carboxylic acid methyl ester;

(2S,4S)-4-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2,6-difluoro-benzylamide);

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 2-[(3-bromo-5-carbamoyl-phenyl)-amide] 1-[(1-carbamoyl-1H-indol-3-yl)-amide];

(2S,4R)-4-Fluoro-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[3-chloro-2-fluoro-5-(2-methoxy-ethylcarbamoyl)-benzylamide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-isopropyl-isoxazol-5-yl)-amide];

(S)-Pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-[(3-phenyl-isoxazol-5-yl)-amide];

3-{2-[(S)-2-(3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[(2S,4R)-4-Fluoro-2-(2-fluoro-3-trifluoromethoxy-phenylcarbamoyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-(2-{(1S,2S,5R)-2-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-hydroxy-ethylcarbamoyl]-3-azabicyclo[3.1.0]hex-3-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide;

3-{2-[(2S,3R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-3-hydroxy-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[(2S,4S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-dimethylaminomethyl-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-(2-{(2S,4R)-2-[(R)-1-(3-Chloro-2-fluoro-phenyl)-3-hydroxy-propylcarbamoyl]-4-fluoro-4-methyl-pyrrolidin-1-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide;

3-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-(2-{(1R,3S,5R)-3-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-hydroxy-ethyl carbamoyl]-2-aza-bicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide;

3-{2-[(S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-thiazolidin-3-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-hydroxymethyl-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-methoxy-indole-1-carboxylic acid amide;

3-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-(2-hydroxy-ethoxy)-indole-1-carboxylic acid amide;

3-{2-[(1R,3S,5S)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-5-methoxymethyl-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

5-(2-Hydroxy-ethoxy)-3-{2-oxo-2-[(1R,3S,5R)-3-(3-trifluoromethoxy-phenylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-ethyl}-indole-1-carboxylic acid amide;

3-(2-{(1R,3S,5R)-3-[(5-Chloro-thiophen-2-ylmethyl)-carbamoyl]-2-aza-bicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide;

3-(2-{(1R,3S,5R)-3-[(R)-1-(3-Chloro-2-fluoro-phenyl)-3-hydroxy-propylcarbamoyl]-2-azabicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide;

3-(2-{(1R,3S,5R)-3-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-dimethylamino-ethylcarbamoyl]-2-aza-bicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide;

3-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidin-1-yl]-2-oxo-ethyl}-5-(2-hydroxy-ethoxy)-indole-1-carboxylic acid amide;

3-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-5-fluoro-indole-1-carboxylic acid amide;

3-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-2-methyl-indole-1-carboxylic acid amide;

3-{2-[(S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-thiazolidin-3-yl]-2-oxo-ethyl}-5-(2-hydroxy-ethoxy)-indole-1-carboxylic acid amide;

3-(2-{(1R,2S,5S)-2-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-hydroxy-ethylcarbamoyl]-3-azabicyclo[3.1.0]hex-3-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide;

3-(2-{(1R,3S,5R)-3-[(S)-1-(3-Chloro-2-fluoro-phenyl)-2-methoxy-ethylcarbamoyl]-2-aza-bicyclo[3.1.0]hex-2-yl}-2-oxo-ethyl)-indole-1-carboxylic acid amide;

3-{2-[(1S,2S,5R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-3-aza-bicyclo[3.1.0]hex-3-yl]-2-oxo-ethyl}-5-(2-hydroxy-ethoxy)-indole-1-carboxylic acid amide;

3-{2-[(2S,3S,4S)-3-Amino-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[(1R,3S,5S)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[(2S,4S)-4-Amino-2-(3-chloro-2-fluoro-benzylcarbamoyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[5-(3-Chloro-benzylcarbamoyl)-pyrazolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[(2S,4S)-4-Aminomethyl-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[(2S,4S)-4-Aminomethyl-2-(3-chloro-2,6-difluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-indole-1-carboxylic acid amide;

3-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-5-(2-dimethylamino-ethoxy)-indole-1-carboxylic acid amide;

(1-Carbamoyl-3-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indol-6-yl)-acetic acid;

3-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-6-(2-hydroxy-ethyl)-indole-1-carboxylic acid amide;

1-{2-[(1R,3S,5R)-3-(3-Chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amid;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-7-methoxy-1H-indole-3-carboxylic acid amide;

(S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-piperidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

6-Bromo-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-5-fluoro-1H-indole-3-carboxylic acid amide;

3-[({(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carbonyl}-amino)-methyl]-5-chloro-4-fluoro-benzoic acid methyl ester;

1-{2-[(2S,4R)-2-(3-Bromo-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide;

(2S,4R)-1-[2-(3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (5-chloro-thiophen-2-ylmethyl)-amide;

(2S,3S,4S)-1-[2-(3-Acetyl-5-methoxy-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-phenylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide;

(2S,3S,4S)-1-[2-(3-Acetyl-6-methoxy-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

5-Chloro-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide ;

7-Chloro-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide ;

(1R,3S,5S)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-5-methoxymethyl-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

6-Chloro-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-5,6-difluoro-1H-indole-3-carboxylic acid amide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-trifluoromethoxy-1H-indole-3-carboxylic acid amide;

(1R,3S,5R)-2-[2-(3-Acetyl-5-methoxy-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-{2-[3-(2,2,2-Trifluoro-acetyl)-indol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-5-methoxy-1H-indole-3-carboxylic acid amide;

(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-5-cyano-2-fluoro-benzylamide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-methoxy-1H-indole-3-carboxylic acid amide;

(2S,4R)-1-[2-(3-Acetyl-6-methoxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(S)-1-[2-(3-Acetyl-5-methoxy-indol-1-yl)-acetyl]-piperidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-pyrrolo[3,2-c]pyridin-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

5-Benzyloxy-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide;

(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(R)-1-(3-chloro-2-fluoro-phenyl)-3-hydroxy-propyl]-amide;

(2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,2S,5S)-3-[2-(3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-5-benzyloxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-6-trifluoromethoxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,4S)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[2.2.1]heptane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(S)-3-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-thiazolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid (2-fluoro-3-trifluoromethoxy-phenyl)-amide;

(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [3-bromo-5-(2H-tetrazol-5-yl)-phenyl]-amide;

(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-bromo-2-fluoro-benzylamide;

1-{2-[(2S,4R)-4-Fluoro-2-(2-fluoro-3-trifluoromethyl-phenylcarbamoyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide;

(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid methylamide ;

(2S,3S,4S)-1-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-5-(1H-tetrazol-5-yl)-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-dimethylamino-ethyl]-amide;

3-[({(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carbonyl}-amino)-methyl]-5-chloro-4-fluoro-benzoic acid methyl ester;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[3,2-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-5-(1H-tetrazol-5-yl)-benzylamide;

3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-6-carboxylic acid methyl ester;

(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-5-cyano-2-fluoro-benzylamide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-difluoromethoxy-1H-indole-3-carboxylic acid amide;

6-Benzyloxy-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide ;

(2S,4R)-1-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-6-chloro-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-6-cyano-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-methoxy-ethyl]-amide;

(2S,4R)-1-[2-(3-Acetyl-6-benzyloxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-methoxy-ethyl]-amide;

(1R,3S,5R)-2-[2-(3-Acetyl-6-benzyloxy-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,2S,5S)-3-[2-(3-Acetyl-pyrrolo[3,2-c]pyridin-1-yl)-acetyl]-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,2S,5S)-3-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-5-trifluoromethoxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-5-carboxylic acid methyl ester;

3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluorobenzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-7-carboxylic acid methyl ester;

3-Acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-6-carboxylic acid methyl ester;

(2S,4R)-4-Fluoro-1-{2-[3-(2-hydroxy-acetyl)-indol-1-yl]-acetyl}-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1S,2S,5R)-3-[2-(3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indol-6-yl)-acetic acid methyl ester;

(2S,4R)-4-Fluoro-1-{2-[3-(2,2,2-trifluoro-acetyl)-indol-1-yl]-acetyl}-pyrrolidine-2-carboxylic acid 3-bromo-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

3-Acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-6-carboxylic acid methyl ester;

(3-Acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indol-6-yl)-acetic acid methyl ester;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluorobenzylamide;

(2S,4R)-4-Fluoro-1-{2-[3-(2-hydroxy-acetyl)-indol-1-yl]-acetyl}-pyrrolidine-2-carboxylic acid [(S)-1-(3-bromo-phenyl)-2-fluoro-ethyl]-amide;

(2S,4R)-1-[2-(3-Acetyl-pyrrolo[2,3-c]pyridin-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[3,2-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-4-Fluoro-4-methyl-1-{2-[3-(2,2,2-trifluoro-acetyl)-indol-1-yl]-acetyl}-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2R,3S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-dimethylamino-3-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-{2-[3-(2-Hydroxy-acetyl)-indol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(R)-1-(3-chloro-2-fluoro-phenyl)-3-hydroxy-propyl]-amide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (3-trifluoromethoxy-phenyl)-amide;

(S)-1-[2-(3-Formyl-indol-1-yl)-acetyl]-pyrrolidine-2-carboxylic acid (3-trifluoromethoxy-phenyl)-amide;

(2S,4R)-4-Fluoro-1-[2-(3-formyl-5-methoxy-indol-1-yl)-acetyl]-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-4-Fluoro-1-{2-[3-(2,2,2-trifluoro-acetyl)-indol-1-yl]-acetyl}-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid (2-fluoro-3-trifluoromethoxy-phenyl)-amide;

(2S,4R)-4-Fluoro-1-{2-[3-(2-hydroxy-acetyl)-indol-1-yl]-acetyl}-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-4-Fluoro-1-{2-[3-(2-hydroxy-acetyl)-indol-1-yl]-acetyl}-pyrrolidine-2-carboxylic acid 3-bromo-2-fluoro-benzylamide;

(2S,4R)-4-Fluoro-1-{2-[3-(2-methoxy-acetyl)-indol-1-yl]-acetyl}-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-hydroxymethyl-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide;

1-{2-[(S)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-thiazolidin-3-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide ;

(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-methoxy-ethyl]-amide;

(2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-3-ethoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid [(R)-1-(3-chloro-2-fluoro-phenyl)-ethyl]-amide;

(2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-ethyl]-amide;

(2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid [1-(3-chloro-phenyl)-cyclopropyl]-amide;

(2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid [1-(4-chloro-phenyl)-cyclopropyl]-amide;

1-{2-[(2S,3S,4S)-3-Amino-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-3-carboxylic acid amide;

(2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-3-amino-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2R,3S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-amino-3-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-5-hydroxy-1H-indole-3-carboxylic acid amide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-hydroxy-1H-indole-3-carboxylic acid amide;

(2S,4R)-1-[2-(3-Acetyl-5-hydroxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-5-hydroxy-indol-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-5-hydroxy-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-6-hydroxy-indol-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-6-hydroxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(3-Acetyl-6-hydroxy-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-(1H-tetrazol-5-ylmethoxy)-1H-indole-3-carboxylic acid amide;

(2S,4R)-1-{2-[3-Acetyl-6-(1H-tetrazol-5-ylmethoxy)-indol-1-yl]-acetyl}-4-fluoro-yrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-[2-(3-Acetyl-5-methoxy-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-{2-[3-Acetyl-5-(pyridin-2-ylmethoxy)-indol-1-yl]-acetyl}-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-{2-[3-Acetyl-5-(pyrimidin-2-ylmethoxy)-indol-1-yl]-acetyl}-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-(2-methoxy-ethoxy)-1H-indole-3-carboxylic acid amide;

(3-Carbamoyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indol-6-yloxy)-acetic acid methyl ester;

(3-Carbamoyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indol-6-yloxy)-acetic acid;

1-{2-[(2S,4R)-2-(3-Chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-6-(2-hydroxy-ethoxy)-1H-indole-3-carboxylic acid amide;

(3-Acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indol-6-yl)-acetic acid;

(3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indol-6-yl)-acetic acid;

3-Acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-6-carboxylic acid;

3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-6-carboxylic acid;

3-Acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-4-methyl-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indole-6-carboxylic acid;

(2S,3S,4S)-4-Fluoro-3-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-[(1-carbamoyl-1H-indol-3-yl)-amide] 2-(3-chloro-2-fluoro-benzylamide);

3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-7-carboxylic acid;

4-(3-Acetyl-1-{2-[(2S,4R)-2-(3-chloro-2-fluoro-benzylcarbamoyl)-4-fluoro-pyrrolidin-1-yl]-2-oxo-ethyl}-1H-indol-6-yloxymethyl)-benzoic acid;

3-Acetyl-1-{2-[(1R,3S,5R)-3-(3-chloro-2-fluoro-benzylcarbamoyl)-2-aza-bicyclo[3.1.0]hex-2-yl]-2-oxo-ethyl}-1H-indole-5-carboxylic acid;

(2S,4R)-1-[2-(3-Acetyl-6-hydroxymethyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

3-[({(2S,4R)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-pyrrolidine-2-carbonyl}-amino)-methyl]-5-chloro-4-fluoro-benzoic acid;

3-[({(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carbonyl}-amino)-methyl]-5-chloro-4-fluoro-benzoic acid;

(2S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-aminomethyl-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-methylamino-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-(2-methoxy-ethylamino)-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5S)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5S)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-5-hydroxymethyl-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1S,2S,5R)-3-[2-(3-Acetyl-indol-1-yl)-acetyl]-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2hydroxy-ethyl]-amide;

(1R,3S,5R)-2-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide;

(2S,4R)-1-[2-(3-Acetyl-pyrrolo[2,3-b]pyridin-1-yl)-acetyl]-4-fluoro-4-methyl-pyrrolidine-2-carboxylic acid [(S)-1-(3-chloro-2-fluoro-phenyl)-2-hydroxy-ethyl]-amide;

(1R,3S,5R)-2-{2-[3-Acetyl-5-(N,N-dimethyl-carbamimidoyl)-indol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-{2-[3-Acetyl-6-(N,N-dimethyl-carbamimidoyl)-indol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,4R)-1-{2-[3-Acetyl-6-(1H-tetrazol-5-yl)-indol-1-yl]-acetyl}-4-fluoro-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-{2-[3-Acetyl-6-(1H-tetrazol-5-yl)-indol-1-yl]-acetyl}-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,3S,4S)-1-[2-(3-Acetyl-*d3*-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(2S,3S,4S)-1-[2-(3-Acetyl-indol-1-yl)-acetyl]-4-fluoro-3-methoxy-*d3*-pyrrolidine-2-carboxylic acid 3-chloro-2-fluoro-benzylamide;

(1R,3S,5R)-2-[2-(1-Acetyl-imidazo[1,5-a]pyridin-3-yl)-acetyl]-2-aza-bicyclo[3.1.0]hexane-3-carboxylic acid 3-chloro-2-fluoro-benzylamide; and

{(1R,3S,5R)-2-[2-(3-Acetyl-indol-1-yl)-acetyl]-2-aza-bicyclo[3.1.0]hex-3-ylmethyl}-carbamic acid 3-chloro-2-fluoro-phenyl ester.

18. A pharmaceutical composition comprising one or more pharmaceutically acceptable carriers and a therapeutically effective amount of a compound of any one of claims 1-17.

19. A combination, in particular a pharmaceutical combination, comprising a therapeutically effective amount of the compound according to any one of claims 1-17 and a second therapeutically active agent.

20. A method of modulating complement alternative pathway activity in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound according to any one of claims 1-17.

21. A method of treating a disorder or a disease in a subject mediated by complement activation, in particular mediated by activation of the complement alternative pathway, wherein the method comprises administering to the subject a therapeutically effective amount of the compound according to any one of claims 1-17.

22. The method of claim 20, in which the disease or disorder is selected from the group consisting of age-related macular degeneration, geographic atrophy, diabetic retinopathy, uveitis, retinitis pigmentosa, macular edema, Behcet's uveitis, multifocal

choroiditis, Vogt-Koyangi-Harada syndrome, imtermediate uveitis, birdshot retino-chorioditis, sympathetic ophthalmia, ocular dicatricial pemphigoid, ocular pemphigus, nonartertic ischemic optic neuropathy, post-operative inflammation, retinal vein occlusion, neurological disorders, multiple sclerosis, stroke, Guillain Barre Syndrome, traumatic brain injury, Parkinson's disease, disorders of inappropriate or undesirable complement activation, hemodialysis complications, hyperacute allograft rejection, xenograft rejection, interleukin-2 induced toxicity during IL-2 therapy, inflammatory disorders, inflammation of autoimmune diseases, Crohn's disease, adult respiratory distress syndrome, myocarditis, post-ischemic reperfusion conditions, myocardial infarction, balloon angioplasty, post-pump syndrome in cardiopulmonary bypass or renal bypass, atherosclerosis, hemodialysis, renal ischemia, mesenteric artery reperfusion after aortic reconstruction, infectious disease or sepsis, immune complex disorders and autoimmune diseases, rheumatoid arthritis, systemic lupus erythematosus (SLE), SLE nephritis, proliferative nephritis, liver fibrosis, hemolytic anemia, myasthenia gravis, tissue regeneration, neural regeneration, dyspnea, hemoptysis, ARDS, asthma, chronic obstructive pulmonary disease (COPD), emphysema, pulmonary embolisms and infarcts, pneumonia, fibrogenic dust diseases, pulmonary fibrosis, asthma, allergy, bronchoconstriction, hypersensitivity pneumonitis, parasitic diseases, Goodpasture's Syndrome, pulmonary vasculitis, Pauci-immune vasculitis, immune complex-associated inflammation, antiphospholipid syndrome, glomerulonephritis and obesity.

23. A method of treating age related macular degeneration comprising administering to a subject in need thereof an effective amount of a composition comprising a compound of any one of claims 1 to 17.

24. A compound according to any one of claims 1-17, for use as a medicament.

25. Use of a compound according to any one of claims 1-17 in the manufacture of a medicament for the treatment of a disorder or disease in a subject mediated by complement activation or activation of the complement alternative pathway.

26. Use of a compound according to any one of claims 1-17, for the treatment of age-related macular degeneration.

27. A compound selected from the group consisting of 3-amino-1H-indole-1-carboxamide, 3-isocyanato-1H-indole-1-carboxamide, 1-(3-isocyanato-1H-indol-1-yl)ethanone, 3-isocyanato-N-methyl-1H-indole-1-carboxamide and salts thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/050005

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D403/12 C07D403/14 C07D405/14 C07D409/14
C07D417/12 C07D417/14 C07D471/04 A61K31/403 A61K31/407
A61K31/416 A61P27/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/106980 A2 (PFIZER [US]; BUCHLER INGRID PRICE [US]; HAYES MICHAEL JOSEPH [US]; HEG) 3 September 2009 (2009-09-03) page 2; compound I page 62, paragraph 6 partial structures; page 22 - page 25 examples 390-393 -----	1-27
A	WO 2010/020675 A1 (NOVARTIS AG [CH]; ASTEX THERAPEUTICS LTD [GB]; BESONG GILBERT [GB]; BR) 25 February 2010 (2010-02-25) page 4; compound I page 21, paragraph 1 page 117; example 58 page 118; example 51 -----	1-27

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

☒ See patent family annex.

* Special categories of cited documents :

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

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"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
21 March 2012	29/03/2012

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, Fax: (+31-70) 340-3016	Hoepfner, Wolfgang

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/050005

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009106980 A2	03-09-2009	NONE	
WO 2010020675 A1	25-02-2010	AR 073116 A1	13-10-2010
		AU 2009284098 A1	25-02-2010
		CA 2734802 A1	25-02-2010
		CN 102186856 A	14-09-2011
		CO 6341561 A2	21-11-2011
		DO P2011000057 A	31-07-2011
		EA 201100355 A1	31-10-2011
		EC SP11010843 A	31-05-2011
		EP 2331547 A1	15-06-2011
		JP 2012500785 A	12-01-2012
		KR 20110052713 A	18-05-2011
		MA 32555 B1	01-08-2011
		PE 04192011 A1	13-07-2011
		TW 201014858 A	16-04-2010
		US 2010105653 A1	29-04-2010
		US 2011152244 A1	23-06-2011
		UY 32067 A	26-03-2010
		WO 2010020675 A1	25-02-2010

Moduladores de la Vía del Complemento y Usos de los Mismos

CAMPO DE LA INVENCIÓN

La invención se refiere a la inhibición de la vía alternativa del complemento y en particular a la inhibición del factor D, en pacientes que sufren de condiciones y enfermedades asociadas con la activación de la vía alternativa del complemento, tales como la degeneración macular relacionada con la edad, retinopatía diabética y enfermedades oftálmicas relacionadas.

FUDAMENTO DE LA INVENCIÓN

El sistema del complemento es un componente crítico en el sistema de inmunidad innata y cuenta con un grupo de proteínas que normalmente se presentan en un estado inactivo. Estas proteínas se organizan en tres vías de activación: La vía clásica, la vía de lectina y la vía alternativa (V. M. Holers, In Clinical Immunology: Principles and Practice, ed. R.R. Rich, Mosby Press; 1996, 363- 391). Moléculas de microorganismos, anticuerpos o componentes celulares pueden activar estas vías que resultan en la formación de complejos de proteasa conocidos como la C3- convertasa y la C5- convertasa. La vía clásica es una cascada dependiente de calcio/magnesio, que normalmente se activa por la formación de complejos antígeno- anticuerpo. También se puede activar de una manera independiente de anticuerpos mediante la unión de un complejo de proteína C- reactiva con ligando y mediante muchos agentes patógenos incluyendo bacterias gram- negativas. La vía alternativa es una cascada dependiente de magnesio que es activada por depósito y activación de C3 sobre ciertas superficies sensibles (ej., polisacáridos de la pared celular de levaduras y bacterias, y ciertos materiales biopolímeros).

El factor D puede ser una diana adecuada para la inhibición de esta amplificación de las vías del complemento debido a que su concentración plasmática en seres humanos es muy baja (alrededor de 1,8 μg/ml), y se ha demostrado que es la enzima limitante para la activación de la vía alternativa del complemento (P.H. Lesavre y H.J. Müller- Eberhard J. Exp. Med., 1978, 148: 1498- 1510; J.E. Volanakis et al., New Eng. J. Med., 1985; 312:395- 401).

La degeneración macular es un término clínico que se utiliza para describir una familia de enfermedades que se caracterizan por una pérdida progresiva de la visión central asociada con anormalidades de la membrana de Bruch, la coroides, la retina neural y/o el epitelio

pigmentario de la retina. En el centro de la retina se encuentra la mácula lútea, que tiene un diámetro de aproximadamente 1/3 a ½ cm. La mácula proporciona la visión detallada, en particular en el centro (la fóvea), porque los conos tienen mayor densidad y debido a la alta proporción de células ganglionares a células fotorreceptoras. Los vasos sanguíneos, células ganglionares, capa nuclear interna y células, y las capas plexiformes todas desplazadas hacia el lado (en lugar de descansar sobre las células fotorreceptoras), permitiendo a la luz, de este manera, un camino más directo a los conos. Bajo la retina está la coroides, una parte del tracto uveal, y el epitelio pigmentario de la retina (EPR), que se encuentra entre la retina neural y la coroides. Los vasos sanguíneos coroideos proporcionan nutrición a la retina y sus células visuales.

La degeneración macular relacionada con la edad (AMD), la forma más frecuente de degeneración macular, está asociada con la pérdida progresiva de la agudeza visual en la parte central del campo visual, los cambios en la visión del color, y adaptación y sensibilidad anormal a la oscuridad . Dos principales manifestaciones clínicas de la AMD se han descrito como la forma seca o atrófica, y la forma neovascular o exudativa. La forma seca se asocia con la muerte celular atrófica de la retina o mácula central, que es necesaria para la visión fina que se usa para actividades tales como leer, conducir o el reconocimiento de caras. Cerca de 10-20% de estos pacientes con AMD progresan a la segunda forma de AMD, conocida como AMD neovascular (también conocida como la AMD húmeda).

La AMD neovascular se caracteriza por el crecimiento anormal de los vasos sanguíneos bajo la mácula y la fuga vascular, lo que resulta en el desplazamiento de la retina, hemorragia y cicatrización. Esto resulta en un deterioro de la visión durante un período de semanas a años. Los casos de AMD neovascular se originan a partir de AMD seca intermedia o avanzada. La forma neovascular representa el 85% de la ceguera legal por AMD. En AMD neovascular, como los vasos sanguíneos anormales filtran fluido y sangre, se forma tejido cicatrizante que destruye la retina central.

Los nuevos vasos sanguíneos en AMD neovascular por lo general se derivan de la coroides y se denominan neovascularización coroidea (CNV). La patogénesis de nuevos vasos coroideos no se comprende bien, pero los factores tales como inflamación, isquemia, y producción local de factores angiogénicos se consideran importantes. Un estudio publicado sugiere que la CNV es causada por la activación del complemento en un modelo láser de ratón (Bora PS, J. Immunol 2005; 174, 491- 497).

Evidencia genética humana implica la participación del sistema del complemento, sobre todo la vía alternativa, en la patogénesis de la degeneración macular relacionada con la edad

(AMD). Se han encontrado asociaciones significativas entre AMD y polimorfismos en el factor H del complemento (CFH) (AO Edwards, et al. Polimorfismo de factor H de complemento y degeneración macular relacionada con la edad. Science. 2005 15 de abril, 308 (5720): 421- 4; Hageman GS, et al Un haplotipo común en el factor H del gen regulador de complemento (HF1/CFH) predispone a los individuos a la degeneración macular relacionada con la edad. Proc Natl Acad Sci U S A. 2005 May 17;102(20):7227- 32; Haines JL. La variante del factor de complemento H aumenta el riesgo de degeneración macular relacionada con la edad. Science. 2005 Abril 15, 308 (5720): 419- 21, Klein RJ, polimorfismo de factor H de complemento en la degeneración macular relacionada con la edad. Science. 2005 Abril 15, 308 (5720):385- 9; Lau Li, et al Asociación del polimorfismo de Y402H con el gen del factor H del complemento y degeneración macular neovascular relacionada con la edad en pacientes chinos. Invest Ophthalmol Vis Sci. 2006 Aug;47(8):3242- 6; Simonelli F. Polimorfismo p.402Y> H en la proteína del factor H del complemento es un factor de riesgo para la degeneración macular relacionada con la edad en una población italiana. Br J Ophthalmol. 2006 Sep; 90 (9) :1142- 5, y Zareparsi S, Fuerte asociación de la variante Y402H en el factor H del complemento en 1q32 con susceptibilidad a la degeneración macular relacionada con la edad. Am J Hum Genet. 2005 Jul;77(1):149- 53.), factor B de complemento (CFB) y complemento C2 (Gold B. La variación en el factor B (BF) y genes del componente 2 de complemento (C2) se asocia con la degeneración macular relacionada con la edad. Nat Genet. 2006 Abril;38(4):458- 62 y Jakobsdottir J. Genes C2 y CFB en la maculopatía relacionada con la edad y la acción conjunta con CFH y genes de LOC387715. PLoS One. 2008 Mayo 21;3(5):e2199), y más recientemente en C3 de complemento (Despriet DD, et al Componente del Complemento C3 y riesgo de degeneración macular relacionada con la edad. Ophthalmology. 2009 Marzo 116(3):474-480.e2; Maller JB, et al., La variación en factor del complemento 3 está asociada con la degeneración macular relacionada con la edad. Nat Genet. 2007 Oct;39(10):1200- 1 y Park KH, halotipos del componente de complemento 3 (C3) y riesgo de avanzada degeneración macular relacionada con la edad. Invest Ophthalmol Vis Sci. 2009 Jul;50(7):3386- 93. Epub 2009 Feb 21.) Tomados en conjunto, las variaciones genéticas en los componentes CFH, CFB, y C3 de la vía alternativa pueden predecir el resultado clínico en casi el 80% de los casos.

En la actualidad no existe una terapia médica probada para AMD seca y muchos pacientes con AMD neovascular se vuelven legalmente ciegos a pesar del tratamiento actual con agentes anti- VEGF como Lucentis. Por lo tanto, sería deseable proporcionar agentes terapéuticos para el tratamiento o prevención de enfermedades mediadas por el complemento y en particular para el tratamiento de AMD.

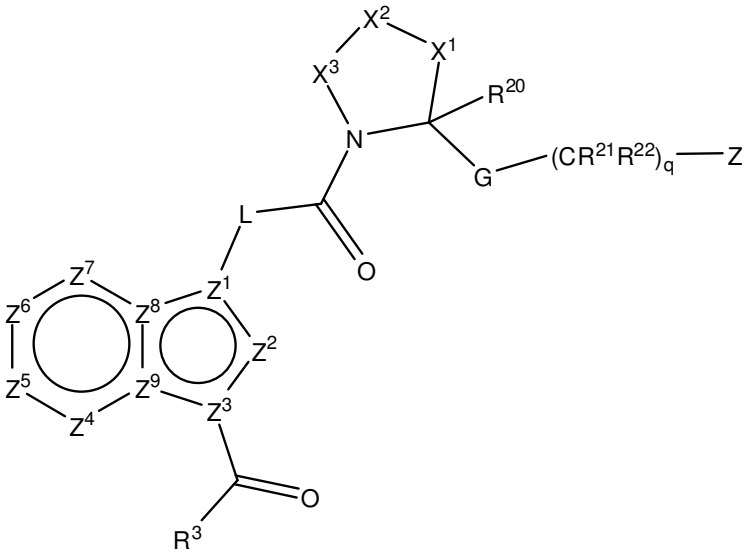
RESUMEN DE LA INVENCIÓN

La presente invención proporciona compuestos que modulan, y preferiblemente inhiben la activación de la vía alternativa del complemento. En ciertas realizaciones, la presente invención proporciona compuestos que modulan, y preferiblemente inhiben la actividad del factor D y/o activación de la ruta del complemento mediada por el factor D. Tales moduladores del factor D preferiblemente son inhibidores del Factor D de alta afinidad que inhiben la actividad catalítica del factor D del complemento, tales como el Factor D de primate y, particularmente, el factor D humano.

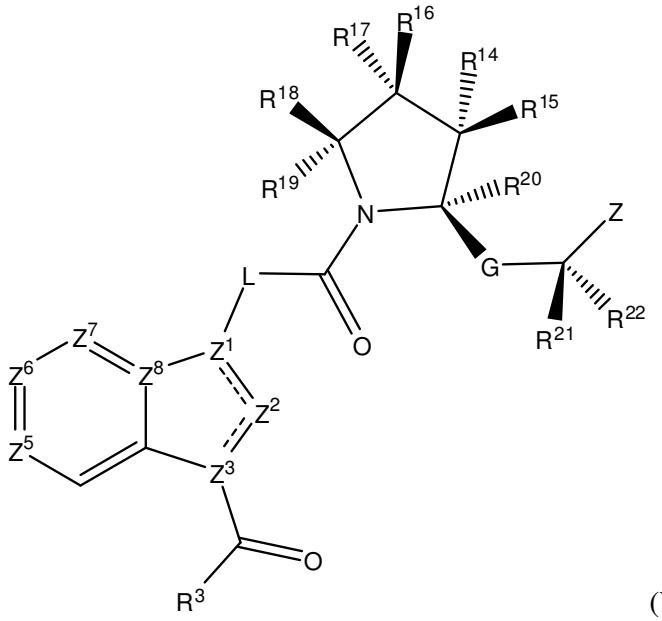
Los compuestos de la presente invención inhiben o suprimen la amplificación del sistema del complemento causada por la activación de C3 independientemente del mecanismo inicial de activación (incluyendo, por ejemplo, la activación de las vías clásica, de lectina o ficolina).

Varias realizaciones de la invención se describen en la presente. Se reconocerá que las características especificadas en cada realización pueden combinarse con otras características especificadas para proporcionar realizaciones adicionales.

Dentro de ciertos aspectos, los moduladores del Factor D proporcionados en la presente son compuestos de la fórmula I y sales de los mismos:



Dentro de ciertos otros aspectos, los moduladores del Factor D proporcionados en este documento son aquellos compuestos de la Fórmula VII y sales de los mismos:



(VII),

En otra realización, la invención proporciona una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto de acuerdo con la definición de la fórmula (I) o subfórmulas de la misma y uno o más vehículos farmacéuticamente aceptables

En otra realización, la invención proporciona una combinación, en particular, una combinación farmacéutica, que comprende una cantidad terapéuticamente eficaz del compuesto de acuerdo con la definición de la fórmula (I) o subfórmulas de la misma y uno o más compuestos terapéuticamente activos.

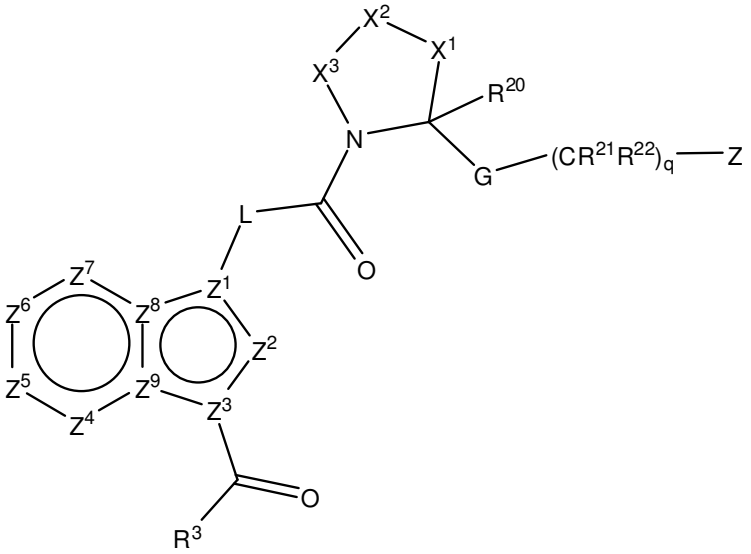
La invención proporciona además métodos de tratamiento o prevención de enfermedades mediadas por complemento, el método comprendiendo las etapas de identificar un paciente en necesidad de la terapia de modulación de complemento y la administración de un compuesto de Fórmula (I) o subfórmulas del mismo. Enfermedades mediadas por complemento incluyen enfermedades oftalmológicas (incluyendo degeneración macular orneovascular temprana relacionada con la edad y atrofia geográfica), enfermedades autoinmunes (como la artritis, artritis reumatoide), enfermedades respiratorias, enfermedades cardiovasculares.

Otros aspectos de la invención se discuten a continuación

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Como se señaló anteriormente, la presente invención proporciona compuestos que modulan la activación del factor D y/o transducción de señales mediadas por factor D del sistema del complemento. Tales compuestos pueden utilizarse in vitro o in vivo para modular (preferiblemente inhibir) la actividad del Factor D en una variedad de contextos.

En una primera realización, la invención proporciona compuestos de la Fórmula I y las sales farmacéuticamente aceptables de los mismos, que modulan la vía alternativa del sistema del complemento. Los compuestos de la Fórmula I están representados por la estructura:



(I)

o una sal farmacéuticamente aceptable del mismo, en donde

Z^1 es C y L es un residuo divalente seleccionado del grupo que consta de –N(H)– y –C(H)(R^1)–, or

Z^1 es N y L es CH_2;

R^1 es hidrógeno, hidróxilo, o amino;

Z^2 es C(R^2) o N;

Z^3 es C o N,

Z^4 es C(R^4) o N;

Z^5 es C(R^5) o N, o un N- óxido del mismo;

Z^6 es C(R^6) o N, o un N- óxido del mismo;

Z^7 es C(R^7) o N, o un N- óxido del mismo;

Z^8 es C o N;

Z^9 es C o N;

en donde uno de Z^1, Z^3, Z^8 y Z^9 es N y tres de Z^1, Z^3, Z^8 y Z^9 son C;

en donde 0, 1, o 2 o 3 de Z^2, Z^4, Z^5, Z^6 y Z^7 son N;

R^2 es hidrogen o C_1- C_6alquilo;

R^3 se selecciona del grupo que consta de hidrógeno, C_1- C_4alquilo, hidroxiC_1- C_4alquilo, C_1- C_4alcoxiC_1- C_4alquilo, haloC_1- C_4alquilo, amino o metilamino;

R^4 se selecciona del grupo que consta de hidrógeno, halogen, y C_1- C_6alquilo;

R^5 y R^6 se seleccionan independientemente del grupo que consta de hidrógeno, halógeno, hidróxilo, NR^8R^9, ciano, CO_2H, $CONR^{10}R^{11}$ SO_2C_1- C_6alquilo, y SO_2NH_2, $SO_2NR^{10}R^{11}$, C_1- C_6alcoxicarbonilo, - $C(NR^{10})NR^8R^9$, C_1- C_6alquilo, haloC_1- C_6alquilo, C_2- C_6alquenilo, C_1- C_6alcoxilo, haloC_1- C_6alcoxilo, C_2- C_6alqueniloxilo, en donde cada alquilo, alquenilo, alcoxilo y alqueniloxilo es sustituido o no sustituido con hasta 4 sustituyentes independientemente seleccionados a partir de halógeno, hidróxilo, tetrazol, C_1- C_4alcoxilo, C_1- C_4haloalcoxilo, CO_2H, C_1- C_6alcoxicarbonilo, $C(O)NR^{10}R^{11}$, NR^8R^9, fenilo opcionalmente sustituido, heterociclo que tiene 4 a 7 átomos de anillo y 1, 2, o 3 heteroátomos de anillo seleccionados a partir de N, O o S, heteroarilo que tiene 5 o 6 átomos de anillo y 1 o 2 heteroátomos de anillo seleccionados a partir de N, O o S, y en donde sustituyentes opcionales de fenilo se seleccionan a partir de halógeno, hidróxilo, C_1- C_4alquilo, C_1- C_4alcoxilo y CO_2H;

R^5 y $R^{6,}$ tomados en combinación con los átomos a los que están unidos, forman un ciclo que tiene 4 a 7 átomos de anillo y 0, 1 o 2 átomos N, O o S de anillo adicionales;

R^7 se selecciona del grupo que consta de hidrógeno, halógeno, C_1- C_6alquilo, C_1- C_6alcoxilo, haloC- C_6alquilo, haloC- C_6alcoxilo, C_1- C_6alcoxicarbonilo, CO_2H y $C(O)NR^{10}R^{11}$;

R^8 y R^9 se seleccionan independientemente del grupo que consta de hidrógeno, y C_1- C_6alquilo, haloC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, hidroxiC_1- C_6alquilo, o NR^8R^9, tomados en combinación, forman un heterociclo que tiene 4 a 7 átomos de anillo y 0 o 1 átomos N, O o S de anillo adicionales,cuyo heterociclo se sustituye por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de C_1- C_4alquilo, halógeno, hidróxilo, C_1- C_4alcoxilo;

R^{10} y R^{11}, son cada uno independientemente seleccionados del grupo que consta de hidrógeno y C_1- C_6alquilo, haloC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, o hidroxiC_1- C_6alquilo;

X^1 es $CR^{14}R^{15}$ o azufre;

X^2 es $CR^{16}R^{17}$, azufre de oxigeno, N(H) o N(C_1- C_6alquilo), en donde al menos uno entre X^1 y X^2 es carbono; o

X^1 y X^2, en combinación, forma una olefina de la fórmula $–C(R^{16})=C(H)-$ o $–C(R^{16})=C(C_1$- C_4alquilo)- , en donde el $C(R^{16})$ está fijado a X^3;

X^3 es $(CR^{18}R^{19})_m$ o N(H) en donde m es 0,1 o 2, en donde X^3 es $CR^{18}R^{19}$ o $(CR^{18}R^{19})_2$ cuando cualquiera X^1 o X^2 es azufre o X^2 es oxigeno; o

X^2 y X^3, tomados en combinación, son –N=C(H)– o –N=C(C_1- C_4alquilo)– en los cuales el C(H) o C(C_1- C_4alquilo) está fijado a X^1;

R^{14} se selecciona del grupo que consta de hidrógeno, halógeno, hidróxilo, amino y C_1-C_6alquilo;

R^{15} se selecciona del grupo que consta de hidrógeno, hidróxilo, halógeno, C_1-C_6alquilo, haloC_1- C_6alquilo, C_2- C_6alquenilo, C_2- C_6alquinilo, C_1- C_6alcoxilo, haloC_1-C_6alcoxilo, NR^8R^9, N(H)C(O)C_1- C_6alquilo, N(H)C(O)OC_1- C_6alquilo y OC(O)$NR^{10}R^{11}$ cada no de los sustituyentes de alquilo, alcoxilo, alquenilo, y alquinilo pueden ser sustituidos por 0, 1, o 2 grupos independientemente seleccionados en cada ocurrencia a partir del grupo que consta de halógeno, hidróxilo, C_1- C_6alquilo, C_1- C_6alcoxilo, y NR^8R^9;

R^{16} es hidrógeno, halógeno, hidróxilo, azida, ciano, COOH, C_1- C_6alcoxicarbonilo, C_1-C_6alquilo, C_1- C_6alcoxilo, C_1- C_6haloalquilo, C_1- C_6haloalcoxilo, NR^8R^9, N(H)C(O)C_1-C_6alquilo, hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, o C_1- C_6alquilo sustituido por NR^8R^9, N(H)C(O)H o N(H)C(O)(C_1- C_4alquilo);

R^{17} es hidrógeno, halógeno, hidróxilo, ciano, C_1- C_6alquilo, C_1- C_6alcoxilo, hidroxiC_1-C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, haloC_1- C_6alquilo, o C_1- C_6haloalcoxilo;

R^{18} se selecciona del grupo que consta de hidrógeno, fenilo y C_1- C_6alquilo, tal grupo alquilo es sustituido o no sustituido por hidróxilo, amino, azida, y NHC(O)C_1- C_6alquilo;

R^{19} y R^{20} son cada uno independientemente seleccionados a partir de hidrógeno y C_1-C_6alquilo; o

$CR^{16}R^{17}$, tomado en combinación forma un carbocilo espirocíclico de 3 a 6 miembros que se sustituye por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de halógeno y metilo; o

R^{16} y R^{17}, tomados en combinación, forman un metilideno exocíclico (=CH_2);

R^{15} y R^{16} tomados en combinación forman un anillo de epoxido o un sistema de anillo carbocíclico de 3 a 6 miembros cuyo anillo carbocíclico es sustituido por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de halógeno, metilo, etilo, hidroxiC_1-C_4alquilo, C_1- C_6alcoxiC_1- C_4alquilo, C_1- C_4alcoxicarbonilo, CO_2H, y C_1- C_4alquilo sustituido por NR^8R^9; o

R^{16} y R^{18} o R^{17} y R^{19}, tomados en combinación, forman un sistema de anillo carbocíclico de 3 miembros fusionado que se sustituye por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de halógeno, metilo, etilo, hidroxiC_1-

C_4alquilo, C_1- C_6alcoxiC_1- C_4alquilo, C_1- C_4alcoxicarbonilo, CO_2H, y C_1- C_4alquilo sustituido por NR^8R^9; o

R^{14} y R^{20} tomados en combinación forman un sistema de 3 anillos carbocíclicos fusionados;

R^{14} y R^{19} tomados en combinación forman un enlazador de alquileno de 1 a 3 carbonos;

R^{17} y R^{20} tomados en combinación forman un enlazador de alquileno de 1 a 3 carbonos;

G es un residuo divalente seleccionado a partir de C(O)- N(H), CH_2- N(H)–$S(O)_2$–, CH_2–N(H)–C(O), CH_2- N(H)- C(O)- O, CH_2N(H), CH_2- N(H)- C(O)- N(H), CH_2- N(H)- C(O)- N(Me), CH_2N(H)- $S(O)_2$- N(H)- , y CH_2N(H)- $S(O)_2$- N(Me)- , en donde el residuo más a la derecha está fijado a $–(CR^{21}R^{22})_q$;

q es 0, 1, 2, 3 o 4;

R^{21} se selecciona independientemente en cada ocurrencia a partir del grupo que consta de hidrógeno, hidróxilo, halógeno, C_1- C_6alquilo, haloC_1- C_6alquilo, fenilo, CO_2H, C_1- C_6alcoxi- carbonilo, $C(O)NH_2$, hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, C_1- C_6alquilo sustituido por NR^8R^9, imidazoilC_1- C_6alquilo heterocicloC_1- C_6alquilo, donde el heterociclo se selecciona a partir de azetidinilo, pirrolidinilo, piperidinilo, morfolinilo, 1- oxa- 6- aza- espiro[3.3]heptano, 2- oxa- 6- aza- espiro[3.3]heptano, piperazinilo, 1,6- diaza- espiro[3.3]heptano, y 2,6- diaza- espiro[3.3]heptano cada uno de los cuales es opcionalmente sustituido por 1 o 2 sustituyentes seleccionados a partir de flúor, hidróxilo, C_1- C_4alquilo o C_1- C_4alcoxilo;

R^{22} se selecciona independientemente en cada ocurrencia a partir de hidrógeno o C_1- C_6alquilo; o

cuando q es 1, 2, 3 o 4, R^{21} y un sustituyente de R^{22}, tomados en combinación con los átomos de carbono a los que están unidos, forman un carbociclo de 3 a 6 miembros o heterociclo de a 6 miembros que tiene un oxigeno o nitrógeno de anillo; o

cuando q es 2, 3 o 4, dos residuos R^{21} o R^{22}, localizados en átomos de carbono adyacentes, forman, junto con los átomos de carbono a los que están unidos, un carbociclo de 3 a 6 miembros; y

Z es C_1- C_6alquilo, C_1- C_6haloalquilo, fenilo, fenoxilo, naftilo, naftiloxilo, C_3- C_7cicloalquilo, indanilo, un heterociclo monocíclico o bicíclico saturado o parcialmente insaturado de 5, 6, 9 o 10 miembros que tiene 1, 2, o 3 heteroátomos de anillo seleccionados a partir de N, O, o S, o un heteroarilo o heteroariloxilo de 5 o 6 miembros, tal heteroarilo tiene 1 o 2 heteroátomos de anillo seleccionados a partir de N, O o S siempre que el anillo no tenga 2 átomos O o S, cada residuo es sustituido o no sustituido por 1, 2, 3, o 4 sustituyentes que se

seleccionan independientemente del grupo que consta de C_1- C_6alquilo sustituido o no sustituido, C_1- C_6haloalquilo, halógeno, CN, hidróxilo, CO_2H, tetrazolilo, $C(O)R^{25}$, $S(O)_2R^{26}$, C_1- C_6alcoxilo sustituido o no sustituido, haloC_1- C_6alcoxilo, fenoxilo, $NR^{23}R^{24}$, $CH_2NR^{23}R^{24}$, heteroarilo de 5 o miembrosy fenilo sustituido o no sustituido, tal fenilo sustituido tiene1 o 2 sustituyentes independientemente seleccionados del grupo que consta de ciano, halo, C_1- C_6alquilo o C_1- C_6haloalquilo, OH, COOH, COR^{25}, $S(O)_2R^{26}$, amino, y CH_2NH_2, y tal alquilo o alcoxilo sustituido tiene un sustituyente seleccionado a partir de hidróxilo, C_1- C_4alcoxilo, ciano, CO_2H, tetrazol o $NR^{23}R^{24}$;

R^{23} es hidrógeno o C_1- C_6alquilo;

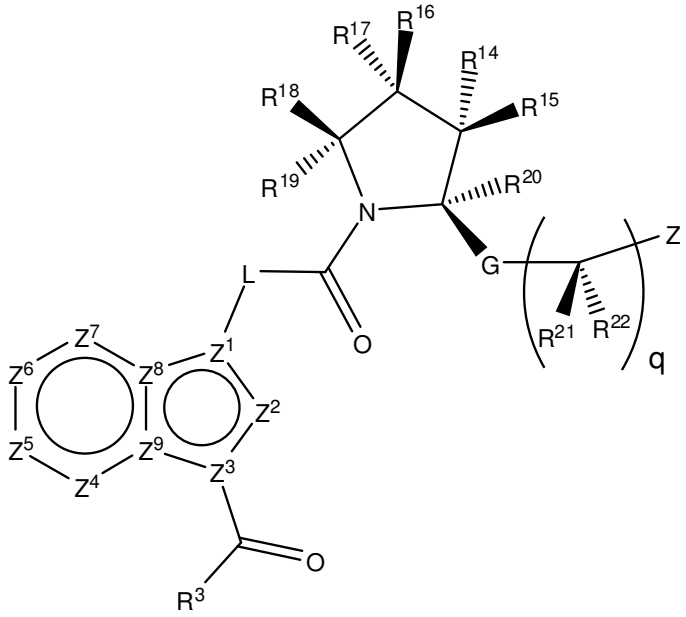
R^{24} es hidrógeno, C_1- C_6alquilo, hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, aminoC_1- C_6alquilo, mono- y di- C_1- C_6alquilaminoC_1- C_6alquilo; o

$NR^{23}R^{24}$, tomados en combinación forman un heterociclo de 4, 5 o 6 miembros que tiene 0 o 1 heteroátomos de anillo adicionales seleccionados del grupo que consta de N, O o S, y que se sustituye por 0, 1 o 2 sustituyentes independientemente seleccionados a partir de flúor, hidróxilo, C_1- C_4alquilo o C_1- C_4alcoxilo;

R^{25} se selecciona independientemente en cada ocurrencia a partir del grupo que consta de C_1- C_6alcoxilo y $NR^{23}R^{24}$; y

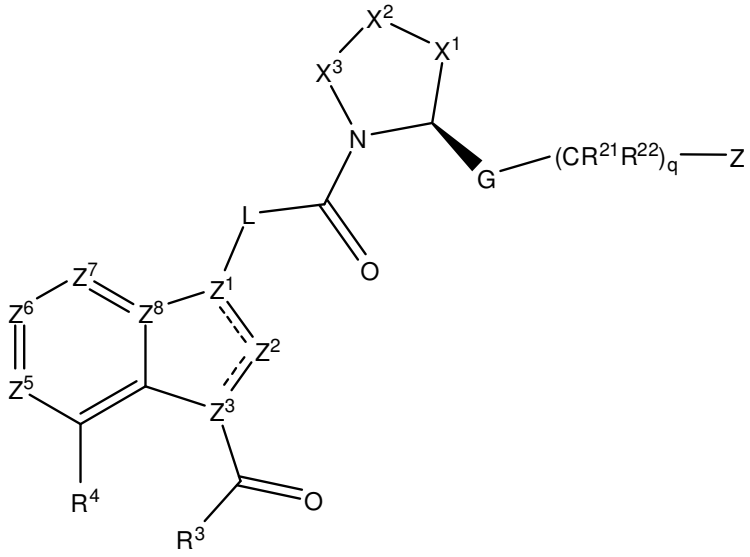
R^{26} se selecciona del grupo que consta de amino, hidróxilo, C_1- C_6alquilo, y, mono- y di- C_1- C_6alquilamino.

En ciertos aspectos, los compuestos de la fórmula (I) preferiblemente tienen la estereoquímica de los compuestos representada por la fórmula (Ia):



(Ia),

En un aspecto, los compuestos de la fórmula (I) incluyen los compuestos representados por la fórmula (II):



(II)

en donde:

Z^2 es CH o N;

X^1 es CHR^{15} o S;

X^2 es $CR^{16}R^{17}$ o S, en donde al menos uno entre X^1 y X^2 no es azufre;

X^3 es $CR^{18}R^{19}$ o N(H);

R^{15} se selecciona a partir del grupo que consta de hidrógeno, hidróxilo, halógeno, C_1-C_6alquilo, haloC_1- C_6alquilo, C_1- C_6alcoxilo, haloC_1- C_6alcoxilo, NR^8R^9, N(H)C(O)C_1-C_4alquilo, N(H)C(O)OC_1- C_4alquilo y OC(O)$NR^{10}R^{11}$, cada alquilo y alcoxilo pueden ser sustituidos por 0, 1, o 2 grupos independientemente seleccionados en cada ocurrencia a partir del grupo que consta de hidróxilo, C_1- C_6alquilo, C_1- C_6alcoxilo, y NR^8R^9;

R^{16} es hidrógeno, halógeno, hidróxilo, amino, ciano, C_1- C_4alquilo, C_1- C_4alcoxilo, C_1-C_4haloalquilo, C_1- C_4haloalcoxilo, heterocicloC$_0$- C_4alquilo, NR^8R^9, N(H)C(O)C_1- C_4 alquilo, hidroxiC_1- C_4alquilo, C_1- C_4alcoxiC_1- C_4alquilo o C_1- C_4alquilo sustituido por NR^8R^9;

R^{17} es hidrógeno, halógeno, hidróxilo, C_1- C_4alquilo, hidroxiC_1- C_4alquilo o C_1- C_2alcoxiC_1-C_4alquilo;

R^{18} se selecciona del grupo que consta de hidrógeno, fenilo y C_1- C_6alquilo, tal grupo alquilo es sustituido o no sustituido por hidróxilo, amino, NHC(O)C_1- C_6alquilo, amida o mono- o di- C_1-C_4alquil- amida;

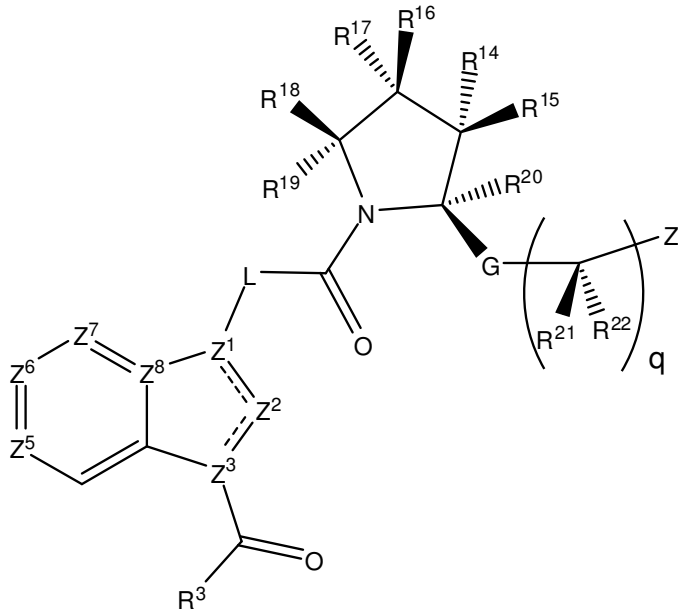
R^{19} es hidrógeno; o

$CR^{16}R^{17}$, tomado en combinación, forma un carbocilo espirocíclico de 3 a 6 miembros; o

R^{15} y R^{16}, tomados en combinación, forman un anillo de ciclopropilo que se sustituye por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de halógeno, metilo, etilo, hidroximetilo, hidroxietilo, metoximetilo; o

R^{17} y R^{19} tomados en combinación forman un anillo de ciclopropilo.

En otra realización, la invención proporciona los compuestos de la fórmula (VII):



(VII),

o una sal farmacéuticamente aceptable del mismo, en donde

L es un residuo divalente seleccionado del grupo que consta de –N(H)– y –C(H)(R^1)–,

R^1 es hidrógeno, hidróxilo, o amino;

Z^1 es C o N;

Z^2 es C(H) o N;

Z^3 es C o N,

Z^5 es C(R^5), N o un N óxido del mismo;

Z^6 es C(R^6), N o un N óxido del mismo;

Z^7 es C(R^7), N o un N óxido del mismo;

Z^8 es C o N

en donde uno de Z^1 y Z^3 es N y el otro es C;

en donde 0, 1, 2 o 3 de Z^2, Z^5, Z^6, Z^7 y Z^8 son N;

R^3 se selecciona del grupo que consta de hidrógeno, C_1- C_4alquilo, hidroxiC_1- C_4alquilo, C_1- C_4alcoxiC_1- C_4alquilo, haloC_1- C_4alquilo, amino o metilamino;

R^5 y R^6 se seleccionan independientemente del grupo que consta de hidrógeno, halógeno, hidróxilo, NR^8R^9, ciano, CO_2H, $CONR^{10}R^{11}$ SO_2C_1- C_6alquilo, y $SO_2NR^{10}R^{11}$, C_1- C_6alcoxicarbonilo, $C(NR^8)NR^8R^9$, C_1- C_6alquilo, haloC_1- C_6alquilo, C_2- C_6alquenilo, C_1- C_6alcoxilo, haloC_1- C_6alcoxilo, C_2- C_6alqueniloxilo, en donde cada alquilo, alquenilo, alcoxilo y alqueniloxilo es sustituido o no sustituido con hasta 4 sustituyentes independientemente seleccionados a partir de halógeno, hidróxilo, tetrazol, C_1- C_4alcoxilo, C_1- C_4haloalcoxilo,

CO_2H, C_1- C_6alcoxicarbonilo, $C(O)NR^{10}R^{11}$, NR^8R^9 fenilo opcionalmente sustituido, heterociclo que tiene 4 a 7 átomos de anillo y 1, 2, o 3 heteroátomos de anillo seleccionados a partir de N, O o S, heteroarilo que tiene 5 o 6 átomos de anillo y 1 o 2 heteroátomos de anillo seleccionados a partir de N, O o S, y en donde sustituyentes opcionales de fenilo se seleccionan a partir de halógeno, hidróxilo, C_1- C_4alquilo, C_1- C_4alcoxilo y CO_2H;

R^5 y $R^{6,}$ tomados en combinación con los átomos a los que están unidos, forman un ciclo que tiene 4 a 7 átomos de anillo y 0 o 1 átomos N, O o S de anillo adicionales;

R^7 se selecciona del grupo que consta de hidrógeno, halógeno, C_1- C_6alquilo, C_1- C_6alcoxilo, haloC- C_6alquilo, haloC- C_6alcoxilo C_1- C_6alcoxicarbonilo, CO_2H y $C(O)NR^{10}R^{11}$;R^8 y R^9 se seleccionan independientemente del grupo que consta de hidrógeno, y C_1- C_6alquilo, haloC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, hidroxiC_1- C_6alquilo, o NR^8R^9, tomados en combinación, forman a heterociclo que tiene 4 a 7 átomos de anillo y 0 o 1 átomos N, O o S de anillo adicionales,dicho heterociclo se sustituye por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de C_1- C_4alquilo, halógeno, hidróxilo, C_1- C_4alcoxilo;

R^8 y R^9 se seleccionan independientemente del grupo que consta de hidrógeno, y C_1- C_6alquilo, haloC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, hidroxiC_1- C_6alquilo, o NR^8R^9, tomados en combinación, forman a heterociclo que tiene 4 a 7 átomos de anillo y 0 o 1 átomos N, O o S de anillo adicionales, dicho heterociclo se sustituye por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de C_1- C_4alquilo, halógeno, hidróxilo, C_1- C_4alcoxilo;

R^{10} y R^{11}, son cada uno independientemente seleccionados del grupo que consta de hidrógeno y C_1- C_6alquilo, haloC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, o hidroxiC_1- C_6alquilo;

R^{14} se selecciona del grupo que consta de hidrógeno, halógeno, hidróxilo, amino y C_1- C_6alquilo;

R^{15} se selecciona a partir del grupo que consta de hidrógeno, hidróxilo, halógeno, C_1- C_6alquilo, haloC_1- C_6alquilo, C_2- C_6alquenilo, C_2- C_6alquinilo, C_1- C_6alcoxilo, haloC_1- C_6alcoxilo, NR^8R^9, $N(H)C(O)C_1$- C_6alquilo, $N(H)C(O)OC_1$- C_6alquilo y $OC(O)NR^{10}R^{11}$ cada uno de los sustituyentes de alquilo, alcoxilo, alquenilo, y alquinilo pueden ser sustituidos por 0, 1, o 2 grupos independientemente seleccionados en cada ocurrencia a partir del grupo que consta de halógeno, hidróxilo, C_1- C_6alquilo, C_1- C_6alcoxilo, y $NR^{10}R^{11}$;

R^{16} es hidrógeno, halógeno, hidróxilo, azida, ciano, COOH, C_1- C_6alcoxicarbonilo, C_1- C_6alquilo, C_1- C_6alcoxilo, C_1- C_6haloalquilo, C_1- C_6haloalcoxilo, NR^8R^9, $N(H)C(O)C_1$-

C_6alquilo, hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, o C_1- C_6alquilo sustituido por NR^8R^9, N(H)C(O)H o N(H)C(O)(C_1- C_4alquilo);

R^{17} es hidrógeno, halógeno, hidróxilo, C_1- C_6alquilo, C_1- C_4alcoxilo, hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, o C_1- C_6haloalcoxilo;

R^{18} se selecciona del grupo que consta de hidrógeno, fenilo y C_1- C_6alquilo, tal grupo alquilo es sustituido o no sustituido por hidróxilo, amino, azida, y $NHC(O)C_1$- C_6alquilo;

R^{19} y R^{20} son cada uno independientemente seleccionados a partir de hidrógeno y C_1- C_6alquilo; o

$CR^{16}R^{17}$, tomado en combinación, forma un carbocilo espirocíclico de 3 a 6 miembros que se sustituye por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de halógeno y metilo; o

R^{16} y R^{17}, tomados en combinación, forman un metilideno exocíclico (=CH_2);

R^{15} y R^{16} o R^{14} y R^{17} tomados en combinación forman un anillo de epóxido o un sistema de anillo carbocíclico de 3 a 6 miembros cuyo anillo carbocíclico es sustituido por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de halógeno, metilo, etilo, hidroxiC_1- C_4alquilo, C_1- C_6alcoxiC_1- C_4alquilo, C_1- C_4alcoxicarbonilo, CO_2H, y C_1- C_4alquilo sustituido por NR^8R^9; o

R^{17} y R^{19} o R^{16} y R^{18}, tomados en combinación, forman un sistema de anillo carbocíclico de 3 miembros fusionado que se sustituye por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de halógeno, metilo, etilo, hidroxiC_1- C_4alquilo, C_1- C_4alcoxicarbonilo, CO_2H, y C_1- C_4alquilo sustituido por NH^8R^9; o

R^{14} y R^{20} tomados en combinación forman un sistema de 3 anillos carbocíclicos fusionados;

R^{14} y R^{19}, tomados en combinación, forman un enlazador de alquileno de 1 a 3 carbonos; o

R^{17} y R^{20}, tomados en combinación, forman un enlazador de alquileno de 1 a 3 carbonos;

G es un residuo divalente seleccionado a partir de C(O)- N(H), CH_2- N(H)–$S(O)_2$–, CH_2–N(H)–C(O), CH_2- N(H)- C(O)- O, CH_2N(H), CH_2- N(H)- C(O)- N(H), CH_2- N(H)- C(O)- N(Me), CH_2N(H)- $S(O)_2$- N(H)- , y CH_2N(H)- $S(O)_2$- N(Me)- , en donde el residuo más a la derecha está fijado a –$(CR^{21}R^{22})_q$;

q es 0, 1, 2, 3 o 4;

R^{21} se selecciona independientemente en cada ocurrencia a partir del grupo que consta de hidrógeno, hidróxilo, halógeno, C_1- C_6alquilo, haloC_1- C_6alquilo, fenilo, CO_2H, C_1-

C_6alcoxilo carbonilo, $C(O)NH_2$, hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, C_1- C_6alquilo sustituido por NR^8R^9, imidazoilC_1- C_6alquilo heterocicloC_1- C_6alquilo, donde el heterociclo se selecciona a partir de azetidinilo, pirrolidinilo, piperidinilo, morfolinilo, 1- oxa- 6- aza- espiro[3.3]heptano, 2- oxa- 6- aza- espiro[3.3]heptano, piperazinilo, 1,6- diaza- espiro[3.3]heptano, y 2,6- diaza- espiro[3.3]heptano cada uno de los cuales se sustituye opcionalmente por 1 o 2 sustituyentes seleccionados a partir de flúor, hidróxilo, C_1- C_4alquilo o C_1- C_4alcoxilo;

R^{22} se selecciona independientemente en cada ocurrencia a partir de hidrógeno o C_1- C_6alquilo; o

cuando q es 1, 2, 3 o 4, R^{21} y un sustituyente de R^{22}, tomados en combinación con los átomos de carbono a los que están unidos, forman un carbociclo de 3 a 6 miembros o heterociclo de 3 a 6 miembros que tiene un oxigeno o nitrógeno de anillo; o

cuando q es 2, 3 o 4, dos residuos R^{21} o R^{22}, localizados en átomos de carbono adyacentes, forman, junto con los átomos de carbono a los que están unidos, un carbociclo de 3 a 6 miembros; y

Z es C_1- C_6alquilo, C_1- C_6haloalquilo, fenilo, fenoxilo, naftilo, naftiloxilo, C_3- C_7cicloalquilo, indanilo, un heterociclo monocíclico o bicíclico saturado o parcialmente insaturado de 5, 6, 9 o 10 miembros que tiene 1, 2, o 3 heteroátomos de anillo seleccionados a partir de N, O, o S, o un heteroarilo o heteroariloxilo de 5 o 6 miembros, tal heteroarilo tiene 1 o 2 heteroátomos de anillo seleccionados a partir de N, O o S siempre que el anillo no tenga 2 átomos O o S, cada residuo es sustituido o no sustituido por 1, 2, 3, o 4 sustituyentes que se seleccionan independientemente del grupo que consta de C_1- C_6alquilo sustituido o no sustituido, C_1- C_6haloalquilo, halógeno, CN, hidróxilo, CO_2H, tetrazolilo, $C(O)R^{25}$, $S(O)_2R^{26}$, C_1- C_6alcoxilo sustituido o no sustituido, haloC_1- C_6alcoxilo, fenoxilo, $NR^{23}R^{24}$, $CH_2NR^{23}R^{24}$, heteroarilo de 5 o miembros y fenilo sustituido o no sustituido, tal fenilo sustituido tiene1 o 2 sustituyentes independientemente seleccionados del grupo que consta de ciano, halo, C_1- C_6alquilo o C_1- C_6haloalquilo, OH, COOH, COR^{25}, $S(O)_2R^{26}$, amino, y CH_2NH_2, y tal alquilo o alcoxilo sustituido tiene un sustituyente seleccionado a partir de hidróxilo, C_1- C_4alcoxilo, ciano, CO_2H, tetrazol o $NR^{23}R^{24}$;

R^{23} es hidrógeno o C_1- C_6alquilo;

R^{24} es hidrógeno, C_1- C_6alquilo, hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, aminoC_1- C_6alquilo, mono- y di- C_1- C_6alquilaminoC_1- C_6alquilo; o

$NR^{23}R^{24}$, tomados en combinación forman un heterociclo de 4, 5 o 6 miembros que tiene 0 o 1 heteroátomos de anillo adicionales seleccionados del grupo que consta de N, O o S,

y que se sustituye por 0, 1 o 2 sustituyentes independientemente seleccionados a partir de flúor, hidróxilo, C_1- C_4alquilo o C_1- C_4alcoxilo;

R^{25} se selecciona independientemente en cada ocurrencia a partir del grupo que consta de C_1- C_6alcoxilo y $NR^{23}R^{24}$; y

R^{26} se selecciona del grupo que consta de amino, hidróxilo, C_1- C_6alquilo, y, mono- y di- C_1- C_6alquilamino.

En otro aspecto, los compuestos de la fórmula (I) o (II) se proporcionan en los cuales X^1 es CHR^{15}; y R^{15} es hidrógeno, flúor, hidróxilo, amino, C_1- C_4alquilo, C_1- C_6alcoxilo, OCH_2CH_2OMe, o C_2- C_4alcoxilo sustituido por NR^8R^9;

X^2 es $CR^{16}R^{17}$;

R^{16} es hidrógeno, halógeno, hidróxilo, C_1- C_4alquilo, C_1- C_4alcoxilo, C_1- C_4haloalquilo, C_1- C_4haloalcoxilo, NR^8R^9, hidroxiC_1- C_4alquilo, C_1- C_4alcoxiC_1- C_4alquilo, C_1- C_4alquilo sustituido por NR^8R^9 o C_2- C_4alcoxilo sustituido por NR^8R^9;

R^{17} es hidrógeno, halógeno, hidroxilo o C_1- C_4alquilo; o

R^{15} y R^{16} tomados en combinación forman un anillo de ciclopropilo; o

R^{17} y R^{19} tomados en combinación forman un anillo de ciclopropilo.

En aún otro aspecto, los compuestos de la fórmula (I) o (II) se proporcionan en los cuales X^1 es S; y X^2 y X^3 son CH_2; o

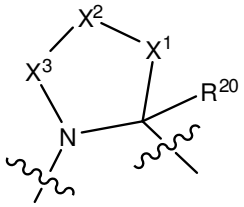
X^1 es CHR^{15}, en donde R^{15} es hidrógeno, flúor, metilo, hidróxilo, metoxilo, etoxilo, metoxietoxilo o amino; X^3 es CH_2; y X^2 es $CR^{16}R^{17}$, en donde R^{16} es flúor, amino, hidroximetilo, metoximetilo, aminometilo o metilo y R^{17} es hidrógeno o flúor; o

X^1 es CHR^{15}, X^2 es $CR^{16}R^{17}$, y X^3 es CHR^{19}, en donde R^{17} y R^{19}, tomados en combinación forman un anillo de ciclopropilo,y R^{16} es hidrógeno, hidroximetilo, o metoximetilo, y R^{15} es hidrógeno; o

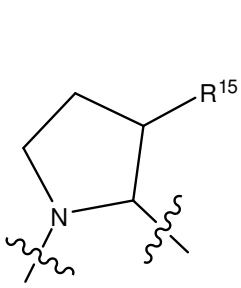
X^1 es CHR^{15}, X^2 es $CR^{16}R^{17}$, y X^3 es CHR^{19}, en donde R^{15} y R^{16}, tomados en combinación forman un anillo de ciclopropilo, R^{17} y R^{19} son hidrógeno; o

X^1 y X^2 son CH_2, y X^3 es N(H).

Otros compuestos de la fórmula (I) o (II) proporcionados en la presente incluyen los compuestos en los cuales el anillo heterocíclico de la fórmula:



se selecciona del grupo que consta de: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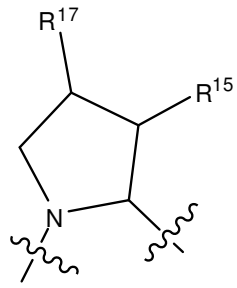
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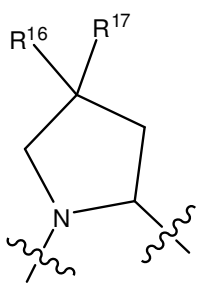
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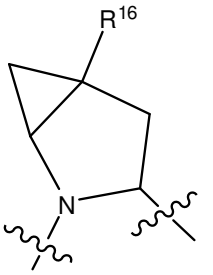
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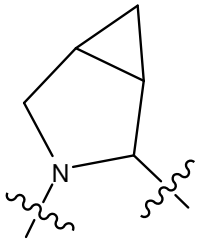
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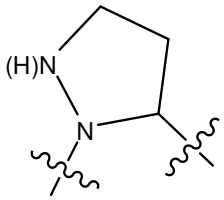
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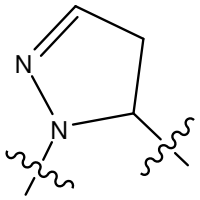
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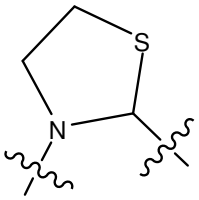
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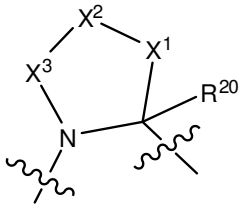
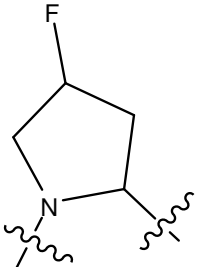
En ciertas realizaciones, el anillo heterocíclico de los compuestos de la fórmula (I) y fórmula (II) de la fórmula:



Es una 4- fluoro pirrolidina, ej., un heterociclo de la fórmula: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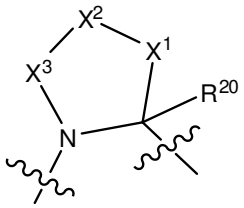
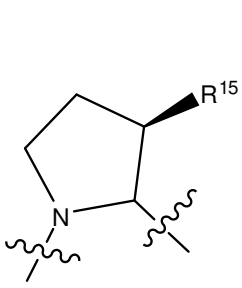
En ciertos aspectos, los compuestos de la fórmula (I) o (II) incluyen compuestos en los cuales el anillo heterocíclico de la fórmula:



se selecciona del grupo que consta de: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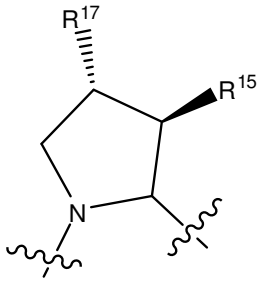
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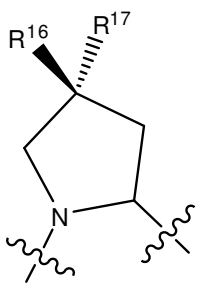
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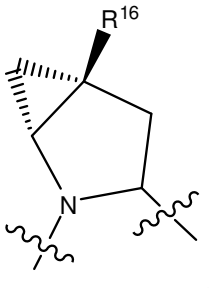
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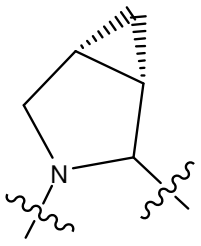
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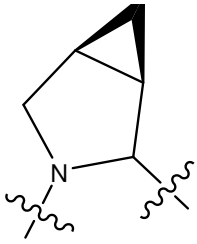
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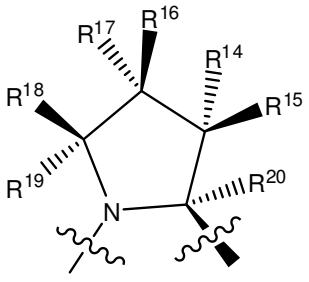
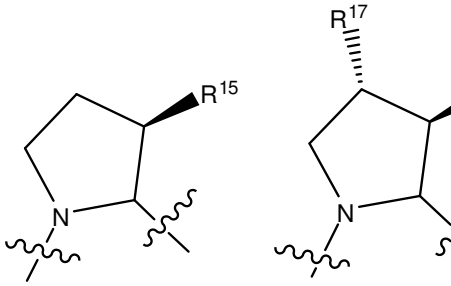
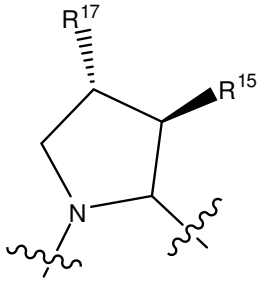
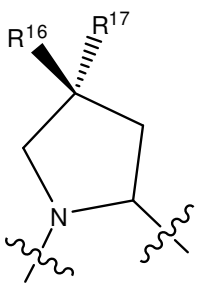
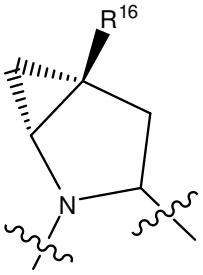
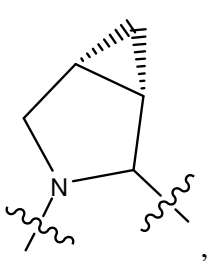
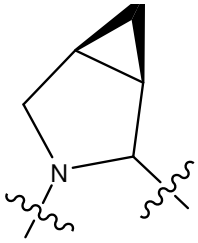
En ciertos aspectos, los compuestos de la fórmula (VII) incluyen compuestos en los cuales el anillo heterocíclico de la fórmula:

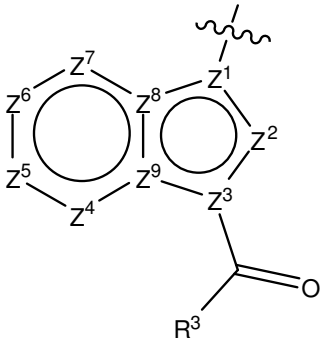


se selecciona del grupo que consta de:

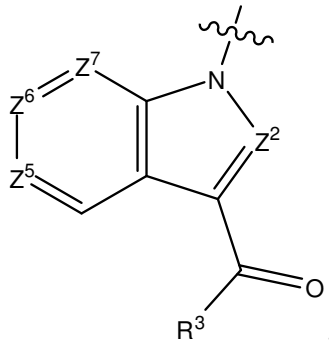
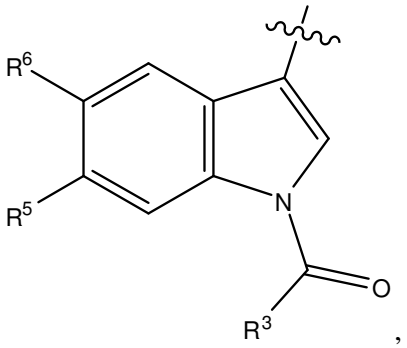







, y .

Otros compuestos de la fórmula (I) proporcionados en la presente incluyen los compuestos en los cuales el sistema de anillo bicíclico de la fórmula:



se selecciona del grupo que consta de:

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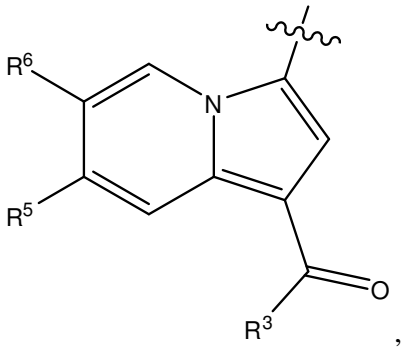

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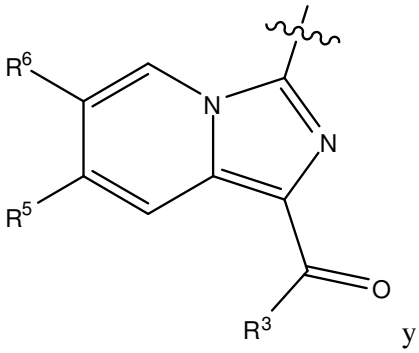

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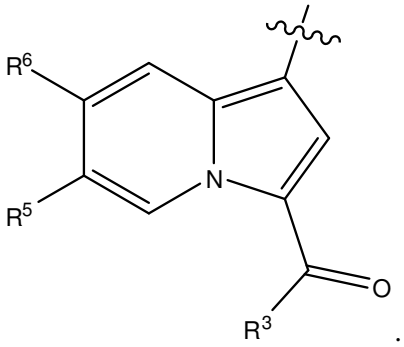
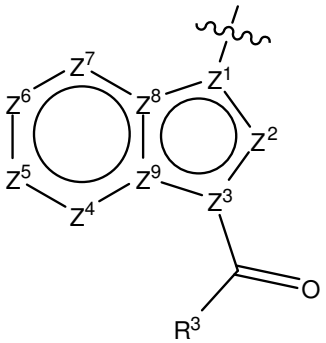
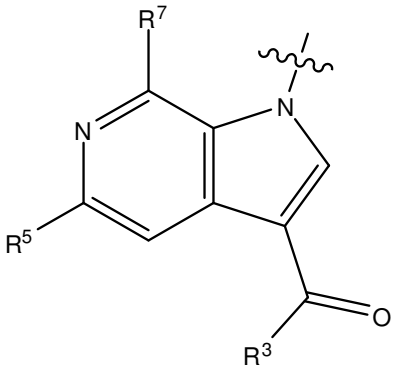
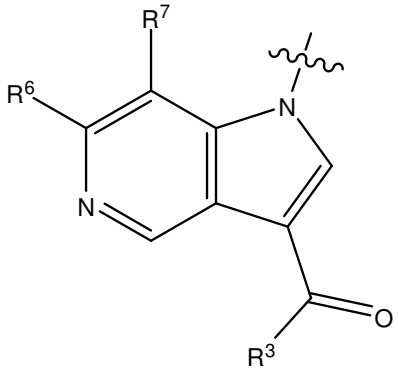
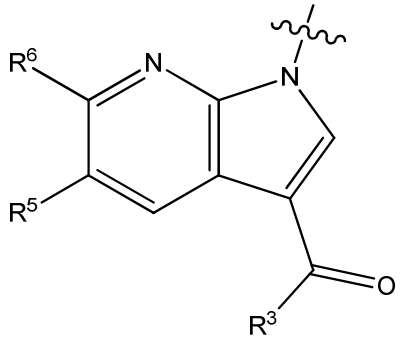
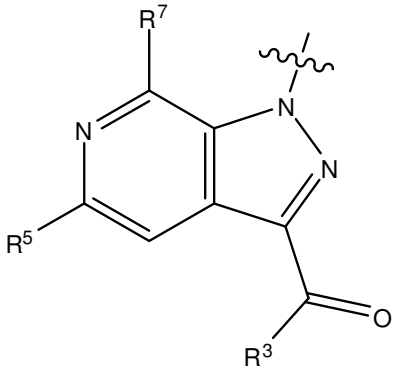
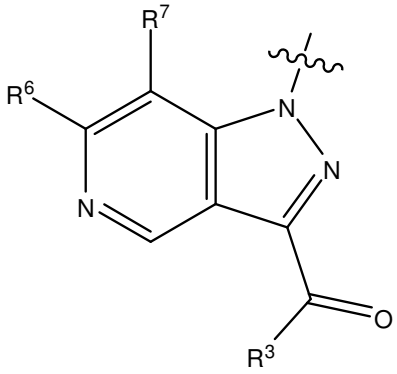
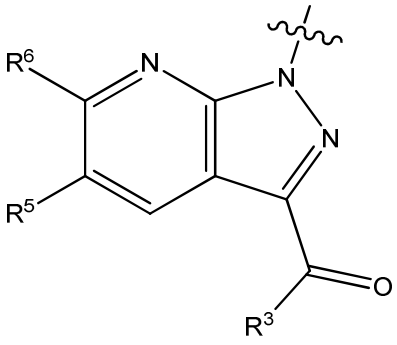


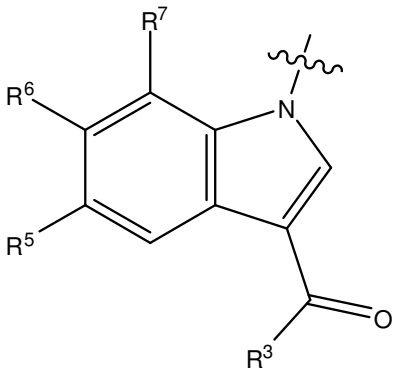
.

Otros ciertos compuestos de la fórmula (I) proporcionados en la presente incluyen los compuestos en los cuales el sistema de anillo bicíclico de la fórmula:



se selecciona del grupo que consta de:


R7
N
N
R5
O
R3
,

R7
R6
N
N
O
R3
,

R6
N
N
R5
O
R3
,

R7
N
N
N
R5
O
R3
,

R7
R6
N
N
N
O
R3
,

R6
N
N
N
R5
O
R3
,



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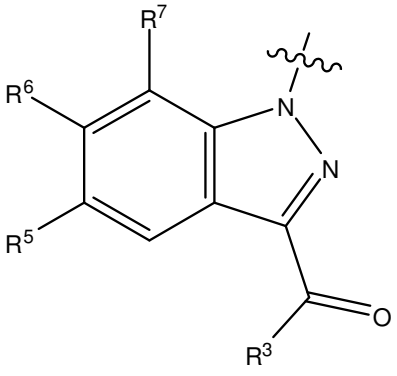

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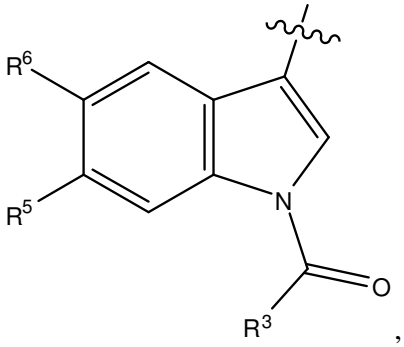

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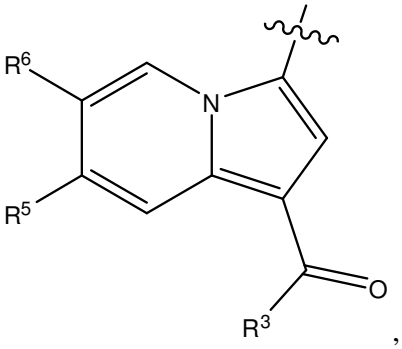

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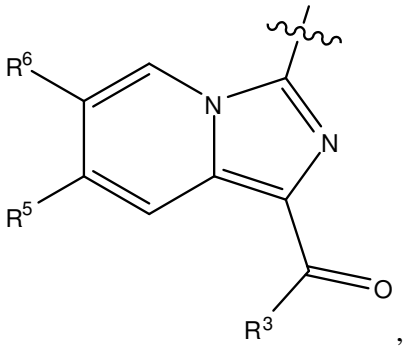
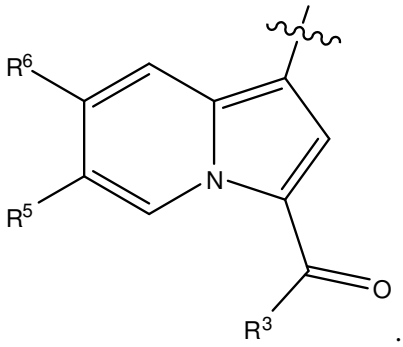


, y


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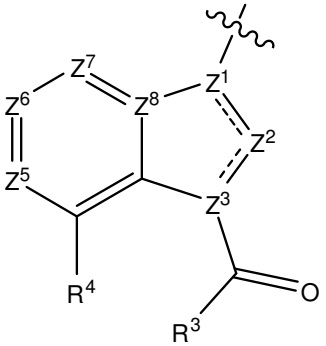
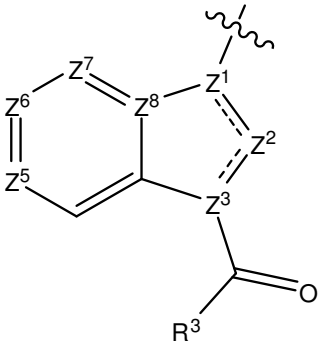
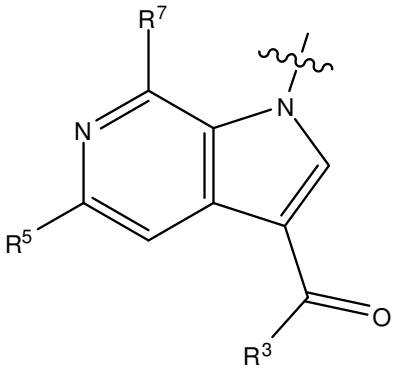
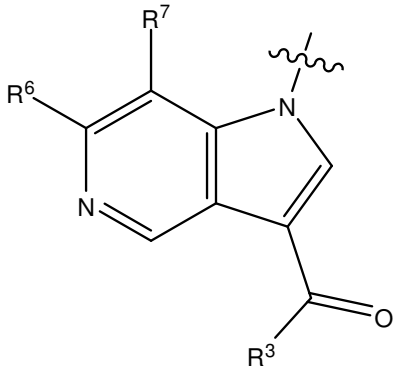
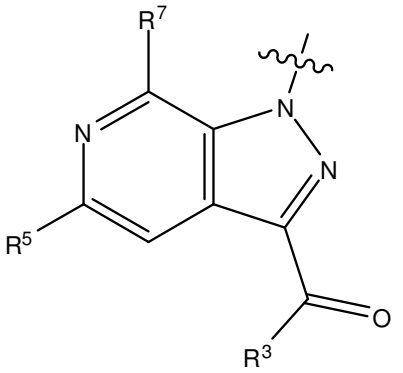
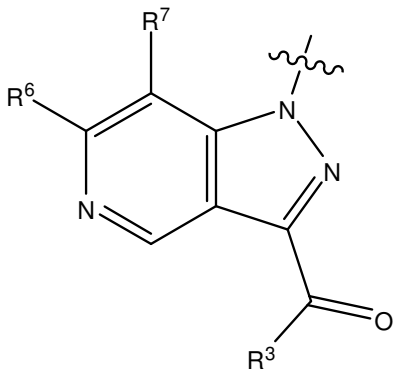
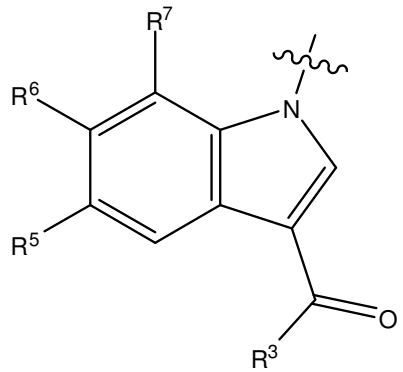
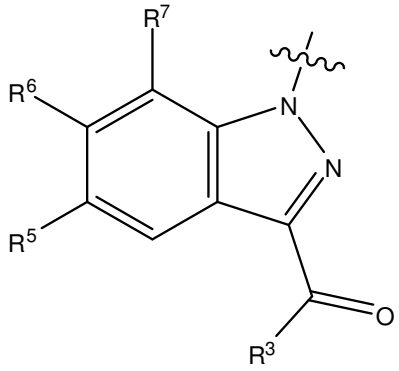
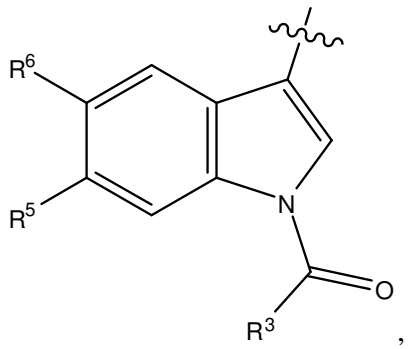
Otros compuestos de la fórmula (II) o fórmula (VII) proporcionados en la presente incluyen los compuestos en los cuales el sistema de anillo bicíclico de la fórmula (II) o fórmula (VII)



o


se selecciona del grupo que consta de:


R7
N
N
R5
O
R3
,

R7
R6
N
N
O
R3
,

R7
N
N
N
R5
O
R3
,

R7
R6
N
N
N
O
R3
,

R7
R6
N
R5
O
R3
,

R7
R6
N
N
R5
O
R3
,



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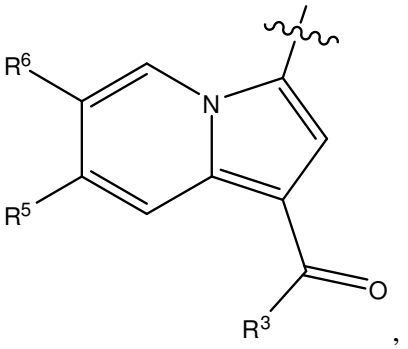

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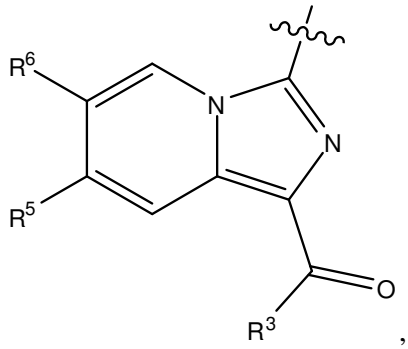
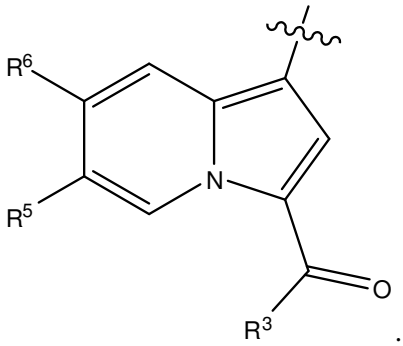


, y


.

Ciertos compuestos preferidos de la fórmula (I), (Ia), (II), (VII) o cualquier subfórmula de los mismos proporcionados en la presente incluyen los compuestos en los que L es –N(H)– o $–CH_2–$. Ciertos otros compuestos preferidos de la fórmula (I), (Ia), (II), (VII) o cualquier subfórmula de los mismos proporcionados en la presente incluyen los compuestos en los que G es –C(O)- N(H)–.

Aún otros compuestos preferidos de la fórmula (I), (Ia), (II) o (VII) o cualquier subfórmula de los mismos proporcionados en la presente incluyen los compuestos en los que q es 0 o 1;

R^{21} se selecciona del grupo que consta de hidrógeno, C_1- C_6alquilo, hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo y C_1- C_6alquilo sustituido por NR^8R^9;

R^{22} es hidrógeno; o

$CR^{21}R^{22}$, tomados en combinación, forman un anillo de ciclopropilo;

Z es fenilo, piridilo, oxalilo, isoxalilo, tiazolilo, pirazolilo, tienilo, cada uno de los cuales es sustituido o no sustituido por 1, 2 o 3 sustituyentes, cada uno de los cuales se selecciona independientemente del grupo que consta de:

halógeno, hidróxilo, C_1- C_4alquilo, C_1- C_4alcoxilo, haloC_1- C_4alquilo, haloC_1- C_4alcoxilo, $NR^{23}R^{24}$, CO_2H, $C(O)NR^{23}R^{24}$, $CO_2(C_1$- C_4alquilo), tetrazol, piperidinilo, piperazinilo, morfolino, y alquilo sustituido por C_1- C_4alcoxilo o $NR^{23}R^{24}$.

En aún otros compuestos preferidos de la fórmula (I), (Ia), (II), o (VII), o cualquier subfórmula de la misma proporcionada en la presente, q es 2;

R^{21}se selecciona, en cada ocurrencia, a partir del grupo que consta de hidrógeno, C_1- C_6alquilo, hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo y C_1- C_6alquilo sustituido por NR^8R^9;

R^{22} es hidrógeno; o

$CR^{21}R^{22}CR^{21}R^{22}$, tomado en combinación, forma un anillo cis o trans de ciclopropano;

Z es fenilo, piridilo, oxalilo, isoxalilo, tiazolilo, pirazolilo, tienilo, cada uno de los cuales es sustituido o no sustituido por 1, 2 o 3 sustituyentes, cada uno de los cuales se selecciona independientemente del grupo que consta de:
halógeno, hidróxilo, C_1- C_4alquilo, C_1- C_4alcoxilo, haloC_1- C_4alquilo, haloC_1- C_4alcoxilo, $NR^{23}R^{24}$, CO_2H, $C(O)NR^{23}R^{24}$, $CO_2(C_1$- C_4alquil), tetrazol, piperidinilo, piperazinilo, morfolino, y alquilo sustituido por C_1- C_4alcoxilo o $NR^{23}R^{24}$.

Aún otros compuestos preferidos de la fórmula (I), (Ia), (II) o (VII) o cualquier subfórmula de los mismos proporcionados en la presente incluyen los compuestos en los que q es 0 o 1;

R^{21} se selecciona del grupo que consta de hidrógeno, C_1- C_6alquilo, hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, aminoC_1- C_6alquilo, y mono- y di- C_1- C_4alquilaminoC_1- C_6alquilo;

R^{22} es hidrógeno; o

$CR^{21}R^{22}$, tomados en combinación, forman un anillo de ciclopropilo; y

Z es fenilo que es sustituido o no sustituido por 1, 2, o 3 sustituyentes, cada uno de los cuales se selecciona independientemente del grupo que consta de halógeno, hidróxilo, C_1- C_4alquilo, C_1- C_4alcoxilo, haloC_1- C_4alquilo, haloC_1- C_4alcoxilo, CO_2H, $C(O)NH_2$, $CO_2(C_1$- C_4alquilo), amino, y mono- y di- C_1- C_4alquilamino, en donde cada residuo N- alquilo es sustituido por 0 o 1 residuo seleccionado del grupo que consta de hidróxilo, C_1- C_4alcoxilo, amino, o mono- o di- C_1- C_2alquilamino.

Aún otros compuestos preferidos de la fórmula (I), (Ia), (II) o (VII) o cualquier subfórmula de los mismos proporcionados en la presente incluyen los compuestos en los que q es 0, 1 o 2;

R^{21} es hidrógeno;

R^{22} es hidrógeno, metilo, o etilo, tal metilo y etilo son sustituidos o no sustituidos por hidróxilo, metoxilo, amino, o mono- o di- metilo amino; o

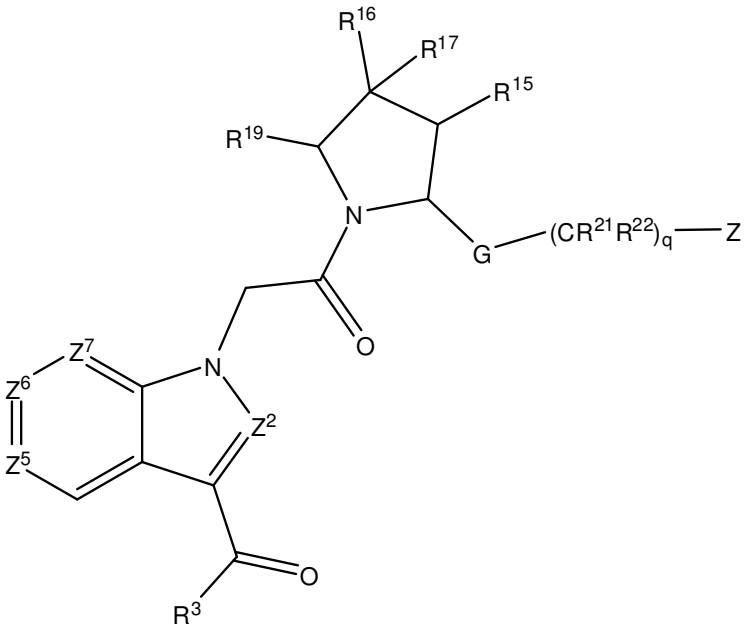
$CR^{21}R^{22}$, tomados en combinación, forman un anillo de ciclopropano;

cuando q es 2, $CR^{21}R^{22}CR^{21}R^{22}$, tomados en combinación forman un anillo cis- o trans de ciclopropano;

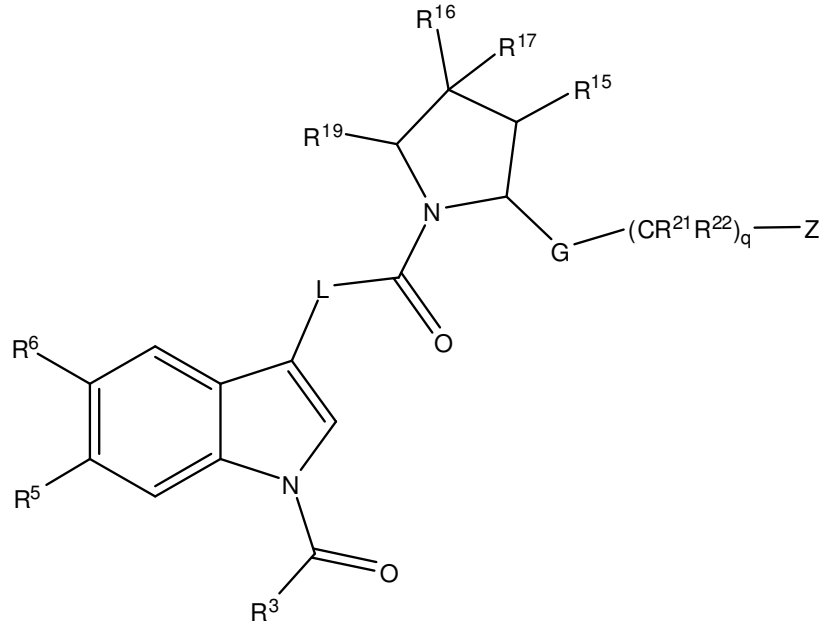
Z es fenilo que es sustituido o no sustituido por 1, 2, o 3 residuos seleccionados del grupo que consta de flúor, cloro, bromo, metilo, trifluorometilo, metoxilo, trifluorometoxilo, amino, mono- y di- C_1- C_2alquilamino, tetrazol o CO_2H; o

Z es piridilo o tienilo, cada uno de los cuales es sustituido o no sustituido por 1 o 2 sustituyentes seleccionados del grupo que consta de flúor, cloro, bromo, metilo, trifluorometilo, metoxilo, o trifluorometoxilo.

En otro aspecto, la invención proporciona los compuestos de la fórmula (I) o fórmula (II) en los cuales los compuestos se representan por las fórmulas (III), (IV) o (V):

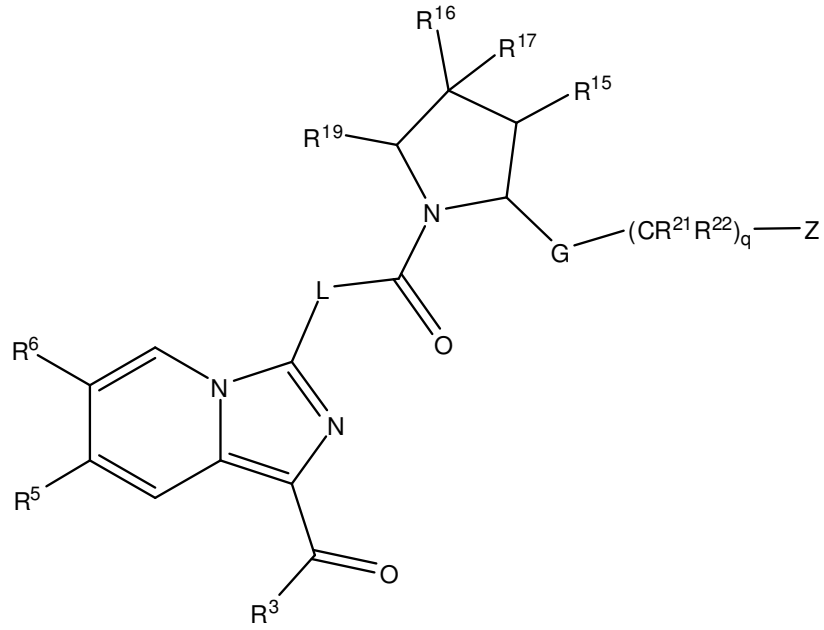


(III)



(IV)

o



(V)

en donde

Z^2 es CH o N;

Z^5 es CR^5 o N;

Z^6 es CR^6 o N;

Z^7 es CH o N, en donde 0, 1 o 2 de Z^5, Z^6 y Z^7 es N;

R^3 es hidrógeno, metilo, etilo, iPr, amino, hidroximetilo, CH2OMe, o mono- , di- y tri-fluorometilo, NHMe;

R^5 es hidrógeno, halógeno, C_1- C_4alquilo, C_1- C_4alcoxilo, C_2- C_4alquenilo, C_2- C_4alqueniloxilo, hidróxilo, CO_2H, tetrazol , C_1- C_4alcoxicarbonilo, ciano, en donde cada grupo alquilo o alcoxilo es sustituido o no sustituido por hasta 5 átomos de halógeno y por 0 o 1 sustituyentes adicionales seleccionados del grupo que consta de hidróxilo, tetrazol,C_1- C_4alcoxilo, CO_2H, C_1- C_4alcoxicarbonilo, fenilo opcionalmente sustituido, piridilo y pirimidinilo, y en donde el fenilo es sustituido o no sustituido por 1 o 2 sustituyentes independientemente seleccionados a partir de halógeno, hidróxilo, metilo, metoxilo y CO_2H;

R^6 es hidrógeno, halógeno, C_1- C_4alquilo, C_1- C_4alcoxilo, C_2- C_4alquenilo, C_2- C_4alqueniloxilo, hidróxilo, CO_2H, C_1- C_4alcoxicarbonilo, ciano, en donde cada grupo alquilo o alcoxilo es sustituido o no sustituido por hasta 5 átomos de halógeno y por 0 o 1 sustituyentes adicionales seleccionados del grupo que consta de hidróxilo, $NR^{10}R^{11}$, tetrazol, ciano, imidazolilo, C_1- C_4alcoxilo, CO_2H, C_1- C_4alcoxicarbonilo, fenilo opcionalmente sustituido, pirrolilo, morfolino, piperidino, piperazino, y piridilo, y en donde el fenilo es sustituido o no sustituido por 1 o 2 sustituyentes independientemente seleccionados a partir de halógeno, hidróxilo, metilo, metoxilo, mono- y dimetilo amino, y CO_2H;

L es CH_2 o NH ;

R^{15} es hidrógeno, flúor, metilo, hidróxilo, metoxilo, etoxilo y OCH_2CH_2OMe, $OCH_2CH_2N(CH_3)_2$, amino o OCH_2CH_2pirrolilo

R^{16} es hidrógeno, flúor, metilo, amino, hidroximetilo, metoximetilo, o aminometilo;

R^{17} es hidrógeno, flúor o metilo;

R^{19} es hidrógeno o R^{19} y R^{17}, tomados en combinación, forman un anillo de ciclopropilo; o

R^{15} y R^{16}, tomados en combinación, forman un anillo de ciclopropilo;

G es - C(O)N(H)- ; y

q es 0, 1, o 2;

R^{21} es hidrógeno, metilo, o etilo, dicho metilo y etilo son sustituidos o no sustituidos por hidróxilo, metoxilo, amino, mono- o di- metil- amino, morfolinometilo, azetidinometilo opcionalmente sustituido, tal anillo azetidino es sustituido por 0 o 1 flúor o metoxilo; o

R^{22} es hidrógeno;

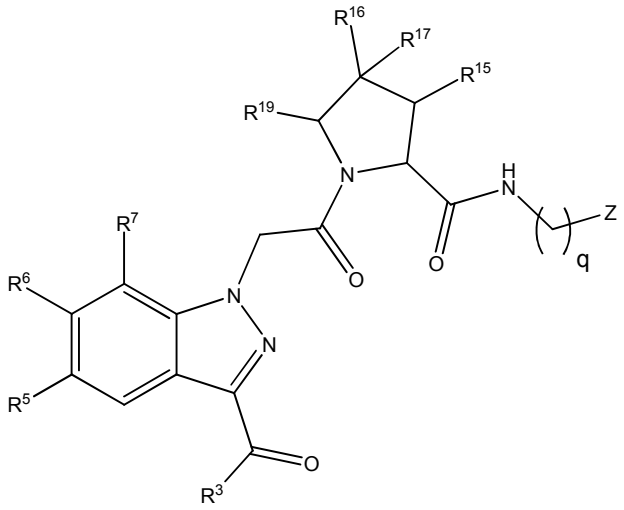
$CR^{21}R^{22}$, tomados en combinación, forman un anillo de ciclopropano; o

cuando q es 2, $CR^{21}R^{22}CR^{21}R^{22}$, tomados en combinación forman un anillo cis- o trans de ciclopropano;

Z es fenilo, piridilo, o tienilo, cada uno de los cuales es sustituido o no sustituido por 1, 2, o 3 residuos seleccionados independientemente en cada ocurrencia del grupo que consta de

halógeno, metilo, metoxilo, hidróxilo, triflúormetilo, triflúormetoxilo, CO_2H, tetrazol, y $NR^{23}R^{24}$.

Ciertos compuestos de la fórmula (III) proporcionados por la invención incluyen compuestos representados por la fórmula (IIIa):



(IIIa)

en donde

R^3 es hidrógeno, metilo, etilo, iPr, amino, hidroximetilo, CH2OMe, o mono- , di- y triflúormetilo, NHMe;

R^5 es hidrógeno, halógeno, C_1- C_4alquilo, C_1- C_4alcoxilo, C_2- C_4alquenilo, C_2- C_4alqueniloxilo, hidróxilo, CO_2H, tetrazol , C_1- C_4alcoxicarbonilo, ciano, en donde cada grupo alquilo o alcoxilo es sustituido o no sustituido con hasta 5 átomos de halógeno y por 0 o 1 sustituyentes adicionales seleccionados del grupo que consta de hidróxilo, tetrazol,C_1- C_4alcoxilo, CO_2H, C_1- C_4alcoxicarbonilo, fenilo opcionalmente sustituido, piridilo y pirimidinilo, y en donde el fenilo es sustituido o no sustituido por 1 o 2 sustituyentes independientemente seleccionados a partir de halógeno, hidróxilo, metilo, metoxilo y CO_2H;

R^6 es hidrógeno, halógeno, C_1- C_4alquilo, C_1- C_4alcoxilo, C_2- C_4alquenilo, C_2- C_4alqueniloxilo, hidróxilo, CO_2H, C_1- C_4alcoxicarbonilo, ciano, en donde cada grupo alquilo o alcoxilo es sustituido o no sustituido con hasta 5 átomos de halógeno y con 0 o 1 sustituyentes adicionales seleccionados del grupo que consta de hidróxilo, $NR^{10}R^{11}$, tetrazol, ciano, imidazolilo, C_1- C_4alcoxilo, CO_2H, C_1- C_4alcoxicarbonilo, fenilo opcionalmente sustituido, pirrolilo, morfolino, piperidino, piperazino, y piridilo, y en donde el fenilo es sustituido o no sustituido por 1 o 2 sustituyentes independientemente seleccionados a partir de halógeno, hidróxilo, metilo, metoxilo, mono- y dimetilo amino, y CO_2H;

R^7 es hidrógeno o metilo;

R^{15} es hidrógeno, flúor, metilo, hidróxilo, metoxilo, etoxilo y OCH_2CH_2OMe, $OCH_2CH_2N(CH_3)_2$, amino o OCH_2CH_2pirrolilo

R^{16} es hidrógeno, flúor, metilo, amino, hidroximetilo, metoximetilo, o aminometilo;

R^{17} es hidrógeno, flúor o metilo;

R^{19} es hidrógeno o R^{19} y R^{17}, tomados en combinación, forman un anillo de ciclopropilo; o

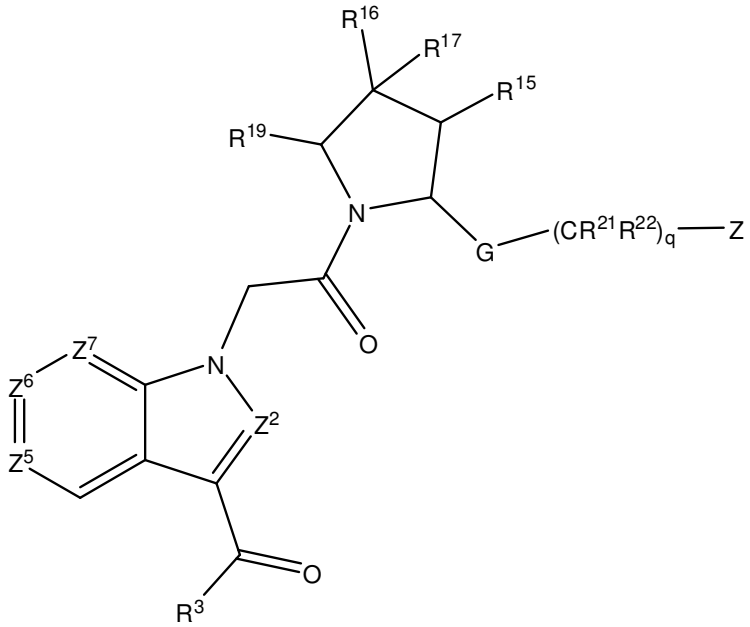
R^{15} y R^{16}, tomados en combinación, forman un anillo de ciclopropilo;

G es - C(O)N(H)- ; y

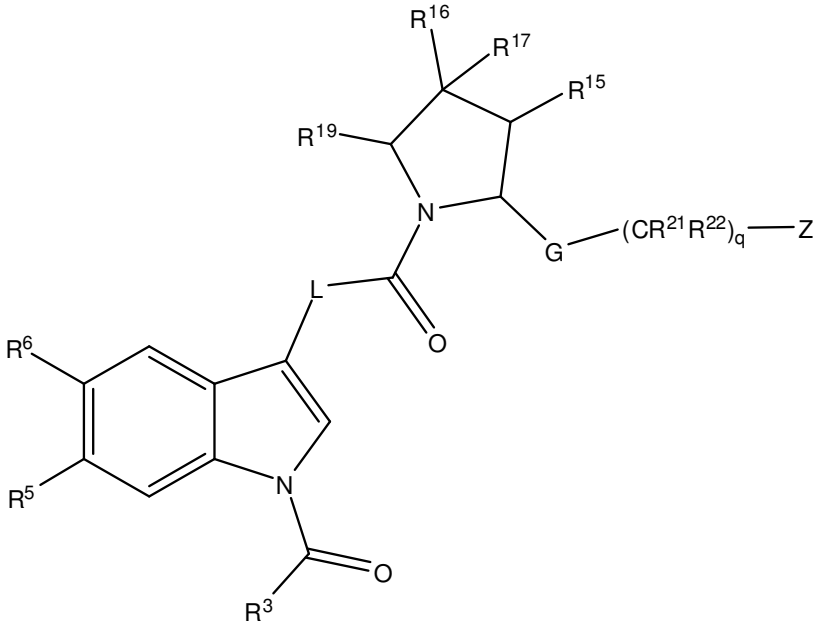
q es 0 o 1;

Z es piridilo, pirazinilo, o tienilo , cada uno de los cuales es sustituido o no sustituido por 1, 2, o 3 residuos seleccionados independientemente en cada ocurrencia del grupo que consta de halógeno, metilo, metoxilo, hidróxilo, trifluorometilo, trifluorometoxilo, CO_2H, tetrazol, y $NR^{23}R^{24}$.

En otra realización, los compuestos de la primera realización incluyen aquellos compuestos representados por una de las fórmulas (IIIb) o (IVb):



(IIIb)



(IVb)

en donde

Z^2 es CH o N;

Z^5 es CR^5 o N;

Z^6 es CR^6 o N;

Z^7 es CH, $C(CH_3)$ o N, en donde 0 o 1 o 2 de Z^5, Z^6 y Z^7 es N;

R^3 es hidrógeno, metilo, etilo, iPr, amino, hidroximetilo, CH2OMe, o mono- , di- y trifluorometilo, NHMe;

R^5 es hidrógeno, halógeno, C_1- C_4alquilo, C_1- C_4alcoxilo, C_2- C_4alquenilo, C_2- C_4alqueniloxilo, hidróxilo, CO_2H, tetrazol , C_1- C_4alcoxicarbonilo, ciano, en donde cada grupo alquilo o alcoxilo es sustituido o no sustituido con hasta 5 átomos de halógeno y con 0 o 1 sustituyentes adicionales seleccionados del grupo que consta de hidróxilo, ciano, tetrazol, C_1- C_4alcoxilo, CO_2H, C_1- C_4alcoxicarbonilo, tetrahidrofuranilo, fenilo opcionalmente sustituido, piridilo y pirimidinilo, y en donde el fenilo es sustituido o no sustituido por 1 o 2 sustituyentes independientemente seleccionados a partir de halógeno, hidróxilo, metilo, metoxilo y CO_2H;

R^6 es hidrógeno, halógeno, C_1- C_4alquilo, C_1- C_4alcoxilo, C_2- C_4alquenilo, C_2- C_4alqueniloxilo, hidróxilo, CO_2H, C_1- C_4alcoxicarbonilo, ciano, en donde cada grupo alquilo o alcoxilo es sustituido o no sustituido con hasta 5 átomos de halógeno y con 0 o 1 sustituyentes adicionales seleccionados del grupo que consta de hidróxilo, $NR^{10}R^{11}$, tetrazol, ciano, imidazolilo, C_1- C_4alcoxilo, CO_2H, C_1- C_4alcoxicarbonilo, fenilo opcionalmente sustituido, pirrolilo, morfolino, piperidino, piperazino, y piridilo, y en donde el fenilo es sustituido o no

sustituido por 1 o 2 sustituyentes independientemente seleccionados a partir de halógeno, hidróxilo, metilo, metoxilo, mono- y dimetilo amino, y CO_2H;

L es CH_2 o NH ;

R^{15} es hidrógeno, flúor, metilo, hidróxilo, metoxilo, etoxilo y OCH_2CH_2OMe, $OCH_2CH_2N(CH_3)_2$, amino o OCH_2CH_2pirrolilo

R^{16} es hidrógeno, flúor, metilo, amino, hidroximetilo, metoximetilo, o aminometilo;

R^{17} es hidrógeno, flúor o metilo;

R^{19} es hidrógeno o R^{19} y R^{17}, tomados en combinación, forman un anillo de ciclopropilo; o

R^{15} y R^{16}, tomados en combinación, forman un anillo de ciclopropilo;

G es - C(O)N(H)- ; y

q es 0 o 1;

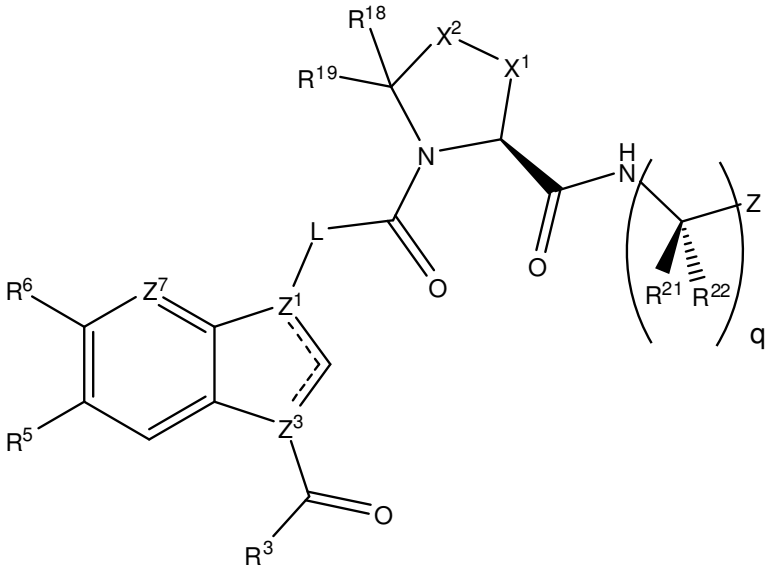
R^{21} es hidrógeno, metilo, o etilo, tal metilo y etilo son sustituidos o no sustituidos por hidróxilo, metoxilo, ciano, amino, mono- o di- metilamino, morfolinometilo, azetidinometilo opcionalmente sustituido, tal anillo de azetidino es sustituido por 0 o 1 flúor o metoxilo; o

R^{22} es hidrógeno;

$CR^{21}R^{22}$, tomados en combinación, forman un anillo de ciclopropano;

Z es fenilo, piridilo, pirazinilo o tienilo, cada uno de los cuales es sustituido o no sustituido por 1, 2, o 3 residuos seleccionados independientemente en cada ocurrencia del grupo que consta de halógeno, metilo, ciclopropilo, metoxilo, hidróxilo, trifluorometilo, trifluorometoxilo, SF_5, CO_2H, tetrazol, y $NR^{23}R^{24}$, fenilo sustituido o no sustituido y piridinilo sustituido o no sustituido, dicho fenilo y piridinilo sustituidos tiene 1 o 2 sustituyentes independientemente seleccionados del grupo que consta de halógeno y metilo.

Ciertos compuestos, o sales de los mismos, proporcionados por la fórmula (I) o fórmula (II) incluyen aquellos compuestos que son representados por la fórmula (VI):



(VI)

en donde

q es 0, 1 o 2;

R^{21} es hidrógeno;

R^{22} es hidrógeno, metilo, o etilo, tal metilo y etilo son sustituidos o no sustituidos por hidróxilo, metoxilo, amino, o mono- o di- metilamino; o

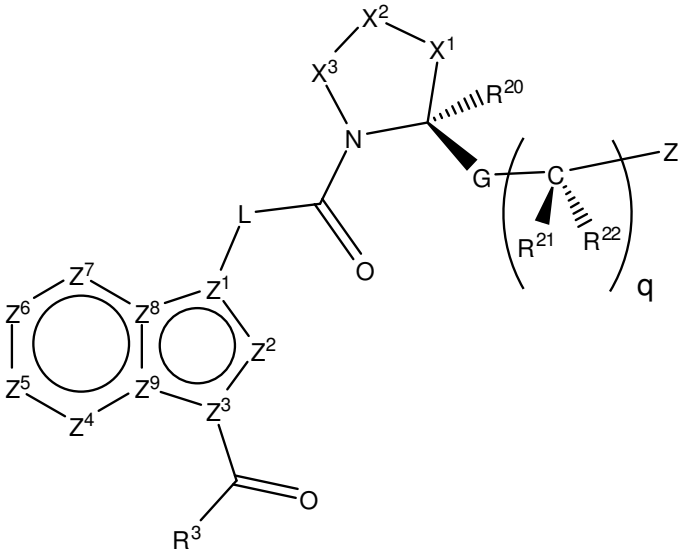
$CR^{21}R^{22}$, tomados en combinación, forman un anillo de ciclopropano;

cuando q es 2, $CR^{21}R^{22}CR^{21}R^{22}$, tomados en combinación forman un anillo cis- o trans de ciclopropano;

Z es fenilo que es sustituido o no sustituido por 1, 2, o 3 residuos seleccionados del grupo que consta de flúor, cloro, bromo, metilo, triflúormetilo, metoxilo, triflúormetoxilo, $NR^{23}R^{24}$, tetrazol o CO_2H; o

Z es piridilo o tienilo, cada uno de los cuales es sustituido o no sustituido por 1 o 2 sustituyentes seleccionados del grupo que consta de flúor, cloro, bromo, metilo, triflúormetilo, metoxilo, o trifluorometoxilo.

En ciertos aspectos, el compuesto de la fórmula (I) se representa por la estructura de la fórmula (VI):



(VI).

En otra realización, compuestos individuales según la invención son aquellos enumerados en la sección de Ejemplos a continuación. En ciertos aspectos el compuesto se selecciona del grupo que consta de:

1- [(1- carbamoil- 1H- indol- 3- il)- amida]2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

2- bencilamida 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1 - [(1 - carbamoil- 1H- indol- 3- il)- amida]- 2- [(piridin- 3- ilmetil)- amida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1 - [(1 - carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- 5- {[(2- metoxi- etil)- metil- amino]- metil}- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1 - [(1 - carbamoil- 1H- indol- 3- il)- amida]- 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida} del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1 - [(1 - carbamoil- 1H- indol- 3- il)- amida]- 2- [(piridin- 4- ilmetil)- amida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1 - [(1 - carbamoil- 1H- indol- 3- il)- amida]- 2- [3- cloro- 2- fluoro- 5- (4- metil- piperazin- 1- il)- bencilamida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1 - [(1 - carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- hidroxi- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [3- cloro- 2- fluoro- 5- (4- metil- piperazin- 1- ilmetil)- bencilamida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(5- cloro- tiofen- 2- ilmetil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 5- dietilamino- metil- 2- fluoro- bencil- amida) del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [((S)- 2- hidroxi- 1- fenil- etil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (2,3- difluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

ester terc- butilo del ácido (2S,3S)- 2- {[(2S,4R)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- 3- metil- pentanoico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [3- cloro- 2- fluoro- 5- (4- metoxi- piperidin- 1- il)- bencilamida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 5- {[(2- dimetilamino- etil)- metil- amino]- metil}- 2- fluoro- bencilamida del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- 5- morfolin- 4- ilmetil- bencilamida) del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- 5- morfolin- 4- il- bencilamida) del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [3- cloro- 2- fluoro- 5- (4- metoxi- piperidin- 1- ilrnetil)- bencilamida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {3- cloro- 2- fluoro- 5- [(2- metoxi- etil)- metil- arnino]- bencilamida} del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {3- cloro- 5- [(2- dimetilamino- etilamino)- metil]- 2- fluoro- bencilamida} del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

Ácido 2- ({[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- metil)- benzoico;

Ácido 2- ({[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 3- carbonil]- amino}- metil)- benzoico;

Ácido (2S,3S)- 2- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- 3- metil- pentanoico;

1- [(1- carbamoil- 1- H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1- H- indol- 3- il)- amida]- 2- fenilamida del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

2- bencilamida 1- [(1- carbamoil- 1- H- indol- 3- il)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico como una sal formiato;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- metil- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- trifluorometil- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- fluoro- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- ciano- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

2- (3- bromo- bencilamida)- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- hidroxi- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

(2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico acid 1- [(1- carbamoil- 1H- indol- 3- il)- amida]

2- (3- metoxi- bencilamida);

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- trifluorometoxi- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- fenoxi- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

2- [(bifenil- 3- ilmetil)- amida]- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico como una sal de formiato;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- pirrol- 1- il- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [3- (5- cloro- tiofen- 2- il)- bencilamida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(5'- cloro- [2,2']bitiofenil- 5- ilmetil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (4- metil- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (4- cloro- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (4- trifluorometil- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (4- trifluorometoxi- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico.

2- (4- hidroxi- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (2- hidroxi- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (2- fluoro- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxilico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (2- cloro- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

2- [(bifenil- 2- ilmetil)- amida]- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (2,3- difluoro- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (5- cloro- 2- metoxi- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1- H- indol- 3- il)- amida]- 2- (3- cloro- 4- metoxi- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (5- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 4- fluoro- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- metil- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (5- cloro- 2- metil- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 4- metil- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3,5- dicloro- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3,4- dicloro- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2,6- difluoro- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(naftalen- 2- ilmetil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(naftalen- 1- ilmetil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(5- metil- tiazol- 2- ilmetil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(5- cloro- tiofen- 2- ilmetil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(4- metil- piridin- 2- ilmetil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {[(S)- 1- (3- cloro- fenil)- etil]- amida} del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico como una sal formiato;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {[(R)- 1- (3- cloro- fenil)- etil]- amida}del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico como una sal formiato;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {[1- (3,5- dicloro- fenil)- 2- hidroxi- etil]- amida} del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {[1- (3- cloro- fenil)- 3- hidroxi- propil]- amida} del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(1- fenil- ciclopropil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

2- benzhydril- amida 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico como una sal de formiato;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- ciclohexilmetil- amida del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [((1R,2S)- 2- hidroxi- ciclohexilmetil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [((1S,2S)- 2- hidroxi- ciclohexilmetil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- ciclohexilamida del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3,4,5,6- tetrahydro- 2H- [1,2']bipiridinil- 3- il)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(6- cloro- indan- 1- il)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(6- cloro- croman- 4- il)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (fenetil- amida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(2- hidroxi- 2- fenil- etil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [((1R,2S)- 2- fenil- ciclopropil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [((R)- 2- fenil- propil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [((S)- 2- fenil- propil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {[2- (3- cloro- fenil)- etil]- amida} del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1Hindol- 3- il)- amida]- 2- {[2- (2- cloro- fenil)- etil]- amida} del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1Hindol- 3- il)- amida]- 2- {[2- (2- fluoro- fenil)- etil]- amida} del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1Hindol- 3- il)- amida]- 2- {[2- (3- fluoro- fenil)- etil]- amida} del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {[2- (3- cloro- 5- fluoro- fenil)- etil]- amida} del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(2- fenoxi- etil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

Ester metilo del ácido (2S,3S)- 2- {[(2S,4S)- 4- amino- 1- (1- carbarnoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- 3- metil- pentanoico;

Ester metilo del ácido (S)- 2- {[(2S,4S)- 4- Amino- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- pentanoico;

Ester metilo del ácido (R)- 2- {[(2S,4S)- 4- amino- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- 3- metil- butírico;

Ester metilo del ácido (S)- 2- {[(2S,4S)- 4- amino- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- 4- metil- pentanoico;

Ester metilo del ácido (S)- 2- {[(2S,4S)- 4- Amino- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- 3- terc- butoxi- propionico;

Ester metilo del ácido (S)- 2- {[(2S,4S)- 4- amino- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- 3- fenil- propionico;

Ester metilo del ácido (S)- {[(2S,4S)- 4- amino- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- fenil- acético;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [((1S,2S)- 1- carbamoil- 2- metil- butil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- etil- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [((1S,2S)- 1- hidroximetil- 2- metil- butil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- isopropil- fenil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

2- bifenil- 3- ilamida- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

Amida del ácido 3- {[(2S,4R)- 2- (bencenosulfonilamino- metil)- 4- fluoro- pirrolidina- 1- carbonil]- amino}- indol- 1- carboxílico;

Amida del ácdio 3- ({(2S,4R)- 4- fluoro- 2- [(3- fluoro- bencenosulfonilamino)- metil]- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico;

Amida del ácido 3- ({(2S,4R)- 4- fluoro- 2- [(3- cloro- bencenosulfonilamino)- metil]- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico;

Amida del ácido 3- ({(2S,4R)- 4- fluoro- 2- [(3- bromo- bencenosulfonilamino)- metil]- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico;

Amida del ácido 3- ({(2S,4R)- 4- fluoro- 2- [(3- trifluorometoxi- bencenosulfonilamino)- metil]- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico;

Amida del ácido 3- ({(2S,4R)- 2- [(3- cloro- 2- fluoro- bencenosulfonilamino)- metil]- 4- fluoro- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico;

Amida del ácido 3- ({(2S,4R)- 2- [(5- cloro- tiofeno- 2- sulfonilamino)- metil]- 4- fluoro- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico;

Amida del ácido 3- ({(S)- 2- [(3- Cloro- bencenosulfonilamino)- metil]- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico;

Amida del ácido 3- {[(2S,4R)- 4- fluoro- 2- (fenilacetilamino- metil)- pirrolidina- 1- carbonil]- amino}- indol- 1- carboxílico;

Ester fenilo del ácido [(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidin- 2- ilmetil]- carbámico;

Ester 3- cloro- 2- fluoro- fenilo del ácido [(1R,3S,5R)- 2- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 3- ilmetil]- carbámico;

Amida del ácido 3- ({(2S,4R)- 2- [(3- cloro- 2- fluoro- bencilamino)- metil]- 4- fluoro- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico;

Amida del ácido 3- ({(S)- 2- [(3- trifluorometoxi- fenilamino)- metil]- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico;

Amida del ácido 1- {2- oxo- 2- [(S)- 2- (3- trifluorometoxi- 3- carboxílico;

(3- trifluorometoxi- fenil)- amida del ácido (S)- 1- [2- (1- acetil- 1H- indol- 3- il)- acetil]- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (1- acetil- 1H- indol- 3- il)- 2- amino- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;

1- [(3- carbamoil- indolizin- 1- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico;

1- [(3- carbamoil- indolizin- 1- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- indolizin- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- ciano- pirrolidina- 1,2 dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R)- 3- metil- pirrolidina- 1,2- dicarboxílico;

Ester terc- butilo del ácido (1- carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 6- il)- acético;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- Metoxi- pirrolidina- 1,2- dicarboxílico;

2- [(1- acetil- 1H- indol- 3- il)- amida]- 3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2hidroxi- etil]- amida} del ácido (1R,3S,5R)- 2- azabiciclo[3.1.0]hexano- 2,3- dicarboxílico;

3- (3- cloro- 2- fluoro- bencilamida) 2- [(1- metilcarbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- azabiciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- hidroxi- pirrolidina- 1,2- dicarboxílico;

1- {[1- carbamoil- 5- (2- metoxi- etoxi)- 1H- indol- 3- il]- amida} 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- 4- metil- pirrolidina- 1,2- dicarboxílico;

Ester metilo del ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- iloxi)- acético;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- [(3- trifluorometoxi- fenil)- amida] del ácido (1S,3S,5S)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (1S,2S,5R)- 3- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- (3- cloro- 2- fluoro- bencilamida) del ácido 2- aza- biciclo[2.1.1]hexano- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- metil- pirrolidina- 1,2- dicarboxílico;

2- (3- bromo- 2- fluoro- bencilamida)- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,5R)- 5- (acetilamino- metil)- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (R)- Pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (1S,2S,5R)- 3- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(2- fluoro- trifluorometoxi- fenil)- amida] del ácido (S)- tiazolidina- 2,3- dicarboxílico;

Ester metilo del ácido 3- cloro- 5- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- benzoico;

Ácido 3- ({[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- metil)- 5- cloro- 4- fluoro- benzoico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- 2,5- Dihidro- pirrola- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,2S,5S)- 6- oxa- 3- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- trifluorometil- pirrolidina- 1,2- dicarboxílico;

3- [(3- bromo- fenil)- amida]- 2- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1 R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 1- (3- cloro- 2- fluoro- bencilamida) del ácido (1S,5R)- 2- aza- biciclo[3.1.0]hexano- 1,2- dicarboxílico;

2- [(3- bromo- fenil)- amida] 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 4- [(3- trifluorometoxi- fenil)- amida] del ácido (R)- 2,2- dimetil- tiazolidina- 3,4- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(4'- ciano- bifenil- 3- il)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico;

Ester metilo del ácido 3- Bromo- 5- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- benzoico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [3- cloro- 5- (2- dimetilamino- etilcarba- moil)- 2- fluoro- bencilamida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- [(5- cloro- tiofen- 2- ilmetil)- amida] del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

Ester metilo del ácido bromo- 4- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- benzoico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- metil- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(6- etil- piridin- 2- il)- amida] del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

Ácido bromo- 5- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- benzoico;

2- [(4- tert- butil- tiazol- 2- il)- amida]- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 4- [(3- trifluorometoxi- fenil)- amida] del ácido (R)- tiazolidina- 3,4- dicarboxílico;

2- {[1- carbamoil- 5- (2- metoxi- etoxi)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(6- etil- piridin- 2- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- hidroxi- 4- metil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- bromo- 4- metil- piridin- 3- il)- amida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

(1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico acid 2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida);

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (1R,2S,5S)- 3- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- [(5- bromo- 2- metil- piridin- 3- il)- amida] 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (2,3- difluoro- bencilamida) del ácido (S)- tiazolidina- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- [(5- bromo- piridin- 3- il)- amida] del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- [(3- fluoro- piridin- 2- il)- amida] del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- (2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- azabiciclo[3.1.0]hexano- 2,3- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (S)- tiazolidina- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- [(2- fluoro- 3- trifluorometoxi- fenil)- amida] del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- [(3- cloro- 2- fluoro- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (2S,3R)- 3- Hidroxi- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- tiazolidina- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,5R)- 5- azidometil- pirrolidina- 1,2- dicarboxílico;

5- [(1- carbamoil- 1H- indol- 3- il)- amida]- 6- (3- cloro- bencilamida) del ácido (S)- 5- aza- espiro[2.4]heptano- 5,6- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- fluoro- 4- hidroximetil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- metil- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- (3- cloro- bencilamida) del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5S)- 5- metoximetil- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- [(3- fluoro- piridin- 4- il)- amida] del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R)- 3- metoxi- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Piperidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(2- fluoro- 3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- ciano- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2R,3S,4R)- 4- dimetilamino- 3- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2R,3R)- 3- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- 2- metil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(5- cloro- piridin- 3- il)- amida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(5- bromo- piridin- 3- il)- amida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 23- (2,3- difluoro- bencilamida) del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Hidroxi- 4- hidroximetil- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (1S,2S,5R)- 6- Oxa- 3- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

Éster metilo del ácido 3- Bromo- 5- {[(S)- 3- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- tiazolidina- 2- carbonil]- amino}- benzoico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(2- metil- 5- fenil- 2H- pirazol- 3- il)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

Éster metilo del ácido (3S,5S)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- 5- (3- cloro- 2- fluoro- bencilcarbamoil)- pirrolidina- 3- carboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 5- (3- cloro- 2- fluoro- bencilamida) del ácido 4,5- Dihidro- pirazol- 1,5- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Hidroxi- 4- hidroximetil- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi-etil]- amida} del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3S,4S)- 4- Fluoro- 3- metoxi- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- 4- metil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3S,4S)- 3- Acetilamino- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi-etil]- amida} del ácido (1S,2S,5R)- 3- Azabiciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2R,3S)- 3- Fluoro- pirrolidina- 1,2- dicarboxílico;

H(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- 4- morfolin- 4- ilmetil- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,2S,5S)- 3- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2R,3S,4R)- 4- Acetilamino- 3- fluoro- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida} del ácido (1R,2S,5S)- 3- Azabiciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R)- 3- Hidroxi- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1S,3S,5R)- 5- Metoximetil- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- fluoro- piridin- 3- ilmetil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 6- metoxi- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

3- {[(S)- 1- (3- bromo- fenil)- 2- hidroxi- etil]- amida} 2- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- Azabiciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(2- fluoro- 3- trifluorometil- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

Éster metilo del ácido 3- {[(S)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- benzoico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- Piperidina- 1,2- dicarboxílico;

carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- (Acetilamino- metil)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (2- fluoro- 3- trifluorometil- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- {[(R)- 1- (3- cloro- 2- fluoro- fenil)- 3- hidroxi- propil]- amida} del ácido (1R,3S,5R)- 2- Azabiciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (2,3- difluoro- 4- metoxi- bencilamida) del ácido (S)- Tiazolidina- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)amida] 3- [(piridin- 3- ilmetil)- amida] del ácido (1R,3S,5R)- 2Azabiciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,3S)- 3- Metil- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(5- cloro- piridin- 3- ilmetil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(R)- 1- (3- cloro- 2- fluoro- fenil)- 3- hidroxi- propil]- amida} del ácido (2S,4R)- 4- Fluoro- 4- metil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- fluoro- piridin- 4- ilmetil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etil]- amida} del ácido (1R,2S,5S)- 3- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- fluoro- 2- trifluorometil- piridin- 4- ilmetil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- sulfamoil- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(3- difluorometoxi- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (2,3- difluoro- 5- metoxi- bencilamida) del ácido (S)- Tiazolidina- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etil]- amida} del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- cloro- piridin- 3- ilmetil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(6- etil- piridin- 2- il)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida} del ácido (2S,4R)- 4- Fluoro- 4- metil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- 5- metilcarbamoil- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Fluoro- 4- fluorometil- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(3- fluoro- piridin- 2- ilmetil)- amida] del ácido 1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

H(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Fluoro- 4- morfolin- 4- ilmetil- pirrolidina- 1,2- dicarboxílico;

Éster metilo del ácido 3- ({[(2S,4R)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- metil)- 5- cloro- 4- fluoro- benzoico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etil]- amida} del ácido (1S,2S,5R)- 3- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

Ácido {[(2S,4R)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- (3- cloro- fenil)- acético;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(5- cloro- piridin- 3- il)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- dimetilamino- etil]- amida} del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- Hidroxi- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [3- cloro- 2- fluoro- 5- (morfolina- 4- carbonil)- bencilamida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(3- metoxi- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 5- dietilamino- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida} del ácido (S)- Tiazolidina- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(3- cloro- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [3- cloro- 2- fluoro- 5- (3- metoxi- Azetidina- 1- carbonil)- bencilamida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- Ciano- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (2S,3S)- 3- Hidroxi- pirrolidina- 1,2- dicarboxílico;

3- bencilamida 2- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- cloro- tiofen- 2- ilmetil)- amida] del ácido (2S,3R)- 3- Hidroxi- pirrolidina- 1,2- dicarboxílico;

1- [(1- acetil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Hidroximetil- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- (2- fluoro- 3- trifluorometil- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (2,3- difluoro- 6- metoxi- bencilamida) del ácido (S)- Tiazolidina- 2,3- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(2- cloro- tiazol- 5- ilmetil)- amida] del ácido (S)- Tiazolidina- 2,3- dicarboxílico;

3- [(1- carbamoil- 5- fluoro- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- Tiazolidina- 2,3- dicarboxílico;

3- (3- cloro- 2- fluoro- bencilamida) 2- [(1- metilcarbamoil- 1H- indol- 3- il)- amida] del ácido (1 R,3S,5S)- 5- Hidroximetil- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- 4- Metileno- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Tiazolidina- 2,3- dicarboxílico;

2- [(5- alliloxi- 1- carbamoil- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 6- metil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etil]- amida} 2- [(1- metilcarbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- acetil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

Éster metilo del ácido 3- Bromo- 5- {[(1R,3S,5R)- 2- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 3- carbonil]- amino}- benzoico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida del ácido (2S,5R)- 5- Fenil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(2- fluoro- 3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

2- [(1- acetil- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5S)- 5- Hidroximetil- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

Éster metilo del ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- trifluorometoxi- fenilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 6- iloxi)- acético;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 5- dimetilcarbamoil- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

Ácido 2- Bromo- 4- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- benzoico;

2- [(5- tert- butil- 2- metil- 2H- pirazol- 3- il)- amida] 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

1- [(6- alliloxi- 1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

2- [(1- acetil- 1H- indol- 3- il)- amida] 3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- dimetilamino- etil]- amida} del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- metilcarbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(2- cloro- tiazol- 5- ilmetil)- amida] del ácido (2S,3R)- 3- Hidroxi- pirrolidina- 1,2- dicarboxílico;

3- (3- cloro- 2- fluoro- bencilamida) 2- [(1- metilcarbamoil- 1H- indol- 3- il)- amida] del ácido (1 R,3S,5S)- 5- Metoximetil- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(3- isopropil- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(6- bromo- 1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida}2- [(1- metilcarbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- Azabiciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 6- etil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- dimetilamino- etil]- amida} 2- [(1- metilcarbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 6- trifluorometil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 6- cloro- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 5- metoxi- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- cloro- tiofen- 2- ilmetil)- amida] del ácido (S)- Tiazolidina- 2,3- dicarboxílico;

2- [(1- carbamoil- 5- fluoro- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(2- cloro- tiazol- 5- ilmetil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- fenil)- 2,2,2- trifluoro- etil]- amida} del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 6- fluoro- 1H- indol- 3- il)- amida] 3- [(3- trifluorometoxi- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 5- metoxi- 1H- indol- 3- il)- amida] 2- [(2- fluoro- 3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Azetidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 5- metoxi- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- 4,4- Difluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- 5,5- Dimetil- pirrolidina- 1,2- dicarboxílico;

1- {[1- carbamoil- 5- (2- metoxi- etoxi)- 1H- indol- 3- il]- amida} 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- fluoro- 4- metil- piridin- 2- ilmetil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- trifluorometil- piridin- 3- ilmetil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

Éster etílico del ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- il)- acético;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 1- [(3- trifluorometoxi- fenil)- amida] del ácido (1S,5R)- 2- Aza- biciclo[3.1.0]hexano- 1,2- dicarboxílico;

1- [(1- carbamoil- 6- difluorometoxi- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(2- metoxi- piridin- 4- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- cloro- piridin- 3- il)- amida] del ácido (S)- Tiazolidina- 2,3- dicarboxílico;

2- [(6- alliloxi- 1- carbamoil- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Hidroximetil- pirrolidina- 1,2- dicarboxílico;

1- [(6- benciloxi- 1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- dimetilamino- etil]- amida} del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

Éster etílico del ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 6- il)- acético;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- Metoxi- pirrolidina- 1,2- dicarboxílico;

2- [(2- tert- butil- piridin- 4- il)- amida] 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

Éster metilo del ácido (1- Carbamoil- 3- {[(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil- pirrolidina- 1- carbonil]- amino}- 1H- indol- 5- iloxi)- acético;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(R)- 1- (3- cloro- fenil)- 2,2,2- trifluoro- etil]- amida} del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- {[(S)- 1- (3- cloro- fenil)- 2- hidroxi- etil]- amida} del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- bromo- piridin- 3- il)- amida] del ácido (S)- Tiazolidina- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [3- cloro- 2- fluoro- 5- (4- metil- piperazina- 1- carbonil)- bencilamida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- fluoro- piridin- 4- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- carbamoil- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- metanosulfonil- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(6- cloro- croman- 4- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico (mezcla de 2 diastereoisómeros);

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- fluoro- piridin- 2- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

H(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Dimetilaminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {3- cloro- 5- [(2- dimetilamino- etil)- metil- amino]- 2- fluoro- bencilamida} del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

3- [(3- tert- butil- fenil)- amida] 2- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1 R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Hidroxi- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- 4,4- Difluoro- pirrolidina- 1,2- dicarboxílico;

Éster etílico del ácido 3- Bromo- 5- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- 4- fluoro- benzoico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(3- trifluorometoxi- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(5- alliloxi- 1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,5R)- 5- Metil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,5S)- 5- Metil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluoromtoxi- fenil)- amida] del ácido (2S,5R)- 5- Etil- pirrolidina- 1,2- dicarboxílico;

Ácido 3- Cloro- 5- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- benzoico;

Ácido 3- Bromo- 5- {[(1R,3S,5R)- 2- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 3- carbonil]- amino}- benzoico;

Ácido 3- Bromo- 5- {[(S)- 3- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- tiazolidina- 2- carbonil]- amino}- benzoico;

Ácido 3- Bromo- 5- {[(1R,3S,5R)- 2- (1- carbamoil- 5- metoxi- 1H- indol- 3- ilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 3- carbonil]- amino}- benzoico;

Ácido 3- Bromo- 5- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- 4- fluoro- benzoico;

3- {[3- bromo- 5- (1H- tetrazol- 5- il)- fenil]- amida} 2- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1 R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

3- {[3- bromo- 5- (1- tert- butil- 1H- tetrazol- 5- il)- fenil]- amida} 2- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [3- cloro- 2- fluoro- 5- (1H- tetrazol- 5- il)- bencilamida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

2- [5- (1 - tert- butil- 1H- tetrazol- 5- il)- 3- cloro- 2- fluoro- bencilamida] 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (2R,3S)- 3- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (2R,3R)- 3- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,5R)- 5- Metil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,5R)- 5- Etil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Hidroximetil- pirrolidina- 1,2- dicarboxílico;

Éster metilo del ácido (3S,5S)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- 5- (3- cloro- 2,6- difluoro- bencilcarbamoil)- pirrolidina- 3- carboxílico;

Ácido (3S,5S)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- 5- (3- cloro- 2,6- difluoro- bencilcarbamoil)- pirrolidina- 3- carboxílico;

2- (3- bromo- 2- fluoro- bencilamida)1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- Hidroximetil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Fluoro- 4- hidroximetil- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1S,3S,5R)- 5- Hidroximetil- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5S)- 5- Hidroximetil- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Difluorometil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,5R)- 5- Hidroximetil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]5- (3- cloro- bencilamida) del ácido 4,5- Dihidro- pirazol- 1,5- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]5- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- 4,5- Dihidro- pirazol- 1,5- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]5- (3- cloro- 2- fluoro- bencilamida) del ácido (R)- 4,5- Dihidro- pirazol- 1,5- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {[(R)- 1- (3- cloro- 2- fluoro- fenil)- etil]- amida} del ácido (2S,3R)- 3- Hidroxi- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- etil]- amida} del ácido (2S,3R)- 3- Hidroxi- pirrolidina- 1,2- dicarboxílico;

1- {[1- (2- hidroxi- acetil)- 1H- indol- 3- il]- amida}- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

1- [(1- acetil- 6- ciano- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

1- [(1- acetil- 6- difluorometoxi- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 6- hidroxi- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 5- hidroxi- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;
2- [(1- carbamoil- 5- hidroxi- 1H- indol- 3- il)- amida]- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
2- [(1- carbamoil- 5- hidroxi- 1H- indol- 3- il)- amida]- 3- (2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
2- [(1- carbamoil- 5- cianometoxi- 1H- indol- 3- il)- amida]- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
Ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- iloxi)- acético;
Ácido (1- Carbamoil- 3- {[(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil- pirrolidina- 1- carbonil]- amino}- 1H- indol- 5- iloxi)- acético;
Ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 6- iloxi)- acético;
Ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- il)- acético;
Ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 6- il)- acético;
2- {[1- carbamoil- 5- (2- hidroxi- etoxi)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
3- {[1- carbamoil- 5- (2- hidroxi- etoxi)- 1H- indol- 3- il]- amida}- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- Tiazolidina- 2,3- dicarboxílico;
2- {[1- carbamoil- 5- (2- hidroxi- etoxi)- 1H- indol- 3- il]- amida}- 3- [(3- trifluorometoxi- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
3- {[1- carbamoil- 5- (2- hidroxi- etoxi)- 1H- indol- 3- il]- amida} 2- (3- cloro- 2- fluoro- bencilamida) del ácido (1S,2S,5R)- 3- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
1- {[1- carbamoil- 5- (2- hidroxi- etoxi)- 1H- indol- 3- il]- amida}- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- 4- metil- pirrolidina- 1,2- dicarboxílico;
2- {[1- carbamoil- 6- (2- hidroxi- etil)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- {[1- carbamoil- 5- (2- hidroxi- etil)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
2- {[1- carbamoil- 5- (2- hidroxi- 2- metil- propoxi)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
2- {[1- carbamoil- 5- (2- dimetilamino- etoxi)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- {[1- carbamoil- 5- (2- pirrolidin- 1- il- etoxi)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
2- {[1- carbamoil- 5- (2- imidazol- 1- il- etoxi)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
Ester terc- butilo del ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- iloxi)- acético;
Ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- iloxi)- acético;
2- [(1- carbamoil- 6- hidroxi- 1H- indol- 3- il)- amida]- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
1- [(1- carbamoil- 6- hidroxi- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;
Ester metilo del ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 6- iloxi)- acético;
2- {[1- carbamoil- 6- (2- hidroxi- etoxi)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3S,4R)- 4- Amino- 3- metoxi- pirrolidina- 1,2- dicarboxílico;
1- [(6- benciloxi- 1- carbamoil- 1H- indol- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido
(2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (S)- Piperazina- 1,2- dicarboxílico;
2- [(4'- aminometil- bifenil- 3- il)- amida]- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;
2- [(4'- aminometil- 2'- fluoro- bifenil- 3- il)- amida]- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,5R)- 5- Aminometil- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- Aminometil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- Aminometil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Aminometil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Dimetilaminometil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Aminometil- 4- hidroxi- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Fluoro- 4- formilaminometil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2,6- difluoro- bencilamida) del ácido (2S,4S)- 4- Aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- acetil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

2- {[(S)- 1- (3- bromo- fenil)- 2- fluoro- etil]- amida}- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- Aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- Aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- acetil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3S,4S)- 3- Amino- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R,4S)- 4- Amino- 3- hidroxi- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R)- 3- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- acetil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R)- 3- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2,2,2- trifluoro- etil]- amida} del ácido (2S,3R)- 3- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3S)- 3- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (2S,3S)- 3- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R)- 3- Acetilamino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R)- 3- (2- Metoxi- etilamino)- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Fluoro- 4- metilaminometil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Metilamino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- (2- Metoxi- etilamino)- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Dimetilamino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- 4,4- Dimetoxi- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3S,4R)- 4- Amino- 3- hidroxi- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2R,3S,4R)- 4- Amino- 3- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluorobencilamida) del ácido (2S,3S,4S)- 3- Amino- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

Amida del ácido 3- {2- [(S)- 5- (3- Cloro- 2- fluoro- bencilcarbamoil)- pirazolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico;

Amida del ácido 3- {2- [(R)- 5- (3- Cloro- 2- fluoro- bencilcarbamoil)- pirazolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]5- (3- cloro- bencilamida) del ácido Pirazolidina- 1,5- dicarboxílico;

Ester metilo del ácido (3S,5S)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- 5- (2- fluoro- 3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 3- carboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2,6- difluoro- bencilamida) del ácido (2S,4S)- 4- Hidroximetil- pirrolidina- 1,2- dicarboxílico;

2- [(3- bromo- 5- carbamoil- fenil)- amida] 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [3- cloro- 2- fluoro- 5- (2- metoxi- etilcarbamoil)- bencilamida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- isopropil- isoxazol- 5- il)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- fenil- isoxazol- 5- il)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;
Amida del ácido 3- {2- [(S)- 2- (3- trifluorometoxi- fenilcarbamoil)- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico;

Amida del ácido 3- {2- [(2S,4R)- 4- Fluoro- 2- (2- fluoro- 3- trifluorometoxi- fenilcarbamoil)- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- (2- {(1S,2S,5R)- 2- [(S)- 1- (3- Cloro- 2- fluoro- fenil)- 2- hidroxi- etilcarbamoil]- 3- azabiciclo[3.1.0]hex- 3- il}- 2- oxo- etil)- indol- 1- carboxílico;
Amida del ácido 3- {2- [(2S,3R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 3- hidroxi- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- {2- [(2S,4S)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- dimetilaminometil- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- (2- {(2S,4R)- 2- [(R)- 1- (3- Cloro- 2- fluoro- fenil)- 3- hidroxi- propilcarbamoil]- 4- fluoro- 4- metil- pirrolidin- 1- il}- 2- oxo- etil)- indol- 1- carboxílico;
Amida del ácido 3- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- (2- {(1R,3S,5R)- 3- [(S)- 1- (3- Cloro- 2- fluoro- fenil)- 2- hidroxi- etil carbamoil]- 2- aza- biciclo[3.1.0]hex- 2- il}- 2- oxo- etil)- indol- 1- carboxílico;
Amida del ácido 3- {2- [(S)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- Tiazolidin- 3- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- hidroximetil- pirrolidin- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 5- metoxi- indol- 1- carboxílico;
Amida del ácido 3- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 5- (2- hidroxi- etoxi)- indol- 1- carboxílico;
Amida del ácido 3- {2- [(1R,3S,5S)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 5- metoximetil- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 5- (2- Hidroxi- etoxi)- 3- {2- oxo- 2- [(1R,3S,5R)- 3- (3- trifluorometoxi- fenilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- etil}- indol- 1- carboxílico;
Amida del ácido 3- (2- {(1R,3S,5R)- 3- [(5- Cloro- tiofen- 2- ilmetil)- carbamoil]- 2- aza- biciclo[3.1.0]hex- il}- 2- oxo- etil)- indol- 1- carboxílico;
Amida del ácido 3- (2- {(1R,3S,5R)- 3- [(R)- 1- (3- Cloro- 2- fluoro- fenil)- 3- hidroxi- propilcarbamoil]- 2- azabiciclo[3.1.0]hex- 2- il}- 2- oxo- etil)- indol- 1- carboxílico;
Amida del ácido 3- (2- {(1R,3S,5R)- 3- [(S)- 1- (3- Cloro- 2- fluoro- fenil)- 2- dimetilamino- etilcarbamoil]- 2- aza- biciclo[3.1.0]hex- 2- il}- 2- oxo- etil)- indol- 1- carboxílico;

Amida del ácido 3- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil-pirrolidin- 1- il]- 2- oxo- etil}- 5- (2- hidroxi- etoxi)- indol- 1- carboxílico;
Amida del ácido 3- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro-pirrolidin- 1- il]- 2- oxo- etil}- 5- fluoro- indol- 1- carboxílico;
Amida del ácido 3- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza-biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 2- metil- indol- 1- carboxílico;
Amida del ácido 3- {2- [(S)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- Tiazolidin- 3- il]- 2-oxo- etil}- 5- (2- hidroxi- etoxi)- indol- 1- carboxílico;
Amida del ácido 3- (2- {(1R,2S,5S)- 2- [(S)- 1- (3- Cloro- 2- fluoro- fenil)- 2- hidroxi-etilcarbamoil]- 3- azabiciclo[3.1.0]hex- 3- il}- 2- oxo- etil)- indol- 1- carboxílico;
Amida del ácido 3- (2- {(1R,3S,5R)- 3- [(S)- 1- (3- Cloro- 2- fluoro- fenil)- 2- metoxi-etilcarbamoil]- 2- aza- biciclo[3.1.0]hex- 2- il}- 2- oxo- etil)- indol- 1- carboxílico;
Amida del ácido 3- {2- [(1 S,2S,5R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 3- aza-biciclo[3.1.0]hex- 3- il]- 2- oxo- etil}- 5- (2- hidroxi- etoxi)- indol- 1- carboxílico;
Amida del ácido 3- {2- [(2S,3S,4S)- 3- Amino- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4-fluoro- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- {2- [(1R,3S,5S)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 5- hidroximetil-2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- {2- [(2S,4S)- 4- Amino- 2- (3- cloro- 2- fluoro- bencilcarbamoil)-pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- {2- [5- (3- Cloro- bencilcarbamoil)- pirazolidin- 1- il]- 2- oxo- etil}- indol-1- carboxílico;
Amida del ácido 3- {2- [(2S,4S)- 4- Aminometil- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4-fluoro- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- {2- [(2S,4S)- 4- Aminometil- 2- (3- cloro- 2,6- difluoro- bencilcarbamoil)-4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza-biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 5- (2- dimetilamino- etoxi)- indol- 1- carboxílico;
Ácido (1- Carbamoil- 3- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza-biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 6- il)- acético;
Amida del ácido 3- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza-biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 6- (2- hidroxi- etil)- indol- 1- carboxílico;
Amida del ácido 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza-biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;

Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;

Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 7- metoxi- 1H- indol- 3- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- piperidina- 2- carboxílico;

Amida del ácido 6- Bromo- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 5- fluoro- 1H- indol- 3- carboxílico;

Ester metilo del ácido 3- [({(1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carbonil}- amino)- metil]- 5- cloro- 4- fluoro- benzoico;

Amida del ácido 1- {2- [(2S,4R)- 2- (3- Bromo- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

(5- cloro- tiofen- 2- ilmetil)- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- 5- metoxi- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico;

Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- fenilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- 6- metoxi- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico;

Amida del ácido 5- Cloro- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;

Amida del ácido 7- Cloro- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5S)- 2- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 5- metoximetil- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

Amida del ácido 6- Cloro- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;

Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 5,6- difluoro- 1H- indol- 3- carboxílico;

Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 6- trifluorometoxi- 1H- indol- 3- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- 5- metoxi- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- {2- [3- (2,2,2- Trifluoro- acetil)- indol- 1- il]- acetil}- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;

Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- metoxi- 1H- indol- 3- carboxílico;

3- cloro- 5- ciano- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;

Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- metoxi- 1H- indol- 3- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 6- metoxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (S)- 1- [2- (3- Acetil- 5- metoxi- indol- 1- il)- acetil]- piperidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- pirrolo[3,2- c]piridin- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico;

Amida del ácido 5- Benciloxi- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- oxo- etil}- 1H- indol- 3- carboxílico;

[(R)- 1- (3- cloro- 2- fluoro- fenil)- 3- hidroxi- propil]- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (1R,2S,5S)- 3- [2- (3- Acetil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 3- aza- biciclo[3.1.0]hexano- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 5- benciloxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 6- trifluorometoxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;

cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,4S)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[2.2.1]heptane- 3- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (S)- 3- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- Tiazolidina- 2- carboxílico;

(2- fluoro- 3- trifluorometoxi- fenil)- amida del ácido (2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;

[3- bromo- 5- (2H- tetrazol- 5- il)- fenil]- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

3- bromo- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;

Amida del ácido 1- {2- [(2S,4R)- 4- Fluoro- 2- (2- fluoro- 3- trifluorometil- fenilcarbamoil)- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;

[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido (2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;

metilamida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- 5- (1H- tetrazol- 5- il)- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;

[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- dimetilamino- etil]- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

Ester metilo del ácido 3- [({(2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carbonil}- amino)- metil]- 5- cloro- 4- fluoro- benzoico;

3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[3,2- c]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

3- cloro- 2- fluoro- 5- (1H- tetrazol- 5- il)- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

Ester metilo del ácido 3- Acetil- 1- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- il]- 2- oxo- etil}- 1H- indol- 6- carboxílico;

Cloro- 5- ciano- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 6- difluorometoxi- 1H- indol- 3- carboxílico;
Amida del ácido 6- Benciloxi- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 6- cloro- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- 6- ciano- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etil]- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 6- benciloxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;
[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etil]- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- 6- benciloxi- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,2S,5S)- 3- [2- (3- Acetil- pirrolo[3,2- c]piridin- 1- il)- acetil]- 3- aza- biciclo[3.1.0]hexano- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,2S,5S)- 3- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 3- aza- biciclo[3.1.0]hexano- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 5- trifluorometoxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;
Ester metilo del ácido 3- Acetil- 1- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 5- carboxílico;
Ester metilo del ácido 3- Acetil- 1- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluorobencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 7- carboxílico;
Ester metilo del ácido 3- Acetil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 4- Fluoro- 1- {2- [3- (2- hidroxi- acetil)- indol- 1- il]- acetil}- 4- metil- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (1S,2S,5R)- 3- [2- (3- Acetil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 3- aza- biciclo[3.1.0]hexano- 2- carboxílico;

Ester metilo del ácido (3- Acetil- 1- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 6- il)- acético;

3- bromo- 2- fluoro- bencilamida del ácido (2S,4R)- 4- Fluoro- 1- {2- [3- (2,2,2- trifluoro- acetil)- indol- 1- il]- acetil}- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;

Ester metilo del ácido 3- Acetil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- carboxílico;

Ester metilo del ácido (3- Acetil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- il)- acético;

3- cloro- 2- fluorobencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

[(S)- 1- (3- bromo- fenil)- 2- fluoro- etil]- amida del ácido (2S,4R)- 4- Fluoro- 1- {2- [3- (2- hidroxi- acetil)- indol- 1- il]- acetil}- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[3,2- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 4- Fluoro- 4- metil- 1- {2- [3- (2,2,2- trifluoro- acetil)- indol- 1- il]- acetil}- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2R,3S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- dimetilamino- 3- fluoro- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- {2- [3- (2- Hidroxi- acetil)- indol- 1- il]- acetil}- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

[(R)- 1- (3- cloro- 2- fluoro- fenil)- 3- hidroxi- propil]- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

(3- trifluorometoxi- fenil)- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

(3- trifluorometoxi- fenil)- amida del ácido (S)- 1- [2- (3- Formil- indol- 1- il)- acetil]- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 4- Fluoro- 1- [2- (3- formil- 5- metoxi- indol- 1- il)- acetil]- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 4- Fluoro- 1- {2- [3- (2,2,2- trifluoro- acetil)- indol- 1- il]- acetil}- pirrolidina- 2- carboxílico;

(2- fluoro- 3- trifluorometoxi- fenil)- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 4- Fluoro- 1- {2- [3- (2- hidroxi- acetil)- indol- 1- il]- acetil}- pirrolidina- 2- carboxílico;

3- bromo- 2- fluoro- bencilamida del ácido (2S,4R)- 4- Fluoro- 1- {2- [3- (2- hidroxi- acetil)- indol- 1- il]- acetil}- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 4- Fluoro- 1- {2- [3- (2- metoxi- acetil)- indol- 1- il]- acetil}- pirrolidina- 2- carboxílico;

Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- hidroximetil- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;

Amida del ácido 1- {2- [(S)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- Tiazolidin- 3- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;

[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etil]- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- 3- etoxi- pirrolidina- 2- carboxílico;

[(R)- 1- (3- cloro- 2- fluoro- fenil)- etil]- amida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico;

[(S)- 1- (3- cloro- 2- fluoro- fenil)- etil]- amida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico;

[1- (3- cloro- fenil)- ciclopropil]- amida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico;

[1- (4- cloro- fenil)- ciclopropil]- amida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico;

Amida del ácido 1- {2- [(2S,3S,4S)- 3- Amino- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 3- amino- 4- fluoro- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2R,3S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- amino- 3- fluoro- pirrolidina- 2- carboxílico;

Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- hidroxi- 1H- indol- 3- carboxílico;

Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- hidroxi- 1H- indol- 3- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 5- hidroxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 5- hidroxi- indol- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- 5- hidroxi- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 6- hidroxi- indol- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 6- hidroxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- 6- hidroxi- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 6- (1H- tetrazol- 5- ilmetoxi)- 1H- indol- 3- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- {2- [3- Acetil- 6- (1H- tetrazol- 5- ilmetoxi)- indol- 1- il]- acetil}- 4- fluoro- irrolidina- carboxílico;

Cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 5- metoxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- {2- [3- Acetil- 5- (piridin- 2- ilmetoxi)- indol- 1- il]- acetil}- 4- fluoro- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- {2- [3- Acetil- 5- (pirimidin- 2- ilmetoxi)- indol- 1- il]- acetil}- 4- fluoro- pirrolidina- 2- carboxílico;

Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 6- (2- metoxi- etoxi)- 1H- indol- 3- carboxílico;

Ester metilo del ácido (3- Carbamoil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- iloxi)- acético;

Ácido (3- Carbamoil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- iloxi)- acético;

Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 6- (2- hidroxi- etoxi)- 1H- indol- 3- carboxílico;

Ácido (3- Acetil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- il)- acético;

Ácido (3- Acetil- 1- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza-biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 6- il)- acético;

Ácido 3- Acetil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin-1- il]- 2- oxo- etil}- 1H- indol- 6- carboxílico;

Ácido 3- Acetil- 1- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza-biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 6- carboxílico;

Ácido 3- Acetil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil-pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- carboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3S,4S)- 4- Fluoro- 3- metoxi- pirrolidina- 1,2- dicarboxílico;

Ácido acetil- 1- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza-biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 7- carboxílico;

Ácido (3- Acetil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro-pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- iloximetil)- benzoico;

Ácido 3- acetil- 1- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza-biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 5- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 6- hidroximetil- indol- 1-il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;

Ácido 3- [({(2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carbonil}-amino)- metil]- 5- cloro- 4- fluoro- benzoico;

Ácido 3- [({(1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3-carbonil}- amino)- metil]- 5- cloro- 4- fluoro- benzoico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4-aminometil- 4- fluoro- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4-metilamino- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- (2-metoxi- etilamino)- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5S)- 2- [2- (3- Acetil- pirrolo[2,3- b]piridin-1- il)- acetil]- 5- hidroximetil- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5S)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 5-hidroximetil- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2hidroxi- etil]- amida del ácido (1S,2S,5R)- 3- [2- (3-Acetil- indol- 1- il)- acetil]- 3- aza- biciclo[3.1.0]hexano- 2- carboxílico;

[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido (2S,4R)- 1- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- {2- [3- Acetil- 5- (N,N- dimetil- carbamimidoil)- indol- 1- il]- acetil}- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- {2- [3- Acetil- 6- (N,N- dimetil- carbamimidoil)- indol- 1- il]- acetil}- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- {2- [3- Acetil- 6- (1H- tetrazol- 5- il)- indol- 1- il]- acetil}- 4- fluoro- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- {2- [3- Acetil- 6- (1H- tetrazol- 5- il)- indol- 1- il]- acetil}- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- d3- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- d3- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (1- Acetil- imidazo[1,5- a]piridin- 3- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico; y
Éster 3- cloro- 2- fluoro- fenilo del ácido {(1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hex- 3- ilmetil}- carbamico.

En otra realización, se proporcionan composiciones farmacéuticas las cuales comprenden uno o más vehículos farmacéuticamente aceptables y una cantidad terapéuticamente efectiva de un compuesto de cualquiera de las fórmulas (I), (Ia), (II), (III), (IV), (V), (VI), (VII), o subfórmulas de los mismos.

En otra realización, se proporcionan combinaciones, en particular combinaciones farmacéuticas, que comprenden una cantidad terapéuticamente efectiva del compuesto de cualquiera de las fórmulas (I), (Ia), (II), (III), (IV), (V), (VI), (VII), o una subfórmula de los mismos.

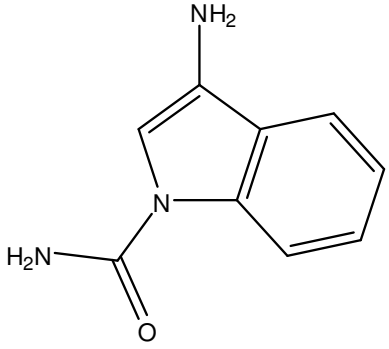
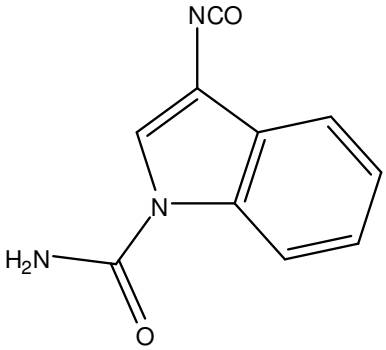
En otra realización, se proporcionan métodos de modulación de la actividad de la vía alternativa de complemento en un sujeto, tales métodos comprenden administrar al sujeto una cantidad terapéuticamente efectiva del compuesto de cualquiera de las fórmulas (I), (Ia), (II), (III), (IV), (V), (VI), (VII), o una subfórmula del mismo.

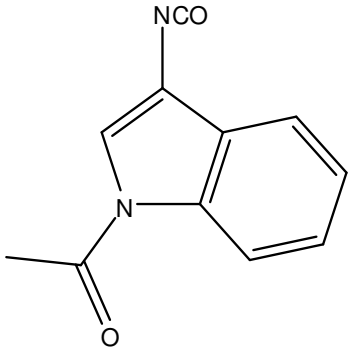
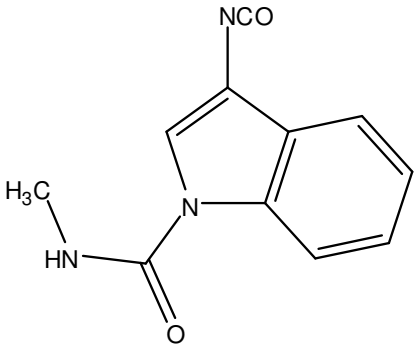
En aún otras realizaciones, se proporcionan métodos de tratar un trastorno o una enfermedad en un sujeto mediada por la activación de complemento, en particular mediada por la activación de la vía alternativa de complemento, tales métodos comprenden administrar al sujeto una cantidad terapéuticamente efectiva del compuesto de cualquiera de las fórmulas (I), (Ia), (II), (III), (IV), (V), (VI), (VII), o una subfórmula de los mismos.

En otra realización, se proporcionan métodos de tratar degeneración macular relacionada con la edad en un sujeto tales métodos comprenden administrar al sujeto una cantidad terapéuticamente efectiva del compuesto de cualquiera de las fórmulas (I), (Ia), (II), (III), (IV), (V), (VI), (VII), o una subfórmula de los mismos.

En otro aspecto, la invención proporciona el uso de compuestos de cualquiera de las fórmulas (I), (Ia), (II), (III), (IV), (V), (VI), (VII), o una subfórmula de los mismos para utilizar en la preparación de un medicamento y más particularmente para utilizar en la fabricación de un medicamento para el tratamiento de un trastorno o enfermedad en un sujeto mediada por la activación de complemento o activation de la vía alternativa de complemento. En ciertos aspectos, la invención proporciona el uso de un compuesto según cualquiera de las fórmulas (I), (Ia), (II), (III), (IV), (V), (VI), (VII), o subfórmulas de los mismos en el tratamiento de degeneración macular relacionada con la edad.

En otra realización, se proporcionan compuestos que son intermedios sintéticos en la preparación de compuestos según cualquiera de las fórmulas (I), (Ia), (II), (III), (IV), (V), (VI), (VII), o una subfórmula de los mismos. En particular, los compuestos proporcionados en la presente como intermedios sintéticos incluyen los compuestos de las fórmulas:

	
3- amino- 1H- indol- 1- carboxamida	3- isocianato- 1H- indol- 1- carboxamida

	
1- (3- isocianato- 1H- indol- 1- il)etanona	3- isocianato- N- metilo- 1H- indole- 1- carboxamida

En una realización, la invención proporciona una combinación, en particular, una combinación farmacéutica, que comprende una cantidad terapéuticamente eficaz del compuesto según la definición de la fórmula (I), (Ia), (II), (VII) o subfórmulas del mismo o cualquiera de los compuestos dados a conocer específicamente de la invención y uno o más agentes terapéuticamente activos (preferiblemente seleccionados de entre los enumerados más adelante).

Para propósitos de interpretar esta especificación, las siguientes definiciones se aplicarán y cuando sea apropiado, los términos utilizados en forma singular también incluirán la forma plural y viceversa.

Como se utiliza en la presente, el término "alquilo" se refiere a una fracción de hidrocarburo ramificada o no ramificada completamente saturada que tiene hasta 20 átomos de carbono. A menos que se indique lo contrario, alquilo se refiere a fracciones de hidrocarburo que tienen 1 a 16 átomos de carbono 1 a 10 átomos de carbono, 1 a 7 átomos de carbono, o 1 a 4 átomos de carbono. Ejemplos representativos de alquilo incluyen, pero no se limitan a, metilo, etilo, n- propilo, iso- propilo, n- butilo, sec- butilo, iso- butilo, tert- butilo, n- pentilo, isopentilo, neopentilo, n- hexilo, 3- metilhexilo, 2,2- dimetilpentilo, 2,3- dimetilpentilo, n- heptilo, n- octilo, n- nonilo, n- decilo y similares.

Como se utiliza en la presente, el término “alquileno” se refiere a un grupo alquilo divalente como se definió en la presente anteriormente que tiene 1 a 20 átomos de carbono. Este comprende 1 a 20 átomos de carbono, A menos que se indique lo contrario, alquileno se refiere a fracciones que tienen 1 a 16 átomos de carbono, 1 a 10 átomos de carbono, 1 a 7 átomos de carbono, o 1 a 4 átomos de carbono. Ejemplos representativos de alquileno incluyen, pero no se limitan a, metileno, etileno, n- propileno, iso- propileno, n- butileno, sec-

butileno, iso- butileno, tert- butileno, n- pentileno, isopentileno, neopentileno, n- hexileno, 3-metilhexileno, 2,2- dimetilpentileno, 2,3- dimetilpentileno, n- heptileno, n- octileno, n-nonileno, n- decileno y similares.

Como se utiliza en la presente, el término “haloalquilo” se refiere a un alquilo como se define en la presente el cual es sustituido por uno o más grupos halo como se define en la presente. El haloalquilo puede ser monohaloalquilo, dihaloalquilo, o polihaloalquilo, incluyendo perhaloalquilo. Un monohaloalquilo puede tener un yodo, bromo, cloro ó fluoro dentro del grupo alquilo. Los grupos dihaloalquilo y polihaloalquilo pueden tener dos o más de los mismos átomos halo o una combinación de diferentes grupos halo dentro del alquilo Típicamente el polihalolaquilo contiene hasta 12, o 10, o 8, o 6, o 4, o 3, o 2 grupos halo. Ejemplos no limitantes de haloalquilo incluyen fluorometilo, difluorometilo, trifluorometilo, clorometilo, diclorometilo, triclorometilo, pentafluoroetilo, heptafluoropropilo, difluoroclorometilo, diclorofluorometilo, difluoroetilo, difluoropropilo, dicloroetilo y dicloropropilo. Un perhaloalquilo se refiere a un alquilo que tiene todos los átomos de hidrógeno reemplazados por átomos halo.

El término "arilo" se refiere a un grupo hidrocarbono aromático que tiene 6- 20 átomos de carbono en la porción cíclica. Típicamente, arilo es arilo monocíclico, bicíclico o tricíclico que tiene 6- 20 átomos de carbono.

Además, el término "arilo” como se utiliza en la presente, se refiere a un sustituyente aromático el cual puede ser un único anillo aromático, o múltiples anillos aromáticos que son fusionados juntos.

Ejemplos no limitantes incluyen fenilo, naftilo o tetrahidronaftilo, cada uno de los cuales puede opcionalmente sustituirse por 1- 4 sustituyentes, tales como alquilo, trifluorometilo, cicloalquilo, halógeno, hidroxilo, alcoxilo, acilo, alquilo- C(O)- O- , arilo- O- , heteroarilo- O- , amino, tiol, alquilo- S- , arilo- S- , nitro, ciano, carboxilo, alquilo- O- C(O)- , carbamoilo, alquilo- S(O)- , sulfonilo, sulfonamido, fenilo, y heterociclilo.

Como se utiliza en la presente, el término “alcoxilo” se refiere a alquilo- O- , en donde alquilo se definió en la presente anteriormente. Ejemplos representativos de alcoxilo incluyen, pero no se limitan a, metoxilo, etoxilo, propoxilo, 2- propoxilo, butoxilo, *tert*- butoxilo, pentiloxilo, hexiloxilo, ciclopropiloxilo- , ciclohexiloxilo- y similares. Típicamente, los grupos alcoxilo tienen aproximadamente 1- 7, más preferiblemente 1- 4 carbonos aproximadamente.

Tal como se utiliza en la presente, el término "heterociclo" o "heterociclilo" se refiere a un anillo no aromático saturado o insaturado o sistema cíclico, por ejemplo, el cual es un sistema de anillo monocíclico de 4- , 5- , 6- , o 7 miembros, bicíclico de 7- , 8- , 9- , 10- , 11- , o

12- miembros o tricíclico de 10- , 11- , 12- , 13- , 14- o 15- miembros y contiene al menos un heteroátomo seleccionado entre O, S y N , donde el N y S también pueden opcionalmente ser oxidados a varios estados de oxidación. El grupo cicloheteroalquilo puede fijarse en un heteroátomo o un átomo de carbono. El heterociclilo puede incluir anillos fusionados o unidos así como también anillos espirocíclicos. Ejemplos de heterociclos incluyen tetrahidrofurano (THF), dihidrofurano, 1,4- dioxano, morfolina, 1,4- ditiano, piperazina, piperidina, 1,3- dioxolano, imidazolidina, imidazolina, pirrolina, pirrolidina, tetrahidropirano, dihidropirano, oxatiolano, ditiolano, 1,3- dioxano, 1,3- ditiano, oxatiano, tiomorfolina, y similares.

El término "heterociclilo" además se refiere a grupos heterocíclicos como se definen en la presente sustituidos por 1 a 5 sustituyentes independientemente seleccionados a partir de los grupos que constan de los siguientes:

(a) alquilo;

(b) hidroxilo (o hidroxilo protegido);

(c) halo;

(d) oxo, es decir, =O;

(e) amino, alquilamino o dialquilamino;

(f) alcoxilo;

(g) cicloalquilo;

(h) carboxilo;

(i) heterociclooxi, en donde heterociclooxi denota un grupo heterocíclico unido a través de un puente de oxígeno;

(j) alquilo- O- C(O)- ;

(k) mercapto;

(l) nitro;

(m) ciano;

(n) sulfamoilo o sulfonamido;

(o) arilo;

(p) alquilo- C(O)- O- ;

(q) arilo- C(O)- O- ;

(r) arilo- S- ;

(s) ariloxilo;

(t) alquilo- S- ;

(u) formilo, es decir, HC(O)- ;

(v) carbamoilo;

(w) aril- alquilo- ; y

(x) arilo sustituido con alquilo, cicloalquilo, alcoxilo, hidroxilo, amino, alquilo- C(O)- NH- , alquilamino, dialquilamino o halógeno.

Como se utiliza en la presente, el término "cicloalquilo" se refiere a grupos hidrocarburos monocíclicos, bicíclicos o tricíclicos saturados o no saturados de 3- 12 átomos de carbono. A menos que se indique lo contrario, cicloalquilo se refiere a grupos hidrocarburo cíclicos que tienen entre 3 y 9 átomos de carbono cíclicos o entre 3 y 7 átomos de carbono cíclicos, cada uno de los cuales puede opcionalmente sustituirse por uno, o dos, o tres, o más sustituyentes independientemente seleccionados a partir del grupo que consta de alquilo, halo, oxo, hidroxilo, alcoxilo, alquilo- C(O)- , acilamino, carbamoilo, alquilo- NH- , (alquilo)2N- , tiol, alquilo- S- , nitro, ciano, carboxilo, alquilo- O- C(O)- , sulfonilo, sulfonamido, sulfamoilo, y heterociclilo. Grupos hidrocarbono monocíclicos de ejemplo incluyen, pero no se limitan a, ciclopropilo, ciclobutilo, ciclopentilo, ciclopentenilo, ciclohexili y ciclohexenilo y similares. Grupos hidrocarburo bicíclicos de ejemplo incluyen bornilo, indilo, hexahidroindilo, tetrahidronaftilo, decahidronaftilo, biciclo[2.1.1]hexilo, biciclo[2.2.1]heptilo, biciclo[2.2.1]heptenilo, 6,6- dimetilbiciclo[3.1.1]heptilo, 2,6,6- trimetilbiciclo[3.1.1]heptilo, biciclo[2.2.2]octilo y similares. Grupos hidrocarburo tricíclicos de ejemplo incluyen adamantilo y similares.

Como se utiliza en la presente, el término “ariloxilo” se refiere a ambos un grupo - O- arilo y un grupo - O- heteroarilo, en donde arilo y heteroarilo se definen en la presente.

Como se utiliza en la presente, el término "heteroarilo" se refiere a un sistema de anillo monocíclico o bicíclico- o tricíclico- aromático de 5- 14 miembros, que tiene 1 to 8 heteroátomos seleccionados a partir de N, O ó S. Típicamente, el heteroarilo es un sistema de anillo de 5- 10 miembros (ej., monociclo de 5- 7 miembros o un biciclo de 8- 10 miembros) o un sistema de anillo de 5- 7 miembros. Grupos heteroarilo típicos incluyen 2- o 3- tienilo, 2- o 3- furilo, 2- o 3- pirrolilo, 2- , 4- , ó 5- imidazolilo, 3- , 4- , o 5- pirazolilo, 2- , 4- , o 5- tiazolilo, 3- , 4- , o 5- isotiazolilo, 2- , 4- , o 5- oxazolilo, 3- , 4- , o 5- isoxazolilo, 3- o 5- 1,2,4- triazolilo, 4- o 5- 1,2, 3- triazolilo, tetrazolilo, 2- , 3- , o 4- piridilo, 3- o 4- piridazinilo, 3- , 4- , o 5- pirazinilo, 2- pirazinilo, y 2- , 4- , o 5- pirimidinilo.

El término “heteroarilo” también se refiere a un grupo en el cual un anillo heteroaromático es fusionado a uno más anillos arilo, cicloalifáticos, o heterocíclicos, donde el radical o punto de fijación está sobre el anillo heteroaromático. Ejemplos no limitantes

incluyen 1- , 2- , 3- , 5- , 6- , 7- , o 8- indolizinilo, 1- , 3- , 4- , 5- , 6- , o 7- isoindolilo, 2- , 3- , 4- , 5- , 6- , o 7- indolilo, 2- , 3- , 4- , 5- , 6- , o 7- indazolilo, 2- , 4- , 5- , 6- , 7- , o 8- purinilo, 1- , 2- , 3- , 4- , 6- , 7- , 8- , o 9- quinolizinilo, 2- , 3- , 4- , 5- , 6- , 7- , o 8- quinoliilo, 1- , 3- , 4- , 5- , 6- , 7- , o 8- isoquinoliilo, 1- , 4- , 5- , 6- , 7- , o 8- ftalazinilo, 2- , 3- , 4- , 5- , o 6- naftiridinilo, 2- , 3- , 5- , 6- , 7- , o 8- quinazolinilo, 3- , 4- , 5- , 6- , 7- , o 8- cinnolinilo, 2- , 4- , 6- , o 7- pteridinilo, 1- , 2- , 3- , 4- , 5- , 6- , 7- , o 8- 4aH carbazolilo, 1- , 2- , 3- , 4- , 5- , 6- , 7- , o 8- carbazolilo, 1- , 3- , 4- , 5- , 6- , 7- , 8- , o 9- carbolinilo, 1- , 2- , 3- , 4- , 6- , 7- , 8- , 9- , o 10- fenantridinilo, 1- , 2- , 3- , 4- , 5- , 6- , 7- , 8- , o 9- acridinilo, 1- , 2- , 4- , 5- , 6- , 7- , 8- , o 9- perimidinilo, 2- , 3- , 4- , 5- , 6- , 8- , 9- , o 10- fenatrolinilo, 1- , 2- , 3- , 4- , 6- , 7- , 8- , o 9- fenazinilo, 1- , 2- , 3- , 4- , 6- , 7- , 8- , 9- , o 10- fenotiazinilo, 1- , 2- , 3- , 4- , 6- , 7- , 8- , 9- , o 10- fenoxazinilo, 2- , 3- , 4- , 5- , 6- , o l- , 3- , 4- , 5- , 6- , 7- , 8- , 9- , o 10- benzisoquinolinilo, 2- , 3- , 4- , o tieno[2,3- b]furanilo, 2- , 3- , 5- , 6- , 7- , 8- , 9- , 10 - , o 11- 7H- pirazino[2,3- c]carbazolilo,2- , 3- , 5- , 6- , o 7- 2H- furo[3,2- b]- piranilo, 2- , 3- , 4- , 5- , 7- , o 8- 5H- pirido[2,3- d]- o- oxazinilo, 1- , 3- , o 5- 1H- pirazolo[4,3- d]- oxazolilo, 2- , 4- , o 54H- imidazo[4,5- d] tiazolilo, 3- , 5- , o 8- pirazino[2,3- d]piridazinilo, 2- , 3- , 5- , o 6- imidazo[2,1- b] tiazolilo, 1- , 3- , 6- , 7- , 8- , o 9- furo[3,4- c]cinolinilo, 1- , 2- , 3- , 4- , 5- , 6- , 8- , 9- , 10, o 11- 4H- pirido[2,3- c]carbazolilo, 2- , 3- , 6- , o 7- imidazo[1,2- b][1,2,4]triazinilo, 7- benzo[b]tienilo, 2- , 4- , 5- , 6- , o 7- benzoxazolilo, 2- , 4- , 5- , 6- , o 7- benzimidazolilo, 2- , 4- , 4- , 5- , 6- , o 7- benzotiazolilo, 1- , 2- , 4- , 5- , 6- , 7- , 8- , o 9- benzoxapinilo, 2- , 4- , 5- , 6- , 7- , o 8- benzoxazinilo, 1- , 2- , 3- , 5- , 6- , 7- , 8- , 9- , 10- , o 11- 1H- pirrolo[1,2- b][2]benzazapinilo. Grupos heteroarilo típicos condensados incluyen, pero no se limitan a 2- , 3- , 4- , 5- , 6- , 7- , o 8- quinolinilo, 1- , 3- , 4- , 5- , 6- , 7- , o 8- isoquinolinilo, 2- , 3- , 4- , 5- , 6- , o 7- indolilo, 2- , 3- , 4- , 5- , 6- , o 7- benzo[b]tienilo, 2- , 4- , 5- , 6- , o 7- benzoxazolilo, 2- , 4- , 5- , 6- , o 7- benzimidazolilo, y 2- , 4- , 5- , 6- , o 7- benzotiazolilo.

Un grupo heteroarilo puede sustituirse con 1 a 5 sustituyentes independientemente seleccionados a partir de los grupos que constan de los siguientes:

(a) alquilo;

(b) hidroxilo (o hidroxilo protegido);

(c) halo;

(d) oxo, es decir, =O;

(e) amino, alquilamino o dialquilamino;

(f) alcoxilo;

(g) cicloalquilo;

(h) carboxilo;

(i) heterociclooxi, en donde heterociclooxi denota un grupo heterocíclico unido a través de un puente de oxígeno;

(j) alquilo- O- C(O)- ;

(k) mercapto;

(l) nitro;

(m) ciano;

(n) sulfamoilo o sulfonamido;

(o) arilo;

(p) alquilo- C(O)- O- ;

(q) arilo- C(O)- O- ;

(r) arilo- S- ;

(s) ariloxilo;

(t) alquilo- S- ;

(u) formilo, es decir, HC(O)- ;

(v) carbamoilo;

(w) aril- alquilo- ; y

(x) arilo sustituido con alquilo, cicloalquilo, alcoxilo, hidroxilo, amino, alquilo- C(O)- NH- , alquilamino, dialquilamino o halógeno.

Como se utiliza en la presente, el término “halógeno” o “halo” se refiere a fluoro, cloro, bromo, y yodo.

Como se utiliza en la presente, el término “opcionalmente sustituido” a menos que se especifique lo contrario se refiere a un grupo que no es sustituido o es sustituido por uno o más, típicamente 1, 2, 3 o 4, sustituyentes no hidrogéno apropiados, cada uno de los cuales es independientemente seleccionado del grupo que consta de:

(a) alquilo;

(b) hidroxilo (o hidroxilo protegido);

(c) halo;

(d) oxo, es decir, =O;

(e) amino, alquilamino o dialquilamino;

(f) alcoxilo;

(g) cicloalquilo;

(h) carboxilo;

(i) heterociclooxi, en donde heterociclooxi denota un grupo heterocíclico unido a través de un puente de oxígeno;

(j) alquilo- O- C(O)- ;

(k) mercapto;

(l) nitro;

(m) ciano;

(n) sulfamoilo o sulfonamido;

(o) arilo;

(p) alquilo- C(O)- O- ;

(q) arilo- C(O)- O- ;

(r) arilo- S- ;

(s) ariloxilo;

(t) alquilo- S- ;

(u) formilo, es decir, HC(O)- ;

(v) carbamoilo;

(w) aril- alquilo- ; y

(x) arilo sustituido con alquilo, cicloalquilo, alcoxilo, hidroxilo, amino, alquilo- C(O)- NH- , alquilamino, dialquilamino o halógeno.

Como se utiliza en la presente, el término “isómeros” se refiere a diferentes compuestos que tienen la misma fórmula molecular pero difieren en disposición y configuración de los átomos. También como se utiliza en la presente, el término “un isómero óptico” o “un estereoisómero” se refiere a cualquiera de las diferentes configuraciones estereoisoméricas que pueden existir para un compuesto dado del presente invento e incluyen isómeros geométricos. Se entiende que un sustituyente será fijado a un centro quiral de un átomo de carbono. Por lo tanto, el invento incluye enantiómeros, diastereoisómeros o racematos del compuesto. Los “enantiómeros” son un par de estereoisómeros que son imágenes especulares que no pueden ser superpuestas entre sí. Una mezcla 1:1 de un par de enantiómeros es una mezcla "racémica”. El término se utiliza para designar una mezcla racémica donde sea apropiado. El asterisco (*) indicado en el nombre de un compuesto designa una mezcla racémica. Los "diaestereoisómeros” son estereoisómeros que tienen al menos dos átomos asimétricos, pero los cuales no son imágenes especulares entre sí. La estereoquímica absoluta es especificada según el sistema R- S de Cahn- lngold- Prelog. Cuando un compuesto es un enantiómero puro la estereoquímica de cada carbono quiral puede especificarse por cualquiera R o S. Compuestos

resueltos cuya configuración absoluta se desconoce pueden designarse (+) o (-) dependiendo de la dirección (dextro- o levorotatoria) que rotan el plano de luz polarizada según la longitud de onda de la línea D del sodio. Ciertos de los compuestos descritos en la presente contienen uno o más centros o ejes asimétricos y pueden por lo tanto dar origen a enantiómeros, diastereoisómeros, y otras formas estereoisoméricas que pueden ser definidas, en términos de estereoquímica absoluta, como (R)- o (S)- . El presente invento pretende incluir todos éstos isómeros posibles, incluyendo mezclas racémicas, formas ópticamente puras y mezclas intermedias. Isómeros ópticamente activos (R)- y (S)- pueden prepararse utilizando sintones quirales o reactivos quirales, o resolverse utilizando técnicas convencionales. Si el compuesto contiene un enlace doble, el sustituyente puede ser de configuración E o Z. Si el compuesto contiene un cicloalquilo disustituido, el sustituyente cicloalquilo puede tener una configuración cis- o - trans. Todas las formas tautoméricas también son incluidas.

Tal como se utiliza en la presente, el término "sales farmacéuticamente aceptables" se refiere a sales que retienen la eficacia biológica y propiedades de los compuestos de esta invención y, que normalmente no son biológicamente o de otro modo indeseables. En muchos casos, los compuestos del presente invento son capaces de formar sales ácidas y/o alcalinas en virtud de la presencia de grupos amino y/o carboxilo o grupos similares de los mismos.

Sales de adición ácida farmacéuticamente aceptables pueden formarse con ácidos inorgánicos y ácidos orgánicos, ej., sales de acetato, aspartato, benzoato, besilato, bromuro/hidrobromuro, bicarbonato/carbonato, bisulfato/sulfato, canforsulfornato, cloruro/hidrocloruro, clorteofilonato, citrato, etanodisulfonato, fumarato, gluceptato, gluconato, glucuronato, hipurato, hidroyoduro/yoduro, isetionato, lactato, lactobionato, laurilsulfato, malato, maleato, malonato, mielato, misilato, metilsulfato, naftoato, napsilato, nicotinato, nitrato, octadecanoato, oleato, oxalato, palmitato, pamoato, fosfato/fosfato de hidrógeno/fosfato de dihidrógeno, poligalacturonato, propionato, estearato, succinato, sulfosalicilato, tartrato, tosilato y sales de trifluoroacetato. Ácidos inorgánicos a partir de los cuales las sales pueden derivarse incluyen, por ejemplo, ácido clorhídrico, ácido hidrobrómico, ácido sulfúrico, ácido nítrico, y ácido fosfórico. Ácidos orgánicos de tales sales pueden derivarse incluyendo, por ejemplo, ácido acético, ácido propiónico, ácido glicólico, ácido oxálico, ácido maléico, ácido manólico, ácido succínico, ácido fumárico, ácido tartárico, ácido cítrico, ácido benzóico, ácido mandélico, ácido metanosulfónico, ácido etanosulfónico, ácido toluensulfónico, ácido sulfosalicílico, y similares.

Las Sales de adición alcalina farmacéuticamente aceptables pueden formarse con bases inorgánicas y orgánicas. Bases inorgánicas a partir de las cuales las sales pueden derivarse

incluyen, por ejemplo, sales y metales de amonio de las columnas I a XII de la tabla periódica. En ciertas realizaciones, las sales se derivan a partir de sodio, potasio, amonio, calcio, magnesio, hierro, plata, zinc, y cobre; sales particularmente apropiadas incluyen sales de amonio, potasio, sodio, calcio y magnesio. Bases orgánicas a partir de las cuales pueden derivarse las sales incluyen, por ejemplo, aminas primarias, secundarias y terciarias, aminas sustituidas incluyendo aminas sustituidas de ocurrencia natural, aminas cíclicas, resinas de intercambio de iones alcalinos, y similares. Ciertas aminas orgánicas incluyen esopropilamina, benzatina, colinato, dietanolamina, dietilamina, lisina, meglumina, piperazina y trometamina.

Las sales farmacéuticamente aceptables de la presente invención pueden sintetizarse a partir de un compuesto precursor, una fracción alcalina o ácida, mediante métodos químicos convencionales. Generalmente, tales sales pueden prepararse al reaccionar formas ácidas libres de estos compuestos con una cantidad estequiométrica de la base apropiada (tales como hidróxido, carbonato, bicarbonato de Na, Ca, Mg, o K o similares), o al reaccionar formas alcalinas libres de estos compuestos con una cantidad estequiométrica del ácido apropiado. Típicamente, tales reacciones se realizan en agua o en un solvente orgánico, o en una mezcla de los dos. Generalmente, el uso de medios no acuosos tipo éter, acetato de etilo, etanol, isopropanol, o acetonitrilo es deseable, donde pueda realizarse. Listas de sales apropiadas adicionales pueden encontrarse, ej., en "*Remington's Farmaceutical Sciences*", 20th ed., Mack Publishing Company, Easton, Pa., (1985); y en "*Handbook of Farmaceutical Salts: Properties, Selection, and Use*" de Stahl y Wermuth (Wiley- VCH, Weinheim, Alemania, 2002).

Cualquiera fórmula dada en la presente también tiene el propósito de representar formas no rotuladas así como también formas isotopicamente rotuladas de los compuestos. Los compuestos isotopicamente rotulados tienen estructuras representadas por las fórmulas dadas en la presente excepto que uno o más átomos son reemplazados por un átomo que tiene un número de masa o masa atómica seleccionados. Ejemplos de isótopos que pueden incorporarse en compuestos del invento incluyen isótopos de hidrógeno, carbono, nitrógeno, oxigeno, fósforo, flúor, y cloro, tales como ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{125}I respectivamente. El invento incluye varios compuestos isotópicamente rotulados como se definió en la presente, por ejemplo aquellos en los cuales los isótopos radioactivos, tales como ^{3}H, ^{13}C, y ^{14}C , están presentes. Tales compuestos rotulados isotópicamente son útiles en estudios metabólicos (con ^{14}C), estudios cinéticos de reacción (con, por ejemplo ^{2}H o ^{3}H), técnicas de detección o visualización, tales como tomografía de emisión de positrones (PET) o tomografía computarizada de emisión de fotones individuales (SPECT) incluyen ensayo de distribución tisular de sustratos o fármacos, o tratamientos radioactivos de pacientes. En particular, un ^{18}F o

un compuesto rotulado pueden ser particularmente deseados para estudios PET o SPECT. Los compuestos isotópicamente rotulados de este invento y profármacos de los mismos generalmente pueden prepararse mediante la realización de los procedimientos divulgados en los esquemas o en los ejemplos y preparaciones descritos a continuación al sustituir un reactivo isotopicamente rotulado fácilmente disponible por un reactivo no isotopicamente rotulado.

Además, la sustitución con isótopos más pesados, particularmente deuterio (es decir,., ^{2}H o D) pueden proporcionar ciertas ventajas terapéuticas que resultan a partir de la mayor estabilidad metabólica, por ejemplo vida media *in vivo* aumentada o requerimientos de dosificación reducidos o una mejora en el índice terapéutico. Se entiende que deuterio en este contexto es considerado como un sustituyente de un compuesto de la fórmula (I). La concentración de tal isótopo más pesado, específicamente deuterio, será definida por el factor de enriquecimiento isotópico. El término "factor de enriquecimiento isotópico" como se utiliza en la presente se refiere a la relación entre la abundancia isotópica y la abundancia natural de un isótopo específico. Si un sustituyente en un compuesto de este invento se denota deuterio, tal compuesto tiene un factor de enriquecimiento isotópico para cada átomo de deuterio designado de al menos 3500 (52.5% de incorporación de deuterio en cada átomo de deuterio designado), al menos 4000 (60% de incorporación de deuterio), al menos 4500 (67.5% de incorporación de deuterio), al menos 5000 (75% de incorporación de deuterio), al menos 5500 (82.5% de incorporación de deuterio), al menos 6000 (90% de incorporación de deuterio), al menos 6333.3 (95% de incorporación de deuterio), al menos 6466.7 (97% de incorporación de deuterio), al menos 6600 (99% de incorporación de deuterio), o al menos 6633.3 (99.5% de incorporación de deuterio).

En ciertas realizaciones, la deuteración selectiva de compuestos de Fórmula (I) incluyen deuteración de R^3, cuando R^3 es alcanoilo, por ejemplo, $C(O)CD_3$. En otras realizaciones, ciertos sustituyentes en el anillo de pirrol se deuterados selectivamente. Por ejemplo, cuando cualquiera de R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, o R^{20} son metoxilo o etoxilo, el residuo alquilo preferiblemente es deuterado, ej., OCD_3 o OC_2D_5. En ciertos otros compuestos, cuando dos sustituyentes del anillo de pirrol se combinan para formar un anillo de ciclopropilo, el carbono de metileno no sustituido es deuterado selectivamente. Ciertos compuestos deuterados preferidos se proporcionan en los Ejemplos 619 y 620 más adelante.

Compuestos isotópicamente rotulados de la fórmula (I) pueden generalmente prepararse mediante técnicas convencionales conocidas por aquellos con experiencia en el estado de la técnica o mediante procesos análogos a aquellos descritos en los Ejemplos y Preparaciones

anexos utilizando un reactivo isotópicamente rotulado apropiado en cambio del reactivo no rotulado previamente empleado.

Los compuestos de la presente invención pueden inherentemente o por diseño formar solvatos con solventes (incluyendo agua) Por lo tanto, se pretende que la invención contemple ambas formas solvatadas y no solvatadas. El término "solvato" se refiere a un complejo molecular de un compuesto de la presente invención (incluyendo sales de los mismos) con una o más moléculas solventes. Tales moléculas solventes son aquellas comúnmente utilizadas en el estado de la técnica farmacéutica, las cuales son conocidas por ser inocuas para el receptor, ej., agua, etanol, dimetilsulfóxido, acetona y otros solventes orgánicos comunes. El término "hidrato"se refiere a un complejo molecular que comprende un compuesto de la invención y agua. Solvatos farmacéuticamente aceptables de acuerdo con la invención incluyen aquellos en donde el solvente de cristalización puede sustituirse isotópicamente, ej. D_2O, d_6- acetona, d_6-DMSO.

Los compuestos de la invención, es decir, los compuestos de la fórmula (I) que contienen grupos capaces de actuar como donantes y/o aceptores de enlaces de hidrógeno pueden ser capaces de formar co- cristales con formadores de co- cristales adecuados. Estos co-cristales pueden prepararse de compuestos de la fórmula (I) mediante procedimientos de formación de co- cristales conocidos. Tales procedimientos incluyen trituración, calentamiento, co- sublimación, co- fundición, o poner en contacto en solución compuestos de la fórmula (I) con el formador de co- cristales bajo condiciones de cristalización y aislamiento de co- cristales así formados. Formadores de co- cristales apropiados incluyen aquellos descritos en WO 2004/078163. Por lo tanto la invención además proporciona co- cristales que comprenden un compuesto de la fórmula (I).

Como se utiliza en la presente, el término " vehículo farmacéuticamente aceptable" incluye cualquiera y todos los solventes, medios de dispersión, recubrimientos, surfactantes, antioxidantes, preservativos (ej., agentes antibacterianos , agentes antimicóticos), agentes isotónicos, agentes retardantes de absorción, preservativos, fármacos, fármacos estabilizadores, aglutinantes, excipientes, agentes de desintegración, lubricantes, edulcorantes, agentes sapófiros, tintes, y similares y combinaciones de los mismos, como se conocerá por aquellos con experiencia en el estado de la técnica (ver, por ejemplo, *Remington's Pharmaceutical Sciences*, 18th Ed. Mack Printing Company, 1990, pp. 1289- 1329). Excepto en lo que respecta a cualquier vehículo convencional incompatible con el ingrediente activo, su uso es contemplado en las composiciones terapéuticas o farmacéuticas.

El término "una cantidad terapéuticamente efectiva" de un compuesto del presente invento se refiere a una cantidad del compuesto de la presente invención que producirá la respuesta biológica o médica de un sujeto, por ejemplo, reducción o inhibición de una enzima o una actividad proteica, o mejorar síntomas, aliviar condiciones, retardar la progresión de la enfermedad, o prevenir una enfermedad, etc. En una realización no limitante, el término "una cantidad terapéuticamente efectiva" se refiere a la cantidad del compuesto de la presente invención que, cuando se administra a un sujeto, es efectiva para (1) al menos parcialmente aliviar, inhibir, prevenir y/o mejorar una condición, o un trastorno o una enfermedad o proceso biológico (ej., regeneración y reproducción de tejido) (i) mediada por el Factor D, o (ii) asociada con actividad del factor D, o (iii) caracterizada por actividad del factor D; o (3) reducir o inhibir la expresión del factor D; o (4) reducir o inhibir la activación del sistema del complemento y particularmente reducir o inhibir la generación de C3a, iC3b, C5a o el complejo de ataque de membrana generado por la activación de la vía alternativa de complemento. En otra realización no limitante, el término "una cantidad terapéuticamente efectiva" se refiere a la cantidad del compuesto de la presente invención que, cuando se administra a una célula, o un tejido, o un material biológico no celular, o un medio, es efectiva para al menos parcialmente reducir o inhibir la actividad del Factor B y/o la ruta alternativa de complemento; o al menos parcialmente reducir o inhibir parcialmente la expresión del Factor D y/o la ruta alternativa de complemento. El significado del término "una cantidad terapéuticamente eficaz" como se ilustra en la realización anterior para el factor D y/o la vía alternativa del complemento.

Como se utiliza en la presente, el término "sujeto" se refiere a un animal. Típicamente el animal es un mamífero. Un sujeto también se refiere a por ejemplo, primates (*ej.*, humanos), vacas, ovejas, cabras, caballos, perros, gatos, conejos, ratas, ratones, peces, aves y similares. En ciertas realizaciones, el sujeto es un primate. En aún otras realizaciones, el sujeto es un humano.

Como se utiliza en la presente, el término "inhibir" o "inhibición" se refiere a la reducción o supresión de una condición, síntoma, o trastorno, o enfermedad dada, o una disminución significativa en la actividad inicial de una actividad o proceso biológico.

Como se utiliza en la presente, el término "tratar", o "tratamiento" de cualquier enfermedad o trastorno se refiere en una realización, a mejorar la enfermedad o trastorno (es decir, retardar o detener o reducir el desarrollo de la enfermedad o al menos uno de los síntomas clínicos de la misma). En otra realización "tratar" o "tratamiento" se refiere a aliviar o mejorar al menos parámetro físico incluyendo aquellos los cuales pueden ser no discernibles por el paciente. En aún otra realización, "tratar" o "tratamiento" se refiere a modular la

enfermedad o trastorno, bien sea físicamente, (*ej.*, estabilización de un síntoma discernible), fisiológicamente, (*ej.*, estabilización de un parámetro físico), o ambos. En aún otra realización, "tratar" o "tratamiento" se refiere a prevenir o retardar el comienzo o desarrollo o progresión de la enfermedad o trastorno.

Como se utiliza en la presente, un sujeto esta "en necesidad de" un tratamiento si tal sujeto se beneficia biológicamente, médicamente o mejora su calidad de vida a partir de tal tratamiento.

Como se utiliza en la presente, el término "un," "una," "el", "los" y términos similares se utilizan en el contexto del presente invento (especialmente en el contexto de las reivindicaciones) para cubrir formas tanto singulares como plurales a menos que se indique lo contrario o claramente sea contradicho por el contexto.

Todos los métodos descritos en la presente pueden realizarse en cualquier orden apropiado a menos que se indique lo contrario en la presente o de otra manera sea contradicho claramente por el contexto. El uso de cualquiera y todos los Ejemplos, o terminología de ejemplo (*ej.,* "tal como") proporcionada en la presente pretende solamente ilustrar mejor el invento y no implica limitación sobre el alcance del invento de otra manera reivindicado.

Cualquier átomo asimétrico (ej., carbono o similares) de los compuestos del presente invento puede presentarse en la configuración racémica o enantioméricamente enriquecida, por ejemplo la configuración (*R*)- , (*S*)- o (*R,S*)- . En ciertas realizaciones, cada átomo asimétrico tiene al menos 50% de exceso enantiomérico, al menos 60 % de exceso enantiomérico, al menos 70 % de exceso enantiomérico, al menos 80 % de exceso enantiomérico, al menos 90 % de exceso enantiomérico, al menos 95 % de exceso enantiomérico, o al menos 99 % de exceso enantiomérico en la configuración (*R*)- o (*S*)- . Los sustituyentes en átomos con enlaces no saturados pueden, si es posible, estar presentes en la forma *cis*- (*Z*)- o *trans*- (*E*)- .

En consecuencia, como se utiliza en la presente un compuesto del presente invento puede estar en la forma de uno de los posibles isómeros, rotámeros, atropisómeros, tautómeros o mezclas de los mismos, por ejemplo, como isómeros geométricos sustancialmente puros (*cis* o *trans*), diastereomeros, isómeros ópticos (antípodos), racematos o mezclas de los mismos.

Cualquier mezcla resultante de isómeros puede ser separada sobre la base de las diferencias fisicoquímicas de los constituyentes, en isómeros geométricos u ópticos puros o sustancialmente puros, diastereoisómeros, racematos, por ejemplo, mediante cromatografía y/o cristalización fraccional.

Los racematos resultantes de los productos finales o intermedios pueden ser resueltos en los antípodos ópticos mediante métodos conocidos, *ej.*, mediante separación de las sales

diastereoisoméricas de los mismos, obtenidas con un ácido o base óptimamente activos, y liberando el compuesto ácido o alcalino ópticamente activo. En particular, una fracción alcalina puede emplearse para separar los compuestos del presente invento en sus antípodos ópticos, *ej.*, mediante cristalización fraccional de una sal formada con un ácido ópticamente activo, *ej.*, ácido tartárico, ácido dibenzoil tartárico, ácido diacetil tartárico, ácido di- O,O'- *p*-toluoil tartárico, ácido mandélico, ácido málico o ácido canfor- 10- sulfónico. Los productos racémicos también pueden separarse mediante cromatografía quiral, *ej.*, cromatografía líquida de alta presión (HPLC) utilizando un absorbente quiral.

Los compuestos del presente invento son obtenidos ya sea en la forma libre, como una sal de los mismos, ó como derivados profarmacológicos de los mismos.

Cuando ambos un grupo alcalino y un grupo ácido están presentes en la misma molécula, los compuestos del presente invento también pueden formar sales internas, ej.,, moléculas zwiteriónicas.

El presente invento también proporciona pro- fármacos de los compuestos del presente invento que se convierten *in vivo* en los compuestos del presente invento. Un pro- fármaco es un compuesto activo o inactivo que es modificado químicamente a través de acción fisiológica *in vivo*, tal como hidrólisis, metabolismo y similares, en un compuesto de este invento después de administración del profármaco a un sujeto. La conveniencia y técnicas involucradas en la preparación y utilización de pro- fármacos son bien conocidas por aquellos con experiencia en el estado de la técnica. Los profármacos pueden dividirse conceptualmente en dos categorías no exclusivas, profármacos bioprecursores o profármacos vehículos. Ver *The Practice of Medicinal Chemistry*, Capítulo. 31- 32 (Ed. Wermuth, Academic Press, San Diego, Calif., 2001). Generalmente, los profármacos bioprecursores son compuestos, los cuales son inactivos o tienen baja actividad en comparación con el compuesto farmacológico activo correspondiente, que contiene uno o más grupos protectores y son convertidos en una forma activa mediante metabolismo o solvólosis. Tanto la forma farmacológica activa como cualquier producto metabólico liberado deben tener toxicidad aceptablemente baja.

Profármacos vehículos son compuestos farmacológicos que contienen una fracción transportadora, *ej.*, que mejoran la captación y/o distribución localizada a un sitio de acción. Deseablemente para tal pro fármaco vehículo, la conexión entre la fracción farmacológica y la fracción transportadora es un enlace covalente, el profármaco es inactivo o menos activo que el compuesto farmacológico, y cualquier fracción transportadora liberada es aceptablemente no tóxica. Para profármacos donde la fracción transportadora pretende mejorar la absorción, típicamente la liberación de la fracción transportadora debe ser rápida. En otros casos, es

deseable utilizar una fracción que proporciona liberación lenta, *ej.*, ciertos polímeros u otras fracciones, tales como ciclodextrinas. Por ejemplo, los profármacos vehículos pueden utilizarse para mejorar una o más de las siguientes propiedades: lipofilicidad aumentada, duración aumentada de efectos farmacológicos, especificidad a sitio aumentada, toxicidad disminuida y reacciones adversas, y/o mejoría en la formulación farmacológica (*ej.*, estabilidad, solubilidad en agua, supresión de una propiedad organoléptica o fisioquímica no deseada). Por ejemplo, la lipofilicidad puede aumentarse mediante esterificación de (a) grupo hidroxilo con ácidos carboxílicos lipofílicos (ej., un ácido carboxílico que tiene al menos una fracción lipofílica), o (b) grupos ácidos carboxílicos con alcoholes lipofílicos (ej., un alcohol que tiene al menos una fracción lipofílica, por ejemplo alcoholes alifáticos).

Profármacos de ejemplo son, *ej.*, ésteres de ácidos carboxílicos libres y derivados S-acilo de tioles y derivados O- acilo de alcoholes o fenoles, en donde acilo tiene un significado como se definió en la presente. Profármacos apropiados son a menudo derivados de éster farmacéuticamente aceptables convertibles mediante solvólosis bajo condiciones fisiológicas en el ácido carboxílico precursor, *ej.*, ésteres de alquilo menor, ésteres de cicloalquilo, ésteres de alquenilo menor, ésteres de bencilo, ésteres de alquilo menor mono- o di- sustituidos, tales como los □- (amino, mono- o di- alquilamino menor, carboxilo, alcoxicarbonil menor)-alquilésteres menores, los (alcanoiloxi menor, alcoxicarbonil menor o di- alquilaminocarbonil menor)- alquilésteres menores, tal como el éster pivaloiloximetílico y similares convencionalmente utilizados en el estado de la técnica. Además, se han enmascarado las aminas como derivados sustituidos de arilcarboniloximetilo los cuales son escindidos mediante esterasas *en vivo* liberando el fármaco libre y formaldehído (Bundgaard, *J. Med. Chem.* 2503 (1989)) Además, los fármacos que contienen un grupo NH ácido, tales como imidazol, imida, indol y similares, han sido enmascarados con grupos N- aciloximetilo (Bundgaard, *Design de Profármacos*, Elsevier (1985)). Los grupos hidroxilo han sido enmascarados como ésteres y éteres. EP 039,051 (Sloan y Little) divulga profármacos de ácido hidroxámico con base Mannich, su preparación y uso.

Además, los compuestos del presente invento, incluyendo sus sales, también pueden obtenerse en la forma de sus hidratos, o incluir otros solvatos utilizados para su cristalización.

Dentro del alcance de este texto, solamente un grupo fácilmente removible que no es un constituyente del producto final deseado particular de los compuestos del presente invento se designa un "grupo protector", a menos que el contexto indique lo contrario. La protección de grupos funcionales mediante tales protectores de grupo, los protectores de grupo mismos, y sus reacciones de escisión se describen por ejemplo en trabajos de referencia estándar, tal como J.

F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London y New York 1973, en T. W. Greene y P. G. M. Wuts, "Protective Groups in Organic Synthesis", Tercera edición, Wiley, New York 1999, en "Los Péptidos "; Volume 3 (editors: E. Gross y J. Meienhofer), Academic Press, London y New York 1981, en "Methoden der organischen Chemie" (Métodos de Química Orgánica), Houben Weyl, 4th edición, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, en H.- D. Jakubke y H. Jeschkeit, "Aminosäuren, Peptide, Proteine" (Aminoacidos, Péptidos, Proteínas), Verlag Chemie, Weinheim, Deerfield Beach, y Basel 1982, y en Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (Quimica de Carbohidratos: Monosacaridos y Derivados), Georg Thieme Verlag, Stuttgart 1974. Una característica de protectores de grupo es que estos se pueden retirar de manera fácil (es decir sin la ocurrencia de reacciones secundarias indeseadas) por ejemplo mediante solvólisis, reducción, fotolisis o alternativamente bajo condiciones fisiológicas (*ej.,* mediante escisión enzimática).

Sales de compuestos del presente invento que tienen al menos un grupo formador de sal pueden prepararse en una forma conocida por aquellos con experiencia en el estado de la técnica. Por ejemplo, sales de compuestos del presente invento que tienen grupos ácidos pueden formarse, por ejemplo, al tratar los compuestos con compuestos metálicos, tal como sales de metales alcalinos de ácidos carboxílicos orgánicos apropiados, ej., la sal de sodio de ácido 2-etilhexanóico, con compuestos orgánicos de metales alcalinos o alcalinotérreos, tal como los hidróxidos correspondientes, carbonatos o carbonatos de hidrógeno, tales como hidróxido de sodio o potasio, carbonato o carbonato de hidrógeno, con compuestos de calcio correspondientes o con amoniaco o una amina orgánica apropiada, cantidades estoiquiométricas o solamente un pequeño exceso del agente formador de sales preferiblemente siendo utilizado. Las sales de adición ácida de los compuestos del presente invento son obtenidas en forma habitual, *ej.,* al tratar los compuestos con un ácido o un reactivo de intercambio aniónico apropiado. Las sales internas de compuestos del presente invento que contienen grupos formadores de sales ácidas y básicas, *ej.,* un grupo carboxilo libre y un grupo amino libre, pueden formarse, *ej.,* mediante la neutralización de sales, tales como sales de adición ácida, hacia el punto isoeléctrico, *ej.,* con bases débiles, o mediante tratamiento con intercambiadores de iones.

Las sales pueden convertirse en los compuestos libres según métodos conocidos por aquellos con experiencia en el estado de la técnica. Las sales metálicas y de amonio pueden convertirse, por ejemplo, mediante tratamiento con ácidos apropiados, y sales de adición ácida, por ejemplo, mediante tratamiento con un agente alcalino apropiado.

Las mezclas de isoméros obtenibles según el invento pueden separarse en una forma conocida por aquellos con experiencia en el estado de la técnica en los isómeros individuales; los diastereoisómeros pueden separarse, por ejemplo, al particionar entre mezclas solventes polifásicas, recristalización y/o separación cromatográfica, por ejemplo sobre gel de sílice o por *ej.,* cromatografía líquida de mediana presión sobre una columna de fase invertida, y los racematos pueden separarse, por ejemplo, mediante la formación de sales con reactivos formadores de sales ópticamente puras y separación de la mezcla de diastereoisómeros así obtenible, por ejemplo por medio de cristalización fraccional, o mediante cromatografía sobre materiales de columna ópticamente activa.

Intermedios y productos finales pueden purificarse según métodos estándar, ej., utilizando métodos cromatográficos, métodos de distribución, (re)- cristalización, y similares.

Lo siguiente aplica en general a todos los procesos mencionados en la presente antes y de aquí en adelante.

Todos los pasos de proceso antes mencionados pueden realizarse bajo condiciones de reacción que son conocidas por aquellos con experiencia en el estado de la técnica, incluyendo aquellas específicamente mencionadas, en ausencia o, comúnmente, en presencia de solventes o diluyentes, incluyendo, por ejemplo, solventes o diluyentes que son inertes a los reactivos utilizados y disolverlos, en ausencia o presencia de catalizadores, agentes de condensación o neutrolizadores, por ejemplo intercambiadores de iones, tales como intercambiadores de cationes, *ej.,* en la forma H+, dependiendo de la naturaleza de la reacción y/o de los reactivos a temperatura reducida, normal o elevada, por ejemplo en un rango de temperatura dentro - 100 ºC y 190 ºC aproximadamente, incluyendo, por ejemplo, desde - 80 ºC a 150 ºC aproximadamente, por ejemplo entre - 80 y - 60 ºC aproximadamente, a temperatura ambiente, desde - 20 a 40 ºC aproximadamente o a temperatura de reflujo, bajo presión atmosférica o en un recipiente cerrado, donde sea apropiado bajo presión, y/o en una atmósfera inerte, por ejemplo bajo una atmósfera de argón o nitrógeno.

En todas las etapas de las reacciones, las mezclas de isoméros que se forman pueden separarse en los isómeros individuales, por ejemplo diastereoisómeros o enantiomeros, o en cualquiera de las mezclas deseadas de isoméros, por ejemplo racematos o mezclas de diastereoisómeros, por ejemplo de manera análoga a los métodos descritos bajo "pasos de proceso adicionales".

Los solventes desde los cuales estos solventes que son apropiados para cualquier reacción particular pueden seleccionarse incluyen aquellos específicamente mencionados o, por ejemplo, agua, ésteres, tales como alquilo inferior- alcanoatos inferiores, por ejemplo acetato de

etilo, éteres, tal como éteres alifáticos, por ejemplo éter dietílico, o éteres cíclicos, por ejemplo tetrahidrofurano o dioxano, hidrocarburos aromáticos líquidos, tales como benceno o tolueno, alcoholes, tales como metanol, etanol o 1- o 2- propanol, nitrilos, tal como acetonitrilos, hidrocarburos halogenados, tales como cloruro de metileno o cloroformo, amidas ácidas, tales como dimetilformamida o acetamida de dimetilo, bases, tales como bases de nitrógeno heterocíclico, por ejemplo piridina o *N*- metilpirrolidin- 2- ona, anhidridos de ácido carboxílicos, tales como anhidridos de ácido alcanoico inferior, por ejemplo anhídrido acético, hidrocarburos cíclicos, lineales o ramificados, tales como ciclohexano, hexano o isopentano, meticiclohexano, o mezclas de estos solventes, por ejemplo soluciones acuosas, a menos que se indique lo contrario en la descripción de los procesos. Tales mezclas solventes también pueden utilizarse en tratamientos finales, por ejemplo mediante cromatografía o particionamiento.

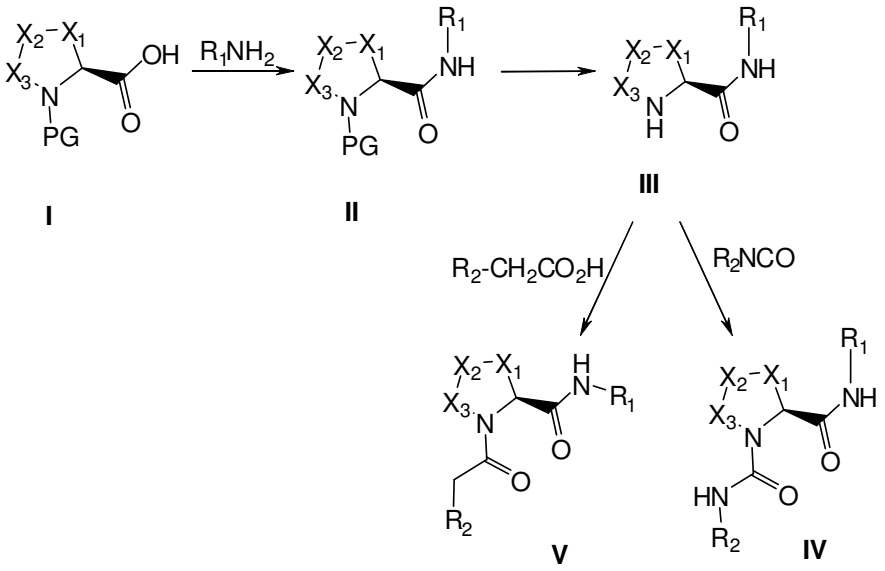
Los compuestos, incluyendo sus sales, también pueden obtenerse en la forma de hidratos, o sus cristales pueden, por ejemplo, incluir el solvente utilizado para cristalización. Diferentes formas cristalinas pueden estar presentes.

La invención también se relaciona con aquellas formas del proceso en las cuales un compuesto obtenible como un intermedio cualquier etapa del proceso se utiliza como material de inicio y se realizan los restantes pasos del proceso, o en los cuales un material de inicio se forma bajo las condiciones de reacción o se utiliza en la forma de un derivado, por ejemplo en una forma protegida o en la forma de una sal, o un compuesto obtenible por el proceso según el invento se produce bajo las condiciones de proceso y se procesa adicionalmente in situ.

Todos los materiales de inicio, componentes fundamentales (materia prima), reactivos, ácidos, bases, agentes deshidratantes, solventes y catalizadores utilizados para sintetizar los compuestos del presente invento están comercialmente disponibles o pueden producirse mediante métodos de síntesis orgánica conocidos por alguien habilidad común en el estado de la técnica (Houben- Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21).

Típicamente, los compuestos de la fórmula (I) pueden prepararse según los Esquemas proporcionados a continuación.

Un compuesto de la fórmula IV o V puede, por ejemplo, prepararse a partir de un aminoácido N- protegido correspondiente como se describe a continuación:



Por reacción de un aminoácido N- protegido I en donde PG es un grupo protector o un derivado reactivo del mismo con un compuesto amino, en condiciones de condensación para obtener un compuesto de la fórmula II. Eliminando el grupo protector y haciendo reaccionar el compuesto de la fórmula III con un isocianato para obtener un compuesto de la fórmula IV o con un ácido o un derivado reactivo del mismo bajo condiciones de condensación para obtener un compuesto de la fórmula V.

La invención también incluye cualquier variante de estos procesos, en los cuales un producto intermedio obtenible en cualquier etapa de los mismos se utiliza como material de partida y el resto de pasos se llevan a cabo, o en los que los materiales de partida se forman *in situ* bajo condiciones de reacción, o en los cuales los componentes de reacción se utilizan en la forma de sus sales o antípodas ópticamente puros.

Los compuestos de la invención y los intermedios también se pueden convertir unos a otros según métodos generalmente conocidos por expertos en el estado de la técnica.

En otro aspecto, el presente invento proporciona una composición farmacéutica que comprende a compuesto del presente invento y un vehículo farmacéuticamente aceptable. La composición farmacéutica puede formularse para rutas particulares de administración tales como administración oral, administración parenteral, y administración oftálmica, etc. Además, las composiciones farmacéuticas de la presente invención pueden integrarse en una forma sólida (incluyendo sin limitación cápsulas, tabletas, píldoras, gránulos, polvos o supositorios), o en una forma líquida (incluyendo sin limitación soluciones, suspensiones o emulsiones, cada uno de los cuales puede ser apropiado para administración oftálmica). Las composiciones farmacéuticas pueden someterse a operaciones farmacéuticas convencionales tales como

esterilización y/o pueden contener diluyentes inertes convencionales, agentes lubricantes, o agentes amortiguadores, así como también adyuvantes, tales como preservativos, estabilizadores, agentes humectantes, emulsificadores y buffers, etc.

Típicamente, las composiciones farmacéuticas son comprimidos o cápsulas de gelatina que comprenden el ingrediente activo junto con

a) diluyentes, *ej*., lactosa, dextrosa, sacarosa, manitol, sorbitol, celulosa y/o glicina;

b) lubricantes, ej., silicio, talco, ácido estearico, su sal de magnesio o calcio y/o glicol de polietileno; para tabletas también

c) aglutinantes, ej, silicato de magnesio y aluminio, pasta de almidón, gelatina, tragacanto, metilcelulosa, carboximetilcelulosa de sodio y/o polivinilpirrolidona; si se desea

d) desintegrantes, ej., almidones, agar, ácido algínico o su sal de sodio, o mezclas efervescentes; y/o

e) absorbentes, colorantes, agentes sapófiros y edulcorantes.

Las tabletas pueden tener revestimiento de película o revestimiento entérico según métodos conocidos en el estado de la técnica.

Composiciones adecuadas para administración oral incluyen una cantidad efectiva de un compuesto del presente invento en la forma de comprimidos, grageas, suspensiones acuosas o aceitosas, polvos o gránulos dispersables, emulsión, cápsulas duras o blandas, o jarabes o elixires. Las composiciones para uso oral son preparadas según cualquier método conocido en el estado de la técnica para la fabricación de composiciones farmacéuticas y tales composiciones pueden contener uno o más agentes seleccionados del grupo que consta de agentes endulzantes, agentes saborizantes, agentes colorantes y agentes preservativos con el objeto de proporcionar preparaciones farmacéuticamente elegantes y de sabor agradable. Las tabletas pueden contener el ingrediente activo en mezcla con excipientes farmacéuticamente aceptables no tóxicos los cuales son apropiados para la fabricación de tabletas. Estos excipientes son, por ejemplo, diluyentes inertes, tales como carbonato de calcio, carbonato de sodio, lactosa, fosfato de calcio o fosfato de sodio; agentes granulantes y desintegrantes, por ejemplo, almidón de maíz, o ácido algínico; agentes aglomerantes, por ejemplo, almidón, gelatina o acacia; y agentes lubricantes, por ejemplo estearato de magnesio, ácido esteárico o talco. Las tabletas son revestidas o no revestidas mediante técnicas conocidas para retardar desintegración y absorción en el tracto gastrointestinal y proporcionar así una acción sostenida

durante un periodo más largo de tiempo. Por ejemplo, puede utilizarse un material retardante tal como monoestearato de glicerilo o diestearato de glicerilo. Las formulaciones para uso oral pueden presentarse como cápsulas de gelatina dura en donde el ingrediente activo es mezclado con un diluyentes sólido inerte, por ejemplo, carbonato de calcio, fosfato de calcio o caolina, o como cápsulas de gelatina suave en donde el ingrediente activo es mezclado con agua o un medio de aceite, por ejemplo, aceite de coco, parafina líquida o aceite de oliva.

Ciertas composiciones inyectables son soluciones o suspensiones acuosas isotónicas, y los supositorios son ventajosamente preparados a partir de emulsiones o suspensiones grasas. Dichas composiciones pueden ser esterilizadas y/o contener adyuvantes, tales como agentes preservantes, estabilizantes, humectantes o emulsificantes, promotores de solución, sales para regular la presión osmótica y/o buffers. Además, también pueden contener otras sustancias terapéuticamente valiosas. Dichas composiciones son preparadas según métodos convencionales de mezclado, granulación o revestimiento, respectivamente, y contienen 0.1-75% aproximadamente, o contienen 1- 50% aproximadamente, del ingrediente activo.

Composiciones apropiadas para aplicación transdérmica incluyen una cantidad efectiva de un compuesto del invento con un vehículo apropiado. Vehículos apropiados para liberación transdérmica incluyen solvatos farmacológicamente aceptables absorbentes para asistir en el pasaje a través de la piel del huésped. Por ejemplo, los dispositivos transdérmicos están en la forma de un vendaje que comprende un miembro de soporte, un depósito que contiene el compuesto opcionalmente con vehículos, opcionalmente una barrera controladora de tasa para liberar el compuesto de la piel del huésped a una tasa controlada y predeterminada durante un periodo de tiempo prolongado, y medios para asegurar el dispositivo a la piel.

Composiciones apropiadas para aplicación tópica, *ej.*, a la piel y ojos, incluyen soluciones acuosas, suspensiones, ungüentos, cremas, geles o formulaciones en atomizador, *ej.*, para liberación mediante aerosol o similares. Tales sistemas de liberación tópica en particular serán apropiados para aplicación oftálmica, ej., para el tratamiento de enfermedades oculares, ej., para uso terapéutico o profiláctico en el tratamiento de degeneración macular relacionada con la edad y otros trastornos oftálmicos mediados por complemento. Estos pueden contener solubilizantes, estabilizadores, agentes mejoradotes de tonicidad, buffer y preservativos.

Como se utiliza en la presente una aplicación tópica también se refiere a una inhalación o a una aplicación intranasal. Estas pueden ser convenientemente liberadas en la forma de un polvo seco (bien sea solo, como una mezcla, por ejemplo una mezcla seca con lactosa, o como partículas de componentes mixtos, por ejemplo con fosfolípidos) a partir de un inhalador de

polvo seco o una presentación de aerosol a partir de un recipiente presurizado, bomba, atomizador, atomizador o nebulizador, con o sin el uso de un propelente apropiado.

Formas de dosificación para la administración tópica o transdérmica de un compuesto de este invento incluyen polvos, aerosoles, ungüentos, pastas, cremas, lociones, geles, soluciones, parches e inhaladores. El compuesto activo puede mezclarse bajo condiciones estériles con un vehículo farmacéuticamente aceptable, y con cualquiera de los preservativos, buffers, o propulsores que puedan ser deseables.

Los ungüentos, pastas, cremas y geles pueden contener, además de un compuesto activo de este invento, excipientes, tales como grasas animales y vegetales, aceites, ceras, parafinas, almidón, tragacanto, derivados de celulosa, glicoles de polietileno, siliconas, bentonitas, ácido silícico, talco y óxido de zinc, o mezclas de los mismos.

Polvos y aerosoles pueden contener, además de un compuesto de este invento, excipientes tales como lactosa, talco, ácido silícico, hidróxido de aluminio, silicatos de calcio y polvo de poliamida, o mezclas de estas sustancias. Los aerosoles pueden contener adicionalmente propulsores habituales, tales como clorofluorohidrocarburos e hidrocarburos no sustituidos volátiles, tales como butano y propano.

Los parches transdérmicos tienen la ventaja agregada de proporcionar liberación controlada de un compuesto del presente invento al cuerpo. Tales formas de dosificación pueden prepararse al disolver o dispersar el compuesto en el medio apropiado. También pueden utilizarse mejoradores de absorción para aumentar el flujo del compuesto a través de la piel. La tasa de tal flujo puede controlarse mediante cualquiera proporcionar una membrana controladora de tasa o dispersar el compuesto activo en una matriz o gel polimérico.

También se contemplan dentro del alcance de este invento las formulaciones oftalmicas, ungüentos oculares, polvos, soluciones y similares.

El presente invento además proporciona composiciones farmacéuticas anhídridas y formas de dosificación que comprenden los compuestos del presente invento como ingredientes activos, puesto que el agua puede facilitar la degradación de ciertos compuestos.

Composiciones farmacéuticas anhídridas y formas de dosificación del invento pueden prepararse utilizando ingredientes anhidros o que contiene baja humedad y condiciones de baja humedad. Una composición farmacéutica anhídrida puede prepararse y almacenarse tal que su naturaleza anhídrida sea mantenida. Por consiguiente, composiciones anhídridas son empacadas utilizando materiales conocidos para prevenir exposición al agua tal que éstas puedan incluirse en kits de formulación apropiados. Ejemplos de empaques apropiados

incluyen, pero no están limitados a aluminios herméticamente sellados, plásticos, recipientes de dosis unitaria (ej., viales), empaques blister, y empaques de tira.

La invención además proporciona composiciones farmacéuticas y formas de dosificación que comprenden uno o más agentes que reducen la tasa mediante la cual el compuesto del presente invento como un ingrediente activo se descompondrá. Tales agentes, los cuales se conocen en la presente como "estabilizadores," incluyen, pero no están limitados a, antioxidantes tales como ácido ascórbico, buffers de pH, o buffers de sales, etc.

Usos profilácticos y Terapéuticos

Los compuestos de la fórmula I en forma libre o en forma de sal farmacéuticamente aceptable, exhiben propiedades farmacológicas valiosas, ej., propiedades moduladoras del Factor D, propiedades moduladoras de la ruta de complemento y modulación de las propiedades de la ruta de complemento alternativa, ej., como se indica en pruebas *in vitro* y *in vivo* como se describe en las siguientes secciones y por lo tanto se indican para terapia.

La presente invención proporciona métodos para tratar una enfermedad o trastorno asociado con la actividad de complemento aumentada mediante la administración a un sujeto que lo necesita una cantidad eficaz de los compuestos de la fórmula (I) de la invención. En ciertos aspectos, se proporcionan métodos para el tratamiento de enfermedades asociadas con el aumento de la actividad del bucle de amplificación C3 de la vía del complemento. En ciertas realizaciones, se proporcionan métodos de tratamiento o prevención de enfermedades mediadas por complemento en los que la activación del complemento es inducida por las interacciones anticuerpo- antígeno, por un componente de una enfermedad autoinmune, o por el daño isquémico.

En una realización específica, la presente invención proporciona un método de tratar degeneración macular relacionada con la edad (AMD) al administrar a un sujeto en necesidad del mismo una cantidad efectiva del compuesto de la Fórmula (I) de la invención. En ciertas realizaciones, los pacientes que son actualmente asintomáticos, pero están en riesgo de desarrollar un trastorno relacionado con la degeneración macular sintomática son adecuados para la administración con un compuesto de la invención. Los métodos de tratamiento o prevención de AMD incluyen, pero no se limitan a, métodos de tratamiento o prevención de uno o más síntomas o aspectos de AMD seleccionados de la formación de drusas oculares, inflamación del ojo o el tejido ocular, pérdida de células fotorreceptoras, pérdida de la visión (incluyendo la pérdida de la agudeza visual o del campo visual), neovascularización (incluyendo CNV), desprendimiento de retina, degeneración de los fotorreceptores,

degeneración RPE, degeneración de la retina, degeneración coriorretiniana, degeneración de conos, disfunción retiniana, daño en la retina en respuesta a la exposición a la luz, daño de la membrana de Bruch, y/o pérdida de la función RPE.

El compuesto de la Fórmula (I) de la invención se puede utilizar, entre otras cosas, para prevenir la aparición de la AMD, para prevenir la progresión de AMD temprana a formas avanzadas de AMD incluyendo AMD neovascular o atrofia geográfica, para retrasar y/o prevenir la progresión de la atrofia geográfica, para tratar o prevenir el edema macular de AMD u otras condiciones (tales como retinopatía diabética, uveítis, o trauma pos quirúrgico o no quirúrgico), para prevenir o reducir la pérdida de la visión por AMD, y para mejorar la visión perdida debido a AMD temprana pre- existente o avanzada. También se pueden utilizar en combinación con terapias anti- VEGF para el tratamiento de pacientes con AMD neovascular o para la prevención de AMD neovascular. La presente invención proporciona además métodos de tratamiento de una enfermedad o trastorno relacionado con el complemento mediante la administración a un sujeto en necesidad del mismo de una cantidad eficaz del compuesto (s) de la invención, en el que dicha enfermedad o trastorno se selecciona de uveítis, degeneración macular en el adulto, retinopatía diabética, retinitis pigmentosa, edema macular, uveítis de Behcet, coroiditis multifocal, síndrome de Vogt- Koyangi- Harada, uveítis intermedia, retinocorioditis tipo perdigón, oftalmía simpática, penfigoide cicatricial ocular, pénfigo ocular, neuropatía óptica isquémica no artértica, inflamación post- operatoria, y oclusión venosa de la retina.

En algunas realizaciones, la presente invención proporciona métodos de tratar una enfermedad o trastorno relacionado con complemento mediante la administración a un sujeto que lo necesita una cantidad eficaz de los compuestos de la invención. Ejemplos de enfermedades o trastornos conocidos relacionados con el complemento incluyen: trastornos neurológicos, esclerosis múltiple, accidente cerebrovascular, síndrome de Guillain Barre, lesión cerebral traumática, enfermedad de Parkinson, trastornos de la activación inapropiada o indeseable del complemento, complicaciones de hemodiálisis, rechazo hiperagudo de injertos, rechazo de xenoinjertos, toxicidad inducida por interleucina- 2 durante la terapia con IL- 2, trastornos inflamatorios, inflamación de las enfermedades autoinmunes, enfermedad de Crohn, síndrome de dificultad respiratoria del adulto, lesión térmica incluyendo quemaduras o congelación, miocarditis, condiciones de reperfusión post- isquémica, infarto de miocardio, angioplastia con balón, síndrome pos bomba en bypass cardiopulmonar o bypass renal, aterosclerosis, hemodiálisis, isquemia renal, reperfusión arterial mesentérica después de reconstrucción aórtica, enfermedad infecciosa o sepsis, trastornos complejos inmunes y

enfermedades autoinmunes, artritis reumatoide, lupus eritematoso sistémico (LES), nefritis por LES, nefritis proliferativa, fibrosis hepática, anemia hemolítica, miastenia gravis, regeneración de tejidos y regeneración neuronal. Además, otras enfermedades relacionadas con el complemento conocidas son las enfermedades pulmonares y trastornos tales como disnea, hemoptisis, SDRA, asma, enfermedad pulmonar obstructiva crónica (EPOC), enfisema, embolias e infartos pulmonares, neumonía, enfermedades por polvos fibrogénicos, polvos inertes y minerales (por ejemplo, silicio, polvo de carbón, berilio, y asbestos), fibrosis pulmonar, enfermedades por polvos orgánicos, lesión química (debido a los gases y productos químicos irritantes, por ejemplo, cloro, fosgeno, dióxido de azufre, sulfuro de hidrógeno, dióxido de nitrógeno, amoníaco, y ácido clorhídrico), lesión de humo, lesión térmica (por ejemplo, quemadura, congelamiento), asma, alergia, broncoconstricción, neumonitis por hipersensibilidad, enfermedades parasitarias, síndrome de Goodpasture, vasculitis pulmonar, vasculitis pauciinmune, inflamación asociada con complejo inmune, uveítis (incluyendo enfermedad de Behcet y otros sub- tipos de uveítis), síndrome antifosfolípido.

En una realización específica, la presente invención proporciona métodos para tratar una enfermedad o trastorno relacionado con el complemento mediante la administración a un sujeto en necesidad del mismo una cantidad eficaz de los compuestos de la invención, en el que dicha enfermedad o trastorno es asma, artritis (por ejemplo, artritis reumatoide), enfermedad autoinmune del corazón, esclerosis múltiple, enfermedades intestinales inflamatorias, lesiones por isquemia- reperfusión, síndrome de Barraquer- Simons, hemodiálisis, lupus sistémico, lupus eritematoso, psoriasis, esclerosis múltiple, trasplantes, enfermedades del sistema nervioso central tales como la enfermedad de Alzheimer y otras enfermedades neurodegenerativas, síndrome urémico atípicamente hemolítico (SHU), glomerulonefritis (incluyendo glomerulonefritis proliferativa de membrana), enfermedades cutáneas eruptivas (incluyendo penfigoide ampollar, pénfigo, y epidermólisis bullosa), penfigoide ocular cicatricial o MPGN II.

En una realización específica, la presente invención proporciona métodos para tratar glomerulonefritis al administrar a un sujeto en necesidad del mismo una cantidad efectiva de una composición que comprende un compuesto de la presente invención. Síntomas de la glomerulonefritis incluyen, pero no se limitan a, proteinuria; reducción de la tasa de filtración glomerular (TFG); cambios de electrolitos séricos incluyendo azotemia (uremia, nitrógeno de urea en sangre excesivo - BUN) y retención de sal, que conduce a la retención de agua resultante en hipertensión y edema; hematuria y sedimentos urinarios anormales, incluyendo residuos de células rojas, hipoalbuminemia, hiperlipidemia, y lipiduria. En una realización

específica, la presente invención proporciona métodos de tratamiento de la hemoglobinuria paroxística nocturna (PNH) mediante la administración a un sujeto en necesidad del mismo una cantidad eficaz de una composición que comprende un compuesto de la presente invención con o sin la administración concomitante de un inhibidor del complemento C5 o inhibidor de la convertasa C5 tales como Soliris.

En una realización específica, la presente invención proporciona métodos de reducir la disfunción de los sistemas inmune y/o hemostático asociados con circulación extracorpórea al administrar a un sujeto en necesidad del mismo una cantidad efectiva de una composición que comprende un compuesto de la presente invención. Los compuestos de la presente invención se pueden utilizar en cualquier procedimiento que implica la circulación de la sangre del paciente desde un vaso sanguíneo del paciente, a través de un conducto, y de vuelta a un vaso sanguíneo del paciente, teniendo el conducto una superficie luminal que comprende un material capaz de provocar al menos una entre activación del complemento, activación de plaquetas, activación de leucocitos o adhesión de plaquetas- leucocitos. Tales procedimientos incluyen, pero no se limitan a, todas las formas de ECC, así como los procedimientos que implican la introducción de un órgano, tejido, o vaso artificial o extraño en el circuito sanguineo de un paciente. Más particularmente, dichos procedimientos incluyen, pero no se limitan a, los procedimientos de trasplante incluyendo procedimientos de trasplante de riñón, hígado, pulmón o corazón y los procedimientos de trasplante de células de los islotes.

En otras realizaciones, los compuestos de la invención son adecuadas para uso en el tratamiento de enfermedades y trastornos asociados con el metabolismo de los ácidos grasos, incluyendo la obesidad y otros trastornos metabólicos.

En otra forma de realización, los compuestos de la invención se pueden usar en ampollas de sangre, kits de diagnóstico y otros equipos utilizados en la recolección y muestreo de sangre. El uso de los compuestos de la invención en tales kits de diagnóstico puede inhibir la activación ex vivo de la vía del complemento asociada con el muestreo de sangre.

La composición farmacéutica o combinación de la presente invención puede ser en dosificación unitaria de 1- 1000 mg aproximadamente de ingrediente activo para un sujeto de 50- 70 kg aproximadamente, o 1- 500 mg aproximadamente o 1- 250 mg aproximadamente o 1- 150 mg aproximadamente o 0.5- 100 mg aproximadamente, o 1- 50 mg aproximadamente de ingredientes activos. La dosificación terapéuticamente efectiva de un compuesto, la composición farmacéutica, o las combinaciones de los mismos, es dependiente de la especie del sujeto, el peso corporal, edad y condición individual, el trastorno o enfermedad o la severidad de la misma. Un médico, médico clínico o veterinario con experiencia común puede fácilmente

determinar la cantidad efectiva de cada uno de los ingredientes activos necesarios para prevenir, tratar o inhibir el progreso del trastorno o enfermedad.

Las propiedades de dosificación antes citadas son demostrables en pruebas *in vitro* y *in vivo* utilizando de manera ventajosa mamíferos, *ej.*, ratones, ratas, perros, monos u órganos aislados, tejidos y preparaciones de los mismos. Los compuestos del presente invento pueden aplicarse *in vitro* en la forma de soluciones, *ej.*, soluciones acuosas, e *in vivo* bien sea de manera entérica, parenteral, de manera ventajosa, intravenosamente, *ej.*, como una suspensión o en solución acuosa. La dosificación *in vitro* puede estar en el rango entre concentraciones 10^{-3} molar y 10^{-9} molar aproximadamente. Una cantidad terapéuticamente efectiva *in vivo* puede estar en el rango dependiendo de la ruta de administración, entre 0.1 y 500 mg/kg aproximadamente, o entre 1 y 100 mg/kg aproximadamente.

La actividad de un compuesto según el presente invento puede evaluarse mediante los siguientes métodos *in vitro & in vivo*.

Los compuestos del presente invento pueden administrarse bien sea simultáneamente con, o antes de o después de, uno o más agentes terapéuticos. Los compuestos del presente invento pueden administrarse de manera separada, mediante la misma o diferente ruta de administración, o juntos en la misma composición farmacéutica como los otros agentes.

En una realización, la invención proporciona un producto que comprende un compuesto de la fórmula (I) y al menos otro agente terapéutico como una preparación combinada para uso simultaneo, separado o secuencial en terapia. En una realización, la terapia es el tratamiento de una enfermedad o condición mediada la ruta de complemento alternativa. Los productos proporcionados como una preparación combinada incluyen una composición que comprende el compuesto de la fómrula (I) y los otros agentes terapéuticos en la misma composición farmacéutica, o el compuesto de la fórmula (I) y los otros agentes terapéuticos en forma separada, *ej.,* en forma de un kit.

En una realización, el invento proporciona una composición farmacéutica que comprende un compuesto de la fórmula (I) y otros agentes terapéuticos. Opcionalmente, la composición farmacéutica puede comprender un excipiente farmacéuticamente aceptable, como se describió anteriormente.

En una realización, el invento proporciona un kit que comprende dos o más composiciones farmacéuticas separadas, al menos una de las cuales contiene un compuesto de la fórmula (I). En una realización, el kit comprende medios para retener de manera separada dichas composiciones, tales como un recipiente, botella dividida, o empaque dividido en

aluminio. Un ejemplo de tal kit es paquete blister, como el que típicamente se utiliza para empacar tabletas, cápsulas y similares.

El kit del invento puede utilizarse para administrar diferentes formas de dosificación, por ejemplo, oral y parenteral, para administrar las composiciones separadas a diferentes intervalos de dosificación, o para titular las diferentes composiciones entre sí. Para ayudar en el cumplimiento terapéutico, el kit del invento típicamente comprende pautas para administración.

En las terapias de combinación del invento, el compuesto del invento y el otro agente terapéutico pueden fabricarse y/o formularse por los mismos o diferentes fabricantes. Además, el compuesto del invento y el otro terapéutico serán llevados juntos en una terapia de combinación: (i) antes de entregar el producto de combinación a los médicos (*ej.* en el caso de un kit que comprende el compuesto del invento y el otro agente terapéutico); (ii) por los médicos mismos (o bajo la pauta del médico) poco antes de administración; (iii) en los pacientes mismos, *ej.* durante administración secuencial del compuesto del invento y el otro agente terapéutico.

Por consiguiente, la invención proporciona el uso de un compuesto de la fórmula (I) para tratar una enfermedad o condición mediada por la ruta alternativa de complemento, en donde el medicamento es preparado para administración con otro agente terapéutico. La invención también proporciona el uso de otro agente terapéutico para tratar una enfermedad o condición mediada por la ruta alternativa de complemento, en donde el medicamento se administra con un compuesto de la Fórmula (I).

La invención también proporciona un compuesto de la fórmula (I) para utilizar en un método de tratar una enfermedad o condición mediada por la ruta alternativa de complemento, en donde el compuesto de la fórmula (I) se prepara para administración con otro agente terapéutico. La invención también proporciona otro agente terapéutico para utilizar en un método de tratar una enfermedad o condición mediada por la ruta alternativa de complemento y/o Factor D, en donde el otro agente terapéutico se prepara para administración con un compuesto de la fórmula (I). La invención también proporciona un compuesto de la fórmula (I) para utilizar en un método de tratar una enfermedad o condición mediada por la ruta alternativa de complemento y/o Factor D, en donde el compuesto de la fórmula (I) se administra con otro agente terapéutico. La invención también proporciona otro agente terapéutico para utilizar en un método de tratar una enfermedad o condición mediada por la ruta alternativa de complemento y/o Factor D, en donde el otro agente terapéutico se administra con un compuesto de la fórmula (I).

La invención también proporciona el uso de un compuesto de la Fórmula (I) para tratar una enfermedad o condición mediada por la ruta alternativa de complemento y/o Factor D, en donde el paciente se ha tratado previamente (ej., dentro de las 24 horas) con otro agente terapéutico. La invención también proporciona el uso de otro agente terapéutico para el tratamiento de una enfermedad o condición mediada por la ruta alternativa de complemento y/o Factor D, en el que el paciente ha sido previamente tratado (por ejemplo, dentro de las 24 horas) con un compuesto de la fórmula (I).

Las composiciones farmacéuticas se pueden administrar solas o en combinación con otras moléculas conocidas por tener un efecto beneficioso sobre la fijación de la retina o tejido retiniano dañado, incluyendo moléculas capaces de reparación y regeneración de tejidos y/o inhibición de la inflamación. Ejemplos de cofactores útiles incluyen agentes anti- VEGF (tal como un anticuerpo o Fab contra el VEGF, por ejemplo, Lucentis o Avastin), factor de crecimiento de fibroblastos básico (bFGF), factor neurotrófico ciliar (CNTF), axokina (una muteína de CNTF), factor inhibidor de leucemia (LIF), neutrotrofina 3 (NT- 3), neurotrofina- 4 (NT- 4), factor de crecimiento nervioso (NGF), factor de crecimiento II tipo insulina, prostaglandina E2, factor de supervivencia 30 kD, taurina y vitamina A. Otros cofactores útiles incluyen cofactores para el alivio de síntomas, incluyendo antisépticos, antibióticos, agentes antivirales y antifúngicos y analgésicos y agentes anestésicos. Agentes adecuados para el tratamiento de combinación con los compuestos de la invención incluyen agentes conocidos en la técnica que son capaces de modular las actividades de los componentes del complemento.

Un régimen de tratamiento combinado puede ser aditivo, o puede producir resultados sinérgicos (por ejemplo, reducciones en la actividad de la vía del complemento más de lo esperado para el uso combinado de los dos agentes). En algunas formas de realización, la presente invención proporciona una terapia de combinación para prevenir y/o tratar AMD u otra enfermedad ocular relacionada con complemento como se describió anteriormente con un compuesto de la invención y un agente anti- angiogénico, tal como un agente anti- VEGF (incluyendo Lucentis y Avastin) o terapia fotodinámica (tal como verteporfina).

En algunas realizaciones, la presente invención proporciona una terapia de combinación para la prevención y/o tratamiento de enfermedades autoinmunes tal como se describe anteriormente con un compuesto de la invención y un agente de modulación de células B o de células T (por ejemplo, ciclosporina o análogos de la misma, rapamicina, RAD001 o análogos de los mismos, y similares). En particular, para la terapia de esclerosis múltiple puede incluir la combinación de un compuesto de la invención y un segundo agente MS seleccionado de fingolimod, cladribina, tysarbi, laquinimod, rebif, avonex y similares.

En una realización, la invención proporciona un método de modular la actividad de la vía alternativa del complemento en un sujeto, en el que el método comprende administrar al sujeto una cantidad terapéuticamente eficaz del compuesto según la definición de la fórmula (I). La invención proporciona además métodos de modular la actividad de la vía alternativa del complemento en un sujeto al modular la actividad del Factor D, en el que el método comprende administrar al sujeto una cantidad terapéuticamente eficaz del compuesto según la definición de la fórmula (I).

En una realización, la invención proporciona un compuesto según la definición de la fórmula (I), (Ia), (VII) o cualquier subfórmula del mismo, para uso como un medicamento.

En una realización, la invención proporciona el uso de un compuesto según la definición de la fórmula (I), (Ia), (VII) o cualquier subfórmula del mismo, para el tratamiento de un trastorno o enfermedad en un sujeto mediada por la activación del complemento. En particular, la invención proporciona el uso de un compuesto según la definición de la fórmula (I), (Ia), (VII) o cualquier subfórmula del mismo, para el tratamiento de un trastorno o enfermedad mediada por la activación de la vía alternativa de complemento.

En una realización, la invención proporciona el uso de un compuesto según la definición de la fórmula (I), (Ia), en la fabricación de un medicamento para el tratamiento de un trastorno o enfermedad en un sujeto caracterizada por la activación del sistema de complemento. Más particularmente en la fabricación de un medicamento para el tratamiento de una enfermedad o trastorno en un sujeto que se caracteriza por la sobre activación de de la vía alternativa del complemento.

En una realización, la invención proporciona el uso de un compuesto según la definición de la fórmula (I), (Ia), o subfórmulas del mismo para el tratamiento de un trastorno o enfermedad en un sujeto caracterizado por la activación del sistema de complemento. Más particularmente, la invención proporciona usos de los compuestos proporcionados en este documento en el tratamiento de una enfermedad o trastorno caracterizado por la sobre activación de la vía alternativa del complemento o el bucle de amplificación C3 de la vía alternativa. En ciertas realizaciones, el uso es en el tratamiento de una enfermedad o trastorno seleccionado de enfermedades de la retina (tales como la degeneración macular relacionada con la edad).

La presente invención proporciona el uso de los compuestos de la invención para tratar una enfermedad o trastorno asociado con la actividad de complemento aumentada mediante la administración a un sujeto que lo necesita una cantidad eficaz de los compuestos de la fórmula (I) de la invención. En ciertos aspectos, se proporcionan usos para el tratamiento de

enfermedades asociadas con la actividad aumentada del bucle de amplificación C3 de la vía del complemento. En ciertas realizaciones, se proporcionan usos de tratamiento o prevención de enfermedades mediadas por complemento en los que la activación del complemento es inducida por las interacciones anticuerpo- antígeno, por un componente de una enfermedad autoinmune, o por el daño isquémico.

En una realización específica, la presente invención proporciona el uso de los compuestos de la invención para el tratamiento o la prevención de la degeneración macular relacionada con la edad (AMD). En ciertas realizaciones, los pacientes que son actualmente asintomáticos, pero están en riesgo de desarrollar un trastorno relacionado con la degeneración macular sintomática son adecuados para la administración con un compuesto de la invención. El uso en el tratamiento o prevención de AMD incluyen, pero no se limitan a, uos de tratamiento o prevención de uno o más síntomas o aspectos de AMD seleccionados de la formación de drusas oculares, inflamación del ojo o el tejido ocular, pérdida de células fotorreceptoras, pérdida de la visión (incluyendo la pérdida de la agudeza visual o del campo visual), neovascularización (incluyendo CNV), desprendimiento de retina, degeneración de los fotorreceptores, degeneración RPE, degeneración de la retina, degeneración coriorretiniana, degeneración de conos, disfunción retiniana, daño en la retina en respuesta a la exposición a la luz, daño de la membrana de Bruch, y/o pérdida de la función RPE.

El compuesto de la Fórmula (I) de la invención se puede utilizar, entre otras cosas, para prevenir la aparición de la AMD, para prevenir la progresión de AMD temprana a formas avanzadas de AMD incluyendo AMD neovascular o atrofia geográfica, para retrasar y/o prevenir la progresión de la atrofia geográfica, para tratar o prevenir el edema macular de AMD u otras condiciones (tales como retinopatía diabética, uveítis, o trauma pos quirúrgico o no quirúrgico), para prevenir o reducir la pérdida de la visión por AMD, y para mejorar la visión perdida debido a AMD temprana pre- existente o avanzada. También se pueden utilizar en combinación con terapias anti- VEGF para el tratamiento de pacientes con AMD neovascular o para la prevención de AMD neovascular. La presente invención proporciona además métodos de tratamiento de una enfermedad o trastorno relacionado con el complemento mediante la administración a un sujeto en necesidad del mismo de una cantidad eficaz del compuesto (s) de la invención, en el que dicha enfermedad o trastorno se selecciona de uveítis, degeneración macular en el adulto, retinopatía diabética, retinitis pigmentosa, edema macular, uveítis de Behcet, coroiditis multifocal, síndrome de Vogt- Koyangi- Harada, uveítis intermedia, retinocorioditis tipo perdigón, oftalmía simpática, penfigoide cicatricial ocular, pénfigo ocular,

neuropatía óptica isquémica no artértica, inflamación post- operatoria, y oclusión venosa de la retina.

En algunas realizaciones, la presente invención proporciona usos para el tratamiento de una enfermedad o trastorno relacionado con el complemento. Ejemplos de enfermedades o trastornos conocidos relacionados con el complemento incluyen: trastornos neurológicos, esclerosis múltiple, accidente cerebrovascular, síndrome de Guillain Barre, lesión cerebral traumática, enfermedad de Parkinson, trastornos de la activación inapropiada o indeseable del complemento, complicaciones de hemodiálisis, rechazo hiperagudo de injertos, rechazo de xenoinjertos, toxicidad inducida por interleucina- 2 durante la terapia con IL- 2, trastornos inflamatorios, inflamación de las enfermedades autoinmunes, enfermedad de Crohn, síndrome de dificultad respiratoria del adulto, lesión térmica incluyendo quemaduras o congelación, miocarditis, condiciones de reperfusión post- isquémica, infarto de miocardio, angioplastia con balón, síndrome pos bomba en bypass cardiopulmonar o bypass renal, aterosclerosis, hemodiálisis, isquemia renal, reperfusión arterial mesentérica después de reconstrucción aórtica, enfermedad infecciosa o sepsis, trastornos complejos inmunes y enfermedades autoinmunes, artritis reumatoide, lupus eritematoso sistémico (LES), nefritis por LES, nefritis proliferativa, fibrosis hepática, anemia hemolítica, miastenia gravis, regeneración de tejidos y regeneración neuronal. Además, otras enfermedades relacionadas con el complemento conocidas son las enfermedades pulmonares y trastornos tales como disnea, hemoptisis, SDRA, asma, enfermedad pulmonar obstructiva crónica (EPOC), enfisema, embolias e infartos pulmonares, neumonía, enfermedades por polvos fibrogénicos, polvos inertes y minerales (por ejemplo, silicio, polvo de carbón, berilio, y asbestos), fibrosis pulmonar, enfermedades por polvos orgánicos, lesión química (debido a los gases y productos químicos irritantes, por ejemplo, cloro, fosgeno, dióxido de azufre, sulfuro de hidrógeno, dióxido de nitrógeno, amoníaco, y ácido clorhídrico), lesión de humo, lesión térmica (por ejemplo, quemadura, congelamiento), asma, alergia, broncoconstricción, neumonitis por hipersensibilidad, enfermedades parasitarias, síndrome de Goodpasture, vasculitis pulmonar, vasculitis pauciinmune, inflamación asociada con complejo inmune, uveítis (incluyendo enfermedad de Behcet y otros sub- tipos de uveítis), síndrome antifosfolípido.

En una realización específica, la presente invención proporciona el uso de los compuestos de la invención para tratar una enfermedad o trastorno relacionado con el complemento, en el que dicha enfermedad o trastorno es asma, artritis (por ejemplo, artritis reumatoide), enfermedad autoinmune del corazón, esclerosis múltiple, enfermedades intestinales inflamatorias, lesiones por isquemia- reperfusión, síndrome de Barraquer- Simons,

hemodiálisis, lupus sistémico, lupus eritematoso, psoriasis, esclerosis múltiple, trasplantes, enfermedades del sistema nervioso central tales como la enfermedad de Alzheimer y otras enfermedades neurodegenerativas, síndrome urémico atípicamente hemolítico (SHU), glomerulonefritis (incluyendo glomerulonefritis proliferativa de membrana), enfermedades cutáneas eruptivas (incluyendo penfigoide ampollar, pénfigo, y epidermólisis bullosa), penfigoide ocular cicatricial o MPGN II.

En una realización específica, la presente invención proporciona el uso de los compuestos de la invención para el tratamiento de la glomerulonefritis. Síntomas de la glomerulonefritis incluyen, pero no se limitan a, proteinuria; reducción de la tasa de filtración glomerular (TFG); cambios de electrolitos séricos incluyendo azotemia (uremia, nitrógeno de urea en sangre excesivo - BUN) y retención de sal, que conduce a la retención de agua resultante en hipertensión y edema; hematuria y sedimentos urinarios anormales, incluyendo precipitados de glóbulos rojos, hipoalbuminemia, hiperlipidemia, y lipiduria. En una realización específica, la presente invención proporciona métodos de tratamiento de la hemoglobinuria paroxística nocturna (PNH) mediante la administración a un sujeto en necesidad del mismo una cantidad eficaz de una composición que comprende un compuesto de la presente invención con o sin la administración concomitante de un inhibidor del complemento C5 o inhibidor de la convertasa C5 tales como Soliris.

En una realización específica, la presente invención proporciona el uso de los compuestos de la invención para reducir la disfunción de los sistemas inmune y/o hemostático asociados con circulación extracorpórea. Los compuestos de la presente invención se pueden utilizar en cualquier procedimiento que implica la circulación de la sangre del paciente desde un vaso sanguíneo del paciente, a través de un conducto, y de vuelta a un vaso sanguíneo del paciente, teniendo el conducto una superficie luminal que comprende un material capaz de provocar al menos una entre activación del complemento, activación de plaquetas, activación de leucocitos o adhesión de plaquetas- leucocitos. Tales procedimientos incluyen, pero no se limitan a, todas las formas de ECC, así como los procedimientos que implican la introducción de un órgano, tejido, o vaso artificial o extraño en el circuito sanguineo de un paciente. Más particularmente, dichos procedimientos incluyen, pero no se limitan a, los procedimientos de trasplante incluyendo procedimientos de trasplante de riñón, hígado, pulmón o corazón y los procedimientos de trasplante de células de los islotes.

Los siguientes ejemplos tienen el propósito de ilustrar la invención y no deben interpretarse como limitaciones de la misma. Las temperaturas son dadas en grados centigrados (°C). Si no se menciona lo contrario, todas las evaporaciones son realizadas bajo presión

reducida, preferiblemente entre 15 mm Hg y 100 mm Hg aproximadamente (=20- 133 mbar). La estructura de los productos finales, intermedios y materiales de inicio es confirmada por métodos analíticos estándar, ej., microanálisis y características espectroscópicas, ej., MS, IR, RMN. Las abreviaturas utilizadas son las convencionales en la técnica.

Todos los materiales de inicio, componentes fundamentales (materia prima), reactivos, ácidos, bases, agentes deshidratantes, solventes y catalizadores utilizados para sintetizar los compuestos del presente invento están comercialmente disponibles o pueden producirse mediante métodos de síntesis orgánica conocidos por alguien con habilidad común en el estado de la técnica (Houben- Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21). Además, los compuetos de la presente invención pueden producirse mediante métodos de síntesis orgánica conocidos por un experto en el estado de la técnica como se muestra en los siguientes ejemplos.

Entre otras se pueden utilizar las siguientes pruebas in vitro

Ensayo de Factor D de complemento humano: Método 1:

El factor recombinante humano D (expresado en E. coli y purificado utilizando métodos estándar) a una concentración de 10 nM se incuba con compuesto de ensayo a diversas concentraciones durante 1 hora a temperatura ambiente en buffer Hepes 0.1 M, pH 7,5, que contiene MgCl2 1 mM, NaCl 1M y CHAPS al 0,05%. Un sustrato sintético Z- Lys- tiobencilo y 2,4- dinitrobencenosulfonilo- fluoresceína se añadió a concentraciones finales de 200 µM y 25 µM, respectivamente. El aumento de la fluorescencia se registra a una excitación de 485 nm y emisión a 535 nm en un espectrofluorímetro de microplaca. Los valores IC_{50} se calculan a partir del porcentaje de inhibición de actividad del factor de complemento D como función de la concentración del compuesto de prueba.

Ensayo de Factor D de complemento humano: Método 2:

El factor recombinante humano D (expresado en E. coli y purificado utilizando métodos estándar) a una concentración de 10 nM se incuba con compuesto de ensayo a diversas concentraciones durante 1 hora a temperatura ambiente en PBS 0.1 pH 7.4, que contiene MgCl2 7.5 mM, y CHAPS al 0,075% (peso/volumen). El factor del veneno de cobra y el complejo de sustrato del factor de complemento humano B se añade a una concentración final de 200 nM. Después de 1 hora de incubación a temperatura ambiente, la reacción enzimática se detuvo mediante la adición de buffer de carbonato sódico 0,1 M pH 9,0 que contiene NaCl 0,15

M y EDTA 40 mM. El producto de la reacción, Ba, se cuantificó por medio de un ensayo inmunosorbente ligado a enzima. Los valores IC_{50} se calculan a partir del porcentaje de inhibición de actividad del factor D como función de la concentración del compuesto de prueba.

Los siguientes Ejemplos, mientras que representan realizaciones preferidas de la invención, sirven para ilustrar la invención sin limitar su alcance.

Abreviaturas:

abs.	Absoluto
Ac	acetilo
EtOAc	acetato de etilo
AcOH	ácido acético
aq	acuoso
cc	concentrado
c- hexano	ciclohexano
CSA	Ácido canfor sulfónico
DIPEA	N, N- diisopropiletilamina
DBU	1,8- diazabiciclo[5.4.0]undec- - 7- eno
DCC	N,N- diciclohexilcarbodiimida
DIBALH	hidruro de diisobutilaluminio
DMF	dimetilformamida
DMSO	dimetilsulfóxido
DPPA	Azida de difenilfosforilo
EDCI	Hidrocloruro de 1- (3- Dimetilaminopropil)- 3- etilcarbodiimida
Eter	dietileter
Et_3N	trietilamina
Et_2O	dietileter
EtOH	etanol
Flujo:	Tasa de flujo:
h	Horas (s)
HMPA	hexametilfosforoamida
HOBt	1- hidroxibenzotriazol

HBTU	Tetrafluoroborato de 2- (1H- benzotriazol- 1- il)- 1,1,3,3- tetrametiluronio
HPLC	Cromatografía líquida de alto desempeño
iPrOH	isopropanol
L	litros
KHMDS	hexametildisilazano potásico
LC- MS	Cromatografía líquida/Espectrometría de masas
LDA	diisopropilamida de litio
Me	metilo
MeI	Yoduro de metilo
MeOH	metanol
MesCl	Cloruro de Mesilo
min	minuto(s)
mL	mililitro
MS	Espectrometría de masas
NBS	N- Bromo succinimida
NMM	4- metilmorfolina
NMR	Resonancia magnética nuclear
Pd/C	paladio sobre carbón vegetal
Ph	fenilo
PiBOP	(benzotriazol- 1- iloxi)- tripirrolidinofosfonio- Hexafluorofosfato
SEM- Cl	Cloruro de 2- (Trimetilsilil)etoximetilo
RT	temperatura ambiente
TBAF	Fluoruro de tetra- butilamonio
TBDMS- Cl	Cloruro de terc- butildimetilsililo
TBDMS	*terc*- butildimetilsililo
TBME	terc- butilmetiléter
TEA	trietilamina
TMEDA	tetrametiletilenodiamina
TEMPO	Radical libre de 2,2,6,6,- tetrametil- 1- piperidiniloxilo
TFA	ácido trifluoroacético
THF	tetrahidrofurano
T_3P	anhidrido propilfosfónico

RP	fase inversa
Prep	Preparativa
TLC	Cromatografía de Capa Delgada
t_r	tiempo de retención

Celite marca registrada	= Celite® (La Corporación Celite) = ayuda de filtración basada en tierra diatomacea
NH_2 Isoluto	(= Isolute® NH_2, Isolute® se registra para Argonaut Technologies, Inc.) = intercambio iónico con grupos amino basado en gel de sílice
Nucleosil	= Nucleosil®, marca registrada de Machery & Nagel, Düren, FRG para Materiales HPLC
Membrana PTFE	= Cromafil O- 45/15MS Politetrafluoroetileno producida por Macherey Nagel)
Cartucho PL Tiol	= Stratosphere® SPE, PL- Tiol MP SPE+, 500mg por Tubo de 6 mL, 1.5 mmol (nominal)

Las temperaturas son dadas en grados centígrados. A menos que se indique lo contrario, las reacciones se llevan a cabo a temperatura ambiente.

Separador de Fase: Biotage – Separador de Fase de Isoluto (Part Nr: 120- 1908- F para 70 mL y Parte No: 120- 1909- J para 150 mL)

Condiciones TLC : valores R_f para TLC se miden en placas TLC de 5 x 10 cm, gel de sílice F_{254}, Merck, Darmstadt, Alemania.

Condiciones HPLC:

HPLC se realizaron usando un instrumento Agilent serie 1100 o 1200. Los espectros de masas y LC/MS se determinaron usando un instrumento Agilent de la serie 1100.

a: Waters Symmetry C18, 3.5um, 2.1x50mm, 20- 95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/2 min, CH_3CN y H_2O conteniendo TFA al 0.1%, flujo: 0,6 mL/min

b: Agilent Eclipse XDB- C18; 1,8um; 4.6x50mm 20- 100% CH_3CN/H_2O/6min, 100%CH_3CN/1.5min, CH_3CN y H_2O que contiene TFA al 0.1%, flujo: 1 mL/min

c. Agilent Eclipse XDB- C18, 1.8um, 4.6x50mm, 5- 100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, CH_3CN y H_2O que contiene TFA al 0.1%, flujo: 1 mL/min

d. Waters XBridge C18, 2.5um, 3x30mm, 10- 95% CH_3CN/H_2O/1.7 min/flujo: 1.4 mL/min, 95% CH_3CN/flujo: 0.7 min/1.6 mL/min, CH_3CN que contiene TFA al 0.05%, H_2O que contiene TFA al 0.05% y CH_3CN al 5%

e. Waters XBridge C18, 2.5um, 3x30mm, 1% CH_3CN/H_2O/0.5 min/flujo: 1.4 mL/min, 1- 95% CH_3CN/H_2O/1.7 min/flujo: 1.4 mL/min, 95% CH_3CN/flujo: 0.7 min/1.6 mL/min, CH_3CN que contiene TFA al 0.05%, H_2O que contiene TFA al 0.05% y CH_3CN al 5%

f. Waters Sunfire C18, 2.5um, 3x30mm, 10- 98% en 2.5 min, CH_3CN y H_2O que contiene TFA al 0.1%, flujo: 1,4 mL/min

g. Waters Sunfire C18, 2.5um, 3x30mm, 0- 10% en 0.5 min, 10- 98% en 2.5 min, CH_3CN y H_2O que contiene TFA al 0.1% , flujo: 1,4 mL/min

h. Waters Sunfire C18, 2.5um, 3x30mm, 10- 98% en 4.5 min, CH_3CN y H_2O que contiene TFA al 0.1%, flujo: 1,4 mL/min

i. Waters Sunfire C18, 5um, 21x50mm, 20- 95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/2 min, CH_3CN y H_2O que contiene HCOOH al 0.1%, flujo: 0,6 mL/min

j. Waters Atlantis; 2.1x30mm, 20- 95% CH_3CN/H_2O/2.5 min, 95% CH_3CN/H_2O/0.05 min, 20- 95- 20% CH_3CN/H_2O/0.45 min CH_3CN y H_2O que contiene 0.1% de HCOOH, flujo: 0,6 mL/min

k. Agilent Eclipse XDB- C18; 1,8um; 2.1x30mm 5- 100% CH_3CN/H_2O/3 min, 100% CH_3CN/0.75 min, CH_3CN y H_2O que contiene 0.1% de TFA, flujo: 0,6 mL/min

l. Agilent Eclipse XDB- C18; 1,8um; 2.1x30mm 20- 100% CH_3CN/H_2O/3min, 100%CH_3CN/0.75 min, CH_3CN y H_2O que contiene 0.1% de TFA, flujo: 0,6 mL/min

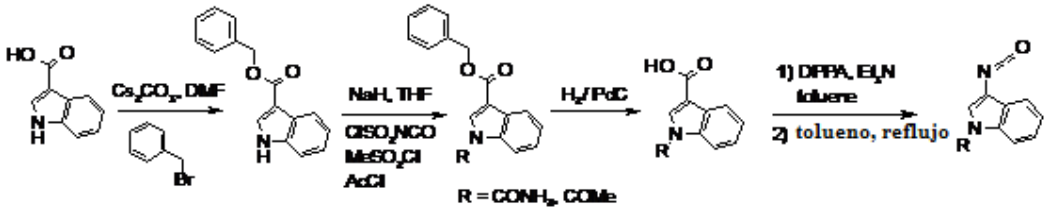
Condiciones UPLC:

m. UPLC/MS: Waters Acquity; columna UPLC: Waters Acquility HSS T3; 1,8um; 2.1x50mm 10- 95% CH_3CN/H_2O/1.5 min, H_2O que contiene 0.05% HCOOH y CH_3CN que contiene 0.04%HCOOH + 3.75 mM NH_4OAc, flujo 1.2 mL/min

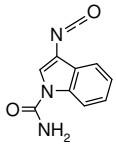
El asterisco (*) indicado en el nombre de un compuesto designa una mezcla racémica.

Parte A: Síntesis de precursores aromáticos o heteroaromáticos sustituidos:

Esquema A1: Protocolo general para la preparación de precursores de síntesis de isocianato



Amida del ácido 3- isocianato- indol- 1- carboxílico



A. Ester bencilo del ácido 1H- indol- 3- carboxílico

A una solución del ácido 1H- indol- 3- carboxílico (5 g, 31 mmol) en DMF (70 ml) bajo atmósfera de nitrógeno a 0 º C se añadió carbonato de cesio (11 g, 31 mmol) y bromuro de bencilo (4,05 ml, 34,1 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 48 h y se vertió en agua. Se añadió EtOAc y las capas se separaron, la fase acuosa se extrajo de nuevo tres veces con EtOAc. Las capas orgánicas combinadas se lavaron con agua, se secaron sobre Na2SO4, se filtraron y se concentraron. El residuo se recogió en Et2O y el precipitado resultante se filtró para dar el compuesto del título. TLC, R_f (c- hexano/EtOAc 01:01) = 0,55; MS (LC- MS): 252,1 [M + H] +, 274,0 [M + Na] +, 525,1 [2M + Na] +, 250,1 [MH] - ; t_R (condiciones de HPLC a) 3,77 min.

B. Éster bencilo del ácido 1- carbamoil- 1H- indol- 3- carboxílico

A una solución de éster bencilo del ácido 1H- indol- 3- carboxílico (3,5 g, 13,9 mmol) en THF (70 ml) a 5 º C, se le añadió NaH (60% en aceite mineral, 557 mg, 13,9 mmol). La mezcla se agitó a 5 ° C durante 30 min antes de la adición lenta gota a gota de isocianato de clorosulfonilo (2,42 ml, 27,9 mmol) manteniendo la temperatura entre 5 °C y 10 °C. La solución de color amarillo pálido se agitó adicionalmente a temperatura ambiente durante 3,5 h. Se añadió ácido acético (22,5 ml) (exotérmica), y la solución resultante se agitó a temperatura ambiente durante 1,5 h antes de la adición de cubos de hielo y agua (100 ml). La suspensión espesa blanca se agitó a temperatura ambiente durante 30 min y el precipitado se filtró, se recogió en MeOH y se filtró de nuevo para proporcionar el compuesto deseado. 1H- RMN (400 MHz, DMSO): δ (ppm) 8,64 (s, 1H), 8,29 (d, 1H), 8,04 (d, 1H), 7,90 (m, 2H), 7,50 (d, 2H), 7,42 (t, 2H), 7,36- 7,30 (m, 3H), 5,38 (s, 2H).

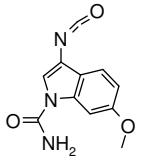
C. ácido 1- carbamoil- 1H- indol- 3- carboxílico

Ester bencilo del ácido 1- carbamoil- 1H- indol- 3- carboxílico (1,33 g, 4,52 mmol) se disolvió en una mezcla de DMF/THF 1:1 (28 ml), se añadió Pd/C (10%, 250 mg) y la solución se desgasificó 3 veces reemplazando aire por nitrógeno y, finalmente nitrógeno por hidrógeno. La mezcla de reacción se agitó adicionalmente en atmósfera de hidrógeno durante la noche y se eliminó el catalizador a través de una almohadilla de Celite y se lavó con THF. Los solventes se concentraron a alto vacío para proporcionar un sólido de color amarillento que se recogió en Et2O y se filtró para proporcionar el compuesto del título. 1H- RMN (400 MHz, DMSO): δ (ppm) 12,6 (m, 1H), 8,54 (s ancho, 1H), 8,28 (d, 1H), 8,05 (d, 1H), 7,85 (m, 2H), 7,34 - 7,27 (m, 2H).

D. Amida del ácido 3- isocianato- indol- 1- carboxílico

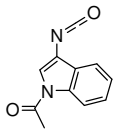
A una suspensión del ácido 1- carbamoil- 1H- indol- 3- carboxílico (1,31 g, 6,42 mmol) en tolueno (30 ml, CH_2Cl_2 también se puede utilizar en lugar de tolueno) en atmósfera de nitrógeno se le añadió Et3N (893 µl, 6,42 mmol) . Después de 15 minutos se añadió DPPA (1,54 ml, 6,42 mmol) y la mezcla de reacción se agitó adicionalmente a temperatura ambiente durante la noche. El tolueno se concentró, el residuo se recogió en CH_2Cl_2 y el el precipitado se filtró para proporcionar el intermedio azida de acilo (565 mg). Se añadió tolueno (20 ml) y la suspensión se calentó a reflujo durante 1,5 h en atmósfera de nitrógeno hasta que no se detectó más azida de acilo por TLC. El tolueno se concentró al vacío y el isocianato deseado se utilizó directamente en la siguiente etapa sin purificación adicional. 1H- RMN (400 MHz, CDCl3): δ (ppm) 8,18 (d, 1H), 7,61 (d, 1H), 7,44 (t, 1H), 7,35 (t, 1H), 7,23 (s, 1H), 5,39 (s ancho, 2H).

Amida del ácido 3- isocianato- 6- metoxi- indol- 1- carboxílico



Se preparó a partir de ácido 6- metoxi- indol- 3- carboxílico usando el protocolo descrito para la preparación de amida del ácido 3- isocianato- indol- 1- carboxílico Esquema A1.

1 - (3- isocianato- indol- 1- il)- etanona



A. Ester bencilo del ácido 1- Acetil- 1H- indol- 3- carboxílico

A una solución de éster bencilo de 1H- indol- 3- carboxílico (600 mg, 2,39 mmol) en THF (10 ml) a 0 °C en atmósfera de nitrógeno se añadió NaH (60% en aceite mineral, 191 mg, 4,78 mmol). La mezcla se agitó durante 20 min a 0 °C, se añadió cloruro de acetilo (339 µl, 4,78 mmol) y la suspensión resultante se agitó a temperatura ambiente durante 48 h. El solvente se concentró y el residuo se vertió en agua y se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre Na2SO_4, se filtraron y se concentraron. El residuo crudo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano a c-hexano/EtOAc 75:25) para proporcionar el producto deseado como un sólido blanco. TLC, R_f (c- hexano/EtOAc 3:1) = 0,38; MS (LC- MS): 294,1 [M + H] +, 316,0 [M + Na] +; t_R (condiciones HPLC a): 4,69 min.

B. Ácido 1- acetil- 1H- indol- 3- carboxílico

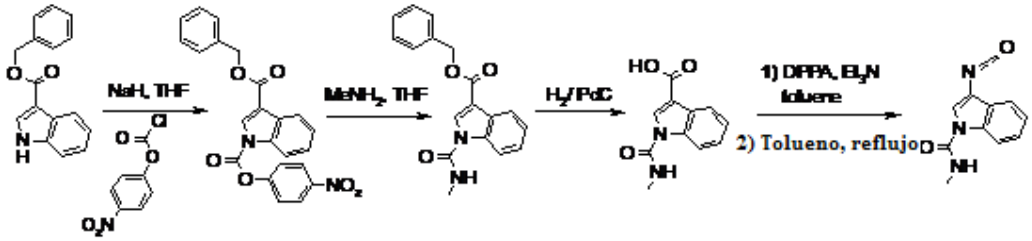
Ester bencilo de ácido 1- acetil- 1H- indol- 3- carboxílico (300 mg, 1,02 mmol) se disolvió en MeOH (10 ml), se añadió Pd/C al 10% (60 mg) y la solución se desgasificó 3 veces reemplazando aire por nitrógeno y, finalmente, el nitrógeno por hidrógeno. La mezcla de reacción se agitó adicionalmente en atmósfera de hidrógeno 2 h y se eliminó el catalizador a través de una almohadilla de Celite y se lavó con MeOH. El solvente se concentró al vacío para proporcionar una mezcla de ácido 1- acetil- 1H- indol- 3- carboxílico y éster bencílico del ácido 1- acetil- 2,3- dihidro- 1H- indol- 3- carboxílico en una relación ~ 7:3 tal como se mide por RMN. El compuesto deseado no se purificó en esta etapa, pero se utilizó directamente en el siguiente paso. Ácido 1- acetil- 1H- indol- 3- carboxílico: TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0,31; MS (LC- MS): 204,1 [M + H] +, 202,1 [MH] - ; tR (Condiciones HPLC a): 3,14 min. Ester bencilo del ácido 1- acetil- 2,3- dihidro- 1H- indol- 3- carboxílico: MS (LC- MS): 206,1 [M + H] +, 228,1 [M + Na] +, 433,0 [2M + Na] +, 204,1 [MH] - ; t_R Condiciones HPLC): 1,93 min.

C. 1 - (3- isocianato- indol- 1- il)- etanona

A una suspensión de ácido 1- acetil- 1H- indol- 3- carboxílico (que contenía aproximadamente 30% de éster bencilo del ácido 1- acetil- 2,3- dihidro- 1H- indol- 3- carboxílico 194 mg) en tolueno (5 ml) se añadió Et3N (130 l, 0,935 mmol) y la solución resultante se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 15 min. Se

añadió DDPA (225 µl, 0,935 mmol) y la mezcla de reacción se agitó adicionalmente a temperatura ambiente durante la noche. El tolueno se concentró al vacío y el residuo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano a c- hexano/EtOAc 1:1) para proporcionar el intermedio de azida de acilo deseado como un polvo blanco (96 mg; t_R condiciones HPLC a: 3,86 min). Se añadió tolueno (3 ml) y la mezcla se calentó a reflujo durante 1,5 h hasta la finalización de la reacción. El tolueno se concentró al vacío para proporcionar el isocianato deseado. TLC, R_f (c- hexano/EtOAc 1:2) = 0,58; t_R (condiciones HPLC a): 3,92 min. 1H- RMN (400 MHz, CDCl3): δ (ppm): 8,44 (m, 1H), 7,56 (d, 1H), 7,44 (t, 1H), 7,36 (t, 1H), 7,23 (d, 1H), 2,60 (s, 3H).

Esquema A2: Preparación de metilamida del ácido 3- isocianato- indol- 1- carboxílico



A. Ester 3- bencilo del ácido Indol- 1,3- dicarboxílico - éster 1- (4- nitro- fenilo)

A una solución de éster bencilo del ácido 1H- indol- 3- carboxílico (100 mg, 0,398 mmol) en THF seco (2 ml) a 0 ° C en atmósfera de nitrógeno se le añadió NaH (60% en aceite mineral, 32 mg, 0,796 mmol) . La solución resultante se agitó a 0 °C durante 10 min, y se añadió gota a gota a una solución agitada de 4- nitrofenil cloroformiato (160 mg, 0,796 mmol) en THF seco (2 ml) se enfrió a 0 °C. La solución resultante se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 48 h. La mezcla se vertió en agua y se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó sucesivamente por cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano a c- hexano/EtOAc 7:3) y por HPLC preparativa (Waters SunFire C18- ODB, 5 micras, 19x50 mm, 20% de CH3CN/H2O 2,5 min, 20- 100% CH_3CN/H_2O en 10 min, CH_3CN/H_2O que contiene 0,1% HCOOH flujo: 20 ml/min) para proporcionar después de la extracción de las fracciones puras del compuesto deseado. TLC, R_f (c- hexano/EtOAc 1:1) = 0,8; MS (LC/MS): 439,0 [M+Na] +; t_R (condiciones HPLC a): 4,58 min.

B. éster bencílico del ácido 1- metilcarbamoil- 1H- indol- 3- carboxílico

A una solución de ester 3- bencilo del ácido indol- 1,3- dicarboxílico - éster 1 - (4- nitro- fenilo) (45 mg, 0,108 mmol) en THF seco (1 ml) se añadió metilamina (2 M en THF, 270 µl, 0,54 mmol) y la reacción se agitó a temperatura ambiente durante 15 min. La mezcla se concentró y el residuo se recogió en Et2O y se filtró para proporcionar el compuesto deseado. TLC, Rf (c- hexano/EtOAc 01:01) = 0,52; MS (LC/MS): 309,1 [M + H] +, 331,1 [M + Na] +, 639,2 [2M + Na] +, 353,2 [M + HCOO] - ; t_R (condiciones de HPLC A): 3,86 min.

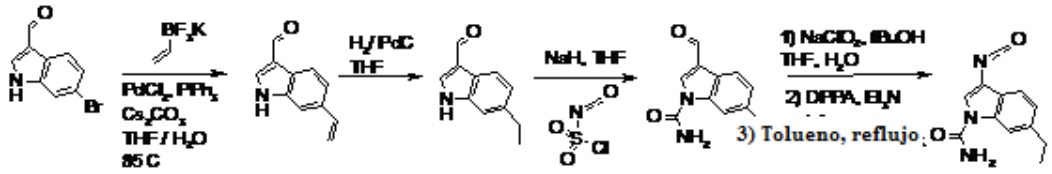
C. Ácido 1- metilcarbamoil- 1H- indol- 3- carboxílico

A ester bencilo del ácido 1- metilcarbamoil- 1H- indol- 3- carboxílico (115 mg, 0,373 mmol) disuelto en una mezcla de MeOH/CH_2Cl_2 1- 1 (4 ml), y se añadió Pd/C al 10% (20 mg) y la solución se desgasificó 3 veces reemplazando aire por nitrógeno y, finalmente nitrógeno por hidrógeno. La mezcla de reacción se agitó adicionalmente en atmósfera de hidrógeno durante 1 h. La mezcla se colocó bajo una atmósfera de nitrógeno y el catalizador se eliminó a través de una almohadilla de Celite y se lavó con MeOH. Los solventes se concentraron al vacío para proporcionar el compuesto deseado. MS (LC/MS): 219,1 [M + H] +; t_R (condiciones de HPLC A): 2,54 min.

D. Metilamida del ácido 3- isocianato- indol- 1- carboxílico

Una solución de ácido 1- metilcarbamoil- 1H- indol- 3- carboxílico (80 mg, 0,367 mmol) y Et_3N (51 l, 0,367 mmol) en una mezcla de tolueno/THF 1/1 (4 ml) se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 30 min. Se añadió DPPA (90%, 88 µl, 0,367 mmol) y la mezcla de reacción se agitó adicionalmente a temperatura ambiente bajo nitrógeno durante la noche. Los solventes se concentraron al vacío y el residuo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1- 1) para proporcionar el intermedio azida de acilo en forma de cristales blancos (83 mg, t_R (condiciones de HPLC a): 3,40 min) . El intermedio de azida de acilo se sometió a reflujo en tolueno (2 ml) durante 1 h para proporcionar después de la concentración del solvente, el isocianato deseado. El compuesto se usó directamente en la siguiente etapa sin purificación adicional.

Esquema A3: Preparación de la amida del ácido 6- etil- 3- isocianato- indol- 1- carboxílico



A. 6- Vinil- 1H- indol- 3- carbaldehído

Se combinó 6- bromoindol- 3- carboxaldehído (5 g, 22,3 mmol), viniltrifluoroborato de potasio (4,48 g, 33,5 mmol), PdCl2 (396 mg, 2,23 mmol), PPh3 (1,75 mg, 6,7 mmoles) y $Cs2CO_3$ (2,18 mg, 66,9 mmol) se combinaron en un matraz de 500 ml colocado bajo una atmósfera de nitrógeno. Se añadieron THF (135 ml) y H2O (15 ml) y la solución de color amarillo se calentó a 85 ° C durante 2 días. La reacción se dejó enfriar a temperatura ambiente, se añadió agua y la mezcla se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano a c- hexano/EtOAc 1:1) para proporcionar el compuesto del título. TLC, R_f (c- hexano/EtOAc 1:1) = 0,4; MS (LC/MS): 172,0 [M + H] + 170,1 [MH] - ; t_R (condiciones de HPLC A): 2,95 min.

B. 6- etil- 1H- indol- 3- carbaldehído

6- Vinil- 1H- indol- 3- carbaldehído (1,5 g, 8,76 mmol) se disolvió en THF (45 ml), se añadió Pd/C al 10% (300 mg) y la solución se desgasificó 3 veces reemplazando aire por nitrógeno y finalmente nitrógeno por hidrógeno. La mezcla de reacción se agitó adicionalmente en atmósfera de hidrógeno 4h y el catalizador se eliminó a través de una almohadilla de Celite y se lavó con THF. El solvente se concentró y el residuo crudo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano a c- hexano/EtOAc 1:1) para proporcionar el compuesto deseado. TLC, R_f (c- hexano/EtOAc 1:1) = 0,40; MS (LC/MS): 174,1 [M + H] +, 196,1 [M + Na] +, 172,1 [MH] - ; t_R (condiciones de HPLC a): 3,05 min.

C. Amida del ácido 6- etil- 3- formil- indol- 1- carboxílico

A una solución de NaH (60% en aceite mineral, 259 mg, 6,47 mmol) en THF (10 ml) enfriada a 5 °C en atmósfera de nitrógeno, se agregó lentamente una solución de 6- etil- 1H- indol- 3- carbaldehído (1,12 g, 6,47 mmol) en THF (20 ml) y la mezcla se agitó a 5 ° C durante 30 min. Mientras se mantuvo la temperatura interna entre 5 °C y 10 °C se añadió por goteo clorosulfonil isocianato (1,12 ml, 12,9 mmol) y la solución se agitó adicionalmente a temperatura ambiente durante la noche. Se añadió ácido acético (15 ml) (ligeramente

exotérmico) y la solución se agitó a temperatua ambiente durante 1,5 h. Se añadieron cubos de hielo y agua (25 ml), y la solución se agitó adicionalmente a temperatura ambiente durante 30 min. Se añadió agua y la mezcla se extrajo con EtOAc. La capa acuosa se extrajo de nuevo dos veces con EtOAc. Las capas orgánicas combinadas se secaron (Na2SO4), se filtraron y se concentraron. El residuo crudo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano a EtOAc) para proporcionar el compuesto deseado. LC/MS: 290,0 [M + H] +, 312,0 [M + Na] +; t_R (condiciones de HPLC a): 3,02 min.

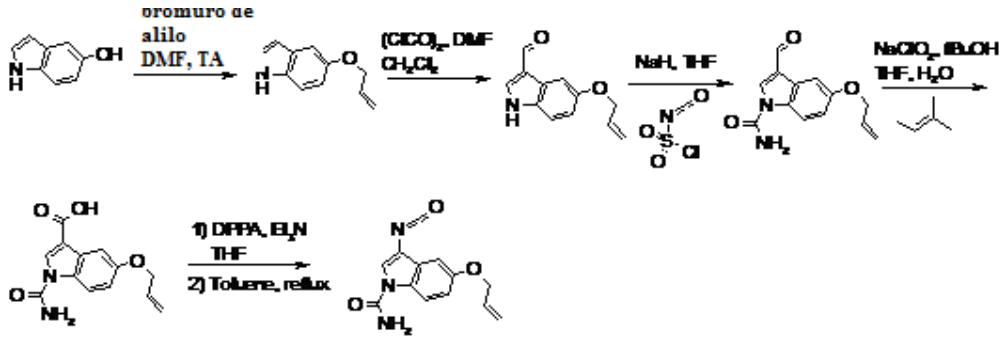
D. Ácido 1- carbamoil- 6- etil- 1H- indol- 3- carboxílico

Se disolvió amida de ácido 6- etil- 3- formil- indol- 1- carboxílico (720 mg, 3,33 mmol) en una mezcla de THF (60 ml) y t- butanol (18 ml). Se añadió 2- metil- 2- buteno (solución 2 M en THF, 66,6 ml, 133 mmol), seguido por una solución acuosa (16 ml) de NaClO2 (80%, 3,76 g, 33,3 mmoles) y NaH_2PO_4 (3,20 g, 26,6 mmoles). La solución resultante se agitó a temperatura ambiente durante 4 h y THF se concentró. Se añadió EtOAc y las capas se separaron. La capa acuosa se acidificó mediante la adición de HCl 1 N y se extrajo dos veces con EtOAc. Los extractos orgánicos combinados se secaron (Na2SO4), se filtraron y se concentraron. El residuo crudo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (eluyente: c- hexano a EtOAc a CH2Cl2/MeOH 8:2) para proporcionar el compuesto deseado. t_R (condiciones de HPLC a): 2,17 min. 1H- RMN (400 MHz, CDCl3): δ (ppm): 12,9 (m, 1H), 8,81 (s, 1H), 8,66 (s ancho, 1H), 8,23 (d, 1H),), 8,09 (m, 2H), 7,70 (dd, 1H).

E. Amida del ácido 6- etil- 3- isocianato- indol- 1- carboxílico

A una solución de ácido 1- carbamoil- 6- etil- 1H- indol- 3- carboxílico (330 mg, 1,42 mmol) en tolueno (8 ml) se añadió trietilamina (0,198 ml, 1,42 mmol) y la suspensión resultante se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 15 min. Se añadió DPPA (0,34 ml, 1,42 mmol) y la mezcla de reacción se agitó adicionalmente a temperatura ambiente durante 3 h. TLC indicó la finalización de la reacción. La mezcla se concentró, se añadió CH_2Cl_2 y la suspensión se filtró para proporcionar el intermedio de azida de acilo. Se añadió tolueno (4 ml) y la mezcla de reacción se calentó a reflujo durante 3 h. El compuesto en crudo se usó directamente en el siguiente paso.

Esquema A4: protocolo general descrito para la preparación de amida del ácido 5- aliloxi- 3- isocianato- indol- 1- carboxílico



A. 5- aliloxi- 1H- indol

A una suspensión de 5- hidroxiindol (1,23 g, 9,24 mmol) y carbonato de cesio (3,01 g, 9,24 mmol) en DMF (40 ml) bajo atmósfera de nitrógeno a 0 ºC se añadió bromuro de alilo (879 µl, 10,16 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h y se vertió en agua y se extrajo con EtOAc (x3). Las capas orgánicas combinadas se lavaron dos veces con agua, se secaron sobre Na2SO_4, se filtraron y se concentraron. El residuo crudo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano a c-hexano/EtOAc 09:01) para proporcionar el compuesto deseado. TLC, R_f (c- hexano/EtOAc 1:1) = 0,76; tR (Condiciones a): 3,46 min.

B. 5- aliloxi- 1H- indol- 3- carbaldehído

A una solución de cloruro de oxalilo (1,22 ml, 14,1 mmol) en CH_2Cl_2 seco (20 ml) se añadió a 0ºC en atmósfera de nitrógeno una solución de DMF seca (1,3 ml) en CH_2Cl_2 seco (20 ml). La mezcla se agitó a 0 °C durante 30 min y se añadio una solución de 5- aliloxi- 1H- indol (1,25 g, 7,22 mmol) en CH_2Cl_2 (10 ml). La solución resultante se dejó que alcanzara la temperatura ambiente y se agitó durante 4 h. El solvente se concentró y el residuo se disolvió en THF (35 ml) y acetato de amonio acuoso al 20% (48 ml) y se calentó a reflujo durante 30 min, se enfrió, se trató con una solución acuosa saturada de $NaHCO_3$, y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se secaron sobre Na2SO4, se filtraron y se concentraron. El sólido crudo se recogió en CH_2Cl_2 y se filtró para proporcionar el compuesto deseado. TLC, R_f (c- hexano/EtOAc 01:02) = 0,56; MS (LC/MS): 202,0 [M + H] +, 224,1 [M + Na] +, 200,1 [MH] - , 159,1 [MH- alil] - ; t_R (a) Condiciones de HPLC: 2,89 min.

C. Amida de ácido 5- aliloxi- 3- formil- indol- 1- carboxílico

A una suspensión de NaH (60% en aceite mineral, 352 mg, 8,79 mmol) en THF (12 ml) bajo atmósfera de nitrógeno a 5 °C se añadió una solución de 5- aliloxi- 1H- indol- 3- carbaldehído (1,18 g , 5,86 mmol) en THF (28 ml) y la mezcla resultante se agitó a 5 °C durante 30 min antes de la adición lenta de clorosulfonil isocianato (11,02 ml, 11,7 mmoles) mientras se mantuvo la temperatura entre 5 °C y 10 °C. La solución se agitó adicionalmente a temperatura ambiente durante 4 h, se añadió ácido acético (11 ml) y la solución se agitó a temperatura ambiente durante 1h. Se añadieron cubitos de hielo y agua (100 ml) y la mezcla se agitó a temperatura ambiente durante 30 min. La solución se extrajo dos veces con EtOAc y los extractos orgánicos combinados se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (100% c- hexano a 100% EtOAc) para proporcionar el compuesto del título. TLC, R_f (c- hexano/EtOAc 1:2) = 0,36; MS (LC/MS): 245,1 [M + H] +, 267,0 [M + Na] +, 200,1 [M- CONH2] - ; t_R (HPLC Condiciones a): 2,95 min.

D. Ácido 5- aliloxi- 1- carbamoil- 1H- indol- 3- carboxílico

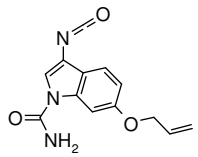
Se disolvió amida del ácido 5- aliloxi- 3- formil- indol- 1- carboxílico (530 mg, 2,17 mmol) en una mezcla de THF (38 ml) y t- butanol (12 ml). Se añadió solución de 2- metil- 2- buteno 2 M en THF (40 ml, 80 mmol), seguido por una solución acuosa (9,5 ml) de NaClO2 (80%, 2,45 g, 21,7 mmoles) y NaH2PO4 (2,08 g, 17,4 mmol). La solución resultante se agitó a temperatura ambiente durante 1 h, hasta consumir el material de partida. Se añadió HCl 1N (3 ml), y los solventes orgánicos se concentraron. La capa acuosa restante se filtró y el precipitado resultante se lavó con agua y Et2O para proporcionar el compuesto deseado. TLC, R_f (c- hexano/EtOAc 01:02) = 0,08; LC/MS: 261,1 [M + H] +, 259,0 [MH] - , 216,1 [M- CONH2] - , 519,1 [2M- H] - ; tR (Condiciones de HPLC a): 2,8 min.

E. Amida del ácido 5- aliloxi- 3- isocianato- indol- 1- carboxílico

A una suspensión de ácido 5- aliloxi- 1- carbamoil- 1H- indol- 3- carboxílico (500 mg, 1,92 mmol) en THF (10 ml) se añadió Et3N (267 µl, 1,92 mmol) y la solución resultante se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 15 min. Se añadió DDPA (462 l, 1,92 mmol) y la reacción se agitó adicionalmente a temperatura ambiente bajo nitrógeno durante 1 h. TLC indicó el consumo del material de partida. THF se concentró y el residuo se recogió en CH_2Cl_2 y se separó por filtración para proporcionar el intermedio crudo de azida de acilo (TLC, R_f (c- hexano/EtOAc 1:2) = 0,65; t_R (Condiciones de HPLC a): 3,50 min). El intermedio de azida de acilo se suspendió en tolueno (7 ml) y se calentó a reflujo en atmósfera

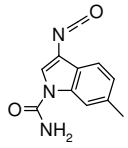
de nitrógeno durante 2 horas hasta la finalización de la reacción. El isocianato crudo se usó como estaba en el siguiente paso.

Amida del ácido 6- aliloxi- 3- isocianato- indol- 1- carboxílico



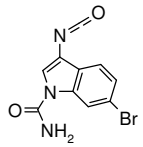
se preparó a partir de 6- hidroxi- indol usando el protocolo descrito para la preparación de amida del ácido 5- aliloxi- 3- isocianato- indol- 1- carboxílico en el Esquema A4.

Amida del ácido 6- metil- 3- isocianato- indol- 1- carboxílico



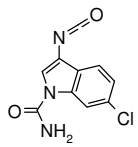
se preparó a partir de 6- metil- 1H- indol- 3- carbaldehído usando el protocolo descrito para las etapas C, D y E en el esquema A4 para la preparación de amida del ácido 5- aliloxi- 3- isocianato- indol- 1- carboxílico.

Amida del ácido 6- bromo- 3- isocianato- indol- 1- carboxílico



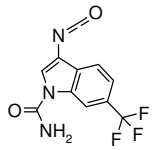
se preparó a partir de 6- bromo- 1H- indol- 3- carbaldehído usando el protocolo descrito para las etapas C, D y E en el esquema A4 para la preparación de amida del ácido 5- aliloxi- 3- isocianato- indol- 1- carboxílico.

Amida del ácido 6- cloro- 3- isocianato- indol- 1- carboxílico



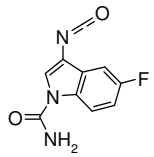
se preparó a partir de 6- cloroindol usando el protocolo descrito para los pasos de B- E en el esquema A4 para la preparación de amida del ácido 5- aliloxi- 3- isocianato- indol- 1- carboxílico.

Amida del ácido 6- trifluorometil- 3- isocianato- indol- 1- carboxílico



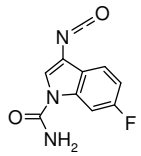
se preparó a partir de 6- trifluorometilindol utilizando el protocolo descrito para los pasos de B- E en el esquema A4 para la preparación de amida del ácido 5- aliloxi- 3- isocianato- indol- 1- carboxílico, excepto que el intermedio de azida de acilo se preparó en 1,2 dimetoxietano en lugar de tolueno.

Amida del ácido 5- fluoro- 3- isocianato- indol- 1- carboxílico



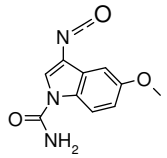
se preparó a partir de 5- fluoro- 1H- indol- 3- carbaldehído usando el protocolo descrito para las etapas C, D y E en el esquema A4 para la preparación de amida del ácido 5- aliloxi- 3- isocianato- indol- 1- carboxílico.

Amida del ácido 6- fluoro- 3- isocianato- indol- 1- carboxílico



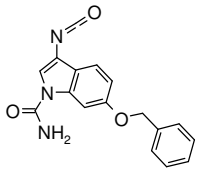
se preparó a partir de 6- fluoro- 1H- indol- 3- carbaldehído [2795- 41- 7] usando el protocolo descrito para las etapas C, D y E en el esquema A4 para la preparación de amida del ácido 5- aliloxi- 3- isocianato- indol- 1 - carboxílico.

Amida del ácido 3- isocianato- 5- metoxi- indol- 1- carboxílico



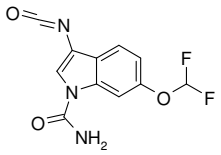
se preparó a partir de 5- metoxi- 1H- indol- 3- carbaldehído usando el protocolo descrito para las etapas C, D y E en el esquema A4 para la preparación de amida del ácido 5- aliloxi- 3- isocianato- indol- 1- carboxílico.

Amida del ácido 6- benciloxi- 3- isocianato- indol- 1- carboxílico



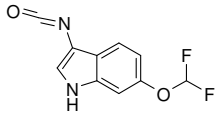
se preparó a partir de 6- benciloxiindol utilizando el protocolo descrito para los pasos B- E en el esquema A4 para la preparación de amida del ácido 5- aliloxi- 3- isocianato- indol- 1- carboxílico.

Amida del ácido 6- difluorometoxi- 3- isocianato- indol- 1- carboxílico



se preparó a partir de 6- difluorometoxi- 1H- indol [200207- 21- 2] usando el protocolo descrito para los pasos de B- E en el Esquema A4 para la preparación de amida del ácido 5- aliloxi- 3- isocianato- indol- 1- carboxílico.

6- difluorometoxi- 3- isocianato- 1H- indol



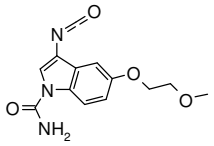
A una suspensión del ácido 1- carbamoil- 6- difluorometoxi- 1H- indol- 3- carboxílico (180 mg, 0,66 mmol) en THF (6 ml) se añadió Et3N (111 µl, 0,8 mmol) y la solución resultante se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 10 min. Se añadió DDPA (220 l, 0,8 mmol) y la reacción se agitó adicionalmente a temperatura ambiente bajo nitrógeno durante 3 h. TLC indicó el consumo del material de partida. La mezcla de reacción se concentró y el residuo en crudo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 4:1- 1:1) para proporcionar 6- difluorometoxi- 1H- indol- 3- carbonil azida (MS: 251 [MH] - ; t_R (condiciones de HPLC k): 3,57 min) y azida (MS: 1- carbamoil- 6- difluorometoxi- 1H- indol- 3- carbonilo: 251 [M- CONH2] - ; 268 [M- N2] + ; tR

(condiciones de HPLC k): 3,46 min). Se suspensió el intermedio de azida de 6- difluorometoxi- 1H- indol- 3- carbonilo en tolueno (6 ml) y se calentó a reflujo bajo nitrógeno durante 3 h hasta la finalización de la reacción. El isocianato crudo se usó como tal en el siguiente paso.

Ácido 1- carbamoil- 6- difluorometoxi- 1H- indol- 3- carboxílico

se preparó a partir de 6- difluorometoxi- 1H- indol [200207- 21- 2] usando el protocolo descrito para los pasos de B- D en el Esquema A4 para la preparación de amida del ácido 5- aliloxi- 3- isocianato- indol- 1- carboxílico.

Amida del ácido 3- isocianato- 5- (2- metoxi- etoxi)- indol- 1- carboxílico

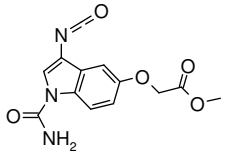


se preparó a partir de 5 - (2- metoxi- etoxi)- 1H- indol usando el protocolo descrito para los pasos de B- E en el esquema A4 para la preparación de amida de ácido 5- aliloxi- 3- isocianato- indol- 1- carboxílico.

5 - (2- metoxi- etoxi)- 1H- indol

Se disolvió 5- hidroxiindol (5 g, 15 mmol) en acetona (75 ml), se añadió carbonato de cesio (5,38 g, 16,5 mmoles) y éter 2- bromoetilmetílico (1,55 ml, 16,5 mmol) y la mezcla de reacción se agitó a reflujo bajo nitrógeno durante la noche. La acetona se concentró. El residuo se disolvió en agua y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se secaron sobre $Na2SO_4$, se filtraron y se concentraron. El residuo crudo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano para c- hexano/EtOAc 7/3) para proporcionar el material deseado. TLC, R_f (c- hexano/EtOAc 1:1) = 0,6; MS (LC-MS): 192,1 [M + H] +, 214,0 [M + Na] +, 405,1 [2M + Na] +; tR (condiciones HPLC f): 1,56 min.

Ester metilo del ácido (1- carbamoil- 3- isocianato- 1H- indol- 5- iloxi)- acético

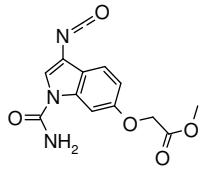


se preparó a partir de ester metilo del ácido (1H- indol- 5- iloxi)- acético utilizando el protocolo descrito para los pasos de B- E en el esquema A4 para la preparación de amida del ácido 5- aliloxi- 3- isocianato- indol- 1- carboxílico.

Ester metilo del ácido (1H- indol- 5- iloxi)- acético

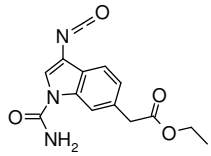
Se añadió una solución de 5- hidroxiindol (5,07 g, 38,1 mmol) y carbonato de cesio (12,4 g, 38,1 mmol) en acetona (150 ml) se enfrió a 0 °C y bromoacetato de metilo (3,96 ml, 41,9 mmol). La mezcla de reacción se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 2 h. La mezcla de reacción se concentró. El residuo se diluyó con agua y se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre Na2SO4, se filtraron y se concentraron. El sólido resultante se recogió en Et2O y se filtró al material deseado. TLC, R_f (c- hexano/EtOAc 01:01) = 0,55; MS (LC- MS): 206,1 [M + H] +, 433,0 [2M + Na] +; $_tR$ (condiciones de HPLC f): 1,64 min.

Ester metilo del ácido (1- carbamoil- 3- isocianato- 1H- indol- 6- iloxi)- acético



se preparó a partir de ester metilo del ácido (1H- indol- 6- iloxi)- acético utilizando el protocolo descrito para la preparación de ester metilo del ácido (1- carbamoil- 3- isocianato- 1H- indol- 5- iloxi)- acético.

Ester etilo del ácido (1- carbamoil- 3- isocianato- 1H- indol- 6- il)- acético



se preparó a partir de éster etílico del ácido (1H- indol- 6- il)- acético usando el protocolo descrito para los pasos de B- E en el esquema A4 para la preparación de amida del ácido 5- aliloxi- 3- isocianato- indol- 1- carboxílico.

Ester etilo del ácido (1H- indol- 6- il)- acético

A una solución de éster metilo del ácido 6- etoxicarbonilmetil- indol- 1- carboxílico (965 mg, 3,25 mmol) en EtOH (10 ml) se añadió dimetilamina (~ 5,6 M en EtOH, 24,4 ml, 48,8

mmol) y la solución se agitó a temperatura ambiente durante la noche. EtOH se concentró y el residuo crudo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano a c- hexano/EtOAc 85:15) para proporcionar el material deseado. MS (UPLC): 204,2 [M + H] +, 221,2 [M + NH4] +, 248,2 [M + HCOO] - ; t_R (condiciones de HPLC f): 1,87 min.

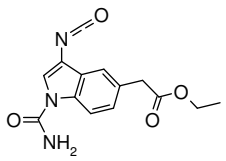
Éster metilo del ácido 6- etoxicarbonilmetil- indol- 1- carboxílico

Una mezcla de éster metilo del ácido 6- bromo- indol- 1- carboxílico (1,12 g, 4,43 mmol), acetoacetato de etilo (1,23 ml, 9,74 mmol), acetato de paladio (20 mg, 0,089 mmol), 2- di- terc- butilfosfino - 2'- metilbifenilo (55 mg, 0,177 mmoles) y K_3PO4 (2,58 g, 12,2 mmol) en tolueno (6 ml) se calentó a 100° C bajo nitrógeno durante la noche. La reacción se vertió en agua y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se secaron sobre Na2SO4, se filtraron y se concentraron. El material crudo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano a c- hexano/EtOAc 93:7) para proporcionar el material deseado. TLC, R_f (c- hexano/EtOAc 04:01) = 0,3; EM (UPLC): 262,2 [M + H] +, 279,2 [M + NH4] +, 284,2 [M + Na] +, 523,3 [M + Na] +, 545,3 [2M + Na] +; tR (condiciones de HPLC f): 2,11 min.

Éster metílico del ácido 6- bromo- indol- 1- carboxílico

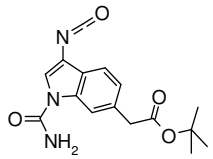
A una solución de 6- bromoindol (1,46 g, 7,44 mmol) en DMF (35 ml) bajo atmósfera de nitrógeno, se añadió NaH (60% en aceite mineral, 327 mg, 8,19 mmol), seguido de cloroformiato de metilo (652 l, 8,19 mmol) y la solución resultante se agitó a temperatura ambiente durante la noche. La mezcla se vertió en agua y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se lavaron de nuevo con agua, se secaron sobre Na2SO4, se filtraron y se concentraron. El residuo crudo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano a c- hexano/EtOAc 88:12) para proporcionar el material deseado. TLC, R_f (EtOAc) = 0,75; EM (UPLC): 254.2/255.2[M + H] +; t_R (condiciones de HPLC f): 2,32 min.

<u>Ester etilo del ácido (1- carbamoil- 3- isocianato- 1H- indol- 5- il)- acético</u>



se preparó a partir de 5- bromoindol como se describe para la síntesis de éster etílico del ácido (1- carbamoil- 3- isocianato- 1H- indol- 6- il)- acético.

Éster terc- butilo del ácido (1- carbamoil- 3- isocianato- 1H- indol- 6- il)- acético

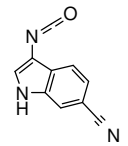


se preparó a partir de ester terc- butilo del ácido (1H- indol- 6- il)- acético usando el protocolo descrito para los pasos de B- E en el esquema A4 para la preparación de amida del ácido 5- aliloxi- 3- isocianato- indol- 1- carboxílico.

Ester terc- butilo del ácido (1H- indol- 6- il)- acético

A una solución de 6- bromoindol (2 g, 10,2 mmol) en THF (20 ml) en atmósfera de nitrógeno se añadió KH (30% en aceite mineral desengrasado con pentano, 1,5 g, 11,22 mmol) y la mezcla se agitó a temperatura ambiente durante 30 min antes de la adición de $[P(t\text{-}Bu)_3PdBr]_2$ (40 mg, 0,051 mmol) diluido en THF (20 ml). La mezcla resultante se añadió a una solución de cloruro de 2- terc- butoxi- 2- oxoetilzinc (0,5 M en Et2O, 22,4 ml, 11,2 mmol) se agitó en atmósfera de nitrógeno y la mezcla se agitó adicionalmente a temperatura ambiente durante 24 h. La mezcla de reacción se diluyó con EtOAc, y se lavó con una solución acuosa saturada de NaHCO3, a continuación, con agua. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo crudo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano a c- hexano/EtOAc 94:6 a c- hexano/EtOAc 8:2) para proporcionar el material deseado. TLC, R_f (c- hexano/EtOAc 4:1) = 0,3; MS (UPLC): 232,2 $[M + H]^+$, 176,1 [MH- tBu]+, 249,2 [M + NH4] +, 463,4 [2M + H] +, 273,3 [M + HCOO] - .

3- Isocianato- 1H- indol- 6- carbonitrilo



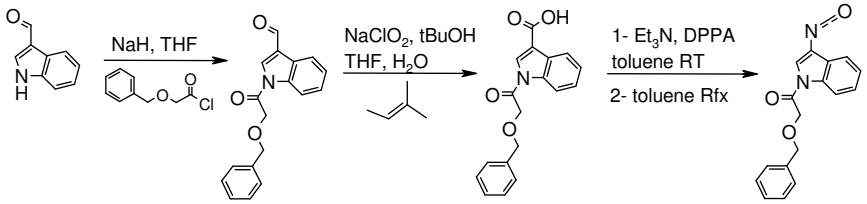
A una solución de ácido 1- carbamoil- 6- ciano- 1H- indol- 3- carboxílico (210 mg, 0,916 mmol) en tolueno (6 ml) se añadió Et_3N (128 µl, 0,916 mmol) y la suspensión de color amarillo resultante se agitó a temperatura ambiente en atmósfera de nitrógeno 15 min antes de

la adición de DDPA (220 µl, 0,916 mmol). La mezcla de reacción se agitó adicionalmente a temperatura ambiente durante la noche. La mezcla de reacción cruda se concentró y se purificó por cromatografía en columna ultrarrápida (c- hexano a c- hexano/EtOAc 1:01) para proporcionar la azida 6- ciano- 1H- indol- 3- carbonilo (TLC, Rf (EtOAc) = 1) ; t_R (condiciones de HPLC a): 3,29 min; 1H- RMN (400 MHz, DMSO): δ (ppm): 12,7 (s ancho, 1H), 8,45 (s, 1H), 8,20 (d, 1H), 8,04 (s ancho , 1H), 7,62 (dd, 1H). Se añadió tolueno (4 ml) y la mezcla de reacción se calentó a reflujo durante 3 h para generar el isocianato correspondiente, que se utilizó sin purificación en la siguiente etapa.

Ácido 1- carbamoil- 6- ciano- 1H- indol- 3- carboxílico

se preparó a partir de 6- ciano- indol usando el protocolo descrito para los pasos de B- E en el esquema A4 para la preparación de la amida del ácido 5- aliloxi- 3- isocianato- indol- 1- carboxílico.

Esquema A5: Preparación de 2- benciloxi- 1- (3- isocianato- indol- 1- il)-



etanona

A. 1 - (2- benciloxi- acetil)- 1H- indol- 3- carbaldehído

A una solución de indol- 3- carboxaldehído (2 g, 13,8 mmol) en THF (70 ml) a 5 º C, se añadió NaH (60% en aceite mineral, 551 mg, 13,8 mmol) bajo atmósfera de nitrógeno. La mezcla se agitó a 5 °C durante 30 min antes de la adición gota a gota de cloruro de benciloxiacetilo (2,6 ml, 16,53 mmol) durante 20 min manteniendo la temperatura interna entre 5 °C y 10 °C. La solución oscura resultante se agitó adicionalmente a temperatura ambiente durante 1h. Como la reacción no se completó se añadió cloruro de benciloxiacetilo (1 ml, 6,44 mmol, 0,5 eq) y NaH (60% en aceite mineral, 551 mg, 13,8 mmol) se y la mezcla se agitó adicionalmente a temperatura ambiente durante 3 días. La mezcla de reacción se concentró, y el residuo se recogió en CH_2Cl_2 y se lavó con agua. La capa orgánica se secó sobre Na_2SO_4, se filtró, y se concentró. El material en crudo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano a c- hexano/EtOAc 4- 1) correspondiente al compuesto deseado. TLC, R_f (c- hexano/EtOAc 01:01) = 0,61; MS (LC/MS): 294,1 [M + H] +, 316,1 [M + Na] +; t_R (condiciones de HPLC a): 3,87 min.

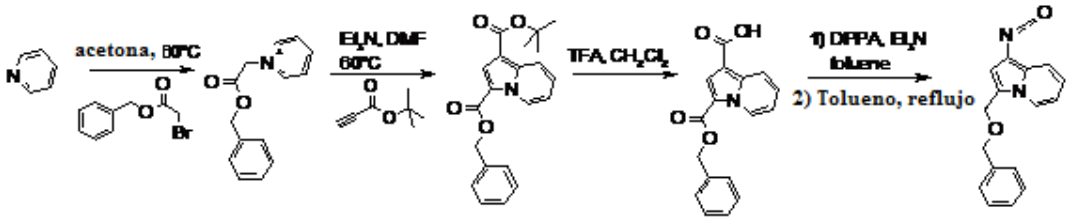
B. Ácido 1- (2- benciloxi- acetil)- 1H- indol- 3- carboxílico -

A una solución de 1 - (2- benciloxi- acetil)- 1H- indol- 3- carbaldehído (1,53 g, 5,22 mmol) en una mezcla de THF (80 ml) y t- butanol (24 ml). Se añadió una solución de 2- metil- 2- buteno 2M en THF (104 ml, 209 mmol), seguido por una solución acuosa (20 ml) de NaClO2 (80%, 5,9 g, 52,2 mmoles) y NaH_2PO_4 (5 g, 41,7 mmoles). La solución de color amarillo resultante se agitó a temperatura ambiente durante 2 h. Los solventes se concentraron y la capa acuosa se filtró y el precipitado resultante se lavó con Et2O para proporcionar el compuesto deseado. LC/MS: 310.1 [MH] - , 332,0 [M + Na] +, 308,0 [MH] - , 617,0 [2M- H] - ; t_R (condiciones de HPLC a): 3,62 min.

C. 2- Benciloxi- 1- (3- isocianato- indol- 1- il)- etanona

Una solución de ácido 1- (2- benciloxi- acetil)- 1H- indol- 3- carboxílico (200 mg, 0,647 mmol) y Et3N (90 µl, 0,647 mmol) en tolueno (3 ml) se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 15 min. Se añadió DDPA (90%, 155 µl, 0,647 mmol) y la mezcla de reacción se agitó adicionalmente a temperatura ambiente durante 3 h. El tolueno se concentró para proporcionar el intermedio de azida de acilo (TLC R_f (c- hexano/EtOAc 1:1) = 0,73; t_R (condiciones de HPLC a) = 4,26 min). La azida cruda se calentó a reflujo en tolueno (3 ml) durante 1 h y el tolueno se concentró para proporcionar el isocianato deseado que se usó en la siguiente etapa sin purificación adicional.

<u>Esquema A6: Preparación de éster bencílico del ácido 1- isocianato- indolizina- 3- carboxílico</u>



A. Bromuro de 1- benciloxicarbonilmetil- piridinio

A una solución de bromoacetato de bencilo (10 g, 43,7 mmol) en acetona (200 ml) se añadió una solución de piridina (3,51 ml, 43,7 mmol) en acetona (20 ml) y la mezcla resultante se agitó a 60 ° C en atmósfera de nitrógeno durante el fin de semana. Luego se dejó enfriar a temperatura ambiente y se concentró para proporcionar el material deseado. MS (LC/MS): 228,1 [MH] +.

B. Éster 3- bencilo del ácido indolizina- 1,3- dicarboxílico - éster 1- terc- butilo

A una suspensión de bromuro de 1- benciloxicarbonilmetil- piridinio (1,50 g, 9,74 mmol) y propiolato de terc- butilo (1,34 ml, 9,74 mmol) en DMF (80 ml) se añadió una solución de trietilamina (4,1 ml, 29,2 mmoles) en DMF (10 ml). La mezcla se agitó vigorosamente 4 horas a 60 °C bajo atmósfera de aire. La solución se dejó enfriar a temperatura ambiente, se vertió en agua y se extrajo con EtOAc (2x). Los extractos orgánicos combinados se secaron sobre $Na2SO_4$, se filtraron y se concentraron. El residuo crudo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano a c- hexano/EtOAc 8:2) para proporcionar el material deseado. TLC, R_f (c- hexano/EtOAc 08:02) = 0,6; MS (LC/MS): 725,3 [2M + Na] +; t_R (condiciones de HPLC a): 4,84 min.

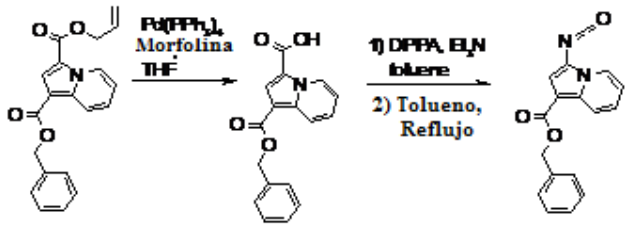
C. Éster 3- bencilo del ácido indolizina- 1,3- dicarboxílico

Una solución de ester 3- bencilo del ácido indolizina- 1,3- dicarboxílico - éster 1- terc- butilo (400 mg, 1,14 mmol) y TFA (872 µl, 11,4 mmol) en CH_2Cl_2 (10 ml) se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró y el sólido crudo se recogió en una mezcla de MeOH y CH_2Cl_2, el precipitado se filtró y se lavó con un mínimo de MeOH para proporcionar el compuesto deseado en forma de un polvo blanco. El filtrado se concentró y se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (CH_2Cl_2 a CH_2Cl_2/MeOH 95:5) para proporcionar de nuevo el compuesto deseado. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0,6; MS (LC/MS): 296,0 [M + H] + 294,1 [MH] - ; t_R (condiciones de HPLC a): 3,64 min.

D. Ester bencilo del ácido 1- isocianato- indolizina- 3- carboxílico

se preparó a partir de ester 3- bencilo del ácido indolizina- 1- ,3- dicarboxílico utilizando el protocolo descrito en el paso E esquema A4 para la preparación de amida del ácido 5- aliloxi- 3- isocianato- indol- 1- carboxílico.

Esquema A7: Preparación de éster bencilo del ácido 3- isocianato- indolizina- 1- carboxílico



Éster ester 3- alilo del ácido indolizina- 1,3- dicarboxílico - éster 1- bencilo

El compuesto del título se preparó usando el protocolo descrito en los pasos A y B para la preparación de éster bencilo del ácido 1- isocianato- indolizina- 3- carboxílico esquema A6 usando ester alilo del ácido bromo- acético en el paso A y éster bencilo del ácido propiónico en el paso B . TLC, R_f (c- hexano/EtOAc 1:1) = 0,8; MS (LC/MS): 336,1 [M + H] +, 358,1 [M + Na] +, 693,2 [2M + Na] +; t_R (Condiciones de HPLC a): 4,55 min.

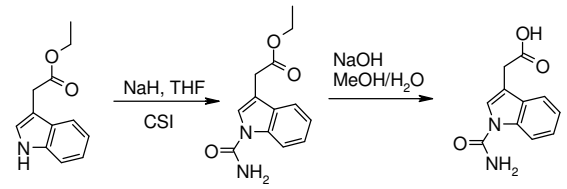
A. Éster 1- bencilo del ácido indolizina- 1,3- dicarboxílico

A una solución de ester 3- alilo del ácido indolizina- 1,3- dicarboxílico - éster 1- bencilo (300 mg, 0,895 mmol) en THF (6 ml) se añadió Pd $(PPh3)_4$ (34,5 mg, 0,09 mmol) y morfolina (260 mg, 8,95 mmol). La mezcla de reacción se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 30 min. La mezcla de reacción se diluyó en EtOAc, se extrajo dos veces con HCl 1 N y los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre Na2SO4, se filtraron y se concentraron para proporcionar el compuesto deseado que se usó sin purificación adicional en la siguiente etapa TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0,4: MS (LC/MS): 294,0 [MH] - ; t_R (condiciones de HPLC a): 3,62 min.

B. Ester bencilo del ácido 3- Isocianato- indolizina- 1- carboxílico

El compuesto del título se preparó a partir de ester 1- bencilo del ácido indolizina- 1,3- dicarboxílico utilizando el protocolo descrito en el paso E esquema A4 para la preparación de amida del ácido 5- aliloxi- 3- isocianato- indol- 1- carboxílico.

<u>Esquema A8: Preparación del ácido (1- carbamoil- 1H- indol- 3- il)- acético</u>



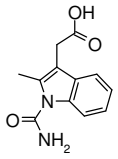
A. Ester etilo del ácido (1- carbamoil- 1H- indol- 3- il)- acético

A una solución de ester etilo del ácido (1H- indol- 3- il)- acético (2,5 g, 12,30 mmol) en THF (58 ml) a 0 º C se añadió hidruro de sodio (60% en aceite mineral, 0,354 g, 14,8 mmol) en porciones en atmósfera de argón. La solución de color marrón oscuro se agitó a 0 ° C durante 45 min antes de la adición gota a gota de isocianato de clorosulfonilo (2,14 ml, 24,6 mmol). La mezcla de reacción se dejó calentar a temperatura ambiente durante la noche bajo agitación. Luego se agregó ácido acético (3 ml) a la mezcla que se agitó a temperatura ambiente durante 20 min. Se añadió hielo a la mezcla que se agitó durante 60 min después se diluyó con agua y se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron (separador de fases) y se concentró al vacío. El aceite residual se purificó por medio de cromatografía en columna ultrarrápida sobre gel de sílice (EtOAc/ciclohexano 1:3- 2:3) para proporcionar el material deseado. TLC, R_f (EtOAc/ciclohexano 1:1) = 0,35; MS: 247 [M + H] +, 493 [2M + H] +; t_R (condiciones de HPLC b) 3,51 min.

B. Ácido (1- carbamoil- 1H- indol- 3- il)- acético

A una suspensión de ester etilo del ácido (1- carbamoil- 1H- indol- 3- il)- acético en metanol (61 ml) y agua (6,1 ml) se añadió una solución acuosa 1N de NaOH (12,2 ml, 12,2 mmol) y la solución de color amarillo resultante se agitó a temperatura ambiente durante 4 h. La mezcla de reacción se concentró a presión reducida y el residuo se suspendió en HCl 1N. La mezcla acuosa se extrajo con EtOAc (3x), los extractos orgánicos combinados se secaron (separador de fases) y se concentraron al vacío. El producto crudo se usó directamente en la siguiente etapa sin ninguna purificación adicional. MS: 219 [M + H]+, 437 [2M + H]+; t_R (condiciones de HPLC b) 2,16 min.

Ácido (1- carbamoil- 2- metil- 1H- indol- 3- il)- acético

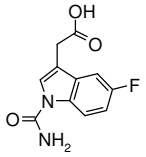


se preparó de una manera similar como se describe en el Esquema A8 Paso B para el ácido (1- carbamoil- 1H- indol- 3- il)- acético a partir de ester etilo del ácido (1- carbamoil- 2- metil- 1H- indol- 3- il) - acético. El producto crudo (sólido pardusco) obtenido después de tratamiento de extracción se utilizó directamente en la siguiente etapa sin purificación. MS: 233 [M + H] +; t_R (condiciones de HPLC b) 3,26 min.

Ester etilo del ácido (1- carbamoil- 2- metil- 1H- indol- 3- il)- acético

El compuesto del título se preparó de una manera similar a la descrita en el Esquema A8 Etapa A a partir de éster etilo del ácido (2- metil- 1H- indol- 3- il)- acético [21909- 49- 9] (1,20 g, 5,52 mmol) , NaH (60% en aceite mineral, 331 mg, 8,28 mmol) e isocianato de clorosulfonilo (0,959 ml, 11,1 mmol). La purificación por cromatografía en columna ultrarrápida sobre gel de sílice (EtOAc/c- hexano 1:4- 1:1) proporcionó un sólido de color amarillento. TLC, R_f (EtOAc/c- hexano 1:1) = 0.31; MS: 261 [M + H]+; t_R (condiciones de HPLC b) 3,54 min.

<u>Ácido (1- carbamoil- 5- fluoro- 1H- indol- 3- il)- acético</u>

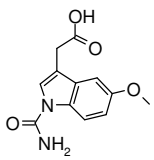


se preparó de una manera similar como se describe en el Esquema A8 Paso B para el ácido (1- carbamoil- 1H- indol- 3- il)- acético a partir de éster etílico del ácido (1- carbamoil- 5- fluoro- 1H- indol- 3- il) - acético. El producto en crudo (sólido amarillento) obtenido después de tratamiento de extracción se utilizó directamente en la siguiente etapa sin purificación. MS: 236,9 [M + H] +; t_R (condiciones de HPLC B) 2,4 min.

Ester etilo del ácido (1- carbamoil- 5- fluoro- 1H- indol- 3- il)- acético

El compuesto del título se preparó de una manera similar a la descrita en el Esquema A8 de la Etapa A a partir de ester metilo del ácido (5- fluoro- 1H- indol- 3- il)- acético [497258- 29- 4] (150 mg, 0,724 mmol) , NaH (60% en aceite mineral, 37,4 mg, 0,869 mmol) e isocianato de clorosulfonilo (0,126 ml, 1,45 mmol). La purificación por cromatografía en columna ultrarrápida sobre gel de sílice (EtOAc/c- hexano gradiente de 1:3- 2:3) proporcionó el compuesto del título. TLC, R_f (EtOAc/c- hexano 1:1) = 0,16; MS: 261 [M+H]+, 501 [2M+H]+; t_R (condiciones de HPLC b) 3,2 min.

<u>Ácido (1- carbamoil- 5- metoxi- 1H- indol- 3- il)- acético</u>

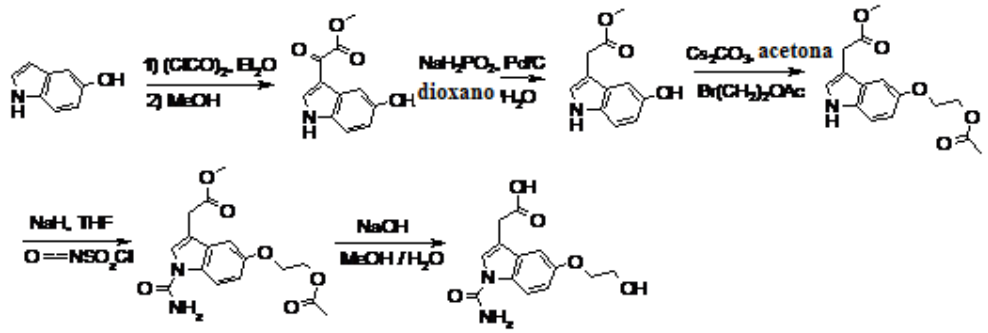


se preparó a partir del éster metilo del ácido 5- metoxi- 3- indolilacético de acuerdo con el protocolo descrito esquema A8 para la preparación de ácido (1- carbamoil- 1H- indol- 3- il)- acético. Rf, TLC (EtOAc) = 0,2; MS (LC/MS): 248,9 [M + H] +, 271,0 [M + Na] +, 247,1 [MH] - , 495,1 [2M - H], 204,1 [M- CONH2] - ; t_R (condiciones de HPLC f): 1,54 min.

Éster metilo del ácido 5- metoxi- 3- indolilacético

A una suspensión del ácido 5- metoxi- 3- indolilacético (500 mg, 2,44 mmol) en CH_2Cl_2 (7 ml) se añadieron DCC (553 mg, 2,68 mmol), DMAP (30 mg, 0,244 mmol) y metanol (99 µl, 2,44 mmoles). La suspensión blanca resultante se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 2,5 h. La mezcla se filtró y el filtrado se concentró para proporcionar un aceite marrón que se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (hexano- c a c- hexano/EtOAc 8- 2) para proporcionar el material deseado como un aceite marrón. TLC, Rf (EtOAc) = 0,82; MS (LC- MS): 220,0 [M + H] +, 242,1 [M + Na] +, 461,0 [2M + Na] +, 218,1 [MH] - ; t_R (condiciones de HPLC f) 3,2 min.

<u>Esquema A9: Ácido [1- carbamoil- 5- (2- hidroxi- etoxi)- 1H- indol- 3- il]- acético</u>



A. Éster metilo del ácido (5- hidroxi- 1H- indol- 3- il) - oxo- acético

A una solución de cloruro de oxalilo (3.18 ml, 37.6 mmol) en éter seco (50 ml) se añadió 5- hidroxiindol (2.5 g, 18.8 mmol) en pequeñas porciones durante 15 min a - 5 °C en atmósfera de nitrógeno, y la mezcla resultante se agitó a temperatura ambiente durante 30 min. La suspensión se filtró y el residuo se lavó con Et_2O. Se añadió MeOH seco (60 ml) cuidadosamente, y la mezcla resultante se agitó a temperatura ambiente durante 1 h. La suspensión se filtró y se lavó sucesivamente con MeOH y Et_2O para proporcionar el material deseado. TLC, R_f (EtOAc) = 0,75; MS (LC- MS): 220,0 [M+H]+, 242,1 [M+Na]+, 461,0 [2M+Na]+, 218,1 [MH] - ; t_R (condiciones de HPLC f): 1.02 min.

B. éster metílo del ácido (5- hidroxi- 1H- indol- 3- il)- acético

A una suspensión de éster metilo del ácido (5- hidroxi- 1H- indol- 3- il)- oxo- acético (1 g, 4.56 mmol) en dioxano (14 ml) se añadió Pd/C al 10% (400 mg) y un solución de $NaH_2PO_2.H_2O$ (4.84 g, 45.6 mmol) en agua (2,35 ml). La mezcla de reacción se agitó y se calentó a reflujo durante 1.5 h. Después de completar la mezcla de reacción se enfrió a temperatura ambiente, y el catalizador se retiró mediante filtración a través de una almohadilla de Celite y se lavó con MeOH. Los solventes se concentraron, y el residuo se disolvió en CH_2Cl_2 y se lavó con agua. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró para proporcionar el material deseado. TLC, R_f (EtOAc) = 0,85; MS (LC- MS): 206,1 [M+H]+. 1H-RMN (400 MHz, DMSO): δ (ppm): 10,64 (bs, 1H), 8,64 (s, 1H), 7,14 (m, 2H), 6,78 (d, 1H), 6,60 (dd, 1H), 3,65 (s, 3H), 3,58 (s, 2H).

C. Éster metilo del ácido [5 (2- acetoxi- etoxi)- 1H- indol- 3- il]- acético

A una solución de éster metilo del ácido (5- hidroxi- 1H- indol- 3- il)- acético (670 mg, 3.26 mmol) en acetona (15 ml) se añadió carbonato de cesio (1.17 g, 3.59 mmol) y acetato de 2-bromoetilo (395 µl, 3.59 mmol). La suspensión se sometió a reflujo durante toda la noche en atmósfera de nitrógeno. La acetona se concentró y el residuo se disolvió en agua y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano para c- hexano/EtOAc 6:4) para proporcionar el material deseado. TLC, R_f (c- hexano/EtOAc 01:01) = 0,45; MS (LC- MS): 292,1 [M+H]+, 314,0 [M+Na]+, 290,0 [MH] - ; t_R (condiciones de HPLC f): 1,70 min.

D. Éster metilo del ácido 5 - (2- acetoxi- etoxi)- 1- carbamoil- 1H- indol- 3- il]- acético

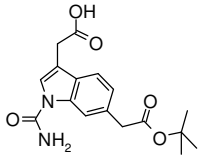
Una suspensión de NaH (en aceite mineral al 60%, 43 mg, 1.06 mmol) en THF (2.5 ml) en atmósfera de nitrógeno se enfrió a 5 °C y se añadió una solución de éster metílo del ácido [5 - (2- acetoxi- etoxi)- 1H- indol - 3- ilo]- acético (249 mg, 0.71 mmol) en THF (2.5 ml). La mezcla se agitó 30 min antes de la adición lenta de isocianato de clorosulfonilo (123 µl, 1.42 mmol) a 5 °C. Luego la solución resultante se agitó durante la noche permitiendo que la temperatura alcanzara lentamente la temperatura ambiente. Se añadió ácido acético (1.3 ml), y la solución se agitó a temperatura ambiente durante 1 h, antes de la adición de hielo y agua (16 ml). La mezcla se agitó adicionalmente a temperatura ambiente durante 30 min y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se lavaron con agua, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (100% c- hexano a 100% EtOAc) para proporcionar el

material deseado. TLC, R_f (EtOAc) = 0,7; MS (LC- MS): 335,0 [M+H]+, 357,1 [M+Na]+, 333,1 [MH] - , 290,0 [M- CONH2] - , 379,0 [M + HCOO] - ; t_R (condiciones de HPLC f): 1,63 min.

E. Ácido [1- carbamoil- 5- (2- hidroxi- etoxi)- 1H- indol- 3- il]- acético

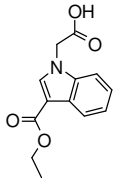
Se disolvió éster metilo del ácido 5 - (2- acetoxi- etoxi)- 1- carbamoil- 1H- indol- 3- il]- acético (54 mg, 0.153 mmol) en MeOH (1.3 ml) y H_2O (130 µl). Se añadió NaOH 1 N (307 µl, 0.307 mmol) y la mezcla se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se concentró, el producto crudo se vertió en HCl 1 N y se extrajo dos veces con CH_2Cl_2. Se formó un precipitado en la capa acuosa y se filtró para proporcionar el material deseado. TLC, R_f (EtOAc) = 0,15; MS (LC/MS): 279,1 [M+H]+, 301,0 [M+Na]+, 277,0 [MH] - , 233,9 [M- $CONH_2$] - ; 1H- RMN (400 MHz, DMSO): δ (ppm): 12,4 (bs, 1H), 8,13 (d, 1H), 7,73 (s, 1H), 7,43 (bs, 2H), 7,05 (d, 1H), 6,89 (dd, 1H), 4,0 (t, 2H), 3,74 (t, 2H), 3,64 (d, 2H).

Ácido (6- terc- butoxicarbonilmetil- 1- carbamoil- 1H- indol- 3- il)- acético



Se preparó a partir de éster terc- butilo del ácido (1H- indol- 6- il) acético (descrito para la preparación de (éster terc- butílo del ácido (1- carbamoil- 3- isocianato- 1H- indol- 6- il)- acético de acuerdo con el protocolo descrito esquema A9 de los pasos A, B, D, E para la preparación de ácido [1- carbamoil- 5- (2- hidroxi- etoxi)- 1H- indol- 3- il]- acético. MS (LC/MS): 350.2/352.2 [M + NH4] +, 687.2/689.2 [2M+Na]+, 277.0/279.0 [MH- tBu]+, 288.0/290.0 [M- $CONH_2$] - , 376.9/378.8 [M + HCOO] - , 662.8/664.7 [2M- H] - ; t_R (condiciones de HPLC f): 1,79 min.

Éster etílo del ácido 1- carboximetil- 1H- indol- 3- carboxílico



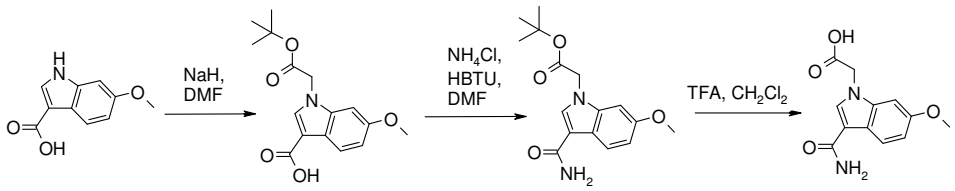
Se disolvió éster etilo del ácido 1- terc- butoxicarbonilmetil- 1H- indol- 3- carboxílico en CH_2Cl_2 (12 ml), TFA (2.65 ml, 34.6 mmol) se añadió y la solución se agitó a temperatura

ambiente durante fin de semana. Se añadió CH_2Cl_2 y agua, las capas se separaron y la fase acuosa se volvió a extraer con CH_2Cl_2 (2x). Las capas orgánicas combinadas se secaron con Na_2SO_4, se filtraron y se concentraron para proporcionar el compuesto deseado. TLC, R_f (EtOAc) = 0,62; MS (LC/MS): 248,1 [M+H]+, 246,0 [MH] - ; t_R (condiciones de HPLC a): 3,03 min.

Éster etílo del ácido 1- terc- butoxicarbonilmetil- 1H- indol- 3- carboxílico

A una suspensión de éster etílo del ácido 1H- indol- 3- carboxílico (800 mg, 4.23 mmol) y carbonato de potasio (1.34 g, 9.72 mmol) en CH_3CN (21 ml) en atmósfera de nitrógeno se añadió bromoacetato de terc- butilo (875 µ, 5.92 mmol) y la mezcla de reacción se calentó a reflujo durante la noche. La mezcla de reacción se dejó enfriar a temperatura ambiente, se añadió EtOAc y agua y las capas se separaron, la fase acuosa se re- extrajo con EtOAc. Las capas orgánicas se lavaron con salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida (c- hexano para c-hexano/EtOAc 1:1) para proporcionar el compuesto deseado. TLC, R_f (EtOAc) = 0,77; MS (LC/MS): 304,1 [M+H]+, 302,0 [MH] - ; t_R (condiciones de HPLC A): 4.01 min.

<u>Esquema A10: preparación del Ácido (3- carbamoil- 6- metoxi- indol- 1- il)- acético</u>



A. Ácido 1- terc- butoxicarbonilmetil- 6- metoxi- 1H- indol- 3- carboxílico

A una suspensión enfriada con hielo de ácido 6- metoxi- 1H- indol- 3- carboxílico (1 g, 5.23 mmol) en DMF (35 ml) se añadió NaH (Suspensión al 60% en aceite; 0.523 g, 13.1 mmol) en una porción, y la mezcla se agitó a 0 °C durante 30 min. Luego se añadió por goteo Terc-butil- 2- bromoacetato (0.85 ml, 5.75 mmol), y la agitación se continuo a temperatura ambiente durante la noche. La mezcla de reacción se neutralizó mediante la adición de NH_4Cl saturado, y luego la solución se ajustó a pH = 2- 3 mediante la adición de HCl 0.1 N. La capa acuosa se extrajo varias veces con CH_2Cl_2, los extractos orgánicos combinados se lavaron con salmuera, se secaron (separador de fases) y se concentraron al vacío. El residuo se disolvió en un pequeño volumen de metanol, seguido de la adición de agua hasta que precipitó un sólido. El precipitado se filtró, se lavó con agua y se secó al vacío para proporcionar el compuesto del título como un

Sólido blanco.MS (LC/MS): 306 [M+H]+, 328 [M+Na]+; t_R (condiciones de HPLC c): 4,67 min.

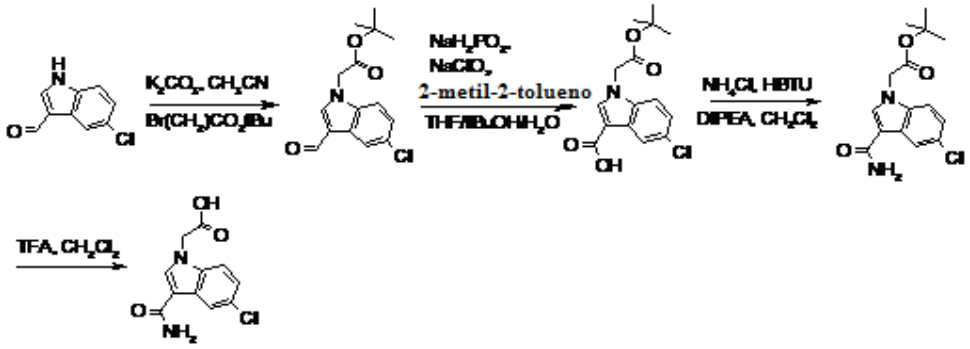
B. Éster terc- butilo del ácido (3- carbamoil- 6- metoxi- indol- 1- il)- acético

A una mezcla del ácido 1- terc- butoxicarbonilmetil- 6- metoxi- 1H- indol- 3- carboxílico (500 mg, 1.28 mmol) en DMF (6 ml) se añadió sucesivamente De NH_4Cl (137 mg, 2.55 mmol), HBTU (1.21 g, 3.19 mmoles) y DIPEA (0.90 ml, 5.11 mmoles), y se continuó la agitación a temperatura ambiente durante 16 h. Se añadió alícuotas adicionales de NH_4Cl (2 equiv) y DIPEA (4 equiv) a la mezcla de reacción. Después de agitar durante 16 h, se añadió agua y la capa acuosa se extrajo varias veces con EtOAc. Los extractos orgánicos combinados se lavaron con solución acuosa saturada de $NaHCO_3$ y salmuera, se secaron (separador de fases) y se concentraron al vacío. La purificación mediante HPLC preparativa (Macherey Nagel, VP250/40, Nucleosil C18 100- 10, eluyente: 20- 100% CH_3CN/H_2O/20 min, 100% de CH_3CN/2 min, CH_3CN y H_2O que contiene TFA al 0.1%, flujo: 40 ml/min) y la liofilización de las fracciones purificadas produjo el compuesto del título como un sólido de color beige. MS: 305 [M+H]+, 609 [2M+H]+; t_R (condiciones de HPLC c): 4.26 min.

C. Ácido (3- carbamoil- 6- metoxi- indol- 1- il)- acético

A una solución de éster terc- butilo del ácido (3- carbamoil- 6- metoxi- indol- 1- il)- acetato (300 mg, 0.99 mmol) en CH_2Cl_2 (9 ml) se añadió TFA (4.5 ml) a temperatura ambiente, y Se continuó agitando durante 2 h. El metanol se añadió después a la mezcla de reacción, y los volátiles se eliminaron al vacío. El residuo se recogió en metanol y se concentró bajo presión reducida para proporcionar el compuesto del título como un sólido de color gris: MS: 249 [M+H]+, 497 [2M+H]+; t_R (condiciones de HPLC c): 2.86 min. El material así obtenido se usó en la siguiente etapa de reacción sin purificación adicional.

Esquema A11: Preparación del ácido (3- carbamoil- 5- cloro- indol- 1- il)- acético



A. éster terc- butilo del ácido (5- cloro- 3- formil- indol- 1- il)- acético

A una suspensión de 5- cloro- 1H- indol- 3- carbaldehído [827- 01- 0] (500 mg, 2.78 mmol) y K_2CO_3 (885 mg, 6.40 mmol) en (14 ml) se añadió terc- butílico del ácido 2 - bromoacetato (0.576 ml, 3.90 mmol) por goteo a temperatura ambiente. Luego la mezcla resultante se calentó a reflujo durante 18 h. Después de enfriar a temperatura ambiente, la mezcla se diluyó con EtOAc y agua. La capa orgánica se separó, se lavó posteriormente con agua (1x) y salmuera (1x), se secó (separador de fases) y se concentró al vacío para proporcionar el compuesto del título crudo. MS (LC/MS): 294 [M+H]+; t_R (condiciones de HPLC B): 5.45 min. El producto se usó en la siguiente etapa de reacción sin purificación adicional.

B. Ácido 1- terc- butoxicarbonilmetil- 5- cloro- 1H- indol- 3- carboxílico

A una solución de éster terc- butilo del ácido (5- cloro- 3- formil- indol- 1- il)- acético (902 mg, 2.92 mmol) en THF (12 ml) y terc- butanol (4.80 ml) se añadió sucesivamente 2- metil- 2- buteno (9.27 ml, 88.0 mmol), una solución de $NaClO_2$ (2.64 g, 29.2 mmoles) y dihidrógeno fosfato de sodio (2.80 g, 23.3 mmol) en agua (4.80 ml), seguido de agitación a temperatura ambiente durante 18 h. La mezcla de reacción se acidificó con HCl 0.1 N (pH de 2 a 3) y se extrajo con EtOAc (3x). Los extractos orgánicos combinados se secaron (separador de fases) y se concentraron al vacío. El residuo se trituró con éter dietílico, el sólido se separó por filtración, se lavó con éter dietílico y se secó al vacío para proporcionar el compuesto del título como un Sólido blanco. MS (LC/MS): 310 [M+H]+; t_R (condiciones de HPLC b): 5.16 min.

C. Éster terc- butilo del ácido (3- carbamoil- 5- cloro- indol- 1- il) –acético

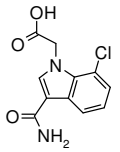
A una mezcla del ácido 1- terc- butoxicarbonilmetil- 5- cloro- 1H- indol- 3- carboxílico (400 mg, 1.29 mmol) en CH_2Cl_2 (6 ml) se añadió sucesivamente NH_4Cl (138 mg, 2.58 mmol), HBTU (1.22 g, 3.23 mmol) y DIPEA (0.902 ml, 5.17 mmol). Se continuó la agitación a

temperatura ambiente durante 16 h. Se añadió alícuotas adicionales de NH_4Cl (2 equiv) y DIPEA (4 equiv) a la mezcla de reacción. Después de agitar durante 4 h, la mezcla de reacción se diluyó con CH_2Cl_2 y la solución se lavó con agua (2x), HCl acuoso 0.1 N (2x), $NaHCO_3$ acuoso saturado (2x) y salmuera, se secó (separador de fases) y se concentró al vacío. El residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (EtOAc/c- hexano gradiente de 2:1- 1:0) para proporcionar el compuesto del título en forma de un Sólido blanco. TLC R_f (EtOAc/c- hexano 2:1) = 0,20; MS (LC/MS): 309 [M+H]+, 617 [2M+H]+; t_R (condiciones de HPLC b): 4.75 min.

D. Ácido (3- carbamoil- 5- cloro- indol- 1- il)- acético

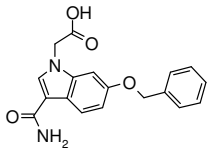
A una solución de éster terc- butílo del ácido (3- carbamoil- 5- cloro- indol- 1- il)- acético (455 mg, 0.973 mmol) en CH_2Cl_2 (6.0 ml) se añadió TFA (3.0 ml) a temperatura ambiente y continuó agitendo durante 2 h. El metanol se añadió después a la mezcla de reacción y los volátiles se eliminaron al vacío. El residuo se recogió en metanol y se concentró de nuevo a presión reducida. El residuo se disolvió en NaOH acuoso 1 N y se lavó con CH_2Cl_2 (3x). La fase acuosa se acidificó a pH 2 mediante la adición de HCl 6 N acuoso para formar una suspensión blanca. El precipitado se separó por filtración, se lavó con agua y se secó al vacío para proporcionar el compuesto del título crudo en forma de un sólido de color blanco. MS (LC/MS): 253 [M+H]+, 505 [2M+H]+; t_R (condiciones de HPLC b): 3.99 min. El producto se usó en la siguiente etapa de reacción sin purificación adicional.

Ácido (3- carbamoil- 7- cloro- indol- 1- il)- acético



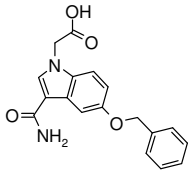
Se preparó a partir de 7- cloro- 1H- indol- 3- carbaldehído [07.07.1008] usando protocolos similares a los descritos en el Esquema A11 para la preparación de (3- carbamoil- 5- cloro- indol- 1- il)- acético ácido. Sólido blanco. MS (LC/MS): 253 [M+H]+, 505 [2M+H]+; t_R (condiciones de HPLC b): 3,32 min.

Ácido (6- benciloxi- 3- carbamoil- indol- 1- il)- acético



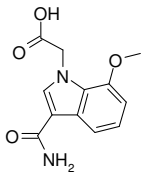
Se preparó a partir de 6- benciloxi- 1H- indol- 3- carbaldehído [92855- 64- 6] usando protocolos similares a los descritos en el Esquema A11 para la preparación del ácido (3- carbamoil- 5- cloro- indol- 1- il)- acético. Sólido blanco. MS (LC/MS): 325 [M+H]+, 649 [2M+H]+; t_R (condiciones de HPLC B): 4.06 min.

Ácido (5- benciloxi- 3- carbamoil- indol- 1- il)- acético



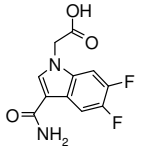
Se preparó a partir de 5- benciloxi- 1H- indol- 3- carbaldehído [6953- 22- 6] usando protocolos similares a los descritos en el Esquema A11 para la preparación del ácido (3- carbamoil- 5- cloro- indol- 1- il)- acético. Sólido blanco. MS (LC/MS): 325 [M+H]+, 649 [2M+H]+; t_R (condiciones de HPLC b): 4.04 min.

Ácido (3- carbamoil- 7- metoxi- indol- 1- il)- acético



Se preparó a partir de 7- metoxi- 1H- indol- 3- carbaldehído [109021- 59- 2] de una manera similar a la descrita en el Esquema A11 para la preparación del ácido (3- carbamoil- 5- cloro- indol- 1- il) - acético. Sólido blanco. MS (LC/MS): 249 [M+H]+, 497 [2M+H]+; t_R (condiciones de HPLC C): 3.05 min.

Ácido (3- carbamoil- 5 ,6- difluoro- indol- 1- il)- acético



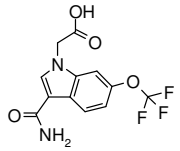
Se preparó a partir de 5,6- difluoro- 1H- indol- 3- carbaldehído de una manera similar como se describe en el Esquema A11 para la preparación de (3- carbamoil- 5- cloro- indol- 1-

il)- acético. El compuesto del título se obtuvo como un Sólido blanco: MS (LC/MS): 255.0 [M+H]+, 509.0 [2M+H]+; t_R (condiciones de HPLC k): 2.58 min.

5,6- difluoro- 1H- indol- 3- carbaldehído

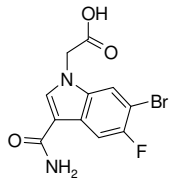
A una solución enfriada con hielo de cloruro de oxalilo (1.21 ml, 13.8 mmol) en CH_2Cl_2 (40 ml) se añadió una solución de DMF (2.02 ml) en CH_2Cl_2 (40,0 ml). La reacción se agitó durante 30 min, luego se añadió 5,6- difluoro- 1H- indol [169674- 01- 5] (2.00 g, 13.1 mmol) en una porción. La mezcla de reacción se dejó calentar a temperatura ambiente durante una noche. Los volátiles se evaporaron, y el residuo se recogió en THF (20 ml) y una solución de acetato de amonio acuoso al 20% (20 ml). La mezcla resultante se calentó a reflujo durante 30 min. Después de enfriar, la mezcla se trató con una solución de $NaHCO_3$ acuoso saturado y se extrajo tres veces con EtOAc. Las capas orgánicas combinadas se secaron (separador de fases) y se evaporaron al vacío para proporcionar el compuesto del título como un sólido de color beige: MS (LC/MS): 182.0 [M+H]+; t_R (condiciones de HPLC c): 3.94 min. El material así obtenido se usó en la siguiente etapa sin purificación adicional.

<u>Ácido (3- carbamoil- 6- trifluorometoxi- indol- 1- il)- acético</u>



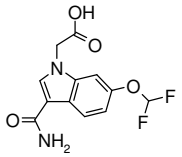
Se preparó a partir de 6- trifluorometoxi- 1H- indol [467451- 91- 8] de una manera similar a la descrita para la preparación de (3- carbamoil- 5 ,6- difluoro- indol- 1- il)- acético. Sólido blanco. MS (LC/MS): 303.0 [M+H]+, 605.0 [2M+H]+; t_R (condiciones de HPLC k): 2.75 min.

<u>Ácido (6- bromo- 3- carbamoil- 5- fluoro- indol- 1- il)- acético</u>



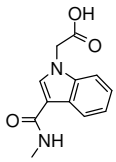
Se preparó a partir de 6- bromo- 5- fluoro- 1H- indol [259860- 08- 7] de una manera similar a la descrita para la preparación del ácido (3- carbamoil- 5 ,6- difluoro- indol- 1- il)- acético. Sólido blanco. MS (LC/MS): 315,0 [M+H]+, 631,0 [2M+H]+; t_R (condiciones de HPLC k): 2.79 min.

Ácido (3- carbamoil- 6- difluorometoxi- indol- 1- il)- acético



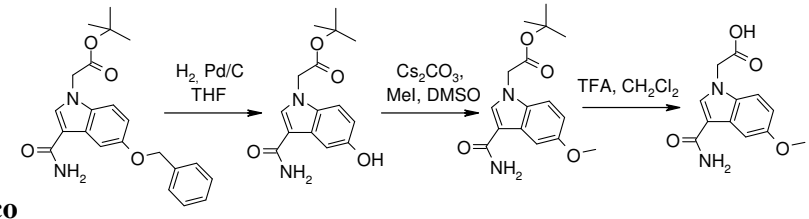
Se preparó a partir de 6- difluorometoxi- 1H- indol [200207- 21- 2] de una manera similar a la descrita para la preparación del ácido (3- carbamoil- 5 ,6- difluoro- indol- 1- il)- acético. Sólido blanco. MS (LC/MS): 285 [M+H]+, 569 [2M+H]+; t_R (condiciones de HPLC k): 2.64 min.

Ácido (3- metilcarbamoil- indol- 1- il)- acético



Se preparó a partir de 1H- indol- 3- carbaldehído usando protocolos similares a los descritos en el Esquema A11 para la preparación del ácido (3- carbamoil- 5- cloro- indol- 1- il)- acético (el uso de hidrocloruro de metilamina en el paso C). MS (LC/MS): 233 [M+H]+; 465 [M+H]+; 231 [MH] - , 463 [M+H] - ; t_R (condiciones de HPLC b): 1.8 min.

Esquema A12: Preparación del Ácido (3- carbamoil- 5- metoxi- indol- 1- il)- acético



A. Éster terc- butilo del ácido (5- benciloxi- 3- carbamoil- indol- 1- il)- acético

El compuesto del título se preparó a partir de 5- benciloxi- 1H- indol- 3- carbaldehído [6953- 22- 6] de una manera similar a la descrita en el Esquema A11 para los pasos de A a C.

B. Éster terc- butilo del ácido (3- carbamoil- 5- hidroxi- indol- 1- il)- acético

Se suspendió éster terc- butílo del ácido (5- benciloxi- 3- carbamoil- indol- 1- il)- acético (250 mg, 0.657 mmol) en THF (13 ml). El aire se retiró del matraz y se reemplazó con nitrógeno tres veces. Se añadió Pd/C al 10% (25 mg) a la solución que se desgasificó de nuevo,

se colocó bajo una atmósfera de hidrógeno y se agitó a temperatura ambiente durante la noche. El catalizador se eliminó a través de un filtro de 0.45 micras y se concentró al vacío. El material crudo se purificó mediante HPLC preparativa (SunFire C18- ODB, 5 µm, 30x100 mm, eluyente: 5- 100% CH_3CN/H_2O/20 min, 100% de CH_3CN/2 min, CH_3CN y H_2O que contiene TFA al 0.1%, flujo: 40 ml/min) para proporcionar después de la liofilización de las fracciones purificadas el compuesto deseado como un Sólido blanco. MS: 291 [M+H]+, 313 [M+Na]+, 581 [2M+H]+, 603 [2M+Na]+; t_R (condiciones de HPLC c): 3.75 min.

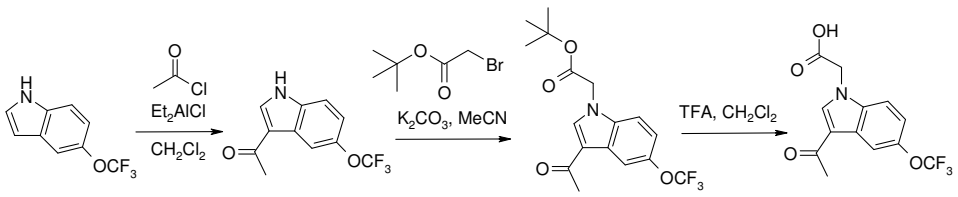
C. Éster terc- butilo del ácido (3- carbamoil- 5- metoxi- indol- 1- il) - acético

A una solución de éster terc- butilo del ácido (3- carbamoil- 5- hidroxi- indol- 1- il)- acético (50 mg, 0.172 mmol) en DMSO (1.7 ml) se le añadió Cs_2CO_3 (336 mg, 1.03 mmol). La mezcla se agitó a temperatura ambiente durante 5 min, seguido de la adición de yoduro de metilo (0.048 ml, 0.774 mmol), y se continuó la agitación a temperatura ambiente durante 3 días. La mezcla de reacción se particionó entre agua y CH_2Cl_2, las capas se separaron y la fase acuosa se extrajo dos veces con CH_2Cl_2. Los extractos orgánicos combinados se lavaron dos veces con salmuera, se secaron (separador de fases) y se concentraron al vacío para proporcionar el compuesto del título como un sólido de color amarillo: MS (LC/MS): 305 [M+H]+, 327 [M+Na]+, 609 [2M+H]+; t_R (condiciones de HPLC C): 4,31 min. El material así obtenido se usó en la siguiente etapa de reacción sin purificación adicional.

D. ácido (3- carbamoil- 5- metoxi- indol- 1- il)- acético

A una solución de éster terc- butílo del ácido (3- carbamoil- 5- metoxi- indol- 1- il)- acético (45.0 mg, 0.118 mmol) en CH_2Cl_2 (2.0 ml) se añadió TFA (1.0 ml) a temperatura ambiente, y agitación se continuó durante 3 h. Luego el metanol se añadió a la mezcla de reacción y los volátiles se eliminaron al vacío. El residuo se recogió en metanol y se concentró de nuevo a presión reducida para proporcionar el compuesto del título como un sólido de color beige: MS (LC/MS): 249 [M+H]+, 277 [M+Na]+; t_R (condiciones de HPLC c): 2,93 min. El material así obtenido se usó en la siguiente etapa de reacción sin purificación adicional.

<u>Esquema A13: Preparación del Ácido (3- acetil- 5- trifluorometoxi- indol- 1- il)- acético</u>



A. 1 - (5- trifluorometoxi- 1H- indol- 3- il)- etanona

A una solución de 5 - (trifluorometoxi)- 1H- indol [262593- 63- 5] (1.00 g, 4.97 mmol) en CH_2Cl_2 (20 ml), se enfrió a 0 °C, se añadió por goteo cloruro de dietil- aluminio (solución 1 M en hexano; 7.46 ml, 7.46 mmoles), y la agitación se continuó durante 30 min. Posteriormente se añadió una solución de cloruro de acetilo (0.532 ml, 7.46 mmol) en CH_2Cl_2 (20 ml), y la mezcla de reacción se agitó a 0 °C durante 1 h. Después se añadió una solución de ácido cítrico acuoso al 5% (100 ml) a 0 °C, y la mezcla se agitó durante 15 min a temperatura ambiente. La mezcla de (dos fases) se filtró, y el precipitado se secó a 50 °C al vacío durante 1 h para proporcionar el compuesto del título. Sólido beige.MS: 244.0 [M+H]+; t_R (condiciones de HPLC c): 4,60 min. El material así obtenido se utilizó directamente en la siguiente etapa sin purificación adicional

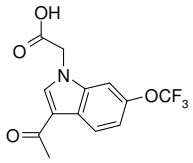
B. Éster de terc- butilo del ácido (3- Acetil- 5- trifluorometoxi- indol- 1- il)- acético

A una solución de 1 - (5- trifluorometoxi- 1H- indol- 3- il)- etanona (0.50 g, 2.06 mmol) en CH_3CN (10 ml) se añadió K_2CO_3 (0.313 g, 2.26 mmol) y 2- bromoacetato de terc- butilo (0.334 ml, 2.26 mmol). La mezcla de reacción se agitó a 90 °C durante la noche. La mezcla de reacción se filtró, y el filtrado se diluyó con CH_2Cl_2. Los orgánicos se lavaron con solución 1M HCl acuoso (5 ml) y solución acuosa saturada de $NaHCO_3$ (5 ml). La capa orgánica se secó (separador de fases) y se evaporó en vacío para proporcionar el compuesto del título como un aceite amarillento: MS: 358.0 [M+H]+; t_R (condiciones de HPLC c): 5,66 min. El material así obtenido se utilizó directamente en la siguiente etapa sin purificación adicional.

C. ácido (3- Acetil- 5- trifluorometoxi- indol- 1- il)- acético

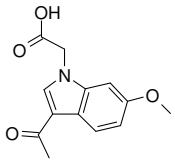
A una solución de éster terc- butilo del ácido (3- acetil- 5- trifluorometoxi- indol- 1- il)- acético (680 mg, 1.90 mmol) en CH_2Cl_2 (10 ml) se añadió TFA (1.47 ml, 19.0 mmoles), y se continuó agitando a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con CH_2Cl_2 y MeOH, y los volátiles se evaporaron bajo presión reducida. El residuo se recogió en MeOH y luego se evaporó de nuevo. El material crudo se recogió en solución acuosa de NaOH 1M (5 ml), y la capa de agua se lavó con CH_2Cl_2 y posteriormente se acidificó a pH = 1 por adición de una solución de HCl 6M. El precipitado se filtró y se secó a 50 °C en vacío durante 1 h para proporcionar el compuesto del título como un sólido blancuzco: MS: 302.0 [M+H]+; t_R (condiciones de HPLC C): 4,40 min. El material así obtenido se utilizó directamente en la siguiente etapa sin purificación adicional.

Ácido (3- Acetil- 6- trifluorometoxi- indol- 1- il)- acético



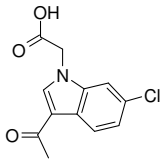
Se preparó a partir de 6- trifluorometoxi- 1H- indol [467451- 91- 8] de una manera similar como se describe en Esquema A13 para la preparación del ácido (3- ccetil- 5- trifluorometoxi- indol- 1- il)- acético. MS: 302.0 [M+H]+; t_R (condiciones de HPLC c): 4,39 min.

Ácido (3- Acetil- 6- metoxi- indol- 1- il)- acético



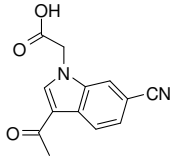
Se preparó a partir de 1 - (6- metoxi- 1H- indol- 3- il)- etanona [99532- 52- 2] de una manera similar como se describe en el paso B y C del Esquema A13 para la preparación del ácido (3- acetil- 5- trifluorometoxi- indol- 1- il)- acético. Sólido marrón. MS: 248 [M+H]+, 517 [2M+Na]+; t_R (condiciones de HPLC k): 2.30 min.

Ácido (3- Acetil- 6- cloro- indol- 1- il)- acético



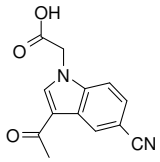
Se preparó a partir de 6- cloro- 1H- indol en una manera similar como se describe en el Esquema A13 para la preparación del ácido (3- acetil- 5- trifluorometoxi- indol- 1- il)- acético. Sólido marrón. MS: 252 [M+H]+, 274 [M+Na]+; t_R (condiciones de HPLC k): 2.89 min.

Ácido (3- Acetil- 6- ciano- indol- 1- il)- acético



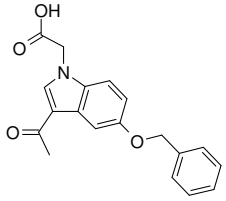
Se preparó a partir de 1H- indol- 6- carbonitrilo de una manera similar como se describe en el Esquema A13 para la preparación del ácido (3- acetil- 5- trifluorometoxi- indol- 1- il)- acético. MS: 243 [M+H]+; t_R (condiciones de HPLC k): 2.72 min.

Ácido (3- Acetil- 5- ciano- indol- 1- il)- acético



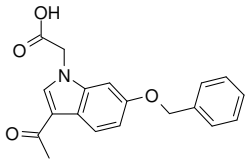
Se preparó a partir de 1H- indol- 5- carbonitrilo de una manera similar como se describe en el Esquema A13 para la preparación del ácido (3- acetil- 5- trifluorometoxi- indol- 1- il)- acético. MS (LC/MS): 241,2 [MH] - , 243,2 [M+H]+; t_R (condiciones de HPLC a): 2.62 min.

Ácido (3- Acetil- 5- benciloxi- indol- 1- il)- acético



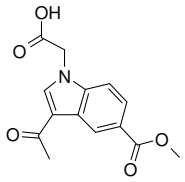
Se preparó a partir de 5- benciloxi- 1H- indol en una manera similar como se describe en el Esquema A13 para la preparación del ácido (3- acetil- 5- trifluorometoxi- indol- 1- il)- acético. MS: 324 [M+H]+, 346 [M+Na]+; t_R (condiciones de HPLC k): 3.34 min.

Ácido (3- Acetil- 6- benciloxi- indol- 1- il)- acético



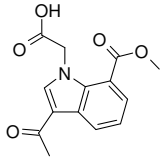
Se preparó a partir de 6- benciloxi- 1H- indol en una manera similar como se describe en el Esquema A13 para la preparación de ácido (3- acetil- 5- trifluorometoxi- indol- 1- il)- acético. MS: 324 [M+H]+, 647 [2M +1]+; t_R (condiciones de HPLC k): 3.38 min.

Éster metilo del ácido 3- acetil- 1- carboximetil- 1H- indol- 5- carboxílico



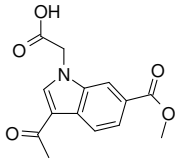
Se preparó a partir del éster metílico del ácido 1H- indol- 5- carboxílico de una manera similar a la descrita en el Esquema A13 para la preparación del ácido (3- acetil- 5- trifluorometoxi- indol- 1- il)- acético. MS: 276 [M+H]+; t_R (condiciones de HPLC k): 2.84 min.

Éster metilo del ácido 3- acetil- 1- carboximetil- 1H- indol- 7- carboxílico



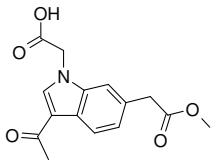
Se preparó a partir del éster metílo del ácido 1H- indol- 7- carboxílico de una manera similar a la descrita en el Esquema A13 para la preparación del ácido (3- acetil- 5- trifluorometoxi- indol- 1- il)- acético. MS: 276 [M+H]+; t_R (condiciones de HPLC k): 2.89 min.

Éster metilo del ácido 3- acetil- 1- carboximetil- 1H- indol- 6- carboxílico



Se preparó a partir del éster metílico del ácido 3- acetil- 1H- indol- 6- carboxílico [106896- 61- 1] en un modo similar al descrito en el paso B y C del Esquema A13 para la preparación de (3- acetil- 5- trifluorometoxi - indol- 1- il)- acético. Sólido de color. MS: 276 [M+H]+; t_R (condiciones de HPLC k): 2.80 min.

Ácido (3- Acetil- 6- metoxicarbonilmetil- indol- 1- il)- acético



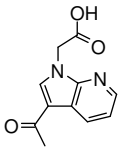
Se preparó a partir del éster metílo del ácido (3- acetil- 1H- indol- 6- il)- acético de una manera similar como se describe en el Esquema A13 para la preparación del ácido (3- acetil- 5-

trifluorometoxi- indol- 1- il) - acético. Sólido marrón. MS: 290 [M+H]+; t_R (condiciones de HPLC k): 2.83 min.

Éster metilo del ácido (3- Acetil- 1H- indol- 6- il)- acético

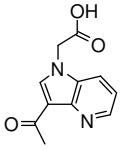
A una solución agitada del ácido (3- acetil- 1H- indol- 6- il)- acético [39689- 58- 2] (500 mg, 2,85 mmol) en MeOH (14 ml), se enfrió a 0 °C se añadió (trimetilsilil) diazometano (solución 2 M en Et_2O, 6.00 ml, 12.0 mmol). Después de agitar a temperatura ambiente durante 30 min, la mezcla de reacción se concentró al vacío para proporcionar el compuesto del título en forma de una cera amarilla. MS: 190 [M+H]+; t_R (condiciones de HPLC k): 3,20 min. El material así obtenido se utilizó directamente en la siguiente etapa sin purificación adicional.

Ácido (3- acetil- pirrolo [2,3- b] piridin- 1- il)- acético



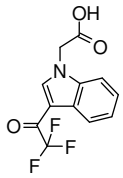
Se preparó de una manera similar como se describe en el paso B y C del Esquema A13 para la preparación de ácido (3- acetil- 5- trifluorometoxi- indol- 1- il)- acético a partir de 1 - (1H- pirrolo [2,3 - b] piridin- 3- il)- etanona [83393- 46- 8]. MS (UPLC/MS): 219,2 [M+H]+, 217,2 [MH] - , 263,3 [M + HCOO] - , 435,3 [2M- H] - ; t_R (condiciones de HPLC f): 1,16 min. 1H- RMN (400 MHz, DMSO): δ (ppm): 8,55 (bs, 1H), 8,49 (dd, 1H), 8,36 (dd, 1H), 7,31 (dd, 1H), 5,12 (s, 2H), 2,48 (s, 3H).

Ácido (3- acetil- pirrolo [3,2- b] piridin- 1- il)- acético



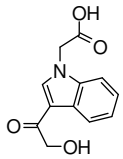
Se preparó de una manera similar como se describe en el paso B y C del Esquema A13 para la preparación del ácido (3- acetil- 5- trifluorometoxi- indol- 1- il)- acético a partir de 1 - (1H- pirrolo [3,2 - b] piridin- 3- il)- etanona (preparada de acuerdo con J. Org. Chem.. 2002, 67, 6226). MS (UPLC/MS): 219,2 [M+H]+, 217,3 [MH] - , 435,3 [2M- H] - ; t_R (condiciones de HPLC f): 1,16 min. 1H- RMN (400 MHz, DMSO): δ (ppm): 8,79 (bs, 1H), 8,64 (m, 2H), 7,64 (m, 1H), 5,33 (s, 2H), 2,67 (s, 3H).

Ácido [3 - (2,2,2- trifluoro- acetil)- indol- 1- il]- ácido acético



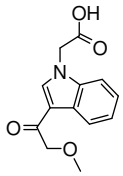
Se preparó a partir de 2,2,2- trifluoro- 1- (1H- indol- 3- il)- etanona de una manera similar como se describe en el Esquema A13 (paso B y C) para la preparación del ácido (3- acetil- 5- trifluorometoxi- indol- 1- il)- acético. Sólido blanco. MS: 272,0 [M+H]+; t_R (condiciones de HPLC C): 4.59 min.

Ácido [3 - (2- hidroxi- acetil)- indol- 1- il]- ácido acético



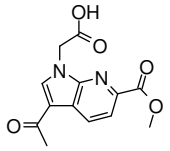
Se preparó a partir de 2- hidroxi- 1- (1H- indol- 3- il)- etanona [2400- 51- 3] de una manera similar a la descrita en el Esquema A13 (paso B y C) para la preparación del ácido (3- acetil - 5- trifluorometoxi- indol- 1- il)- acético. Sólido de color. MS: 234,0 [M+H]+, 489,0 [2M+Na]+; t_R (condiciones de HPLC c): 3,11 min.

Ácido [3 - (2- metoxi- acetil)- indol- 1- il]- acético



Se preparó a partir de 1H- indol en una manera similar como se describe en el Esquema A13 (en el paso A, se utilizó cloruro de 2- metoxiacetilo en lugar de cloruro de acetilo) para la preparación del - ácido (3- acetil- 5- trifluorometoxi- indol- 1- il) acético. Sólido marrón. MS: 248.0 [M+H]+; t_R (condiciones de HPLC c): 3,42 min.

Éster metílico del ácido 3 - acetil- 1- carboximetil- 1H- pirrolo- [2,3- b] piridina- 6- carboxílico



Se preparó a partir de metil 3- acetil- 1H- pirrolo [2,3- b] piridina- 6- carboxilato de metilo usando un protocolo similar al descrito en el Esquema A13, Pasos C y D: MS (LC/MS): 277 [M+H]+; t_R (condiciones de HPLC k): 2,68 min.

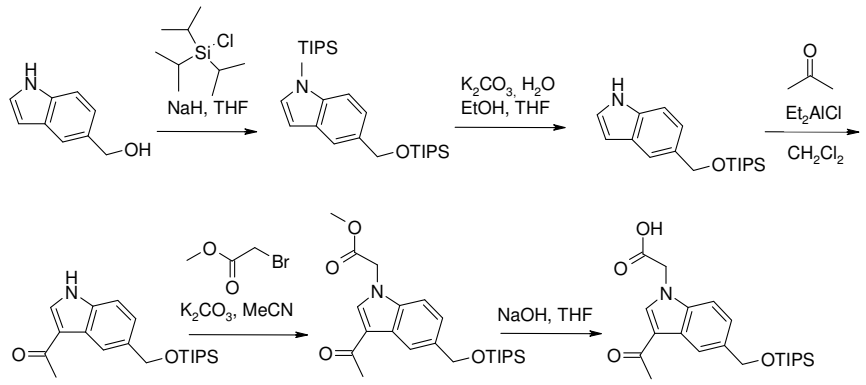
3- acetil- 1H- pirrolo [2,3- b] piridina- 6- carboxilato de metilo

Se preparó a partir de metil 1H- pirrolo [2,3- b] piridina- 6- carboxilato de metilo usando un protocolo similar al descrito en el Esquema A17, Paso A: MS (LC/MS): 219 [M+H]+; t_R (HPLC condiciones k): 2,58 min.

1H- pirrolo [2,3- b] piridina- 6- carboxilato de metilo

A una solución agitada de 1H- pirrolo [2,3- b] piridina- 6- carboxílato de metilo [898746- 35- 5] (500 mg, 3.08 mmol) en MeOH se añadió una solución 2 M de trimetilsilildiazometano en Et_2O a 0 °C, y la mezcla de reacción se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se concentró al vacío para proporcionar el compuesto del título. MS (LC/MS): 177 [M+H]+, 375 [2M+H]+; t^R (condiciones de HPLC k): 2,71

Esquema A14: Preparación del ácido (3- acetil- 5- triisopropilsilaniloximetil- indol- 1- il)- acético



A. 1- triisopropilsilanil- 5- triisopropilsilaniloximetil- 1H- indol

A una solución de (1H- indol- 5- il)- metanol (1.00 g, 6.79 mmol) en THF (60 ml), se enfrió a 0 °C, se añadió hidruro de sodio (en aceite mineral al 60%; 1.36 g, 34.0 mmol) en

porciones. Después de agitar durante 5 min, se añadió cloruro de triisopropilsililo (2.88 ml, 13.6 mmol), y la solución resultante se agitó a temperatura ambiente durante 2 h. La reacción se apagó mediante la adición de una solución acuosa saturada de $NaHCO_3$ a 0 °C. La capa acuosa se extrajo varias veces con EtOAc, y los orgánicos combinados se lavaron con H_2O (1x) y salmuera (1x), se secaron (separador de fases) y se concentraron al vacío. La purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (gradiente de eluyente: c-hexano para c- hexano/EtOAc 9:1) proporcionó el compuesto del título como un Sólido blanco. TLC, R_f (c- hexano/EtOAc 9:01) = 0,72. 1H- RMN (400 MHz, DMSO- d_6): ppm δ 7,61 (s, 1H), 7,49 (d, 1H), 7,32 (d, 1H), 6,93 (d, 1H), 6,57 (d, 1H), 4,92 (s, 2H), 1,60- 1,85 (m, 3H), 1.1- 1.12 (m, 39H).

B. 5- Triisopropilsilaniloximetil- 1H- indol

A una suspensión de 1- triisopropilsilanil- 5- triisopropilsilaniloximetil- 1H- indol (2.80 g, 6.09 mmol) en EtOH (30 ml)/THF (10 ml) / agua (10 ml) se añadió K_2CO_3 (4.21 g, 30.4 mmol) , y la mezcla de reacción se calentó a 85 °C durante 16 h. La reacción se apagó con HCl 1 N a 0 °C. La capa acuosa se extrajo con CH_2Cl_2 (2x) y las capas orgánicas combinadas se lavaron con salmuera, se secaron (separador de fases) y se concentraron bajo presión reducida. El residuo aceitoso se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (gradiente de eluyente: c- hexano para c- hexano/EtOAc 9:1) para proporcionar el compuesto del título como un aceite de color amarillo. TLC, R_f (c- hexano/EtOAc 9:1) = 0.29. t_R (condiciones de HPLC k): 5.02 min. MS (LC/MS): 304 [M+H]+.

C. 1 - (5- Triisopropilsilaniloximetil- 1H- indol- 3- il)- etanona

El compuesto del título se preparó a partir de 5- triisopropilsilaniloximetil- 1H- indol en una manera similar como se describe en el paso A del Esquema A13 para la preparación del ácido (3- acetil- 5- trifluorometoxi- indol- 1- il)- acético. Sólido marrón. MS: 346 [M+H]+; t_R (condiciones de HPLC c): 6,86 min.

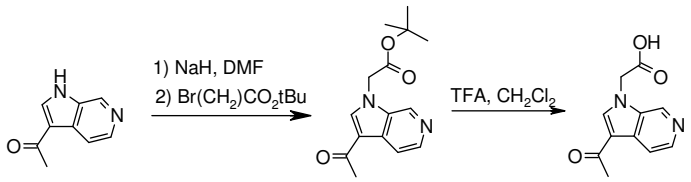
D. Éster metilo del ácido (3- Acetil- 5- triisopropilsilaniloximetil- indol- 1- il)- acético

El compuesto del título se preparó a partir de 1 - (5- triisopropilsilaniloximetil- 1H- indol- 3- il)- etanona de una manera similar a la descrita en el paso B del Esquema A13 para la preparación del ácido (3- acetil- 5- trifluorometoxi- indol- 1- il)- acético. MS: 418 [M+H]+; t_R (condiciones de HPLC k): 4.75 min.

E. Ácido (3- Acetil- 5- triisopropilsilaniloximetil- indol- 1- il)- acético

A una solución éster metilo del ácido (3- acetil- 5- triisopropilsilaniloximetil- indol- 1- il)- acetato (109 mg, 0.138 mmol) en THF (5 ml) y agua (0,5 ml) se añadió NaOH 1 N (0.69 ml, 0.69 mmol) , y se continuó la agitación a temperatura ambiente durante 16 h. La mezcla de reacción se particionó entre EtOAc y $NaHCO_3$ acuoso saturado. La capa acuosa se extrajo con EtOAc (2x), los extractos orgánicos combinados se secaron (separador de fases) y se concentraron al vacío para proporcionar el compuesto del título en forma de una cera amarilla. MS (LC/MS): 404 [M+H]+; t_R (condiciones de HPLC k): 4,35 min.

Esquema A15: Preparación de trifluoroacetato del ácido (3- acetil- pirrolo [2,3- c] piridin- 1- il)- acético



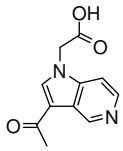
A. Éster de terc- butilo del ácido (3- acetil- pirrolo [2,3- c] piridin- 1- il)- acético

A una suspensión de NaH (en aceite mineral al 60%, 90 mg, 2.25 mmol) en DMF (4.2 ml) se enfrió a 0 ºC se añadió una solución de 1 - (1H- pirrolo [2,3- c] piridin- 3 - etanona)- ilo (preparado de acuerdo con J. Org. Chem.. 2002, 67, 6226) (300 mg, 1.87 mmol) en DMF (4.2 ml) y la suspensión resultante se agitó a 0 °C bajo atmósfera de nitrógeno durante 30 min antes de la adición lenta de bromoacetato de terc- butilo (277 µl, 1.87 mmol). La mezcla de reacción se dejó alcanzar a temperatura ambiente y se agitó adicionalmente a temperatura ambiente durante 1,5 h. Después de la terminación de la reacción, la mezcla se purificó primero por captura de liberación en SiliaPrep Tosic ácido- (2x10 g) (Varian) (eluyente: MeOH (50 ml) por amoniaco 2 M en MeOH (50 ml)) para proporcionar una mezcla de regioisómeros: éster terc- butilo del ácido (3- acetil- pirrolo [2,3- c] piridin- 1- il)- acetato y éster terc- butílo del ácido (3- acetil- pirrolo [2,3- c] piridin- 6- il) - acético seguido de cromatografía ultrarrápida en columna sobre gel de sílice (CH_2Cl_2 a CH_2Cl_2/MeOH 85- 15) para proporcionar éster terc- butilo del ácido (3- acetil- pirrolo [2,3- c] piridin- 1- il)- acético en forma de un polvo de color amarillo. TLC, R_f (CH_2Cl_2/MeOH 9- 1) = 0,50; EM (UPLC/MS): 275,3 [M+H]+, 319,2 [M+HCOO] - ; t_R (f) Condiciones de HPLC: 1,28 min; 1H- RMN (400 MHz, DMSO- d6): δ (ppm): 8,88 (s, 1H), 8,50 (s, 1H), 8,33 (d, 1H), 8,06 (d, 1H), 5,27 (s, 2H), 2,48 (s, 3H), 1,45 (s, 9H).

B. trifluoroacetato del ácido (3- acetil- pirrolo [2,3- c] piridin- 1- il)- acético

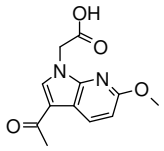
Una solución de éster terc- butilo del ácido (3- acetil- pirrolo [2,3- c] piridin- 1- il)- acético (230 mg, 0.8 mmol) y TFA (0.915 ml, 11.95 mmol) en CH_2Cl_2 (3.1 ml) se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró y el residuo se secó a alto vacío. El sólido resultante se absorbió en Et2O y se filtró para proporcionar el compuesto deseado (sal de TFA) como un polvo de color beige que se utilizó en la siguiente etapa sin purificación. MS (UPLC/MS): 219,2 [M+H]+, 217,2 [MH] - , 1H- RMN (400 MHz, DMSO): δ (ppm): 9,50 (s, 1H), 9,03 (s, 1H), 8,54 (d, 1H), 8,51 (d, 1H), 5,40 (s, 2H), 2,57 (s, 3H).

Trifluoroacetato del ácido (3- acetil- pirrolo [3,2- c] piridin- 1- il)- acético



Se preparó usando procedimientos similares a los descritos para la síntesis del ácido (3- acetil- pirrolo [2,3- c] piridin- 1- il)- acético en el Esquema A15 a partir de 1 - (1H- pirrolo [3,2- c] - etanona) piridin- 3- il)etanona (preparado de acuerdo con J. Org. Chem.. 2002, 67, 6226). MS (UPLC/MS): 219,1 [M+H]+, 217,2 [MH] - , 435,3 [2M- H] - ; 1H- RMN (400 MHz, DMSO): δ (ppm): 9,54 (s, 1H), 8,89 (s, 1H), 8,66 (d, 1H), 8,30 (d, 1H), 5,38 (s, 2H), 2,58 (s, 3H).

Ácido (3- Acetil- 6- metoxi- pirrolo [2,3- b] piridin- 1- il)- acético



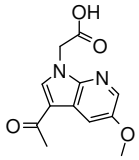
Se preparó usando procedimientos similares a los descritos para la síntesis del ácido (3- acetil- pirrolo [2,3- c] piridin- 1- il)- acético en el Esquema A15 a partir de 1 - (6- metoxi- 1H- pirrolo [2, 3- b] piridin- 3- il)- etanona. MS (UPLC/MS): 249,2 [M+H]+, 497,3 [2M+H]+, 519,3 [2M+Na]+, 247,1 [MH] - , 293,2 [M + HCOO] - , 495,3 [2M + HCOO] - ; t_R (condiciones de HPLC f): 1,55 min. 1H- RMN (400 MHz, DMSO): δ (ppm): 12,3 (bs, 1H), 8,33 (d, 1H), 8,21 (s, 1H), 6,70 (d, 1H), 3,89 (s, 3H), 3,32 (s, 2H), 2,43 (s, 3H).

1 - (6- metoxi- 1H- pirrolo [2,3- b] piridin- 3- il)- etanona

A una suspensión de $AlCl_3$ (1.37 g, 10.3 mmol) en CH_2Cl_2 (40 ml) se añadió 6- metoxi- 7- azaindol (315 mg, 2.07 mmol) y la mezcla se agitó a temperatura ambiente durante 30 min

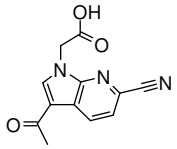
en atmósfera de nitrógeno. Se añadió por goteo cloruro de acetilo (736 l, 10.3 mmol) y la mezcla resultante se agitó a temperatura ambiente durante la noche. MeOH (8 ml) se añadió con precaución para detener la reacción y los solventes se eliminaron al vacío. El residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (CH_2Cl_2 a CH_2Cl_2/MeOH 93- 7) y por HPLC preparativa (Waters Sunfire C18- ODB, 5 micras, 30x100 mm, 5% a 100% de CH_3CN en H_2O en 25 min, CH_3CN y H_2O que contiene 0.1% de TFA, flujo: 40 ml/min) para proporcionar después de la neutralización (acuosa saturada de $NaHCO_3$) y la extracción (CH_2Cl_2) de las fracciones purificadas el compuesto deseado TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0,55; MS (UPLC/MS): 191,2 [M+H]+, 189,1 [MH] - , 379,2 [2M- H] - ; t_R (condiciones de HPLC f): 1,45 min. 1H- RMN (400 MHz, DMSO): δ (ppm): 8,35 (d, 1H), 8,29 (s, 1H), 6,75 (d, 1H), 5,04 (s, 2H), 3,89 (s, 3H), 2,44 (s, 3H).

Trifluoroacetato del ácido (3- Acetil- 5- metoxi- pirrolo [2,3- b] piridin- 1- il)- acético



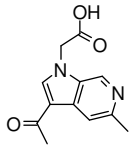
Se preparó usando procedimientos similares a los descritos para la síntesis de (3- acetil- 6- metoxi- pirrolo [2,3- b] piridin- 1- il)- acético en el Esquema A15 de 1H- pirrolo [2,3- b] piridina- 6- carbonitrilo. TLC, R_f (CH_2Cl_2/MeOH 4:1) = 0.50; EM (UPLC/MS): 191,2 [M+H]+, 189,1 [MH] - ; t_R (condiciones de HPLC f): 1,23 min.

Ácido (3- Acetil- 6- ciano- pirrolo [2,3- b] piridin- 1- il)- acético



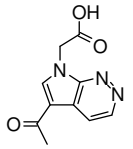
Se preparó usando procedimientos similares a los descritos para la síntesis de (3- acetil- 6- metoxi- pirrolo [2,3- b] piridin- 1- il)- acético en el Esquema A15 de 1H- pirrolo [2,3- b] piridina- 6- carbonitrilo. MS (UPLC/MS): 244,1 [M+H]+, 242,1 [MH] - ; t_R (condiciones de HPLC f): 1,42 min.

Trifluoroacetato del ácido (3- Acetil- 5- metil- pirrolo [2,3- c] piridin- 1- il)- acético



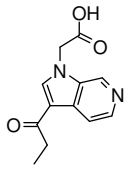
Se preparó usando procedimientos similares a los descritos para la síntesis de (3- acetil- pirrolo [2,3- c] piridin- 1- il)- acético en el Esquema A15 a partir de 1 - (5- metil- 1H- pirrolo [2, 3- c] piridin- 3- il)- etanona (preparado de acuerdo con J. Org. Chem.. 2002, 67, 6226). MS (UPLC/MS): 233,2 [M+H]+, 231,2 [M- H] - .

Ácido (5- Acetil- pirrolo [2,3- c] piridazin- 7- il)- acético



Se preparó usando procedimientos similares a los descritos para la síntesis de (3- acetil- pirrolo [2,3- c] piridin- 1- il)- acético en el Esquema A15 a partir de 1 - (7H- pirrolo [2,3- c] piridazin- 5- il)- etanona (preparada de acuerdo con J. Org. Chem.. 2002, 67, 6226). MS (UPLC/MS): 220,1 [M+H]+, 178,0 [MH- CH_3CO] +, 218,1 [MH] - , 437,2 [2M- H] - .

Trifluoroacetato de ácido (3- propionil- pirrolo [2,3- c] piridin- 1- il)- acético



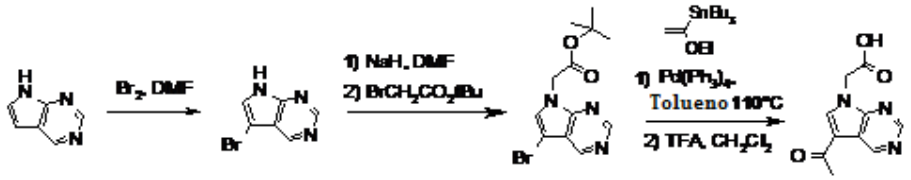
Se preparó usando procedimientos similares a los descritos para la síntesis del ácido (3- acetil- 6- metoxi- pirrolo [2,3- b] piridin- 1- il)- acético en el Esquema A15 a partir de 1 - (1H- pirrolo [2, 3- c] piridin- 3- il)- propan- 1- ona. 1H- RMN (400 MHz, DMSO- d_6): δ (ppm): 9,56 (s, 1H), 9,09 (s, 1H), 8,58 (m, 2H), 5,42 (s, 2H), 3,0 (q, 2H), 1,15 (t, 3H).

1 - (1H- pirrolo [2,3- c] piridin- 3- il)- propan- 1- ona

Se añadió 6- azaindol (500 mg, 4,23 mmol) a una suspensión de $AlCl_3$ (2.82 g, 21.16 mmol) en CH_2Cl_2 (100 ml) bajo atmósfera de argón. La mezcla se agitó a temperatura ambiente durante 30 min y se añadió por goteo cloruro de propionilo (1.84 ml, 21.16 mmol). La mezcla de reacción se agitó durante 2.5 h y se apagó mediante la adición cuidadosa de MeOH (20 ml). Los solventes se eliminaron a presión reducida y el residuo crudo se purificó mediante

cromatografía en columna ultrarrápida sobre gel de sílice (CH_2Cl_2 a CH_2Cl_2/MeOH 87:13). TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0,35; EM (UPLC/MS): 175,2 [M+H]+, 173,1 [MH] - , 347,3 [2M- H], 219,1 [M + HCOO] - ; t_R (f) Condiciones de HPLC: 0,42 min.

Esquema A16: Preparación de trifluoroacetato del ácido (5- acetil- pirrolo [2,3- d] pirimidin- 7- il)- acético



A. 5- bromo- 7H- pirrolo [2,3- d] pirimidina

Se añadió una solución de bromo (0.086 ml, 1.68 mmol) en DMF (5.5 ml) a una solución de 7H- pirrolo [2,3- d] pirimidina (200 mg, 1.68 mmol) en DMF (5.5 ml). La mezcla de reacción se agitó a temperatura ambiente durante 4 h y se vertió en una mezcla de hielo y agua que contenía $Na_2S_2O_3$. Se añadió una solución acuosa saturada de $NaHCO_3$ (hasta pH básico), las capas se separaron y la capa acuosa se extrajo dos veces con EtOAc. Los extractos orgánicos combinados se lavaron con salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron. El material así obtenido se utilizó sin purificación adicional en la siguiente etapa. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0,45; EM (UPLC/MS): 198.1/200.1 [M+H]+, 196.1/198.1 [MH] - .

B. Éster terc- butilo del ácido (5- bromo- pirrolo [2,3- d] pirimidin- 7- il)- acético

A una suspensión de NaH (en aceite mineral al 60%, 34 mg, 0.85 mmol) en DMF (1.5 ml) a 0 °C bajo atmósfera de nitrógeno se añadió una solución de 5- bromo- 7H- pirrolo [2,3- d] pirimidina (140 mg, 0.71 mmol) en DMF (1.5 ml). La mezcla de reacción se agitó a 0 °C durante 30 min y se añadió lentamente bromoacetato de terc- butilo (104 µl, 0.71 mmol). La mezcla se agitó adicionalmente a temperatura ambiente durante 30 min, luego se vertió en agua y se extrajo con EtOAc (x3). Los extractos orgánicos combinados se lavaron con agua, se secaron (Na_2SO_4), se filtraron y se concentraron. MS (UPLC/MS): 312.3/314.2 [M+H]+.

C. Éster terc- butilo del ácido (5- Acetil- pirrolo [2,3- d] pirimidin- 7- il)- acetico

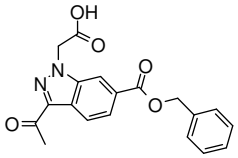
Una solución de éster terc- butilo del ácido (5- bromo- pirrolo [2,3- d] pirimidin- 7- il)- acético (220 mg, 0.71 mmol), tri- butilo (1- etoxivinil)estaño (285 µl, 0.85 mmol) y tetraquis (trifenilfosfina)paladio (16,28 mg, 14,1 mmol) en tolueno (7 ml) se calentó a 110 °C durante

72 h en atmósfera de argón. La mezcla se dejó enfriar a temperatura ambiente, se vertió en agua y se extrajo con EtOAc (x2). Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (CH_2Cl_2 a CH_2Cl_2/MeOH 94:6). TLC, Rf (CH_2Cl_2/MeOH 9:1) = 0,54; MS (UPLC/MS): 276,3 [M+H]+, 320,4 [M + HCOO] - ; t_R (condiciones de HPLC f): 1,40 min.

D. Ácido (5- Acetil- pirrolo [2,3- d] pirimidin- 7- il)- acético

Una solución de éster terc- butilo del ácido (5- acetil- pirrolo [2,3- d] pirimidin- 7- il)- acético (146 mg, 0.53 mmol) y TFA (0.814 ml, 10.62 mmol) en CH_2Cl_2 (2.5 ml) se agitó a temperatura ambiente durante 24 h. Los solventes se eliminaron a presión reducida y el material así obtenido se utilizó sin purificación adicional en la siguiente etapa. 1H- RMN (400 MHz, DMSO): δ (ppm): 9,45 (s, 1H), 9,0 (s, 1H), 8,68 (s, 1H), 7,66- 7,56 (m, 2H), 5,16 (s, 2H), 2,53 (s, 3H).

Éster bencílico del ácido 3- Acetil- 1- carboximetil- 1H- indazol- 6- carboxílico



Se preparó usando protocolos similares a los descritos en el Esquema A16, Paso C y D a partir de éster bencílo del ácido 3- bromo- 1- terc- butoxicarbonilmetil- 1H- indazol- 6- carboxílico. MS (UPLC/MS): 553,4 [M+H]+, 351,4 [MH] - , 703,6 [2M- H] - ; t_R (condiciones de HPLC f): 2.10 min.

Éster bencilo del ácido 3- bromo- 1- terc- butoxicarbonilmetil- 1H- indazol- 6- carboxílico

Se preparó usando el protocolo similar como se describe en el Esquema A20 Paso C a partir del éster bencílo del ácido 3- bromo- 1H- indazol- 6- carboxílico. MS (UPLC/MS): 445.4/447.3 [M+H]+; tR (UPLC condiciones m): 1,45 min.

Éster bencilo del ácido 3- bromo- 1H- indazol- 6- carboxílico

Una solución de éster de 6- bencilo del ácido 3- bromo- indazol- 1 ,6- dicarboxílico - éster 1- terc- butilo (2,05 g, 4,75 mmol) y TFA (3,66 ml, 47,5 mmol) en CH_2Cl_2 (30 ml) se agitó a temperatura ambiente durante 16 h. Se añadió una solución acuosa saturada de $NaHCO_3$, las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (x3). Los extractos

orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron y el material así obtenido se utilizó sin purificación adicional en la siguiente etapa. MS (UPLC/MS): 331.2/333.2 [M+H]+, 329.3/331.2 [MH] - ; t_R (UPLC condiciones m): 1,18 min.

Éster bencilo del ácido de 3- bromo- indazol- 1 ,6- dicarboxílico – éster 1- terc- butilo

Una solución que contiene éster 1- terc- butilo del ácido 3- bromo- indazol- 1 ,6- dicarboxílico (1.80 g, 5.28 mmol), bromuro de bencilo (0.753 ml, 6.33 mmol), Cs_2CO_3 (1.89 g, 5.80 mmol) y yoduro de sodio (0.095 g, 0.633 mmol) en DMF (30 ml) se agitó 16 h a temperatura ambiente. La mezcla se diluyó con agua y se extrajo con EtOAc (x3). Los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron al vacío. El residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (EtOAc/c-hexano 1:04). MS (UPLC/MS): 431.2/433.2 [M+H]+; t_R (condiciones UPLC f): 2,77 min.

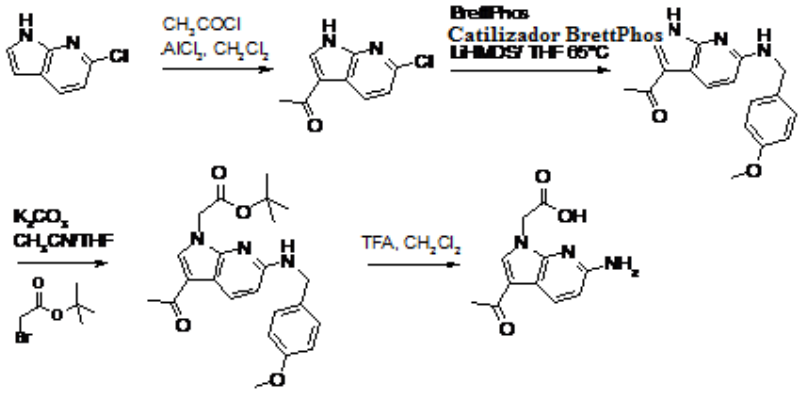
Éster 1- terc- butil del ácido 3- bromo- indazol- 1 ,6- dicarboxílico

Una solución que contiene ácido 3- bromo- 1H- indazol- 6- carboxílico (1.40 g, 5.81 mmol), trietilamina (0.89 ml, 6.39 mmol), DMAP (0.071 g, 0.58 mmol) y $(Boc)_2O$ (1.90 g, 8.71 mmol) en CH_2Cl_2 (60 ml) se agitó 16 horas a 25 °C. Los Volatiles se eliminaron bajo presión reducida, se añadió agua y Et_2O. La capa acuosa se acidificó mediante la adición de $KHSO_4$ (10% en agua) y se extrajo con EtOAc (x3). Los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron al vacío. El material así obtenido se utilizó sin purificación adicional en la siguiente etapa. MS (UPLC/MS): 441.2/443.2 [M+H]+.

Ácido 3- bromo- 1H- indazol- 6- carboxílico

Se añadió por goteo bromo (0.385 ml, 7.48 mmol) a una solución del ácido 1H- indazol-6- carboxílico (1 g, 5.98 mmol) en ácido acético (30 ml) y la mezcla de reacción se agitó durante 16 horas a 25 °C en la oscuridad. La reacción se apagó mediante la adición de una solución acuosa saturada de Na_2SO_3 (12 ml) y salmuera (25 ml) y se extrajo con EtOAc (x3). Los extractos orgánicos combinados se lavaron con salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron. El material así obtenido se utilizó sin purificación adicional en la siguiente etapa. MS (UPLC/MS): 239.1/241.1 [MH] - , 481.3/483.3 [2M- H] - ; t_R (condiciones UPLC f): 1,59 min.

Esquema A17: Ácido (3- Acetil- 6- amino- pirrolo [2,3- b] piridin- 1- il)- acético



A. 1 - (6- cloro- 1H- pirrolo [2,3- b] piridin- 3- il)- etanona

Se añadió 6- cloro- 7- azaindol (1 g, 6.55 mmol) a una suspensión de $AlCl_3$ (4.37 g, 32.8 mmol) en CH_2Cl_2 (150 ml) bajo atmósfera de nitrógeno. La mezcla se agitó a temperatura ambiente durante 30 min, y se añadió por goteo cloruro de acetilo (2.34 ml, 32.8 mmol). La mezcla resultante se agitó adicionalmente a temperatura ambiente durante 2 h. Después de la terminación, se añadió MeOH (40 ml) con precaución y los volatiles se eliminaron a presión reducida. El residuo se diluyó en CH_2Cl_2 y se neutralizó por adición de una solución acuosa saturada de $NaHCO_3$. Las capas se separaron y los extractos orgánicos se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se purificó dos veces mediante cromatografía en columna ultrarrápida sobre gel de sílice (CH_2Cl_2 a CH_2Cl_2/MeOH 95- 5). TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0,5; EM (UPLC/MS): 195.1/197.1 [M+H]+, 193.1/195.1 [MH] - ; tR (condiciones de HPLC f): 1,54 min.

B. 1 - [6 - (4- metoxi- bencilamino)- 1H- pirrolo [2,3- b] piridin- 3- il]- etanona

La reacción se realizó de acuerdo con el protocolo descrito en Org. Lett., 2010, 12 (20), 4438- 4441. Un vial que contiene 1 - (6- cloro- 1H- pirrolo [2,3- b] piridin- 3- il)- etanona (100 mg, 0.49 mmol), BrettPhos (2,62 mg, 4,88 mmol) y precatalizador BrettPhos (3.9 mg , 4.88 mol) y una barra de agitación magnética se selló con un tapón de rosca de teflón, se evacuo y se volvió llenar con argón. Un globo de argón, se colocó en la parte superior del frasco, para permitir un equilibrio de presión y se añadío LiHMDS (1 M en THF, 1.172 l, 1.17 mmol), seguido de 4- metoxibencilamina (76 µl, 0.59 mmol). La mezcla de reacción se agitó y se calentó a 65 °C durante 22 h, después se dejó enfriar hasta temperatura ambiente, se apagó mediante la adición de HCl 1 M (1 ml) se diluyó con EtOAc y se vertió en una solución acuosa saturada de $NaHCO_3$. Después de extraer dos veces con EtOAc, las capas orgánicas combinadas se lavaron con salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron. El

producto crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano a EtOAc). TLC, R_f (EtOAc) = 0,75; EM (UPLC/MS): 296,2 [M+H]+, 591,3 [2M+H]+, 613,2 [2M+Na]+; tR (condiciones de HPLC f): 1,5 min.

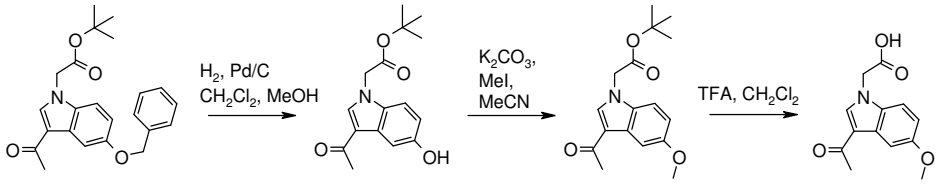
C. Éster terc- butilo del ácido [pirrolo- [3- Acetil- 6- (4- metoxi- bencilamino) 2,3- b] piridin- 1- il]- acetato

Se añadió bromoacetato de terc- butilo (27 µl, 0.18 mmol) a una suspensión de 1 - [6 - (4- metoxi- bencilamino)- 1H- pirrolo [2,3- b] piridin- 3- il]- etanona (0.17 mmol) y carbonato de potasio (27.5 mg, 0.20 mmol) en CH_3CN (0.33 ml) y THF (0.33 ml). La mezcla de reacción se agitó a temperatura ambiente durante 7 h. Se añadió de nuevo carbonato de potasio (27.5 mg, 0.20 mmol) y bromoacetato de terc- butilo (27 µl, 0,18 mmol) y se continuó la agitación durante toda la noche, esta operación se repitió al día siguiente. La suspensión se filtró, el filtrado se concentró bajo presión reducida y el residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (CH_2Cl_2 a CH_2Cl_2/MeOH 98:2). TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0,9; EM (UPLC/MS): 410,2 [M+H]+, 819,4 [2M+H]+, 841,3 [2M+Na]+, 454,1 [M+HCOO] - ; t_R (condiciones de HPLC $_f$): 2,30 min.

D. Trifluoroacetato del ácido (3- Acetil- 6- amino- pirrolo [2,3- b] piridin- 1- il)- acético

Una solución de [3- acetil- 6- (4- metoxi- bencilamino)- pirrolo [2,3- b] piridin- 1- il]- acetato de terc- butilo (51 mg, 0.125 mmol) y TFA (191 µl, 2.49 mmol) en CH_2Cl_2 (0.6 ml) se agitó a temperatura ambiente durante 24 h. Los volatiles se eliminaron bajo presión reducida y el sólido de color pardo así obtenido se usó sin purificación adicional en la siguiente etapa. MS (UPLC/MS): 234,1 [M+H]+, 232,1 [M- H] - . 1H- RMN (400 MHz, DMSO): δ (ppm): 8,08 (d, 1H), 8,02 (s, 1H), 6,83 (m, 2H), 6,44 (d, 1H), 4,90 (s, 2H), 2,38 (s, 3H).

<u>Esquema A18: Preparación del ácido (3- acetil- 5- metoxi- indol- 1- il)- acético</u>



A. Éster terc- butilo del ácido (3- Acetil- 5- hidroxi- indol- 1- il)- acético

A una solución de éster terc- butílo del ácido (3- acetil- 5- benciloxi- indol- 1- il)- acético (MS: 380.0 [M+H]+; t_R (Condiciones de HPLC c): 5.72 min; preparado a partir de 5 - benciloxi- 1H- indol [1215- 59- 4] de una manera similar a la descrita en el Esquema A13 (Paso

A y B)) (3.3 g, 8.70 mmol) en CH_2Cl_2/MeOH (80 ml) se añadió Pd/C (0.093 g, 0.870 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 5 h bajo atmósfera de H_2. La mezcla de reacción se filtró sobre una almohadilla de Celite y se lavó con CH_2Cl_2 y MeOH. Los volátiles se evaporaron, y la mezcla cruda se purificó mediante cromatografía ultrarrápida sobre gel de sílice (gradiente de c- hexano/EtOAc 2:1 a 100% de EtOAc). TLC, R_f (c- hexano/EtOAc 1:1) = 0,35; MS: 312.0 [M+Na]+; t_R (condiciones de HPLC c): 4,27 min.

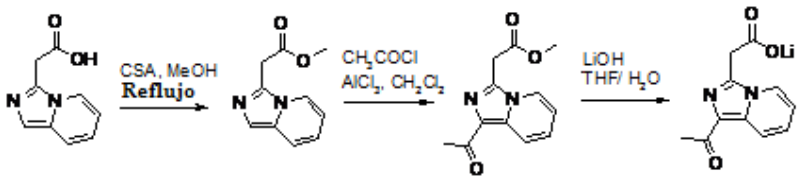
B. Éster terc- butilo del ácido (3- Acetil- 5- metoxi- indol- 1- il)- acético

A una solución de éster terc- butilo del ácido (3- acetil- 5- hidroxi- indol- 1- il)- acético (500 mg, 1,73 mmol) en CH_3CN (15 ml) se añadió K_2CO_3 (358 mg, 2.59 mmol) y yodometano (0.162 ml, 2.59 mmol). La mezcla de reacción se agitó a 50 °C durante la noche. Se añadió K_2CO_3 (716 mg, 5.18 mmoles) y yodometano (0.324 ml, 5.18 mmol) y se continuó el calentamiento durante 2 días. Los volátiles se evaporaron, la mezcla de reacción se recogió en agua y se extrajo dos veces con AcOEt. Las fases orgánicas combinadas se secaron (separador de fase) y se evaporaron para proporcionar el compuesto del título. MS (LC/MS): 304,0 [M+H]+, 629,0 [2M+Na]+; t_R (condiciones de HPLC C): 4,92 min.

C. ácido (3- Acetil- 5- metoxi- indol- 1- il)- acético

A éster terc- butilo del ácido (3- acetil- 5- metoxi- indol- 1- il)- acético (520 mg, 1.71 mmol) en CH_2Cl_2 (15 ml) se añadió TFA (1.32 ml, 17.1 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. Los volátiles se evaporaron, luego el material crudo se recogió en 5 ml de solución acuosa de NaOH 1M y se lavó con CH_2Cl_2 que se desechó. La fase acuosa se acidificó a pH = 1 mediante la adición de una solución acuosa de HCl 6 M, y luego se extrajo dos veces con AcOEt. Las fases orgánicas combinadas se secaron (separador de fase) y se evaporaron para proporcionar el compuesto del título. MS (LC/MS): 248,1 [M+H]+, 246,1 [MH] - ; t_R (condiciones de HPLC C): 3.47 min.

Esquema A19: Preparación del Ácido (3- acetil- 5- trifluorometoxi- indol- 1- il)- acético



A. Éster metílico del ácido imidazo [1,5- a] piridin- 3- il- acético

Una suspensión del ácido imidazo [1,5- a] piridin- 3- il acético (Ellanovalabs, 2 g, 11.35 mmoles) y ácido canforsulfónico (2.9 g, 12.49 mmol) en MeOH (120 ml) se calentó a reflujo durante 4 h. Luego se dejó enfriar a temperatura ambiente y se concentró bajo presión reducida. El residuo crudo se diluyó en CH_2Cl_2 y la capa orgánica se lavó con una solución acuosa saturada de $NaHCO_3$. Los orgánicos se secaron (Na_2SO_4), se filtraron y se concentraron. El material así obtenido se usó en la siguiente etapa sin purificación adicional: TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0,55; EM (UPLC/MS): 191,1 [M+H]+; t_R (F) Condiciones de HPLC: 0,4 min.

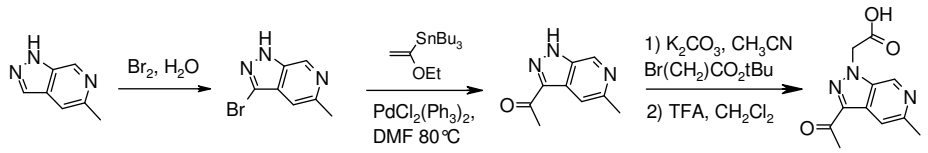
B. éster metílo del ácido (1- acetil- imidazo [1,5- a] piridin- 3- il)- acético

Una solución de éster metílo del ácido imidazo [1,5- a] piridin- 3- il- acético (1.38 g, 7.26 mmol) en CH_2Cl_2 (50 ml) se añadió a una suspensión de $AlCl_3$ (2.9 g, 21.77 mmol) en CH_2Cl_2 (115 ml) y la mezcla se agitó a temperatura ambiente durante 30 min bajo atmósfera de nitrógeno. Se añadió posteriormente por goteo cloruro de acetilo (1.55 ml, 21.77 mmol) y la mezcla se agitó adicionalmente durante una noche. Se añadió $AlCl_3$ (1.94 g, 14.51 mmol) y 15 min más tarde cloruro de acetilo (1.04 ml, 14.51 mmol) y se continuó la agitación durante la noche para completar la reacción. La mezcla de reacción se enfrió con 0 °C y se apagó cuidadosamente mediante la adición cuidadosa de MeOH (35 ml). Los solventes se evaporaron a presión reducida y el residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (eluyente: CH_2Cl_2 a CH_2Cl_2/MeOH 94:6).TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0,60; EM (UPLC/MS): 233,1 [M+H]+, 255,1 [M+Na]+, 487,1 [2M+Na]+; t_R (F) Condiciones de HPLC: 1,27 min.

C. (1- acetil- imidazo [1,5- a] piridin- 3- il)- acetato de litio

A una solución de éster metilo del ácido (1- acetil- imidazo [1,5- a] piridin- 3- il)- acético (1.12 g, 4.82 mmol) en THF (15 ml) y agua (7,5 ml) se añadió LiOH .H_2O (202 mg, 4.82 mmol). La reacción se agitó a temperatura ambiente durante 5.5 h hasta la finalización de la reacción. La mezcla se concentró bajo presión reducida y el material así obtenido se utilizó en la siguiente etapa sin purificación adicional: MS (UPLC/MS): 219,2 [M+H]+, 241,2 [M+Na]+, 217,2 [MH] - ; t_R (F) Condiciones de HPLC: 1,03 min.

Esquema A20: Preparación de trifluoroacetato del ácido (3- Acetil- 5- metil- pirazolo [3,4- c] piridin- 1- il)- acético



A. 3- Bromo- 5- metil- 1H- pirazolo [3,4- c] piridina

Se agitó 5- metil- 1H- pirazolo [3,4- c] piridina (2 g, 15.02 mmoles) y bromo (0.774 ml, 15.02 mmol) en agua (71.5 ml) a temperatura ambiente durante 1 h. La mezcla de reacción se neutralizó con NaOH (20% en agua), el precipitado se filtró, se lavó con agua y se secó a alto vacío. Polvo de color amarillo, MS (UPLC/MS): 212/214 [M+H]+, 210/212 [MH] - ; t_R (condiciones de HPLC f): 0,74 min.

B. 1 - (5- metil- 1H- pirazolo [3,4- c] piridin- 3- il)- etanona

Una solución de 3- bromo- 5- metil- 1H- pirazolo [3,4- c] piridina (2.13 g, 10.04 mmol), tri- butilo (1- etoxivinil)estaño (6.78 ml, 20.09 mmol) y $PdCl_2(PPh_3)_2$ (0.705 mg, 1 mmol) en DMF (12.6 ml) se calentó a 80 °C durante la noche bajo atmósfera de argón. Luego se concentró bajo presión reducida y se diluyó con EtOAc. Se añadió HCl (2N), las capas se separaron y la capa acuosa se basificó mediante la adición de $NaHCO_3$ (1 N en agua) y se extrajo con EtOAc (3x). Los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron. El aceite de color amarillo así obtenido se utilizó sin purificación adicional en la siguiente etapa. TLC, R_f (c- hexano/EtOAc 1:1) = 0.05; EM (UPLC/MS): 176 [M+H]+, 174 [MH] - .

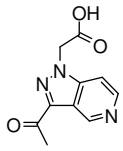
C. Éster terc- butilo del ácido (3- Acetil- 5- metil- pirazolo [3,4- c] piridin- 1- il) - acético

A una solución de 1 - (5- metil- 1H- pirazolo [3,4- c] piridin- 3- il)- etanona (1 g, 5.71 mmol) en CH_3CN (30 ml) se añadió carbonato de potasio (1.81 g, 13.13 mmol) y bromoacetato de terc- butilo (0.927 ml, 6.28 mmol). La mezcla de reacción se agitó a reflujo durante 1 h, después se vertió en agua y se extrajo con EtOAc (x3). Los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:00- 3:02). TLC, R_f (c- hexano/EtOAc 1:1) = 0.25; EM (UPLC/MS): 290 [M+H]+; t_R (condiciones de HPLC f): 1.50 min.

D. Ácido (3- acetil- 5- metil- pirazolo [3,4- c] piridin- 1- il)- acético

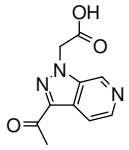
Una solución de (3- acetil- 5- metil- pirazolo [3,4- c] piridin- 1- il)- acético éster terc-butílo del ácido (126 mg, 0.37 mmol) y TFA (0.171 ml, 2.22 mmol) en CH_2Cl_2 (5 ml) se agitó a temperatura ambiente durante 24 h. Los solventes se eliminaron bajo presión reducida, se añadió Et_2O y se filtró el precipitado, se lavó con Et_2O y se secó a alto vacío. El material así obtenido se utilizó sin purificación adicional en la siguiente etapa. MS (UPLC/MS): 234 [M+H]+, 232 [MH] - , 465 [2M- H] - ; t_R (condiciones de HPLC f): 0,53 min.

Trifluoroacetato del ácido (3- Acetil- pirazolo [4,3- c] piridin- 1- il)- acético



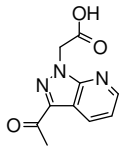
Se preparó usando procedimientos similares a los descritos para la síntesis del ácido (3-acetil- 5- metil- pirazolo [3,4- c] piridin- 1- il)- acético en el Esquema A20 a partir de 1 - (1H-pirazolo [4, 3- c] piridin- 3- il)- etanona (Sphinx Scientific laboratory LLC, número de catálogo: PPY- CS0001). 1H- RMN (400 MHz, DMSO): δ (ppm): 9,57 (s, 1H), 8,52 (m, 1H), 8,08 (m, 1H), 5,56 (s, 2H), 2,69 (s, 3H).

Trifluoroacetato del ácido (3- Acetil- pirazolo [3,4- c] piridin- 1- il)- acético



Se preparó usando procedimientos similares a los descritos para la síntesis de (3- acetil-5- metil- pirazolo [3,4- c] piridin- 1- il)- acético en el Esquema A20 da partir de 1 - (1H-pirazolo [3, 4- c] piridin- 3- il)- etanona (Sphinx Scientific laboratory LLC, número de catálogo: PPY- 1- CS01). MS (UPLC/MS): 220 [M+H]+; t_R (condiciones de HPLC l): 0.69 min.

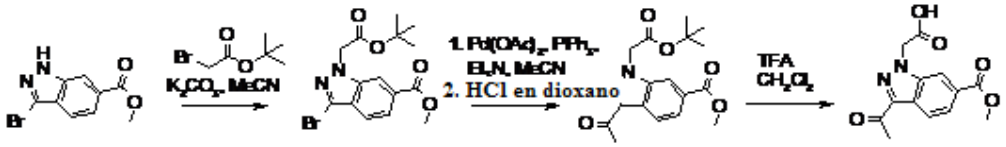
Trifluoroacetato del ácido (3- Acetil- pirazolo [3,4- b] piridin- 1- il)- acético



Se preparó usando procedimientos similares a los descritos para la síntesis del ácido (3-acetil- 5- metil- pirazolo [3,4- c] piridin- 1- il)- acético en el Esquema A20 a partir de 1 - (1H-

pirazolo [3, 4- b] piridin- 3- il)- etanona (Sphinx Scientific laboratory LLC, [889451- 31- 4], PEP- 3- 0043). MS (UPLC/MS): 220 [M+H]+, 218,2 [MH] - ; t_R (condiciones de HPLC k): 2,51 min.

Esquema A21: Preparación del ácido 2 - (3- acetil- 6- (metoxicarbonil)- 1H- indazol- 1- il) acético



A. 3- bromo- 1- (2- terc- butoxi- 2- oxoetil)- 1H- indazol- 6- carboxilato de metilo

El compuesto del título se preparó a partir de 3- bromo- 1H- indazol- 6- carboxilato [192945- 56- 5] en un modo similar al descrito en el paso B del Esquema A13 para la preparación del ácido (3- acetil- 5- trifluorometoxi- indol- 1- il)- acético. MS: 392 [M+Na]+, 313 [M- tBu] +; t_R (condiciones de HPLC k): 4,08 min.

B. 3- acetil- 1- (2- terc- butoxi- 2- oxoetil)- 1H- indazol- 6- carboxilato de metilo

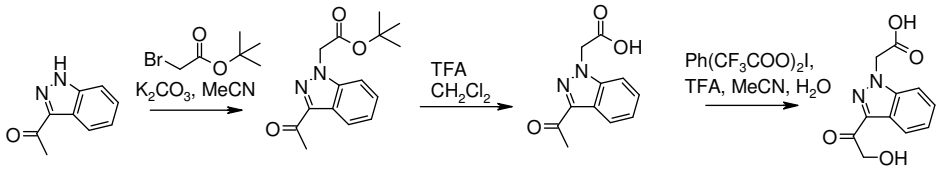
Una solución de 3- bromo- 1- (2- terc- butoxi- 2- oxoetil)- 1H- indazol- 6- carboxilato de metilo (1.00 g, 2.71 mmol), n- butil- vinil- éter (1.75 ml, 13.5 mmol), acetato de paladio (61 mg, 0.27 mmol), trifenilfosfina (142 mg, 0.54 mmol) y trietilamina (0.45 ml, 3.25 mmol) en CH_3CN seco (10 ml) se calentó a 100 °C bajo irradiación de microondas durante 7 h. Luego, la mezcla se calentó adicionalmente a 120 °C durante 5 h bajo irradiación de microondas. El solvente se evaporó, y después el residuo se trató con HCl 4 N/dioxano con agitación a temperatura ambiente durante 16 h. Los volátiles se evaporaron y el residuo se purificó mediante HPLC preparativa (Waters Sunfire, C18- ODB, 5µm, 30x100 mm, flujo: 40 ml/min, eluyente: 5- 100% $CH_3CN/H_2O/_{20}$ min, 100% de CH_3CN/2 min, CH_3CN y H_2O que contiene TFA al 0.1%) para proporcionar después de la liofilización de las fracciones puras el compuesto del título. MS (LC- MS): 333 [M+H]+, 355 [M + Na]; t_R (condiciones de HPLC k): 3.83 min.

C. Ácido 2 - (3- acetil- 6- (metoxicarbonil)- 1H- indazol- 1- il) acético

El compuesto del título se preparó a partir de 3- acetil- 1- (2- terc- butoxi- 2- oxoetil)- 1H- indazol- 6- carboxilato de metilo de una manera similar a la descrita en el paso C del

Esquema A13 para la preparación de (3 - acetil- 5- trifluorometoxi- indol- 1- il)- acético. MS: 277 [M+H]+; t_R (condiciones de HPLC k): 2.95 min.

Esquema A22: Preparación del ácido 2 - (3 - (2- hidroxiacetil)- 1H- indazol- 1- il) acético



A. 2 - (3- acetil- 1H- indazol- 1- il) acetato de terc- butílo

El compuesto del título se preparó a partir de 1 - (1H- indazol- 3- il) etanona [4498- 72- 0] de una manera similar a la descrita en el paso B del Esquema A13 para la preparación del ácido (3- acetil- 5- trifluorometoxi- indol- 1- il)- acético. MS: 275 [M+H]+; t_R (condiciones de HPLC k): 3.78 min.

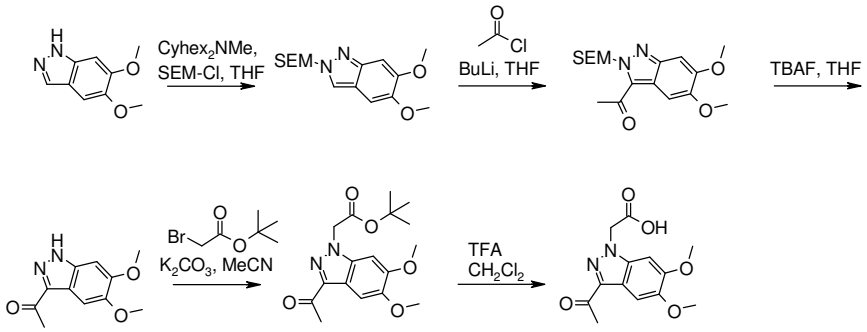
B. Ácido 2 - (3- Acetil- 1H- indazol- 1- il) acético

El compuesto del título se preparó a partir de 2 - (3- acetil- 1H- indazol- 1- il) acetato de terc- butilo de una manera similar a la descrita en el paso C del Esquema A13 para la preparación del ácido (3- acetil- 5- trifluorometoxi- indol- 1- il)- acético. MS: 219 [M+H]+; t_R (condiciones de HPLC k): 2.78 min.

C. Ácido 2 - (3 - (2- hidroxi- acetil)- 1H- indazol- 1- il) acético

El compuesto del título se preparó de una manera similar a la descrita por N.Yoshikawa et al., J. Org. Chem., 2002, 67, 2556- 2565: Una mezcla del ácido 2 - (3- acetil- 1H- indazol- 1- il) acético (100 mg, 0.46 mmol), TFA (0.71 ml, 0.92 mmol) y bis- (trifluoroacetoxi)- yodobenceno (394 mg, 0.92 mmol) en CH_3CN (4 ml) y agua (0.6 ml) se calentó a reflujo (90 °C) durante 16 h. Los solventes se evaporaron y el producto crudo se purificó por HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 30x100 mm, flujo: 40 ml/min, eluyente: 5- 100% CH_3CN/H_2O/20 min, 100% de CH_3CN/2 min, CH_3CN y H_2O que contiene TFA al 0.1%) para proporcionar, después de liofilización de las fracciones purificadas del compuesto del título. MS (LC- MS): 233 [M+H]+; t_R (condiciones de HPLC k): 2.41 min.

Esquema A23: Preparación del ácido 2 - (3- acetil- 5 ,6- dimetoxi- 1H- indazol- 1- il) acético



A. 5,6- dimetoxi- 2- ((2 - (trimetilsilil) etoxi) metil)- 2H- indazol

El compuesto del título se preparó de una manera similar a la descrita por G. Luo et al., J. Org. Chem.. 2006, 71, 5392- 5395: A una solución de 5,6- dimetoxiindazole [7746- 30- 7] (356 mg, 2,00 mmol) en THF (20 ml) se añadió diciclohexilmetilamina (0.51 ml, 2.40 mmol) seguido por SEM - Cl (0.43 ml, 2.40 mmol). La mezcla se agitó a temperatura ambiente durante 24 h, seguido por dilución con EtOAc y se apagó con solución acuosa de NaOH 1N. Las capas se separaron y la capa orgánica se lavó con agua y salmuera, luego se secaron (separador de fases) y se evaporó. El residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 4:1- 1:1) para separar del regioisómero 5,6- dimetoxi- 1- ((2 - (trimetilsilil) etoxi) metil) - 1H- indazol y para proporcionar el compuesto del título. TLC, R_f (c- hexano/EtOAc 1:1) = 0.37; MS (LC/MS): 309 [M+H; t_R (condiciones de HPLC k): 3.70 min.

B. 1 - (5,6- dimetoxi- 2- ((2 - (trimetilsilil) etoxi) metil)- 2H- indazol- 3- il) etanona

El compuesto del título se preparó de una manera similar a la descrita por G. Luo et al., J. Org. Chem. 2006, 71, 5392- 5395: A una solución de 5,6- dimetoxi- 2- ((2 - (trimetilsilil) etoxi) metil)- 2H- indazol (200 mg, 0.65 mmol) en THF (5 ml) a - 78 º C se añadió por goteo una solución de 2.5 M de n- BuLi en hexanos (0.29 ml, 0.71 mmol). La mezcla de reacción se agitó a - 78 °C durante 20 min. Luego se añadió cloruro de acetilo (0.07 ml, 0.97 mmol) por goteo, y la mezcla se agitó a temperatura ambiente durante 16 h. Se añadió solución acuosa saturada de NH_4Cl a la mezcla de reacción, seguido de agitación durante 30 min. La fase acuosa se extrajo dos veces con EtOAc y los extractos orgánicos combinados se lavaron con salmuera, se secaron (separador de fases) y se evaporaron para proporcionar el compuesto del título crudo que se usó directamente en la siguiente etapa sin purificación adicional.

C. 1 - (5,6- dimetoxi- 1H- indazol- 3- il) etanona

El compuesto del título se preparó de una manera similar a la descrita por G. Luo et al., J. Org. Chem. 2006, 71, 5392- 5395: A una solución de 1 - (5,6- dimetoxi- 2- ((2 - (trimetilsilil) etoxi) metil)- 2H- indazol- 3- il) etanona (200 mg, 0.57 mmol) en THF (6 ml) se añadió una solución 1 M en THF de TBAF (2.85 ml, 2.85 mmoles), y la mezcla se calentó a reflujo durante 16 h. La mezcla de reacción se diluyó luego con EtOAc y se lavó sucesivamente con agua y salmuera, después se secó (separador de fases) y se evaporó. El producto crudo se purificó por HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 30x100 mm, flujo: 40 ml/min, eluyente: 5- 100% CH_3CN/H_2O/20 min, 100% de CH_3CN/2 min, CH_3CN y H_2O que contiene 0.1% de TFA) para proporcionar después de la liofilización de las fracciones purificadas del compuesto del título. MS (LC- MS): 221 [M+H]+; t_R (condiciones de HPLC k): 2.61 min.

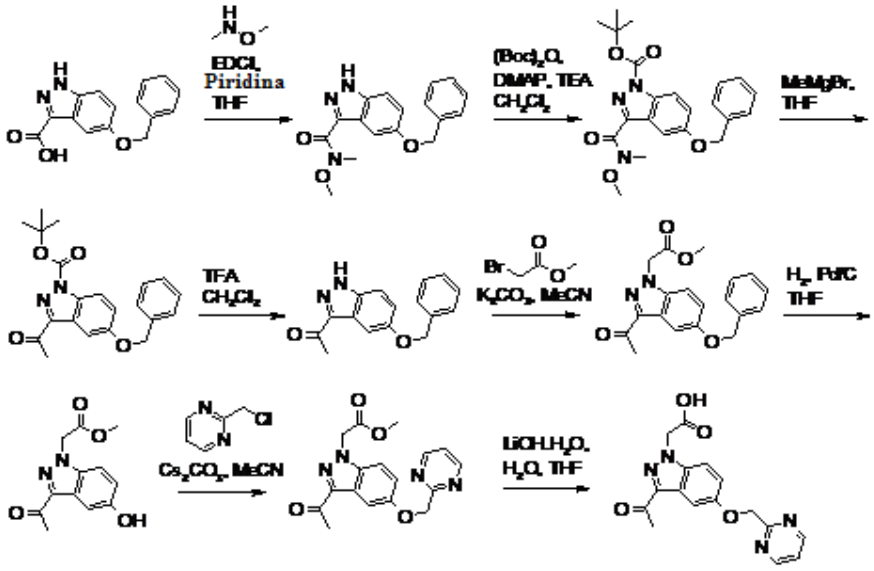
D. 2 - (3- acetil- 5 ,6- dimetoxi- 1H- indazol- 1- il) acetato de terc- butilo

El compuesto del título se preparó a partir de 1 - (5,6- dimetoxi- 1H- indazol- 3- il) etanona de una manera similar a la descrita en el paso B del Esquema A13 para la preparación del ácido (3- acetil- 5- trifluorometoxi- indol - 1- il)- acético. MS: 335 [M+H]+; t_R (condiciones de HPLC k): 3,58 min.

E. Ácido 2 - (3- Acetil- 5 ,6- dimetoxi- 1H- indazol- 1- il) acético

El compuesto del título se preparó a partir de 2 - (3- acetil- 5 ,6- dimetoxi- 1H- indazol- 1- il) acetato de terc- butilo de una manera similar a la descrita en el paso C del Esquema A13 para la preparación del ácido (3 - acetil- 5- trifluorometoxi- indol- 1- il)- acético. MS: 279 [M+H]+; t_R (condiciones de HPLC k): 2.73 min.

Esquema A24: Preparación del ácido 2 - (3- acetil- 5- (pirimidin- 2- ilmetoxi)- 1H- indazol- 1- il) acético



A. 5 - (benciloxi)- N- metoxi- N- metil- 1H- indazol- 3- carboxamida

El compuesto del título se preparó de una manera similar a la descrita por F. Crestey et al, Tetrahedron 2007, 63, 419- 428:. Para el ácido 5 - (benciloxi)- 1H- indazol- 3- carboxílico [177941- 16- 1] (3.50 g, 13.1 mmol) en THF (70 ml) se añadió N, O- dimetilhidroxilamina (1.40 g, 14.4 mmol). La mezcla se enfrió a 0 °C antes de la adición de piridina (2.30 ml, 28.7 mmol). La solución se agitó a 0 ºC durante 1.5 h, y luego a temperatura ambiente durante 1 h. Se añadió piridina (2.10 ml, 26.1 mmoles) y EDCI (5.00 g, 26.1 mmol) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción seguido de extracción (x3) con CH_2Cl_2. Los extractos orgánicos combinados se lavaron con solución acuosa saturada de $NaHCO_3$, después se secaron (separador de fases) y se evaporaron para proporcionar el compuesto del título. MS (LC/MS): 312,0 [M+H]+, 334,0 [M+Na]+, 645,1 [2M+Na]+, 310,0 [MH] - ; t_R (condiciones de HPLC C): 4.44 min.

B. 5 - (benciloxi) - 3 - (metoxi (metil) carbamoil)- 1H- indazol- 1- carboxilato de terc-butilo

El compuesto del título se preparó de una manera similar a la descrita por F. Crestey et al, Tetrahedron 2007, 63, 419- 428: A una solución de 5 - (benciloxi)- N- metoxi- N- metil- 1H- indazol- . 3- carboxamida (3.40 g, 10.9 mmol) en CH_2Cl_2 (70 ml) se añadió DMAP (0.13 g, 1.09 mmol), TEA (1.67 ml, 12.0 mmol) y anhídrido de Boc (3.80 ml, 16.4 mmol) a 0 °C . La mezcla de reacción se agitó a 0 °C durante 1 h y se dejó volver a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con CH_2Cl_2 y se lavó con 50 ml de solución acuosa de HCl 0.1 M y agua. La fase orgánica se secó (separador de fases) y se evaporó para

proporcionar el compuesto del título. MS (LC/MS): 434,0 [M+Na]+, 845,0 [2M+Na]+; t_R (condiciones de HPLC C): 5.79 min.

C. 3- acetil- 5- (benciloxi)- 1H- indazol- 1- carboxilato de etilo y 1 - (5 - (benciloxi)- 1H- indazol- 3- il) etanona de terc- butilo

El compuesto del título se preparó de una manera similar a la descrita por F. Crestey et al, Tetrahedron 2007, 63, 419- 428:. Para 5 - (benciloxi) - 3 - (metoxi (metil) carbamoil)- 1H- indazol- 1- carboxilato de terc- butilo (4.70 g, 11.4 mmol) en THF (60 ml), se enfrió a - 78 °C, se añadió una solución 3 M de MeMgBr (22.9 ml, 68.5 mmol) en Et_2O. La mezcla de reacción se agitó a - 78 º C durante 1 h. Se añadió una solución acuosa saturada de NH_4Cl a la mezcla de reacción y la temperatura se dejó elevar hasta la temperatura ambiente. La mezcla se extrajo dos veces con CH_2Cl_2, se secaron los extractos orgánicos combinados (separador de fases) y se evaporaron para proporcionar la mezcla del título que se usó sin purificación en la siguiente etapa.

D. 1 - (5 - (benciloxi)- 1H- indazol- 3- il) etanona

A la mezcla de 3- acetil- 5- (benciloxi)- 1H- indazol- 1- carboxilato de terc- butilo y 1 - (5 - (benciloxi)- 1H- indazol- 3- il) etanona (3.80 g, 10.4 mmol) en CH_2Cl_2 (50 ml) se añadió TFA (7.99 ml, 104 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con CH_2Cl_2 y se lavó con 100 ml de solución acuosa de NaOH 2N. La fase básica se extrajo dos veces con CH_2Cl_2, luego se secaron las fases orgánicas combinadas (separador de fases) y se evaporaron para proporcionar el compuesto del título. MS (LC/MS): 267,0 [M+H]+, 289,0 [M+Na]+, 265,1 [MH] - ; t_R (condiciones de HPLC c): 4,71 min.

E. 2 - (3- acetil- 5- (benciloxi)- 1H- indazol- 1- il) acetato de metilo

A 1 - (5 - (benciloxi)- 1H- indazol- 3- il) etanona (3.50 g, 13.1 mmol) en CH_3CN (100 ml) se añadió K_2CO_3 (4.54 g, 32.9 mmol) y 2- bromoacetato de metilo (1.33 ml , 14.5 mmol). La mezcla de reacción se agitó a 90 °C durante 90 min. La mezcla de reacción se filtró y el sólido se lavó con CH_3CN. Los volátiles se evaporaron y luego la mezcla cruda se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (Gradiente: c-hexano/EtOAc 1:1- 1:3). TLC, R_f (c- hexano/EtOAc 1:3) = 0,64; MS (LC/MS): 339,0 [M+H]+, 361,0 [M+Na]+; t_R (condiciones de HPLC c): 5.09 min.

F. 2 - (3- acetil- 5- hidroxi- 1H- indazol- 1- il) acetato de metilo

A 2 - (3- acetil- 5- (benciloxi)- 1H- indazol- 1- il) acetato de metilo (3.70 g, 10.9 mmol) en THF (80 ml) se le añadió Pd/C (10%, 400 mg). La mezcla de reacción se agitó a 50 °C durante la noche bajo una atmósfera de H_2. La mezcla de reacción se filtró sobre una almohadilla de Celite y se lavó con CH_2Cl_2, luego los volátiles se evaporaron para proporcionar el compuesto del título. MS (LC/MS): 248,9 [M+H]+, 271,0 [M+Na]+; t_R (condiciones de HPLC c): 3,36 min.

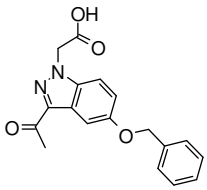
G. 2 - (3- acetil- 5- (pirimidin- 2- ilmetoxi)- 1H- indazol- 1- il) acetato de metilo

A 2 - (3- acetil- 5- hidroxi- 1H- indazol- 1- il) acetato de metilo (1.80 g, 7.25 mmol) en CH_3CN (75 ml) se añadió sal de hidrocloruro 2 - (clorometil) pirimidina (1.32 g, 7.98 mmoles) y Cs_2CO_3 (5.91 g, 18.13 mmol). La mezcla de reacción se agitó a 70 °C durante 2 h. La mezcla de reacción se filtró y se lavó con CH_3CN. El solvente se evaporó y la mezcla crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (gradiente: c-hexano/EtOAc 1:1 a 1:3). TLC, R_f (c- hexano/EtOAc 1:3) = 0,35; MS (LC/MS): 340,9 [M+H]+, 363,0 [M+Na]+; t_R (condiciones de HPLC c): 3.64 min.

H. Ácido 2 - (3- Acetil- 5- (pirimidin- 2- ilmetoxi)- 1H- indazol- 1- il) acético

A 2 - (3- acetil- 5- (pirimidin- 2- ilmetoxi)- 1H- indazol- 1- il) acetato de metilo (1.93 g, 5.67 mmol) en THF (15 ml) y agua (15 ml) se le añadió LiOH . H_2O (0.25 g, 5.95 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1.5 h. Los volátiles se evaporaron y el residuo se liofilizó durante la noche para proporcionar el compuesto del título. MS (LC/MS): 327,0 [M+H]+, 325,1 [M+H]+; t_R (condiciones de HPLC c): 3.24 min.

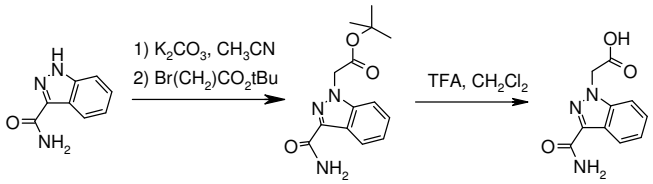
<u>Ácido (3- Acetil- 5- benciloxi- indazol- 1- il)- acético</u>



A una solución de éster metílo del ácido (3- acetil- 5- benciloxi- indazol- 1- il)- acético (preparado como se describe en el Esquema A24, 1.50 g, 4.43 mmol) en MeOH (40 ml) se añadió una solución acuosa de NaOH al 10% (5.32 ml, 13.30 mmol) y la mezcla resultante se agitó a temperatura ambiente durante 16 h. La mezcla se concentró, se diluyó en agua y se acidificó a pH = 2 con HCl 6N. Después, la mezcla se extrajo con EtOAc y la capa orgánica se

secó (Na_2SO_4), se filtró y se concentró. El producto se utilizó en la siguiente etapa sin purificación adicional. MS (UPLC- MS): 325 [M+H]+; t_R (UPLC condiciones m): 0.90 min.

Esquema A25: Preparación del ácido (3- carbamoil- indazol- 1- il)- acético



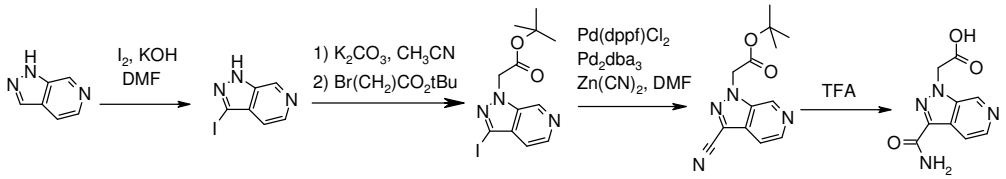
A. 2 - (3- carbamoil- 1H- indazol- 1- il) acetato de terc- butilo

A una suspensión de 1H- indazol- 3- carboxamida [90004- 04- 9] (2.00 g, 12.4 mmoles) y carbonato de potasio (4.12 g, 29.8 mmol) en CH_3CN (60 ml) se añadió bromoacetato de terc-butilo (2.20 ml, 14.9 mmol) por goteo a temperatura ambiente, y la mezcla resultante se calentó a reflujo durante 16 h. Luego la mezcla se enfrió a temperatura ambiente y se filtró, el sólido se lavó con CH_3CN y el filtrado se concentró al vacío. El aceite residual se utilizó directamente en la siguiente etapa de reacción sin purificación adicional.MS (LC/MS): 276,0 [M+H]+; t_R (condiciones de HPLC k): 3.22 min.

B. Ácido (3- carbamoil- indazol- 1- il)- acético

A una solución de 2 - (3- carbamoil- 1H- indazol- 1- il)- acetato de terc- butílo (3.42 g, 12.4 mmol) en CH_2Cl_2 (20 ml) se añadió TFA (10 ml, 130 mmol) y la mezcla resultante se agitó a temperatura ambiente durante 16 h. La mezcla de reacción se concentró al vacío, el sólido residual se suspendió en metanol y se concentró de nuevo al vacío para proporcionar el compuesto del título. MS (LC/MS): 220 [M+H]+; t_R (condiciones de HPLC k): 1.79 min.

Esquema A26: Preparación del ácido 2 - (3- carbamoil- 1H- pirazolo [3,4- c] piridin- 1- il) acético



A. 3- yodo- 1H- pirazolo [3,4- c] piridina

A una solución de 1H- pirazolo [3,4- c] piridina [271- 47- 6] (4.00 g, 33.6 mmol) en DMF (50 ml) se añadieron yodo (12.8 g, 50.4 mmoles) e hidróxido de potasio (4.70 g, 84.0 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 h. La mezcla se

diluyó con tiosulfato de sodio al 10% y agua, luego se extrajo (3x) con EtOAc. Los extractos orgánicos combinados se lavaron con salmuera, después se secaron (separador de fases) y se concentraron al vacío. MS (LC/MS): 246.0 [M+H]+; t_R (condiciones de HPLC k): 0.48 min.

B. 2 - (3- yodo- 1H- pirazolo [3,4- c] piridin- 1- il) acetato de terc- butilo

A una suspensión de 3- yodo- 1H- pirazolo [3,4- c]piridina (6.24 g, 22.9 mmoles) y carbonato de potasio (7.29 g, 52.7 mmol) en acetonitrilo (50 ml) se añadió bromoacetato de terc- butilo (4.06 ml, 27.5 mmol) por goteo a temperatura ambiente y la mezcla resultante se calentó a reflujo durante 2 h. La mezcla se enfrió a temperatura ambiente y se filtró, el sólido se lavó con CH_3CN y el filtrado se concentró al vacío. El aceite residual se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (gradiente de EtOAc/c- hexano 1:4, luego 1:2, luego 1:1).MS (LC/MS): 360,0 [M+H]+; t_R (condiciones de HPLC k): 2.93 min.

C. 2- (3- ciano- 1H- pirazolo [3,4- c] piridin- 1- il)- acetato de - terc- butilo

Una mezcla de 2 - (3- yodo- 1H- pirazolo [3,4- c] piridin- 1- il) acetato de terc- butílo (3.76 g, 10.5 mmol), Zn $(CN)_2$ (1.35 g, 11.5 mmol) , Pd(dppf)Cl_2 (855 mg, 1.05 mmol), $Pd_2(dba)_3$ (959 mg, 1.05 mmol), agua (4 ml) y DMF (30 ml) se agitó a 100 ºC durante 16 h en atmósfera de argón. La mezcla de reacción se diluyó con EtOAc y luego se lavó sucesivamente con agua, $NaHCO_3$ acuoso saturado (2x) y salmuera, se secó (separador de fases) y se concentró al vacío. El aceite residual se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (EtOAc/c- hexano 1:1 luego 100% de EtOAc).MS (LC/MS): 259.0 [M+H]+; t_R (condiciones de HPLC k): 3.10 min. La elución adicional de la columna con CH_2Cl_2/MeOH 8:2 y la posterior purificación por HPLC preparativa (Macherey- Nagel Nucleosil 100- 10 C18, 5 m, 40x250 mm, flujo: 40 mL/min, eluyente: 5- 100% CH_3CN/H_2O/20 min, 100% de CH_3CN/2 min, CH_3CN y H_2O que contiene TFA al 0.1%) proporcionó 2 - (3- carbamoil- 1H- pirazolo [3,4- c] piridin- 1- il) acetato de terc- butílico como un sub- producto. MS (LC/MS): 277,0 [M+H]+; t_R (condiciones de HPLC k): 2.39 min.

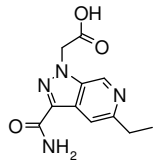
D. Ácido 2 - (3- carbamoil- 1H- pirazolo [3,4- c] piridin- 1- il) acético

Una solución de 2 - (3- ciano- 1H- pirazolo [3,4- c] piridin- 1- il) acetato de terc- butilo (663 mg, 2.40 mmol) en TFA (6 ml) se sometió a irradiación de microondas a 140 °C durante 90 min. La mezcla de reacción se concentró al vacío, el sólido residual se suspendió en MeOH y los volátiles se eliminaron de nuevo al vacío. MS: 221,0 [M+H]+; t_R (condiciones de HPLC k): 0.23 min.

A partir de 2 - (3- carbamoil- 1H- pirazolo [3,4- c] piridin- 1- il) acetato de terc- butilo:

A una solución de 2 - (3- carbamoil- 1H- pirazolo [3,4- c] piridin- 1- il) acetato de terc-butílo (663 mg, 2.40 mmol) en CH_2Cl_2 (20 ml) se añadió TFA (10 ml, 130 mmol), y la mezcla resultante se agitó a temperatura ambiente durante 6 h. La mezcla de reacción se concentró al vacío, el sólido residual se suspendió en metanol y los volátiles se eliminaron de nuevo al vacío para proporcionar el compuesto del título.

Ácido (3- carbamoil- 5- etil- pirazolo [3,4- c] piridin- 1- il)- acético

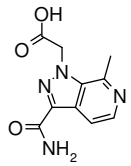


Se preparó a partir de 5- etil- 1H- pirazolo [3,4- c] piridina mediante el uso de los mismos procedimientos que para la preparación del ácido 2 - (3- carbamoil- 1H- pirazolo [3,4-c] piridin- 1- il) acético (Esquema A26). MS (LC- MS): 249 [M+H]+, t_R (condiciones de HPLC k): 0.49 min.

5- etil- 1H- pirazolo [3,4- c] piridina

Se añadió trietilaluminio (21.7 ml, 40.4 mmol, 25% de peso de solución en tolueno) a una solución vigorosamente agitada de 5- bromo- 1H- pirazolo [3,4- c] piridina [929617- 35- 6] (4.00 g, 20.2 mmol) y Pd (PPh_3) 4 (1.17 g, 1,01 mmol) en THF (100 ml) en atmósfera de argón. La mezcla de reacción se agitó a 65 °C durante 60 h. La mezcla se enfrió a temperatura ambiente y se vertió en NH_4Cl acuoso saturado. La suspensión resultante se filtró, el sólido se lavó con agua y se desecho. El filtrado y los lavados combinados se extrajeron con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, después se secaron (separador de fases) y se concentraron bajo presión reducida. El aceite residual se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (EtOAc/c- hexano 50:50, luego 75:25, luego 100:0).TLC, R_f (c- hexano/EtOAc 1:3) = 0.22; MS (LC- MS): 148 [M+H]+, t_R (condiciones de HPLC k): 0.71 min.

Ácido (3- carbamoil- 7- metil- pirazolo [3,4- c] piridin- 1- il)- acético



Se preparó usando el mismo procedimiento que para la preparación del ácido 2 - (3- carbamoil- 1H- pirazolo [3,4- c] piridin- 1- il) acético a partir de 7- metil- 1H- pirazolo [3,4- c] piridina (Esquema A26). MS (LC- MS): 235 [M+H]+, t_R (condiciones de HPLC k): 0.6 min.

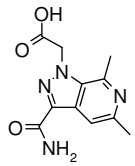
7- metil- 1H- pirazolo [3,4- c] piridina

Se añadió trimetilaluminio (23.9 ml, 47.8 mmol, 2 M sol. en tolueno) a una solución vigorosamente agitada de 7- cloro- 1H- pirazolo [3,4- c] piridina (3.67 g, 23.9 mmol) y Pd $(PPh_3)_4$ (1.38 g, 1.19 mmol) en THF (109 ml) en atmósfera de argón. La mezcla de reacción se agitó a 65 °C durante 16 h. La mezcla se enfrió a temperatura ambiente y se vertió en NH_4Cl acuoso saturado. La suspensión resultante se filtró, el sólido se lavó con agua y se desechó. El filtrado y los lavados combinados se extrajeron con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera y después se secaron (separador de fases) y se concentraron bajo presión reducida para proporcionar 7- metil- 1H- pirazolo [3,4- c] piridina en forma de un sólido. MS (LC- MS): 134 [M+H]+, t_R (condiciones de HPLC k): 0.25 min.

7- cloro- 1H- pirazolo [3,4- c] piridina

Una solución de 2- cloro- 4- metil- piridin- 3- amina [133627- 45- 9] (3.0 g, 21.0 mmol) en ácido acético (300 ml) se trató con una solución de nitrito de sodio (1.45 g, 21.0 mmol) en agua (2.5 ml). La mezcla de reacción se agitó a temperatura ambiente durante 15 min y después se dejó en reposo a temperatura ambiente durante 24 h. Se añadió una solución adicional de nitrito de sodio (500 mg, 7.25 mmol) en agua (1 ml) a la mezcla que se dejó en reposo a temperatura ambiente durante 3 h. El ácido acético se evaporó bajo presión reducida y la solución acuosa residual se particionó entre EtOAc y $NaHCO_3$ acuoso saturado. El sólido insoluble se separó por filtración (se secó al vacío; lote 1) y el filtrado orgánico se lavó con agua y salmuera, después se secó (separador de fases) y se concentró bajo vacío (lote 2). Los dos lotes se combinaron para proporcionar 7- cloro- 1H- pirazolo [3,4- c] piridina en forma de un sólido.MS (LC- MS): 153 [M+H]+, t_R (condiciones de HPLC k): 0.9 min.

<u>Ácido (3- carbamoil- 5 ,7- dimetil- pirazolo [3,4- c] piridin- 1- il)- acético</u>



Se preparó a partir de 5,7- dimetil- 1H- pirazolo [3,4- c] piridina mediante el uso de los mismos procedimientos que los descritos para la preparación del acido 2 - (3- carbamoil- 1H- pirazolo [3,4- c] piridin- 1- il) acético (Esquema A26). MS (LC- MS): 249 [M+H]+, t_R (HPLC condiciones c): 0.9 min.

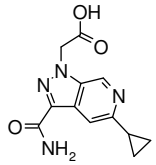
5,7- Dimetil- 1H- pirazolo [3,4- c] piridina

A una solución vigorosamente agitada de 7- bromo- 5- metil- 1H- pirazolo [3,4- c] piridina (3.65 g, 14.6 mmol) y $Pd(PPh_3)_4$ (845 mg, 0.73 mmol) en THF (65 ml) se añadió trimetilaluminio (14.6 ml, 29.3 mmol; 2 M sol en tolueno) en atmósfera de argón. La mezcla de reacción se agitó a 65 °C durante 60 h, y después se enfrió a temperatura ambiente y se vertió en una solución de NH_4Clacuoso saturado. La suspensión resultante se filtró, el sólido se lavó con agua y se desechó. El filtrado y los lavados combinados se extrajeron con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, después se secaron (separador de fases) y se concentraron bajo presión reducida para proporcionar 5,7- dimetil- 1H- pirazolo [3,4- c] piridina en forma de un sólido. MS (LC- MS): 148 [M+H]+, t_R (condiciones de HPLC k): 0,50 min.

7- bromo- 5- metil- 1H- pirazolo [3,4- c] piridina

Una solución de 2- bromo- 4 ,6- dimetilpiridin- 3- amina [104829- 98- 3] (4.00 g, 19.9 mmol) en ácido acético (300 ml) se trató con una solución de nitrito de sodio (1.37 g, 19.9 mmol) en agua (2,5 ml). La mezcla de reacción se agitó a temperatura ambiente durante 15 min y después se dejó en reposo a temperatura ambiente durante 24 h. Se añadió una solución adicional de nitrito de sodio (500 mg, 7.25 mmol) en agua (1 ml) a la mezcla que se dejó en reposo a temperatura ambiente durante 16 h. El ácido acético se evaporó bajo presión reducida y la solución acuosa residual se particionó entre EtOAc y $NaHCO_3$ acuoso saturado. El precipitado se separó por filtración, se lavó y se desechó. Los filtrados combinados se lavaron con agua y salmuera, después se secaron (separador de fases) y se concentró al vacío para proporcionar 7- bromo- 5- metil- 1H- pirazolo [3,4- c] piridina en forma de un sólido.MS (LC- MS): 212 [M+H]+, t_R (condiciones de HPLC k): 2.49 min.

Ácido (3- carbamoil- 5- ciclopropil- 1H- pirazolo [3,4- c] piridin- 1- il) acético



Se preparó mediante el mismo procedimiento como se describe para la preparación del ácido 2 - (3- carbamoil- 1H- pirazolo [3,4- c] piridin- 1- il)- acético y partiendo de 5- ciclopropil- 1H- pirazolo [3,4- c] piridina (Esquema A26). MS (LC- MS): 261 [M+H]+, t_R (condiciones de HPLC c): 1.84 min.

5- ciclopropil- 1H- pirazolo [3,4- c] piridina

Una solución de 6- ciclopropil- 4- metil- piridin- 3- amina (130 mg, 0.88 mmol) en AcOH (10 ml) se trató con una solución de nitrito de sodio (61 mg, 0.88 mmol) en agua (0.5 ml). La mezcla de reacción se agitó a temperatura ambiente durante 15 min y después se dejó en reposo a temperatura ambiente durante 24 h. Se evaporó AcOH bajo presión reducida y la solución acuosa residual se particionó entre EtOAc y $NaHCO_3$ acuoso saturado. La solución orgánica se lavó con agua y salmuera, después se secó (separador de fases) y se concentró bajo.MS (LC- MS): 160 [M+H]+, t_R (condiciones de HPLC c): 2.07 min.

6- ciclopropil- 4- metil- piridin- 3- amina

A una solución de 2- ciclopropil- 4- metil- 5- nitropiridina (201 mg, 0.96 mmol) en MeOH (5 ml) se añadió HCl acuoso 3 N (9.6 ml, 28.8 mmol) y Zn en polvo (376 mg, 5.75 mmol) . La mezcla se agitó 18 h a temperatura ambiente. La solución se neutralizó con una solución Una solución de $NaHCO_3$ acuoso saturado y se extrajo con CH_2Cl_2 (3x). Los extractos orgánicos combinados se secaron (separador de fases) y se concentraron bajo presión reducida.MS (LC- MS): 149 [M+H]+, t_R (condiciones de HPLC c): 2.22 min.

2- ciclopropil- 4- metil- 5- nitropiridina

Ciclopropiltrifluoroborato de potasio (857 mg, 5.79 mmol), 2- cloro- 4- metil- 5- nitropiridina (500 mg, 2.90 mmol), $Pd(OAc)_2$ (26 mg, 0.12 mmol), Cs_2CO_3 (2.83 g, 8.69 mmol) , y n- butil- di- adamantilfosfina (62 mg, 0.17 mmoles) se cargaron en un vial tapado. El vial se purgó con argón y luego se selló con un tapón perforado de laboratorio. Tolueno/H_2O 10:1 (11 ml) se añadió mediante una jeringa y la mezcla se calentó a 100 °C durante 16 h. Se añadió más ciclopropiltrifluoroborato de potasio (857 mg, 5.79 mmol) a la mezcla, que se calentó

adicionalmente a 100 ºC durante 72 h. La mezcla se diluyó con CH_2Cl_2 y se filtró a través de una almohadilla de Celite. El filtrado se secó (separador de fases) y se concentró bajo presión reducida. El residuo se purificó mediante HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 30x100 mm, flujo: 40 ml / min, eluyente: 5- 100% CH_3CN/H_2O/30 min, 100% de CH_3CN/3 min, CH_3CN y H_2O que contiene 0.1% de TFA). MS (LC- MS): 179 [M+H]+, t_R (condiciones de HPLC C): 4.26 min.

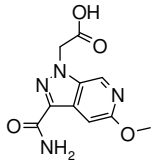
Ácido (3- carbamoil- 5- (trifluorometil)- 1H- pirazolo [3,4- c] piridin- 1- il) acético

Se preparó mediante el mismo procedimiento como se describe para la preparación del ácido 2 - (3- carbamoil- 1H- pirazolo [3,4- c] piridin- 1- il) acético y partiendo de 5- trifluorometil- 1H- pirazolo [3,4- c] piridina (Esquema A26). MS (LC- MS): 289 [M+H]+, t_R (condiciones de HPLC c): 2.93 min.

5- trifluorometil- 1H- pirazolo [3,4- c] piridina

Una solución de 4- metil- 6- (trifluorometil) piridin- 3- amina [944317- 54- 8] (1,00 g, 5.68 mmol) en ácido acético (75 ml) se trató con una solución de nitrito de sodio (392 mg, 5.68 mmoles) en agua (1 ml). La mezcla de reacción se agitó a temperatura ambiente durante 15 min y después se dejó en reposo a temperatura ambiente durante 48 h. El ácido acético se evaporó bajo presión reducida y la solución acuosa residual se particionó entre EtOAc y $NaHCO_3$ acuoso saturado. La solución orgánica se lavó con agua y salmuera, después se secó (separador de fases) y se concentró al vacío.MS (LC- MS): 188 [M+H]+, t_R (condiciones de HPLC k): 2,49 min.

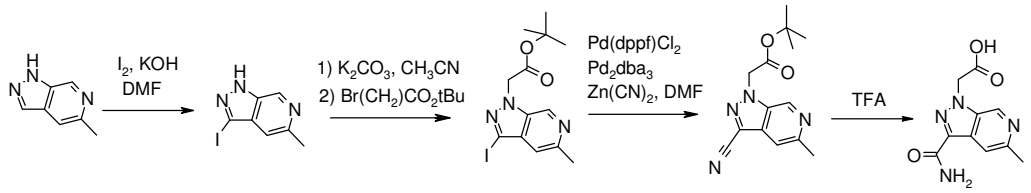
Ácido (3- carbamoil- 5- metoxi- pirazolo [3,4- c] piridin- 1- il)- acético



Se preparó a partir de 5- metoxi- 1H- pirazolo [3,4- c] piridina [76006- 07- 0] mediante el uso de los mismos procedimientos que los descritos para la preparación de ácido 2 - (3-

carbamoil- 1H- pirazolo [3,4- c] piridin- 1- il) - acético (Esquema A26). MS (LC- MS): 251 [M+H]+, t_R (condiciones de HPLC k): 0.62 min.

Esquema A27: Preparación del ácido (3- carbamoil- 5- metil- pirazolo [3,4- c] piridin- 1- il)- acético



A. 3- Yodo- 5- metil- 1H- pirazolo [3,4- c] piridina

A una solución de 5- metil- 1H- pirazolo [3,4- c] piridina [76006- 06- 9] (1.00 g, 7.51 mmol) en DMF (15 ml) se añadió yodo (2.86 g, 11.3 mmol) y hidróxido de potasio (1.05 g, 18.8 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 60 h. La mezcla se diluyó con tiosulfato de sodio al 10% y agua, la suspensión resultante se filtró. El sólido se lavó con agua y después se secó al vacío. MS (LC/MS): 260,0 [M+H]+; t_R (condiciones de HPLC k): 0.28 min.

B. 2 - (3- yodo- 5- metil- 1H- pirazolo [3,4- c] piridin- 1- il) acetato de terc- butílo

A una suspensión de 3- yodo- 5- metil- 1H- pirazolo [3,4- c]piridina (1.00 g, 3.86 mmol), y carbonato de potasio (1.28 g, 9.26 mmol) en acetonitrilo (40 ml) se añadió bromoacetato de- butilo (0.685 ml, 4.63 mmol) por goteo a temperatura ambiente y la mezcla resultante se calentó a reflujo durante 16 h. La mezcla se enfrió a temperatura ambiente y se filtró, el sólido se lavó con acetonitrilo y el filtrado se concentró al vacío. El aceite residual se usó directamente en la siguiente etapa sin purificación adicional. MS (LC/MS): 374,0 [M+H]+; t_R (condiciones de HPLC k): 2.96 min.

C. 2 - (3- ciano- 5- metil- 1H- pirazolo [3,4- c] piridin- 1- il) acetato de terc- butílo

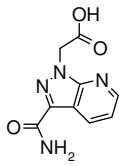
Una mezcla de 2 - (3- yodo- 5- metil- 1H- pirazolo [3,4- c] piridin- 1- il) acetato de terc-butílo(1.00 g, 2.55 mmol), $Zn(CN)_2$ (329 mg , 2.55 mmol), $Pd(dppf)Cl_2$ (208 mg, 0.25 mmol), $Pd_2(dba)_3$ (233 mg, 0.25 mmol), agua (2.7 ml) y DMF (20 ml) se sometió a irradiación de microondas a 120 °C durante 30 min en atmósfera de argón. La mezcla de reacción se filtró a través de una almohadilla de Celite y el filtrado se diluyó con agua y EtOAc. Las fases se separaron y la capa acuosa se extrajo con EtOAc. Los extractos orgánicos combinados se lavaron con salmuera, después se secaron (separador de fases) y se concentraron al vacío. El

aceite residual se purificó mediante cromatografía ultrarrápida sobre gel de sílice (EtOAc/c-hexano 1:2 y luego 1:1).MS (LC/MS): 273.0 [M+H]+; t_R (condiciones de HPLC k): 3.04 min.

D. Ácido (3- carbamoil- 5- metil- pirazolo [3,4- c] piridin- 1- il)- acético

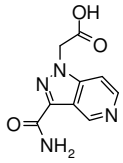
Una solución de 2 - (3- ciano- 5- metil- 1H- pirazolo [3,4- c] piridin- 1- il) acetato de terc- butilo (250 mg, 0.92 mmol) en TFA (4 ml) se sometió a irradiación de microondas a 140 °C durante 90 min. La mezcla de reacción se concentró al vacío, el sólido residual se suspendió en metanol y se concentró de nuevo al vacío. MS: 235,0 [M+H]+; t_R (condiciones de HPLC k): 0.24 min.

Ácido (3- carbamoil- pirazolo [3,4- b] piridin- 1- il)- acético



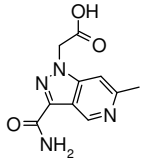
Se preparó a partir de 1H- pirazolo [3,4- b] piridina [271- 73- 8] mediante el uso de los mismos procedimientos que los descritos para la preparación del ácido (3- carbamoil- 5- metil- pirazolo [3,4- c] piridin- 1- il)- acético (Esquema A27). MS (LC- MS): 221 [M+H]+, t_R (condiciones de HPLC k): 0.87 min.

Ácido (3- carbamoil- pirazolo [4,3- c] piridin- 1- il)- acético



Se preparó a partir de 1H- pirazolo [4,3- c] piridina [271- 52- 3] mediante el uso de los mismos procedimientos que para la preparación del ácido (3- carbamoil- 5- metil- pirazolo [3,4- c] piridin- 1- il)- acético (Esquema A27). MS (LC- MS): 221 [M+H]+, t_R (condiciones de HPLC k): 0.19 min.

Ácido (3- carbamoil- 6- metil- pirazolo [4,3- c] piridin- 1- il)- acético

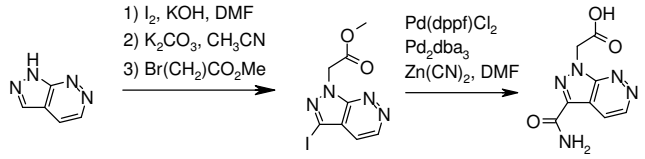


Se preparó a partir de 6- metil- 1H- pirazolo [4,3- c] piridina mediante el uso de los mismos procedimientos que para la preparación del ácido (3- carbamoil- 5- metil- pirazolo [3,4- c] piridin- 1- il)- acético (Esquema A27). MS (LC- MS): 235 [M+H]+, t_R (condiciones de HPLC k): 0,29 min.

6- metil- 1H- pirazolo [4,3- c] piridina

Una solución de 4- cloro- 6- metil- 1H- pirazolo [4,3- c] piridina [1159828- 70- 2] (750 mg, 4,48 mmol) en una mezcla de etanol (25 ml) y THF (10 ml) se hidrogenó sobre Pd al 10% / C (75 mg, 0.07 mmol) a temperatura ambiente durante 24 h. La mezcla de reacción se filtró, el catalizador se lavó con etanol y el filtrado se concentró al vacío. MS (LC- MS): 134 [M+H]+, t_R (condiciones de HPLC k): 0.23 min.

Esquema A28: Preparación del ácido 2 - (3- carbamoil- 1H- pirazolo [3,4- c] piridazin- 1- il) acético



A. 2 - (3- yodo- 1H- pirazolo [3,4- c] piridazin- 1- il) acetato de metilo

A una solución de 1H- pirazolo [3,4- c] piridazina yodo [271- 75- 0] (450 mg, 3.75 mmol) en DMF (10 ml) se añadió (951 mg, 3.75 mmoles) y KOH (525 mg , 9.37 mmol). La mezcla se agitó a temperatura ambiente durante 16 h hasta la finalización de la reacción. Luego se añadió 2- bromoacetato de metilo (0.380 ml, 4,12 mmol) a la mezcla de reacción y se continuó la agitación a temperatura ambiente durante 2 h. La mezcla se diluyó con EtOAc y se lavó con agua (10 ml), la fase orgánica se secó (Na_2SO_4) y se evaporó bajo vacío. La mezcla cruda se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- Hex/EtOAc 66: 33) para proporcionar el compuesto del título como un marrón sólido. TLC, R_f (c- Hex/EtOAc 1:1) = 0.40; MS (LC/MS): 318,9 [M+H]+; t_R (condiciones de HPLC c): 3.35 min.

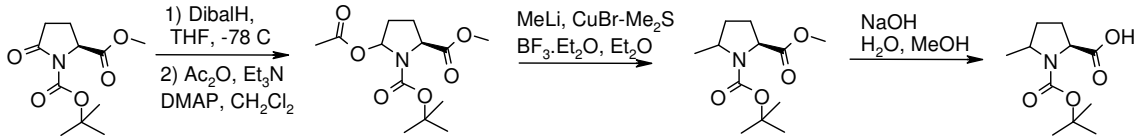
B. Ácido 2 - (3- carbamoil- 1H- pirazolo [3,4- c] piridazin- 1- il) acético

A una solución de 2 - (3- yodo- 1H- pirazolo [3,4- c] piridazin- 1- il) acetato de metilo (675 mg, 2.12 mmol) en DMF (7.5 ml) y se añadió agua (1.5 ml) $Zn(CN)_2$ (274 mg, 2.33 mmol), Pd_2dba_3 (194 mg, 0.21 mmol) y aducto $PdCl_2(dppf).CH_2Cl_2$ (173 mg, 0.21 mmol). La

mezcla de reacción se agitó a 100 ºC durante 16 h. La suspensión resultante se filtró y el filtrado se evaporó bajo vacío. El residuo se suspendió en CH_3CN/MeOH 1:1, el sólido se separó por filtración y el filtrado se purificó mediante HPLC preparativa (Macherey Nagel, VP250/40, Nucleosil C18 100- 10, flujo: 40 ml/min, eluyente: 5 - 100% CH_3CN/H_2O/20 min, 100% de CH_3CN/2 min, CH_3CN y H_2O que contiene TFA al 0.1%) para proporcionar el compuesto del título después de la liofilización. MS (LC/MS): 222,1 $[M+H]+$; t_R (condiciones de HPLC c): 1.34 min.

Parte B: Síntesis de diversos heterociclos de 5 miembros:

Esquema B1: Preparación de éster 1- terc- butilo del ácido (2S, 5R) y (2S, 5S)- 5- metil- pirrolidina- 1 ,2- dicarboxílico en una relación de (7:1) siguiendo un procedimiento similar al descrito en J. Org. Chem.. 2003, 60, 7219.



A. Éster 1- terc- butilo del ácido (S)- 5- acetoxi- pirrolidina- 1 ,2- dicarboxílico - éster de 2- metilo

A una solución de éster 1- terc- butil del ácido (S)- 5- oxo- pirrolidina- 1 ,2- dicarboxílico - éster 2- metilo (preparado de acuerdo con J. Org. Chem.. 2003, 60, 7219) (1.9 g, 7.8 mmoles) en THF (25 ml), se enfrió a - 78 °C, se añadió lentamente Dibalh (1 M en tolueno, 11.0 ml, 11.0 mmol) bajo una atmósfera de argón, seguido de agitación de la solución a - 78 °C durante 1 h. La reacción se apagó mediante la adición de una solución acuosa saturada de NH_4Cl (30 ml). La mezcla se dejó calentar hasta temperatura ambiente, y se añadió posteriormente una solución de Na_2CO_3 acuoso al 10% (20 ml) y CH_2Cl_2 (70 ml). Las capas se separaron y la fase acuosa se extrajo con CH_2Cl_2 (2x50 ml). Los extractos orgánicos combinados se secaron (Na_2SO_4) y se concentraron al vacío. El residuo se disolvió en CH_2Cl_2 (25 ml), anhídrido acético (2.21 ml, 23.4 mmol), NEt_3 (3.26 ml, 23.4 mmol) y se añadió posteriormente 4- dimetilaminopiridina (0.2 g, 1.6 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante la noche. Los orgánicos se lavaron con una solución acuosa saturada de $NaHCO_3$ (10 ml) y HCl acuoso 1 M, se secó (separador de fases) y se concentró al vacío. El residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (gradiente de c- hexano/EtOAc 3:1- 1:1) para proporcionar el compuesto del título. TLC, R_f (c- hexano/EtOAc 1:1) = 0.5; MS: 310.0 $[M+Na]+$, 597.3 $[2M+Na]+$.

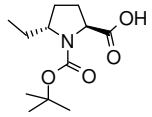
B. Éster 1- terc- butilo del ácido (2S, 5R) y (2S, 5S)- 5- metil- pirrolidina- 1 ,2- dicarboxílico – ester 2- metilo

A una suspensión de complejo bromuro de cobre- sulfuro de dimetilo (1.09 g, 5.32 mmol) en Et_2O (30 ml), se enfrió a - 40 °C, se añadió litio de metilo (1.6 M en Et_2O, 3.32 ml, 5.32 mmol) por goteo bajo una atmósfera de argón ambiente. La solución se agitó durante 45 min, después se enfrió a - 78 °C, y se añadió por goteo boro de trifluoruro (0.67 ml, 5.32 mmol). Después se añadió por goteo 15 min, una solución de éster 1- terc- butilo del ácido (S)- 5- acetoxi- pirrolidina- 1 ,2- dicarboxílico – éster 2- metil (0.51 g, 1.77 mmol) en Et_2O (5 ml). La mezcla de reacción se agitó durante 15 min y luego se calentó a temperatura ambiente durante 1 h, se apagó mediante la adición de un (v/v) mezcla 1:1 de una solución NH_4Cl acuoso saturado y una solución de NH_4OH acuoso al 25% (10 ml. Después de agitar durante 30 min, las dos capas se separaron y la fase acuosa se extrajo con Et_2O (2x50 ml). Los extractos orgánicos combinados se secaron (Na_2SO_4) y se concentraron bajo presión reducida. El residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c-hexano/EtOAc 8:2) para proporcionar el compuesto del título como un (trans: cis) mezcla de diastereoisómeros en una relación de 7:1. TLC, R_f (c- hexano/EtOAc 3:1) = 0,42; MS: 266.0 [M+Na]+, 509,2 [2M+Na]+.

C. Éster 1- terc- butilo del ácido (2S, 5R) - y (2S, 5S)- 5- metil- pirrolidina- 1 ,2- dicarboxílico

A una solución de éster 1- terc- butilo del ácido (2S, 5R) - y (2S, 5S)- 5- metil- pirrolidina- 1 ,2- dicarboxílico - éster 2- metilo (0.33 g, 1.35 mmol; trans: cis relación 7:1) en MeOH (2 ml) se añadió NaOH 1 N (2 ml) y la mezcla de reacción se agitó a temperatura ambiente durante la noche. Se añadió una alícuota adicional de NaOH 1 N (2 ml) y la mezcla se calentó a 50 °C durante 5 h. Los volátiles se eliminaron bajo presión reducida, y la fase acuosa se acidificó a pH 1 por adición de HCl 6 N, seguido de la extracción con CH_2Cl_2 (2x25 ml). Los extractos orgánicos combinados se secaron (separador de fases) y se concentraron para proporcionar el compuesto del título en un (trans: cis) mezcla de diastereoisómeros en una relación de 7:1. TLC, R_f (CH2Cl2/MeOH (10% de AcOH) 9:1) = 0.41; MS (LC/MS): 227,9 [MH] - .

<u>Éster 1- terc- butilo del ácido (2S, 5S)- 5- etil- pirrolidina- 1 ,2- diarboxilico</u>



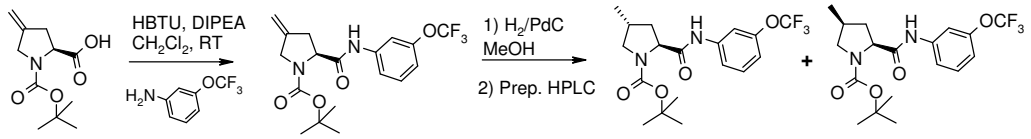
A. Éster 1- terc- butilo del ácido (2S, 5R)- 5- etil- pirrolidina- 1 ,2- dicarboxílico - ester 2- metilo

A una suspensión agitada del complejo de bromuro de cobre- sulfuro de dimetilo (2.15 g, 10.4 mmol) en Et_2O seco (40 ml), se enfrió a - 40 °C, se añadió por goteo cloruro de etil- magnesio (2 M en Et_2O, 5.22 ml, 10.4 mmoles, Aldrich 300330), bajo una atmósfera de argón. Después de agitar durante 45 min, la mezcla se enfrió a - 78 °C, seguido de la adición por goteo de eterato de trifluoruro de boro (1.32 ml, 10.4 mmoles) y agitar durante 15 min. Luego se añadió una solución de éster 1- terc- butílo del ácido (S)- 5- acetoxi- pirrolidina- 1 ,2- dicarboxílico - éster 2- metilo (1.00 g, 3.48 mmoles, preparado como se describe en el Esquema B1) en Et_2O seco (10 ml) se añadió por goteo para proporcionar una suspensión de color negro. La mezcla de reacción se agitó durante 15 min y posteriormente se dejó calentar hasta temperatura ambiente durante un período de 1 h. La reacción se apagó mediante la adición de un (1:1)- mezcla de una solución de NH_4Cl acuoso saturado y una solución acuosa concentrada de NH_3 (10 ml), seguido de agitación durante 30 min. La capa orgánica se separó, y la fase acuosa se extrajo con Et_2O (2x50 ml). Los extractos orgánicos combinados se secaron (Na_2SO_4) y se evaporaron bajo presión reducida. El residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (EtOAc/c- hexano 2:8) para proporcionar el compuesto del título (contenía menos de 10% del (2S, 5S)- diastereoisómero menor según 1H- RMN). TLC R_f (EtOAc/c- hexano 1:3) = 0.48.

B. Éster 1- terc- butilo del ácido (2S, 5S)- 5- etil- pirrolidina- 1 ,2- diarboxilico

A una solución de éster 1- terc- butilo del ácido (2S, 5R)- 5- etil- pirrolidina- 1 ,2- dicarboxílico - 2- metil éster (contenía <10% del (2S, 5R)- diastereómero menor) (340 mg, 1.32 mmol) en MeOH (15 ml) se añadió una solución 2 N de NaOH acuoso (1.32 ml, 2.64 mmol), seguido por agitación de la mezcla de reacción a 50 °C durante la noche. Se añadió una alícuota adicional de NaOH (2 equiv) y la agitación se continuó a 50 °C durante 6 h. Los volátiles se eliminaron bajo presión reducida y el residuo se recogió en agua. La capa acuosa se acidificó (pH 1) mediante la adición de HCl acuoso 6 N, seguido de la extracción con CH_2Cl_2 (2x20 ml). Los extractos orgánicos combinados se secaron (separador de fase) y se evaporaron al vacío para proporcionar el compuesto del título (contenía 10% del (2S, 5S)- diastereoisómero menor). TLC, R_f (CH_2Cl_2/MeOH (AcOH al 2%): 9:1) = 0.40.

Esquema B2: preparación de éster terc- butilo del ácido (2S, 4R) y (2S, 4S) - 2 - (3- trifluorometoxi- fenilcarbamoil)- 4- metil- pirrolidina- 1- carboxilato



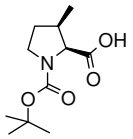
A. Éster terc- butílo del ácido (S) - 2 - (3- trifluorometoxi- fenilcarbamoil)- 4- metileno- pirrolidina- 1- carboxílico

A una suspensión de N- Boc- 4- metilen- L- prolina (1 g, 4.4 mmol) en CH_2Cl_2 (40 ml) se añadió 3 - (trifluorometoxi) anilina (0.71 ml, 5.28 mmol), HBTU (1.14 g, 6.6 mmol) y diisopropiletilamina (1.51 ml, 8.8 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 días. La mezcla se lavó sucesivamente con 30 ml de una solución acuosa saturada de $NaHCO_3$ y una solución de HCl 1M. Las capas orgánicas se secaron (separador de fases) y se concentraron al vacío. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (eluyente: c- hexano/EtOAc: 65/35) para proporcionar el compuesto del título. TLC, R_f (c- hexano/EtOAc: 1:1) = 0,55; MS (LC/MS): 287,0 [M- Boc] +, 385.0 [MH] - .

B. Éster terc- butilo del ácido (2S, 4R) y (2S, 4S) - 2 - (3- trifluorometoxi- fenilcarbamoil)- 4- metil- pirrolidina- 1- carboxílico

A una solución de éster terc- butílo del ácido (S) - 2 - (3- trifluorometoxi- fenilcarbamoil)- 4- metileno- pirrolidina- 1- carboxílico (0.5 g, 1.29 mmol) en EtOAc (15 ml) se añadió Pd/C (10%) y la mezcla de reacción se colocó en atmósfera de hidrógeno durante la noche. La mezcla de reacción se filtró sobre un lecho de Celite, el residuo de catalizador se lavó con EtOAc y el solvente se concentró. El material crudo se purificó mediante HPLC preparativa (waters SunFire C18- ODB, 5 µm, 30x100 mm, eluyente: 20- 100% CH_3CN/H_2O/20 min, 100% de CH_3CN/2 min, CH_3CN y H_2O que contenía TFA al 0.1%, flujo : 40 ml/min, carga de 150 mg por carrera) para proporcionar después de la liofilización de las fracciones purificadas los compuestos deseados: éster terc- butilo del ácido (2S, 4S) - 2 - (3- trifluorometoxi- fenilcarbamoil)- 4- metil- pirrolidina- 1- carboxílico: t_R (condiciones de HPLC b): 5,34 min; LC/MS: 387.0 [MH] - , éster terc- butilo del ácido (2S, 4R) - 2 - (3- trifluorometoxi- fenilcarbamoil)- 4- metil- pirrolidina- 1- carboxílico: t_R (condiciones de HPLC B): 5.53 min; MS (LC/MS): 387.0 [MH] - .

Éster 1- terc- butilo del ácido (2S, 3R)- 3- metil- pirrolidina- 1 ,2- dicarboxílico

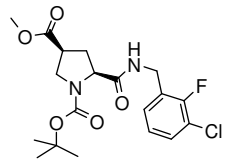


A. Éster bencilo del ácido(2S, 3R)- 3- metil- 1- ((S)- 1- fenil- etil)- pirrolidina- 2- carboxílico se preparó siguiendo el procedimiento descrito en Tet. Lett. 1997, 38 (1), 89- 92 a partir de éster bencilo del ácido [but- 3- enil- ((S)- 1- fenil- etil)- amino]- acético.

B. Éster 1- terc- butílico del ácido (2S, 3R)- 3- metil- pirrolidina- 1 ,2- dicarboxílico

Se disolvió éster bencilo del ácido (2S, 3R)- 3- metil- 1- ((S)- 1- fenil- etil)- pirrolidina- 2- carboxílico (245 mg, 0.758 mmol) y Boc_2O (165 mg, 0.758 mmol) en MeOH (3,5 ml). El aire se retiró del matraz y se reemplazó con nitrógeno tres veces. Se añadió Pd/C al 10% (76 mg) y la solución se desgasificó de nuevo y se colocó bajo una atmósfera de hidrógeno. La mezcla se agitó a temperatura ambiente durante 1.5 h, se filtró a través de una almohadilla de Celite y el solvente se concentró al vacío. El residuo se disolvió en EtOAc y se añadió una solución acuosa saturada de $NaHCO_3$. Las capas se separaron y la fase acuosa se acidificó con HCl 1 N (pH = 1) y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron para proporcionar el compuesto deseado que se usó sin purificación adicional en la siguiente etapa. 1H- RMN (400 MHz, DMSO): δ (ppm): 12,5 (bs, 1H), 4,02 (d, 1H), 3,47 (q, 1H), 3,19 (m, 1H), 2,4 (m, 1H), 1,92 (m, 1H), 1,54 (m, 1H), 1,40 y 1,35 (2s, 9H), 0,96 (d, 3H).

Éster 1- terc- butilo del ácido (3S, 5S) - 5 - (3- cloro- 2- fluoro- bencilcarbamoil)- pirrolidina- 1 ,3- dicarboxílico - éster 3- metilo



A. Éster 1- terc- butilo del ácido (2S, 4S)- 4- ciano- pirrolidina- 1 ,2- dicarboxílico

Una solución de éster metilo N- Boc- cis- 4- ciano- L- prolina (800 mg, 3.15 mmol) en MeOH (27 ml) se enfrió a 0 °C y se añadió LiOH ·H_2O (792 mg, 18.9 mmol). La solución incolora se dejó que alcanzara la temperatura ambiente y se agitó durante 4 h. Se añadió LiOH · H_2O (792 mg, 18.9 mmol) y la reacción se agitó adicionalmente a durante 1 hora para

completar la reacción. MeOH se concentró y el residuo se diluyó en CH_2Cl_2 y se trató con HCl acuoso 1 M ajustando el pH a 1. Las capas se separaron y la fase acuosa se volvió a extraer con CH_2Cl_2 (x2). Los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron para proporcionar el compuesto deseado que se utilizó en la siguiente etapa sin purificación adicional. MS (LC/MS): 263,0 [M+Na]+, 503,2 [2M+Na]+, 239,1 [MH] - .

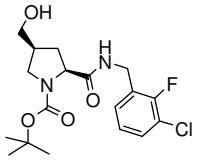
B. Éster terc- butilo del ácido (2S, 4S) - 2 - (3- cloro- 2- fluoro- bencilcarbamoil)- 4- ciano- pirrolidina- 1- carboxilato

A una mezcla de éster 1- terc- butilo del ácido (2S, 4S)- 4- ciano- pirrolidina- 1 ,2- dicarboxílico (700 mg, 2.91 mmol), 3- cloro- 2- fluorobencilamina (558 mg, 3.50 mmol) , se añadió HBTU (1.66 g, 4.37 mmol) en DMF (15 ml) de DIPEA (1.5 ml, 8.74 mmol) y la mezcla resultante se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 48 h. La mezcla se vertió en agua y se extrajo con EtOAc (2x). Los extractos orgánicos combinados se lavaron con agua (1x), se secaron (Na_2SO_4), se filtraron y se concentraron. El material crudo se purificó mediante cromatografía en columna ultrarrápida (c- hexano para c- hexano/EtOAc 1:1) para proporcionar el compuesto deseado. TLC, R_f (c- hexano/EtOAc 1:1) = 0.40; MS: 404.0 [M+Na]+, 380,0 [MH] - , t_R (condiciones de HPLC a): 3,45 min.

C. Éster 1- terc- butilo del ácido (3S, 5S) - 5 (3- cloro- 2- fluoro- bencilcarbamoil)- pirrolidina- 1 ,3- dicarboxílico – éster 3- metilo

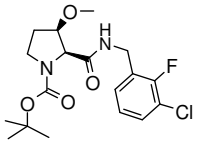
Se añadió por goteo clorotrimetilsilano (5.66 ml, 44.8 mmol) a MeOH seco (7.6 ml) a 0 °C, seguido de una solución de éster tert- butilo del ácido (2S, 4S) - 2 - (3- cloro- 2- fluoro- bencilcarbamoil)- 4- ciano - pirrolidina- 1- carboxílico (900 mg, 2.36 mmol) en CH_2Cl_2 seco (6.7 ml) y la mezcla resultante se agitó a temperatura ambiente durante 5 h. La mezcla se enfrió a 0 °C, se apagó con una solución acuosa saturada de $NaHCO_3$ y se extrajo con CH_2Cl_2 (x3). A los extractos orgánicos se añadió dicarbonato de di- terc- butilo (514 mg, 2.36 mmol) a temperatura ambiente y la solución resultante se agitó durante la noche. La mezcla de reacción se concentró en vacío y el material crudo se purificó mediante cromatografía en columna ultrarrápida (c- hexano para c- hexano/EtOAc 1:1) para proporcionar el compuesto esperado. t_R (Condiciones de HPLC a): 3.50 min.

Éster terc- butílo del ácido (2S, 4S) - 2 - (3- cloro- 2- fluoro- bencilcarbamoil) - 4- hidroximetil- pirrolidina- 1- carboxílico



A una solución de éster 1- terc- butilo del ácido (3S, 5S) - 5 - (3- cloro- 2- fluoro- bencilcarbamoil)- pirrolidina- 1 ,3- dicarboxílico - éster 3- metilo (550 mg, 1.33 mmol) en THF (6 ml) se añadió borohidruro de litio (2 M en THF, 1.46 ml, 2.92 mmol) a temperatura ambiente y la mezcla se agitó adicionalmente durante 2 h bajo atmósfera de N_2. Después terminar se añadió salmuera y CH_2Cl_2, las capas se separaron y la fase acuosa se volvió a extraer con CH_2Cl_2. Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron. El producto crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (eluyente: EtOAc) para proporcionar el material deseado. MS (LC/MS): 409,1 [M+Na]+, 287,0 [MH- Boc] +, 385,1 [MH] - ; t_R (condiciones de HPLC f): 1.82 min.

<u>Éster terc- butilo del ácido (2S, 3R) - 2 - (3- cloro- 2- fluoro- bencilcarbamoil)- 3- metoxi- pirrolidina- 1- carboxílico</u>



A. Éster 1- terc- butilo del ácido (2S, 3R) - 3- metoxi- pirrolidina- ,2- dicarboxílico - éster 2- metilo

A una solución de éster 1- terc- butilo del ácido (2S, 3R)- 3- hidroxi- pirrolidina- 1 ,2- dicarboxílico [186132- 96- 7] (500 mg, 2.16 mmol, Chem- Impex International, Inc.) en acetona (10 ml) se añadieron sucesivamente Ag_2O (1,65 g, 7.14 mmoles) y MeI (0.473 ml, 7.57 mmol), seguido de agitación a temperatura ambiente durante una noche. La mezcla de reacción se filtró, el filtrado se evaporó y el residuo se recogió de nuevo en acetona (10 ml). A esta solución se añadió Ag_2O (1.65 g, 7.14 mmoles) y MeI (0.473 ml, 7.57 mmol) y la mezcla de reacción se agitó durante 60 h. Los sólidos se retiraron por filtración, el filtrado se concentró bajo presión reducida y el residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (EtOAc/c- hexano gradiente de 1:2- 1:1) para proporcionar el compuesto del título en forma de un aceite incoloro .MS (LC/MS): 282 [M+Na]+; 160 [M- BOC] +; t_R (condiciones de HPLC b): 3.37 min.

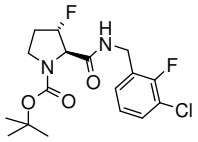
B. Éster 1- terc- butilo del ácido (2S, 3R)- 3- metoxi- pirrolidina- 1 ,2- dicarboxílico

A una solución de éster 1- terc- butilo del ácido (2S, 3R)- 3- metoxi- pirrolidina- 1 ,2- dicarboxílico - éster 2- metilo (150 mg, 0.578 mmol) en THF (4 ml) y agua (2,0 ml) se añadió LiOH (69.3 mg, 2.89 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 40 h. Se añadió otra alícuota de LiOH (69.3 mg, 2.89 mmol). Se continuó la agitación a temperatura ambiente durante 60 h y, posteriormente, a 50 °C durante 16 h para completar la reacción. Se añadió agua y los volátiles se eliminaron bajo presión reducida. La fase acuosa se ajustó a pH 2 a 3 mediante la adición de HCl acuoso 1 N, seguido de extracción con EtOAc (3x). Los extractos orgánicos combinados se secaron (separador de fases) y se concentraron al vacío para proporcionar el compuesto del título como un Sólido blanco.MS (LC/MS): 262 [M+Na]+, 190 [MH- tBu] +, 146 [MH- Boc] +, t_R (condiciones de HPLC b): 3.51 min.

C. Éster terc- butilo del ácido (2S, 3R) - 2 - (3- cloro- 2- fluoro- bencilcarbamoil)- 3- metoxi- pirrolidina- 1- carboxílico

La mezcla de éster 1- terc- butilo (2S, 3R)- 3- metoxi- pirrolidina- 1 ,2- dicarboxílico (60.0 mg, 0.245 mmol), (3- cloro- 2- fluorofenil) metanamina (0.034 ml, 0.269 mmol), HBTU (139 mg, 0.367 mmoles) y DIPEA (0.085 ml, 0.489 mmol) en CH_2Cl_2 (5 ml) se agitó durante 20 h a temperatura ambiente. La mezcla de reacción se diluyó con CH_2Cl_2, y los extractos orgánicos se lavaron posteriormente con HCl acuoso 0.1 N (3x), solución $NaHCO_3$ acuoso (2x) y salmuera. Las capas orgánicas se secaron (separador de fases), se concentraron al vacío y el residuo se purificó por HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 30x100 mm; flujo: 40 ml/min; eluyente: 5- 100% de CH_3CN/H_2O durante 20 min, CH_3CN al 100% durante 2 min, CH_3CN y H_2O que contiene TFA al 0.1%) para proporcionar el compuesto del título como un Sólido blanco. MS (LC/MS): 387 [M+H]+, 331 [MH- tBu] +, 287 [MH- Boc] +; t_R (condiciones de HPLC b): 4.26 min.

<u>Éster terc- butílo del ácido (2R, 3S) - 2 - (3- cloro- 2- fluoro- bencilcarbamoil)- 3- fluoro- pirrolidina- 1- carboxílico</u>



A. Éster 2- bencilo del ácido (2S, 3R)- 3- hidroxi- pirrolidina- 1 ,2- dicarboxílico – ester 1- terc- butilo

A una solución de éster 1- terc- butilo del ácido (2S, 3R)- 3- hidroxi- pirrolidina- 1 ,2- dicarboxílico [186132- 96- 7] (500 mg, 2.162 mmol; Chem- Impex International, Inc.) en

MeOH (9,0 ml), se enfrió a 0 °C, se añadió con agitación una solución de Cs_2CO_3 (704 mg, 2.162 mmol) en agua (6,0 ml). La mezcla se concentró por evaporación rotatoria y el residuo se suspendió en DMF (17.0 ml). La suspensión se enfrió a 0 °C, seguido por adición de bromuro de bencilo (0.514 ml, 4.32 mmoles) y se agitó durante la noche a temperatura ambiente. La mezcla de reacción se filtró, el filtrado se concentró bajo presión reducida y el residuo se disolvió en EtOAc. Los orgánicos se lavaron con $NaHCO_3$ acuoso (2x) y agua (2x), se secaron (separador de fases) y se concentraron al vacío. El residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (EtOAc/c- hexano 2:3) para proporcionar el compuesto del título en forma de un aceite. MS (LC/MS): 322 [M+H]+, 665 [2M+Na]+; t_R (condiciones de HPLC b): 4.12 min.

B. Éster bencílico del ácido (2R, 3S)- 3- fluoro- pirrolidina- 1,2- dicarboxílico – éster 1- terc- butilo

El compuesto del título se preparó de una manera similar como se describe por J.A. Hodges et al., J. Amer. Chem.. Soc. 2005, 127, 15923 a 15932: A una solución de éster 2- bencilo del ácido (2S, 3R)- 3- hidroxi- pirrolidina- 1 ,2- dicarboxílico - éster 1- terc- butilo (490 mg, 1.53 mmol) en CH_2Cl_2 (30 ml), se enfrió a - 78 °C, se añadió por goteo, DAST (1.01 ml, 7.62 mmol). La mezcla de reacción se agitó a - 78 ºC durante 5 h, y después se dejó calentar a temperatura ambiente y se agitó durante la noche. Después de enfriar a 0 °C, la reacción se apagó con MeOH, seguido de la adición de solución acuosa de $NaHCO_3$. Los volátiles se eliminaron bajo presión reducida y el residuo se recogió en EtOAc. Los orgánicos se lavaron con $NaHCO_3$ acuoso (3x), agua y salmuera, se secaron (separador de fases) y se concentraron al vacío. El residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (EtOAc/c- hexano 1:9) para proporcionar el compuesto del título (89% de pureza por HPLC/215 nm). MS (LC/MS): 346 [M+Na]+, 268 [MH- tBu] +, 224 [MH- Boc] +; t_R (condiciones de HPLC b): 5.31 min.

C. Éster terc- butilo del ácido (2R, 3S)- 3- fluoro- pirrolidina- 1 ,2- dicarboxílico

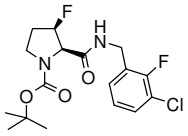
Una solución de éster 2- bencílico del ácido (2R, 3S)- 3- fluoro- pirrolidina- 1 ,2- dicarboxílico - éster 1- terc- butilo (252 mg, 0.778 mmol, 72% de pureza por HPLC/215 nm) en MeOH (20 ml) se hidrogenó a temperatura ambiente (1 atm) sobre Pd/C 10% (35 mg, 10% peso/ peso) durante 24 h. La mezcla de reacción se filtró a través de un filtro de 0.45 micras y se concentró bajo presión reducida para proporcionar el compuesto del título crudo (70% de pureza por HPLC/215 nm) como un Sólido blanco. Este material se usó en la siguiente etapa de

reacción sin purificación adicional. MS (LC/MS): 232 [MH] +; t_R (condiciones de HPLC b): 2.78 min.

D. Éster terc- butílo del ácido (2R, 3S) - 2 - (3- cloro- 2- fluoro- bencilcarbamoil)- 3- fluoro- pirrolidina- 1- carboxílico

A una solución de éster 1- terc- butilo del ácido (2R, 3S)- 3- fluoro- pirrolidina- 1 ,2- dicarboxílico (120 mg, 0.514 mmol) en CH_2Cl_2 (5 ml) se añadió sucesivamente 3- cloro- 2- fluorobencilamina (0.065 ml, 0.514 mmol), HBTU (293 mg, 0.772 mmoles) y DIPEA (0.18 ml, 1.03 mmoles), y se continuó la agitación a temperatura ambiente durante 20 h. La mezcla de reacción se diluyó con CH_2Cl_2, y los extractos orgánicos se lavaron con HCl 0.1 N aqeous (2x), $NaHCO_3$ acuoso (2x) y salmuera (1x), se secaron (separador de fases) y se concentraron al vacío. El residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (EtOAc/c- hexano gradiente de 1:4- 1:3) para proporcionar el compuesto del título como una espuma blanca. TLC R_f (EtOAc/c- hexano 1:1) = 0,62; MS (LC/MS): 397 [M+Na]+, 319 [MH- tBu] +, 275 [MH- Boc] +; t_R (condiciones de HPLC b): 4.72 min.

<u>Éster terc- butílo del ácido (2R, 3R) - 2 - (3- cloro- 2- fluoro- bencilcarbamoil)- 3- fluoro- pirrolidina- 1- carboxílico</u>



A. Ésterbencilo del ácido (2S, 3R)- 3- hidroxi- pirrolidina- 1 ,2- dicarboxílico - éster 1- terc- butilo

A una solución de éster 1- terc- butilo del ácido (2S, 3S)- 3- hidroxi- pirrolidina- 1 ,2- dicarboxílicod [187039- 57- 2] (500 mg, 2.16 mmol) en MeOH (9.0 ml), se enfrió a 0 °C, se añadió con agitación una solución de Cs_2CO_3 (704 mg, 2.162 mmol) en agua (6.0 ml). La mezcla se concentró por evaporación rotatoria y el residuo se suspendió en DMF (17.0 ml). La suspensión se enfrió a 0 °C, seguido por adición de bromuro de bencilo (0.514 ml, 4.32 mmoles) y agitar durante la noche a temperatura ambiente. La mezcla de reacción se filtró, el filtrado se concentró bajo presión reducida y el residuo se disolvió en EtOAc. Los orgánicos se lavaron con $NaHCO_3$ acuoso (2x) y agua (2x), se secaron (separador de fases) y se concentraron al vacío. El residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (EtOAc/c- hexano 2:3) para proporcionar el compuesto del título como un

Sólido blanco. MS (LC/MS): 665 [2M+Na]+, 266 [MH- tBu] +, 222 [MH- Boc] +; t_R (condiciones de HPLC b): 4.18 min.

B. Éster bencílico del ácido (2R, 3R)- 3- fluoro- pirrolidina- 1 ,2- dicarboxílico - éster 1- terc- butilo

El compuesto del título se preparó de una manera similar a la descrita por L. Demange et al, Tetrahedron Letters 2001, 42, 651- 653: A una solución de éster bencilo del ácido (2S, 3R)- 3- hidroxi- pirrolidina- 1 ,2- dicarboxílico - éster 1- terc- butilo (360 mg, 1.12 mmol) en CH_2Cl_2 (30 ml), se enfrió a - 78 °C, se añadió por goteo, DAST (0.740 ml, 5.60 mmol). La mezcla de reacción se agitó a - 78 ºC durante 5 h, y después se dejó calentar a temperatura ambiente y se agitó durante la noche. Después de enfriar a 0 °C, la reacción se apagó con MeOH, seguido de la adición de solución acuosa de $NaHCO_3$. Los volátiles se eliminaron bajo presión reducida y el residuo se recogió en EtOAc. Los orgánicos se lavaron con $NaHCO_3$ acuoso (3x), agua y salmuera, se secaron (separador de fases) y se concentraron al vacío. El residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (EtOAc/c- hexano 1:9) para proporcionar el compuesto del título (99% de pureza por HPLC/215 nm). TLC R_f (EtOAc/c- hexano 1:4) = 0.2; MS (LC/MS): 346 [M+Na]+, 268 [MH- tBu] +, 224 [MH- Boc] +; t_R (condiciones de HPLC b): 5.01 min.

C. Éster 1- terc- butilo del ácido (2R, 3R) - 3- fluoro- pirrolidina- 1 ,2- dicarboxílico

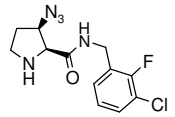
Una solución de éster 2- bencílo del ácido (2R, 3R)- 3- fluoro- pirrolidina- 1 ,2- dicarboxílico - éster 1- terc- butilo (70.0 mg, 0.216 mmol) en MeOH (10 ml) se hidrogenó a temperatura ambiente (1 atm) sobre Pd/C 10% (35 mg, 50% peso/peso) durante 48 h. La mezcla de reacción se filtró a través de un filtro de 0.45 micras y se concentró bajo presión reducida para proporcionar el compuesto del título crudo (> 95% de pureza por 1H- RMN) como un Sólido blanco. MS (LC/MS): 232 [MH] +; t_R (condiciones de HPLC b): 2.26 min. Este material se usó en la siguiente etapa de reacción sin purificación adicional.

D. Éster terc- butílo del ácido (2R, 3R) - 2 - (3- cloro- 2- fluoro- bencilcarbamoil)- 3- fluoro- pirrolidina- 1- carboxílico

A una solución de éster 1- terc- butilo del ácido (2R, 3R)- 3- fluoro- pirrolidina- 1 ,2- dicarboxílico (45.0 mg, 0.193 mmol) en CH_2Cl_2 (5 ml) se añadió sucesivamente 3- cloro- 2- fluorobencilamina (0.024 ml, 0.193 mmol), HBTU (110 mg, 0.289 mmoles) y DIPEA (0.067 ml, 0.386 mmol), y se continuó la agitación a temperatura ambiente durante 20 h. La mezcla de

reacción se diluyó con CH_2Cl_2, y los extractos orgánicos se lavaron con HCl acuoso 0.1 N (2x), $NaHCO_3$ acuoso (2x) y salmuera (1x), se secaron (separador de fases) y se concentraron al vacío. El residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (eluyente: EtOAc/c- hexano gradiente de 1:4- 1:3) para proporcionar el compuesto del título. TLC R_f (EtOAc/c- hexano 1:1) = 0,31; MS (LC/MS): 397 [M+Na]+, 319 [MH- tBu] +, 275 [MH- Boc] +; t_R (condiciones de HPLC b): 4.37 min.

Procedimiento 1 para la preparación de trifluoroacetato (2S, 3R)- 3- azido- pirrolidina- 2- carboxílico ácido 3- cloro- 2- fluoro- bencilamida



A. Éster 1- terc- butilo del ácido 2(2S, 3R)- 3- azido- pirrolidina- 1 ,2- dicarboxílico

A una solución de éster 1- terc- butilo del ácido (2S, 3R)- 3- azido- pirrolidina- 1 ,2- dicarboxílico – éster 2- metilo [361367- 97- 7] (210 mg, 0.777 mmol; Sunshine Ltd) en THF (6 ml) se añadió una solución de LiOH (55.8 mg, 2.33 mmol) en agua (3 ml), seguido de agitación a temperatura ambiente durante 20 h. La mezcla de reacción se concentró bajo presión reducida y la fase acuosa residual se lavó con EtOAc (3x). La fase acuosa se ajustó a pH de 2 a 3 mediante la adición de HCl acuoso 1 N, seguido de extracción con EtOAc (3x). Los extractos orgánicos combinados se secaron (separador de fases) y se concentraron al vacío para proporcionar el compuesto del título crudo en forma de un aceite incoloro. El producto crudo se usó en la siguiente etapa de reacción sin purificación adicional. MS (LC/MS): 279 [M+Na]+, 200 [MH- tBu]+, 157 [MH- Boc]+; t_R (condiciones de HPLC b): 2.77 min.

B. Éster terc- butilo del ácido (2S, 3R)- 3- azido- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- pirrolidina- 1- carboxílico

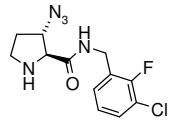
A éster 1- terc- butílico del ácido (2S, 3R)- 3- azido- pirrolidina- 1,2- dicarboxílico (170 mg, 0.663 mmol) en CH_2Cl_2 (12 ml) se añadió sucesivamente 3- cloro- 2- fluorobencilamina (0.092 ml, 0.730 mmol), HBTU (377 mg, 0.995 mmol) de DIPEA (0.232 ml, 1.33 mmol) y se continuó la agitación a temperatura ambiente durante 20 h. La mezcla de reacción se diluyó con CH_2Cl_2 y las fases orgánicas se lavaron con HCl acuoso 1 N (2x), 1 N acuoso de NaOH 1 N (2x) y salmuera, se secaron (separador de fases) y se concentraron al vacío. El producto crudo se purificó en dos pasos: primero por HPLC preparativa (Macherey- Nagel Nucleosil 100- 10 C18, 5 m, 40x250 mm; flujo: 20 ml/min; eluyente: 20- 100% CH_3CN/H_2O durante 20 min, 100

% de CH_3CN durante 2 min, CH_3CN y H_2O que contiene TFA al 0,1%) y posteriormente mediante cromatografía en columna ultrarrápida sobre sílice (EtOAc/c- hexano gradiente de 1:3- 01:1) para proporcionar el compuesto del título como una cera incolora. TLC R_f (EtOAc/c-hexano 1:1) = 0,41; MS (LC/MS): 420 [M+Na]+, 342 [MH- tBu] +, 298 [MH- Boc] +; t_R (condiciones de HPLC b): 4,66 min.

C. Trifluoroacetato de 3- cloro- 2- fluoro- bencilamida del ácido (2S, 3R)- 3- azido- pirrolidina- 2- carboxílico

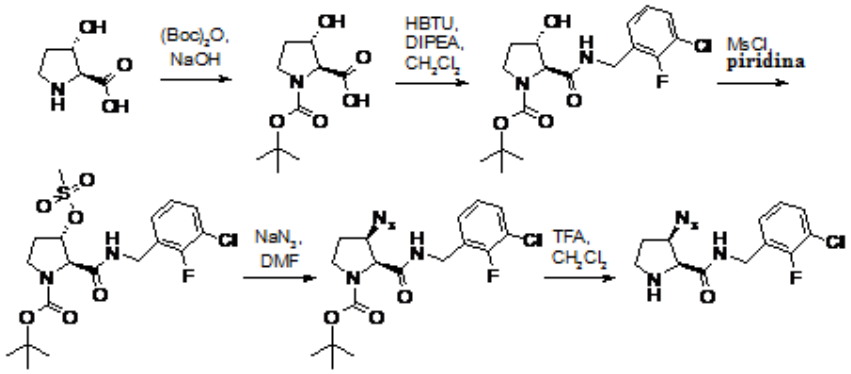
A una solución de éster terc- butilo del ácido (2S, 3R)- 3- azido- 2- (3- cloro- 2- fluoro-bencilcarbamoil)- pirrolidina- 1- carboxílico (87 mg, 0.22 mmol) en CH_2Cl_2 (6 ml) se añadió TFA a temperatura ambiente, y la agitación se continuó durante una noche a temperatura ambiente. Se añadió metanol a la mezcla de reacción y los volátiles se eliminaron bajo presión reducida. El residuo se recogió en MeOH y se concentró al vacío para proporcionar el compuesto del título crudo en forma de una cera incolora. El producto se usó en la siguiente etapa de reacción sin purificación adicional. MS (LC/MS): 298 [M+H]+; t_R (condiciones de HPLC b): 2.71 min.

Trifluoroacetato de 3- cloro- 2- fluoro- bencilamida del ácido (2S, 3S)- 3- azido- pirrolidina- 2- carboxílico



Se preparó de una manera similar a la descrita en el procedimiento 1 para trifluoroacetato de 3- cloro- 2- fluoro- bencilamida3- cloro- 2- fluoro- bencilamida del ácido (2S, 3R)- 3- azido- pirrolidina- 2- carboxílico a partir de éster 1- terc- butilo del ácido (2S, 3S)-3- azido- pirrolidina 1,2- dicarboxílico – éster 2- metilo [361367- 99- 9]. MS (LC/MS): 298 [M+H]+; t_R (condiciones de HPLC b): 2.68 min.

Procedimiento alternativo 2 para la preparación de trifluoroacetato de 3- cloro- 2- fluoro-bencilamida del ácido (2S, 3R)- 3- azido- pirrolidina- 2- carboxílico



A. Éster terc- butilo del ácido (2S, 3S) - 2 - (3- cloro- 2- fluoro- bencilcarbamoil)- 3- hidroxi- pirrolidina- 1- carboxílico

A una solución de éster terc- butilo del ácido (2S, 3S)- 3- hidroxi- pirrolidina- 1 ,2- dicarboxílico (800 mg, 3.46 mmol; Preparado de acuerdo con J. Amer Chem. Soc. **2005**, 127, 15923 - 15932) en CH_2Cl_2 (35 ml) se añadió sucesivamente 3- cloro- 2- fluorobencilamina (0.435 ml, 3.46 mmol), HBTU (1.97 g, 5.19 mmol), DIPEA (1.21 ml, 6.92 mmol). Después de agitar a temperatura ambiente durante 18 h, la mezcla de reacción se diluyó con CH_2Cl_2 y las fases orgánicas se lavaron con agua (2x), HCl acuosa 0.1 N (2x), solución acuosa de $NaHCO_3$ (2x) y salmuera, se secaron (separador de fases) y se concentraron al vacío. El producto crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (EtOAc/c- hexano 1:2- 4:1 después EtOAc) para proporcionar el compuesto del título como una cera incolora. TLC R_f (EtOAc/c- hexano 1:1) = 0,32; MS (LC/MS): 373 [M+H]+, 395 [M+Na]+, 767 [2M+Na]+; t_R (condiciones de HPLC c): 4.42 min.

B. Éster terc- butílo del ácido (2S, 3S) - 2 - (3- cloro- 2- fluoro- bencilcarbamoil)- 3- metanosulfoniloxi- pirrolidina- 1- carboxílico

A una solución enfriada con hielo de éster terc- butilo del ácido (2S, 3S) - 2 - (3- cloro- 2- fluoro- bencilcarbamoil)- 3- hidroxi- pirrolidina- 1- carboxílico (0.98 g, 2.64 mmol) en piridina seca (13 ml) se añadió cloruro de metanosulfonilo (0.31 ml, 3.96 mmol). La reacción se agitó a 0 º C durante 2 h y luego a temperatura ambiente durante 72 h. Los volátiles se evaporaron al vacío y el residuo se particionó entre agua y EtOAc. La capa acuosa se extrajo varias veces con EtOAc, los extractos orgánicos combinados se lavaron con HCl 0.1 N y salmuera, se secaron (separador de fases) y se concentraron al vacío para proporcionar el compuesto del título. Aceite marrón. MS (LC- MS): 451 [M+H]+, 395 [MH- tBu] +, 351 [MH-

Boc]+; t_R (condiciones de HPLC c): 5.08 min. El material así obtenido se utilizó sin ninguna purificación.

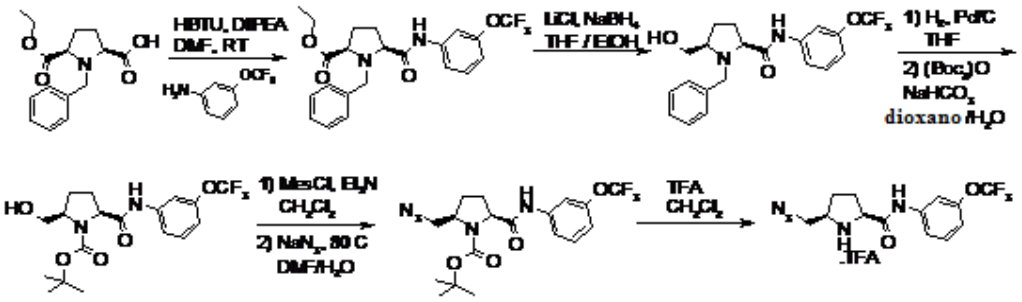
C. Éster terc- butilo del ácido (2S, 3R)- 3- azido- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- pirrolidina- 1- carboxílico

Una mezcla de éster terc- butílo del ácido (2S, 3S) - 2 - (3- cloro- 2- fluoro- bencilcarbamoil)- 3- metanosulfoniloxi- pirrolidina- 1- carboxílico (1.60 g, 2.35 mmol) y NaN_3 (0.370 g, 5.67 mmol) en DMF seca (12 ml) se agitó a 110 º C durante 60 h. La mezcla se particionó entre agua y EtOAc. La capa acuosa se extrajo con EtOAc (3x), los extractos orgánicos combinados se lavaron con salmuera, se secaron (separador de fases) y se concentraron al vacío. El producto crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (EtOAc/c- hexano 1:4- 1:2) para proporcionar el compuesto del título como una espuma incolora. MS (LC- MS): 398 [M+H]+, 342 [MH- tBu]+, 298 [MH- Boc] +; t_R (condiciones de HPLC c): 5.15 min.

D. Trifluoroacetato de 3- cloro- 2- fluoro- bencilamida del ácido (2S, 3R)- 3- azido- pirrolidina- 2- carboxílico

A una solución de éster terc- butílo del ácido (2S, 3R)- 3- azido- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- pirrolidina- 1- carboxílico (560 mg, 1.41 mmol) en CH_2Cl_2 (8 ml) se añadió TFA (4 ml), y la solución se agitó a temperatura ambiente durante 2 h. Luego se añadió metanol, y los volátiles se eliminaron bajo presión reducida. El residuo se recogió en metanol y se concentró al vacío para proporcionar el compuesto del título crudo en forma de una resina amarilla. MS (LC/MS): 298.0 [M+H]+; t_R (condiciones de HPLC c): 3.59 min. El producto se utilizó directamente en la siguiente etapa sin purificación adicional.

<u>Esquema B3: preparación de (3- trifluorometoxi- fenil)- amida del ácido - (2S, 5R)- 5- azidometil- pirrolidina- 2- carboxílico</u>



Éster monoetilo del ácido (2R, 5S)- 1- bencil- pirrolidina- 2 ,5- dicarboxílico

El compuesto del título se preparó de acuerdo con el procedimiento descrito en la Gazzetta Chimica Italiana, 1996, 126, 543 a 554 a partir de éster dietilo del ácido (2R, 5S)- 1- bencil- pirrolidina- 2 ,5- dicarboxílico preparado a partir de bencilamina y dietil- meso dibromoadipato de acuerdo con el procedimiento descrito en J. Med. Chem.. 2006, 49, 11, desde 3068- 3076.

A. Éster etilo del ácido (2R, 5S)- 1- bencil- 5- (3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 2- carboxílico

A una suspensión de éster monoetilo del ácido (2R, 5S)- 1- bencil- pirrolidina- 2 ,5- dicarboxílico (2 g, 7.21 mmol) en DMF (25 ml) se añadió 3 - (trifluorometoxi) anilina (1.53 ml, 8.65 mmol), HBTU (4.19 g, 10.8 mmol) y diisopropiletilamina (3.78 ml, 21.6 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. Se añadió EtOAc y HCl 1N, las capas se separaron y la fase acuosa, se volvieron a extraer con EtOAc (x3). Los extractos orgánicos combinados se lavaron con una solución acuosa que contiene $NaHCO_3$ al 5%, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc gradiente de 100:0 a 80:20) para proporcionar el compuesto del título. MS (LC/MS): 437,2 [M+H]+; t_R (condiciones de HPLC b) 5.50 min.

B. (2S, 5R)- 1- bencil- 5- hidroximetil- pirrolidina- 2- carboxílico ácido (3- trifluorometoxi- fenil)- amida

A una solución de éster etilo del ácido (2R, 5S)- 1- bencil- 5- (3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 2- carboxílico (2.5 g, 5.73 mmol) en una mezcla de THF (40 ml) y EtOH (20 ml) se añadió LiCl (486 mg, 11.5 mmol) seguido de $NaBH_4$ (451 mg, 11.5 mmol) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción cruda se concentró, se añadió EtOAc y HCl 1N las capas se separaron y la acuosa se volvieron a extraer con EtOAc. Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se usó sin purificación adicional en la siguiente etapa. MS (LC/MS): 395 [M+H]+; t_R (condiciones de HPLC b): 3.66 min.

C. (3- trifluorometoxi- fenil)- amida del ácido (2S, 5R)- 5- hidroximetil- pirrolidina- 2- carboxílico

A una solución de (3- trifluorometoxi- fenil)- amida del ácido (2S, 5R)- 1- bencil- 5- hidroximetil- pirrolidina- 2- carboxílico (500 mg, 1.27 mmol) en THF (5 ml) que contenía 5 gotas de MeOH se añadió Pd/C (10%, 27 mg). La solución se desgasificó 3 veces sustitución de aire por nitrógeno y, finalmente, de nitrógeno por hidrógeno. La mezcla de reacción se agitó adicionalmente en atmósfera de hidrógeno durante la noche. El catalizador se eliminó a través de una almohadilla de Celite y se lavó con THF. Los solventes se concentraron y el material resultante se utilizó sin purificación en la siguiente etapa. MS (LC/MS): 305 [M+H]+; t_R (condiciones de HPLC b): 2.89 min.

D. Éster terc- butilo del ácido (2S, 5R)- 5- hidroximetil- 2- (3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 1- carboxílico

Una mezcla de (3- trifluorometoxi- fenil)- amida del ácido (2S, 5R)- 5- hidroximetil- pirrolidina- 2- carboxílico (422 mg, 1.27 mmoles), $(Boc)_2O$ (420 mg, 1.91 mmol) y $NaHCO_3$(161 mg, 1.91 mmol) en agua/dioxano (2.5/2.5 ml) se agitó durante 48 h. Se añadió CH_2Cl_2 y HCl 0.1 N, las capas se separaron y la fase acuosa se volvió a extraer con CH_2Cl_2. Los extractos orgánicos crudos se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc gradiente de 100:0 a 1:1) para proporcionar el compuesto deseado. MS (LC- MS): 403 [MH] - ; t_R (condiciones de HPLC b) 4.76 min.

E. Éster terc- butilo del ácido (2R, 5S)- 2- metanosulfoniloximetil- 5- (3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 1- carboxílico

A una solución de éster terc- butílo del ácido (2S, 5R)- 5- hidroximetil- 2- (3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 1- carboxílico (390 mg, 0.97 mmol) en CH_2Cl_2 (3.5 ml) se añadió a 0 °C bajo atmósfera de nitrógeno Et_3N (296 µl, 2.12 mmol) y cloruro de mesilo (167 µl, 2.12 mmol) y la mezcla se agitó adicionalmente a temperatura ambiente durante 3 h. Se añadió CH_2Cl_2 y HCl 0.1 N, las capas se separaron y la fase acuosa se volvió a extraer con CH_2Cl_2. Los extractos orgánicos crudos se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El material crudo se usó sin purificación en la siguiente etapa. MS (LC- MS): 383 [MH- Boc] +; t_R (condiciones de HPLC b) 5.1 min.

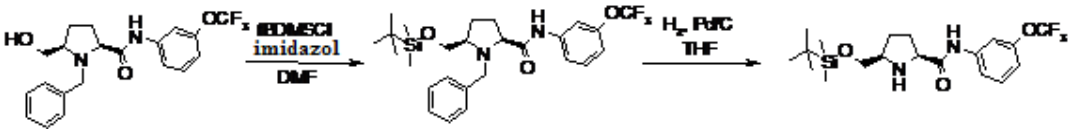
F. Éster terc- butilo del ácido (2R, 5S)- 2- azidometil- 5- (3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 1- carboxílico

A una solución de éster terc- butílo del ácido (2R, 5S)- 2- metanosulfoniloximetil- 5- (3- trifluorometoxi- fenilcarba moil)- pirrolidina- 1- carboxílico (465 mg, 0.97 mmol) en DMF (3 ml) se añadió una solución de azida de sodio (313 mg, 4.82 mmol) en agua (0.5 ml) y la mezcla se agitó a 80 °C en atmósfera de nitrógeno durante la noche. Se añadió EtOAc y una solución acuosa saturada de $NaHCO_3$, las capas se separaron y la fase acuosa volvió a extraer con EtOAc. Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc gradiente de 100:0 a 1:1) para proporcionar el compuesto deseado. MS (LC- MS): 330 [MH- Boc] +; t_R (condiciones de HPLC b) 5.75 min.

G. (3- trifluorometoxi- fenil)- amida del ácido (2S, 5R)- 5- azidometil- pirrolidina- 2- carboxílico

Se disolvió éster terc- butílo del ácido (2R, 5S)- 2- azidometil- 5- (3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 1- carboxílico (100 mg, 0.233 mmol) en CH_2Cl_2 (0.2 ml), Se añadió TFA (0.18 ml, 2.33 mmol) y la solución se agitó a temperatura ambiente 3 h. La solución se concentró a alto vacío para proporcionar la sal de TFA deseada. MS (LC/MS): 328 [M- H] - ; t_R (HPLC Condiciones b): 3.45 min.

(3- trifluorometoxi- fenil)- amida del ácido (2S, 5R) - 5 - (terc- butil- dimetil- silaniloximetil)- pirrolidina- 2- carboxílico



A. (2S, 5R)- 1- bencil- 5- ácido (terc- butil- dimetil- silaniloximetil)- pirrolidina- 2- carboxílico (3- trifluorometoxi- fenil)- amida

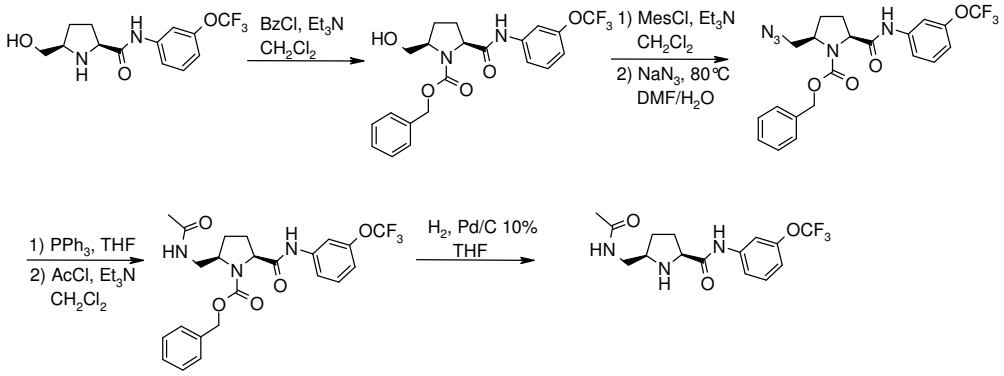
Una mezcla que contiene (3- trifluorometoxi- fenil)- amida del ácido (2S, 5R)- 1- bencil- 5- hidroximetil- pirrolidina- 2- carboxílico (300 mg, 0.76 mmol) (preparado como se describe en el Esquema B3), TBDMSCl (129 mg, 0.84 mmol) e imidazol (57 mg, 0,84 mmol) en DMF (3 ml) se agitó a temperatura ambiente durante la noche. La mezcla se concentró y el residuo se recogió en CH_2Cl_2- , se añadió HCl acuoso 1 N, se separaron las capas y la acuosa volvió a extraer con CH_2Cl_2. Los extractos orgánicos se lavaron poco con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc gradiente de 100:0

a 1:1) para proporcionar el compuesto del título. MS (LC/MS): 509,2 [M+H]+; t_R (condiciones de HPLC b): 5.99 min.

B. (3- trifluorometoxi- fenil)- amida del ácido (2S, 5R) - 5 - ácido (terc- butil- dimetil- silaniloximetil)- pirrolidina- 2- carboxílico

A una solución de (3- trifluorometoxi- fenil)- amida del ácido (2S, 5R)- 1- bencil- 5- (terc- butil- dimetil- silaniloximetil)- pirrolidina- 2- carboxílico (97 mg, 0.19 mmol) en THF (1 ml) se añadió Pd/C(10%, 20 mg). La solución se desgasificó 3 veces remplazando el aire por nitrógeno y, finalmente, de nitrógeno por hidrógeno. La mezcla de reacción se agitó adicionalmente en atmósfera de hidrógeno durante la noche. El catalizador se eliminó a través de una almohadilla de Celite y se lavó con THF. El solvente se concentró y el residuo crudo se purificó por HPLC preparativa (Waters SunFire C18- ODB 5 µm, 19x50, 5- 100% de CH3CN/H2O en 17 min, 100% de CH3CN durante 3 min, CH_3CN y H_2O que contiene TFA al 0.1%, flujo: 20 ml/min) para proporcionar el compuesto deseado. MS (LC/MS): 419 [M+H]+; t_R (condiciones de HPLC b): 5.28 min.

<u>Esquema B4: preparación del ácido del ácido (2S, 5R) - 5 - (acetilamino- metil)- pirrolidina (3- trifluorometoxi- fenil)- amida - 2- carboxílico</u>



A. Éster bencilo del ácido (2R, 5S)- 2- hidroximetil- 5- (3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 1- carboxílico

A una solución de (3- trifluorometoxi- fenil)- amida del ácido (2S, 5R)- 5- hidroximetil- pirrolidina- 2- carboxílico (797 mg, 2.62 mmol) (preparado como se describe en el Esquema B3) en CH_2Cl_2 (10 ml) se añadió en atmósfera de nitrógeno Et_3N (440 µl, 3.14 mmol) y cloroformiato de bencilo (406 µl, 2.88 mmol) y la mezcla se agitó adicionalmente a temperatura ambiente durante la noche. Se añadió CH_2Cl_2 y HCl 0.1 N, las capas se separaron y la fase acuosa se volvió a extraer con CH_2Cl_2. Los extractos orgánicos crudos se lavaron con

salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El material crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc gradiente de 100:0 a 01:01) para proporcionar el compuesto del título. MS (LC- MS): 439 [M+H]+; t_R (condiciones de HPLC b) 4.88 min.

B. Éster bencilo del ácido (2R, 5S)- 2- metanosulfoniloximetil- 5- (3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 1- carboxílico

A una solución de éster bencilo del ácido (2R, 5S)- 2- hidroximetil- 5- (3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 1- carboxílico (500 mg, 1.14 mmol) en CH_2Cl_2 (5 ml) se añadió a 0 °C bajo atmósfera de nitrógeno Et_3N (350 l, 2.5 mmol) y cloruro de mesilo (197 µl, 2.5 mmol) y la mezcla se agitó adicionalmente a temperatura ambiente durante 3 h. Se añadió CH_2Cl_2 y HCl 0.1 N, las capas se separaron y la fase acuosa se volvió a extraer con CH_2Cl_2. Los extractos orgánicos crudos se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El material crudo se usó sin purificación adicional en la siguiente etapa. MS (LC- MS): 517 [MH- Boc]+; t_R (condiciones de HPLC b) 5.15 min.

C. Éster bencilo del ácido (2R, 5S)- 2- azidometil- 5- (3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 1- carboxílico

A una solución de éster bencilo del ácido (2R, 5S)- 2- metanosulfoniloximetil- 5- (3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 1- carboxílico (589 mg, 1.14 mmol) en DMF (4.5 ml) se añadió una solución de azida de sodio (371 mg, 5.7 mmol) en agua (0,5 ml) y la mezcla se agitó a 80 °C en atmósfera de nitrógeno durante la noche. Se añadió EtOAc y agua, las capas se separaron y la fase acuosa volvió a extraer con EtOAc. Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc gradiente de 100:0 a 6:5) para proporcionar el compuesto deseado. MS (LC-MS): 464 [MH- Boc] +; t_R (condiciones de HPLC b) 5.73 min.

D. Éster bencilo del ácido (2R, 5S)- 2- aminometil- 5- (3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 1- carboxílico

Una mezcla de éster bencilo del ácido (2R, 5S)- 2- azidometil- 5- (3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 1- carboxílico (460 mg, 0.99 mmol) y trifenilfosfina (312 mg, 1.19 mmol) en THF (4 ml) se agitó a temperatura ambiente durante la noche. Después de la terminación de la reacción, se eliminó el THF y la mezcla de reacción cruda se purificó por

HPLC preparativa (Waters SunFire C18- ODB 5 µm, 19x50, 5- 100% de CH_3CN/H_2O en 17 min, 100% de CH_3CN durante 3 min, CH_3CN y H_2O que contiene TFA al 0.1% , flujo: 20 ml/min) para proporcionar el compuesto del título. MS: 438 [M+H]+; t_R (condiciones HPLC b):3.8 min.

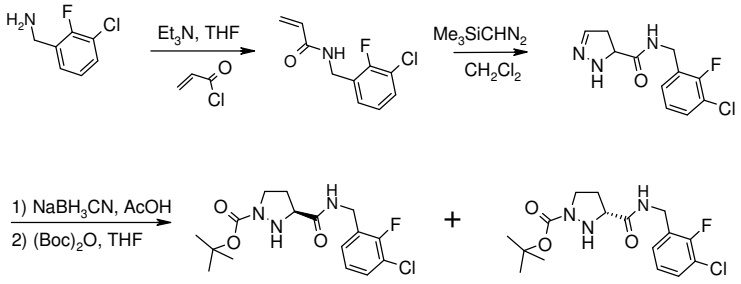
E. Éster bencílico del ácido (2R, 5S) - 2 - (acetilamino- metil) - 5 - (3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 1- carboxílico

Éster bencilo del ácido a una solución de (2R, 5S)- 2- aminometil- 5- (3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 1- carboxílico (200 mg), y Et_3N (77 µL, 0.55 mmol) en CH_2Cl_2 (3 ml) se añadió bajo atmósfera de nitrógeno a 0 ºC cloruro de acetilo (39 µL, 0.55 mmoles) y la mezcla se agitó a 0 °C durante 1 h. Se añadió CH_2Cl_2 y HCl acuoso 1 N, las capas se separaron y la fase acuosa volvió a extraer con CH_2Cl_2. Los extractos orgánicos combinados se lavaron poco con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc gradiente de 100:0 a 0:100) para proporcionar el compuesto del título. MS (LC/MS): 480.1 [M+H]+; t_R (condiciones de HPLC b): 4.69 min.

F. (3- trifluorometoxi- fenil)- amida del ácido (2S, 5R) - 5 - (acetilamino- metil)- pirrolidina- 2- carboxílico

A una solución de éster bencilo del ácido (2R, 5S) - 2 - (acetilamino- metil) - 5 - (3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 1- carboxílico (48 mg, 0.1 mmol) en THF (0.3 ml) se añadió Pd/C (10%, 2.1 mg). La solución se desgasificó 3 veces remplazando aire por nitrógeno y, finalmente nitrógeno por hidrógeno. La mezcla de reacción se agitó adicionalmente en atmósfera de hidrógeno durante 5 h. El catalizador se eliminó a través de una almohadilla de Celite y se lavó con THF. Los solventes se concentraron y el residuo resultante se usó sin purificación adicional en la siguiente etapa. MS (LC/MS): 346 [M+H]+; t_R (condiciones de HPLC b): 2.94 min.

Esquema B5: preparación de 3- cloro- 2- fluoro- bencilamida del ácido 3,4- dihidro- 2H- pirazol- 3- carboxílico



A. N- (3- cloro- 2- fluoro- bencil)- acrilamida

A una solución de 2- fluoro- 3- clorobencilamina (1 g, 6.27 mmol) y TEA (1.05 ml, 7.52 mmol) en THF (20.9 ml) se añadió cloruro de acriloilo (0.61 ml, 7.52 mmol) por goteo y la mezcla de reacción se agitó a 23 °C durante 2 h. La mezcla de reacción se diluyó en EtOAc, se añadió HCl 1 N y se separaron las capas. La capa acuosa se extrajo de nuevo con EtOAc y las capas orgánicas combinadas se secaron, se filtró y se concentró a sequedad. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (xiclohexano / gradiente EtOAc 100:0 a 1:1) para proporcionar el material deseado. TLC, R_f (c-hexano/EtOAc 5:5) = 0.41; MS (LC/MS): 214.0 [M+H]+; t_R (condiciones de HPLC b): 3.35 min.

B. 3- cloro- 2- fluoro- bencilamida del ácido (S) - 3,4- dihidro- 2H- pirazol- 3- carboxílico

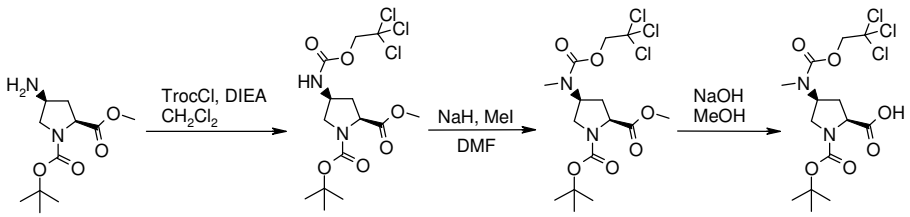
A una solución de N- (3- cloro- 2- fluoro- bencil)- acrilamida (1.25 g, 5.85 mmol) en 1/1 de una mezcla de tolueno (58.5 ml)/hexano (58.5 ml) se añadió trimetilsilildiazometano (5.85 ml, 11,7 mmol, 2 M en hexano). La reacción se agitó a 23 °C durante 20 h hasta que se completó. Los solventes se eliminaron al vacío y después CH_2Cl_2 (58.5 ml) se añadió seguido de TFA (0.49 ml, 6.44 mmol) y la mezcla de reacción se agitó adicionalmente a 23 °C durante 1 h. La mezcla de reacción se apagó con una solución de $NaHCO_3$ acuoso al 5% y se extrajo con CH_2Cl_2. Las capas orgánicas combinadas se secaron, se filtraron y se evaporaron a sequedad. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc gradiente de 100:0 a 0:100) seguido por HPLC preparativa (Waters SunFire C18ODB, 5 m, 30x100, eluyente: 20% CH_3CN/80% de H_2O a 100% de CH_3CN en 20 min, CH_3CN y H_2O que contiene TFA al 0.1%, flujo de 40 ml/min) para proporcionar el material deseado después de la liofilización de las fracciones purificadas. TLC, R_f (EtOAc) = 0.23; MS (LC- MS): 256.0 [M+H]+; t_R (condiciones de HPLC b): 2.53 min.

C. Éster terc- butílo del ácido (S) - 3 - (3- cloro- 2- fluoro- bencilcarbamoil)- pirazolidin- 1- carboxílico y Éster terc- butil- carboxílico ácido (R) - 3 - (3- cloro- 2- fluoro- bencilcarbamoil)- 1- pirazolidina

A una solución de ácido pirazolidin- 3- carboxílico 3- cloro- 2- fluoro- bencilamida (600 mg, 2.35 mmol) en ácido acético glacial (10.4 ml) se añadió $NaCNBH_3$ (369 mg, 5.87 mmol) y la mezcla de reacción se agitó a 23 °C durante 2 h. La mezcla de reacción se diluyó con EtOAc y se apagó con una solución acuosa saturada de K_2CO_3. Las capas se separaron y la fase acuosa se extrajo de nuevo con EtOAc. Las capas orgánicas combinadas se secaron, se filtraron y se evaporaron a sequedad para proporcionar el material deseado que se usó en la siguiente etapa sin purificación. El residuo se disolvió en THF (9,4 ml), Boc_2O (0.817 ml, 3.52 mmol), se añadió TEA (0.654 ml, 4.69 mmol) y DMAP (28.7 mg, 0.235 mmol) y la mezcla de reacción se agitó a 23 °C durante 2 h. El producto crudo se concentró y se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc gradiente de 100:0 a 0:100) para proporcionar el material racémico deseado. TLC, R_f (EtOAc) = 0.4; MS (LC/MS): 380 [M+Na]+, 258 [MH- Boc]+; t_R (condiciones de HPLC b): 4.22 min.

La mezcla racémica se purificó por HPLC preparativa quiral (Chiralpak AD- 00SC JF004, 5 x 50 cm, heptano/isopropanol 90/10, el flujo de 35 mL/min, detección 210 nM) para proporcionar pico 1 (t_R: 61.43 min) y pico 2 (t_R: 99.77 min). Pico 1: Éster terc- butilo del ácido (R §) - 3 - (3- cloro- 2- fluoro- bencilcarbamoil)- pirazolidin- 1- carboxílico, MS: 258,0 [MH +- Boc], 379,9 [MNa +]; tR (HPLC , Chiralpak AD, 250mmx4.6mm, heptano/isopropanol 91/10, flujo de 1 ml / min, detección 220 nM): 14,1 min. Pico 2: Éster terc- butilo del ácido(S §) - 3 - (3- cloro- 2- fluoro- bencilcarbamoil)- pirazolidin- 1- carboxílico, MS: 258,0 [MH +- Boc] [MH +], 379,9 [MNa +]; t_R (HPLC, Chiralpak AD, 250mmx4.6mm, heptano/isopropanol 91/10, flujo de 1 ml/min, detección 220 nM): 22.37 min. La estereoquímica absoluta se ha asignado provisionalmente sobre la base de los resultados de la prueba para los compuestos finales **Ejemplo 432** y el **Ejemplo 433** en el ensayo biológico.

<u>Esquema B6: preparación de éster terc- butilo del ácido ((2S, 4S) - 4 - [metil- (2,2,2- tricloro- etoxicarbonil)- amino]- pirrolidina- 1 ,2- dicarboxílico</u>



A. Éster terc- butilo del ácido (2S, 4S) - 4 - (2,2,2- tricloro- etoxicarbonilamino)- pirrolidina- 1 ,2- dicarboxílico - éster 2- metilo

A una solución de 2- metil- 4- aminopirrolidina- 1 ,2- dicarboxilato de (2S, 4S)- 1- terc- butilo (4.6 g, 10.7 mmol) en CH_2Cl_2 (100 ml) se añadió carbonoclorurato 2,2,2- tricloroetilo (1.73 ml, 12.88 mmol) y DIPEA (2.81 ml, 16.1 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h, después se vertió en agua. El compuesto deseado se extrajo con EtOAc (2 x 100 ml), las fases orgánicas se unieron, se lavaron con HCl 1 N y después con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano para c- hexano/EtOAc 1:1). MS (UPLC): 421 [M+H]+, 419 [MH] - ; t_R (condiciones de HPLC $_f$): 1.11 min.

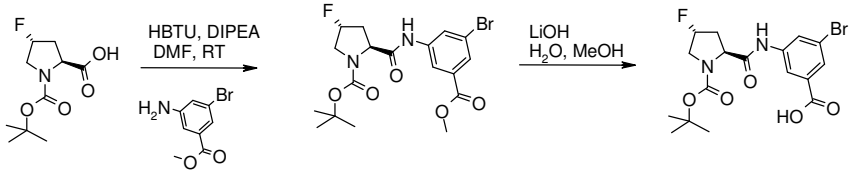
B. Éster 1- terc- butilo del ácido (2S, 4S) - 4 - [metil- (2,2,2- tricloro- etoxicarbonil)- amino] 1- pirrolidina- 1 ,2- dicarboxílico – éster 2- metilo

A una solución de éster 1- terc- butilo del ácido (2S, 4S) - 4 - (2,2,2- tricloro- etoxicarbonilamino)- pirrolidina- 1 ,2- dicarboxílico - éster 2- metilo (420 mg, 1 mmol) y yoduro de metilo (0.18 ml, 3 mmol) en DMF (10 ml) se enfrió a 0 °C bajo argón, se añadió hidruro de sodio (44 mg, 1.1 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h, después se vertió en agua. El compuesto deseado se extrajo con EtOAc (2 x 25 ml), las fases orgánicas se unieron, se lavaron con HCl 1 N y luego con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano para c- hexano/EtOAc 1:1). MS (UPLC): 436 [M+H]+, 434 [MH] - ; t_R (condiciones de HPLC $_f$): 2.35 min.

C. Éster 1- terc- butilo del ácido (2S, 4S) - 4 - [metil- (2,2,2- tricloro- etoxicarbonil)- amino]- pirrolidina- 1 ,2- dicarboxílico

A una solución de éster 1- terc- butilo del ácido ((2S, 4S) - 4 - [metil- (2,2,2- tricloro- etoxicarbonil)- amino]- pirrolidina- 1 ,2- dicarboxílico – éster 2- metilo (360 mg, 0.83 mmol) en MeOH (20 ml) se añadió NaOH acuoso 1 N (1.66 ml, 1.66 mmol). La reacción se agitó a temperatura ambiente durante 16 h y después se concentró. El residuo se acidificó con HCl acuoso 2 N a pH 3, se extrajo con EtOAc. (2 x 25 ml). Las fases orgánicas se unieron, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se usó sin purificación adicional en la siguiente etapa MS (UPLC): 421 [M+H]+, 419 [MH] - ; t_R (condiciones de HPLC $_f$): 1,00 min.

Esquema B7: preparación de éster terc- butílo del ácido (2S, 4R) - 2 - (3- bromo- 5- carboxi- fenilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico



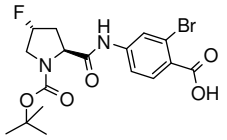
A. Éster terc- butílo del ácido (2S, 4R) - 2 - (3- bromo- 5- metoxicarbonil- fenilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico

A una mezcla de N- Boc- trans- 4- fluoro- L- prolina (500 mg, 2.14 mmol), 3- amino- 5- bromobenzoato de metilo (592 mg, 2.57 mmol) y HBTU (1.22 g, 3.22 mmol) en DMF (6 ml) se añadió DIPEA (734 µl, 4.29 mmol) y la solución resultante se agitó a temperatura ambiente bajo nitrógeno durante la noche. La mezcla se vertió en agua y se extrajo tres veces con EtOAc. Las capas orgánicas combinadas se lavaron dos veces con agua, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano 100% a c- hexano/EtOAc 70:30) para proporcionar el material deseado. TLC, R_f (c- hexano/EtOAc 1:2) = 0,8; MS (LC/MS): 467.0/469.0 [M+Na]+, 345.1/347.0 [MH- Boc] +, 443.1/445.1 [MH] - ; t_R (Condiciones de HPLC a): 3,77 min.

B. Éster terc- butílo del ácido (2S, 4R) - 2 - (3- bromo- 5- carboxi- fenilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico

A una solución de éster terc- butílo del ácido (2S, 4R) - 2 - (3- bromo- 5- metoxicarbonil- fenilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico (480 mg, 1.08 mmol) en MeOH (10 ml), se enfrió a 0 ºC se añadió $LiOH \cdot H_2O$ (271 mg, 6.47 mmol) y la solución resultante se dejó alcanzar a temperatura ambiente y se agitó durante 5 h. MeOH se concentró y el residuo se diluyó en CH_2Cl_2, se añadió HCl 1 M (pH = 1) y las capas se separaron. La capa acuosa se extrajo de nuevo dos veces con CH_2Cl_2 y las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtró y se concentró para proporcionar el material deseado que se usó sin purificación adicional en la siguiente etapa. MS (LC- MS): 453.0/455.0 [M+Na]+, 375.1/377.1 [MH- tBu] +, 331.1/333.1 [MH- Boc] +, 429.0/431.0 [MH] - ; t_R (condiciones de HPLC a): 3.27 min.

Éster terc- butílo del ácido (2S, 4R) - 2 - (3- bromo- 4- carboxi- fenilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico



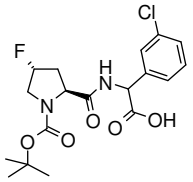
A. Éster terc- butílo del ácido (2S, 4R) - 2 - (3- bromo- 4- metoxicarbonil- fenilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico

Una mezcla de éster 1- terc- butílico del ácido (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico (355 mg, 1.52 mmol), y éster metílo del ácido 4- amino- 2- bromo- benzoico (preparado como se describe en la Parte c) (350 mg, 1.52 mmol), HBTU (865 mg, 2.282 mmoles) y DIPEA (0.531 ml, 3,04 mmol) en CH_2Cl_2 (15 ml) se agitó a temperatura ambiente durante 60 h. Se añadió alícuotas adicionales de éster 1- terc- butilo (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico (180 mg), HBTU (580 mg) y DIPEA (0.265 ml) a la mezcla, y se continuó la agitación a temperatura ambiente durante 20 h y, posteriormente, a 40 °C durante 24 h. La mezcla de reacción se diluyó con CH_2Cl_2 y la capa orgánica se lavó con agua, (3x), solución acuosa de HCl 1N acuosa de $NaHCO_3$ (2x) y salmuera, se secó (separador de fases) y se concentró al vacío. El residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (eluyente: EtOAc/c- hexano gradiente de 1:3- 1:2) para proporcionar el compuesto del título como una espuma blanca. TLC R_f (EtOAc/c- hexano 1:2) = 0.24; MS (LC/MS): 468 [M+Na]+, 388/390 [MH- tBu] +, 345/347 [MH- Boc] +; t_R (condiciones de HPLC b): 4,36 min.

B. Éster terc- butílo del ácido (2S, 4R) - 2 - (3- bromo- 4- carboxi- fenilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico

A una solución de éster ter- butilo del ácido (2S, 4R) - 2 - (3- bromo- 4- metoxicarbonil- fenilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico (400 mg, 0.898 mmol) en MeOH (9 ml) se añadió una solución acuosa de NaOH 2 N (1.78 ml, 3.59 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 20 h y después se evaporó bajo presión reducida. El residuo se recogió en agua y la fase acuosa se acidificó (pH 2 a 3) mediante la adición de HCl acuoso 0.1 N. La suspensión resultante se extrajo con EtOAc (4x) y los extractos orgánicos combinados se concentraron bajo presión reducida para proporcionar el compuesto del título crudo en forma de un sólido de color amarillo pálido. Este producto se usó en la siguiente etapa de reacción sin purificación adicional. MS (LC/MS): 454 [M+Na]+, 374 [MH- tBu] +, 330 [MH- Boc] +; t_R (condiciones de HPLC b): 3.41 min.

<u>Éster terc- butílo del ácido (2S, 4R) - 2 - {[carboxi- (3- cloro- fenil)- metil]- carbamoil}- 4- fluoro- pirrolidina- 1- carboxílico</u>



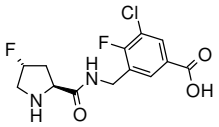
Éster de terc- butilo del ácido (2S, 4R) - 2- {[(3- cloro- fenil)- metoxicarbonil- metil]- carbamoil}- 4- fluoro- pirrolidina- 1- carboxílico

A una mezcla de éster metílico del ácido N- Boc- trans- 4- fluoro- L- prolina (200 mg, 0.86 mmol), amino- (3- cloro- fenil)- acético (233 mg, 0.94 mmol) y HBTU (488 mg, 1.29 mmol) en DMF (2.5 ml) se añadió DIPEA (294 µl, 1,72 mmol) y la mezcla se agitó a temperatura ambiente bajo nitrógeno durante la noche. Luego se vertió en agua y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se lavaron de nuevo con agua, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (CH_2Cl_2 a CH_2Cl_2/MeOH 9:1) para proporcionar el material deseado. TLC, R_f (CH_2Cl_2/MeOH 4:1) = 0,3; MS (LC/MS): 437,0 [M+Na]+, 315,1 [MH- Boc] +, 413,0 [MH] - ; t_R (condiciones de HPLC a): 3.59 min.

Éster terc- butílo del ácido (2S, 4R) - 2 - {[carboxi- (3- cloro- fenil)- metil]- carbamoil}- 4- fluoro- pirrolidina- 1- carboxílico

A una solución de éster terc- butilo del ácido (2S, 4R) - 2 - {[(3- cloro- fenil)- metoxicarbonil- metil]- carbamoil}- 4- fluoro- pirrolidina- 1- carboxílico (mezcla de diastereoisómeros, 365 mg, 0.88 mmol) en MeOH (8 ml) se añadió $LiOH \cdot H_2O$ (222 mg, 5.28 mmol) a 0 °C. La solución se dejó lentamente hasta alcanzar temperatura ambiente y se agitó durante 1 h. MeOH se concentró y el residuo se diluyó en CH_2Cl_2 y se acidificó mediante la adición de HCl 1N. Las capas se separaron y la fase acuosa se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron para proporcionar el material deseado. TLC, R_f (EtOAc) = 0.1; MS (LC- MS): 301.0/303.0 [MH- Boc] +; t_R (condiciones de HPLC a): 3.20 min.

<u>Ácido 3- cloro- 4- fluoro- 5- {[((2S, 4R)- 4- fluoro- pirrolidina- 2- carbonil)- amino]- metil}-</u> <u>benzoico</u>



Éster terc- butílo del ácido (2S, 4R) - 2 - (3- cloro- 2- fluoro- 5- metoxicarbonil- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico

A una mezcla de N- Boc- trans- 4- fluoro- L- prolina (143 mg, 0.61 mmol), éster metílo del ácido 3- aminometil- 5- cloro- 4- fluoro- benzoico (preparado como se describe en la Parte C, 275 mg, 0.61 mmol) y HATU (0.35 g, 0.92 mmol) en DMF (4 ml) se añadió DIPEA (430 µl, 2.45 mmol) y la solución resultante se agitó durante la noche a temperatura ambiente. La mezcla de reacción se dividió en dos lotes y el producto crudo se purificó sin tratamiento acuoso por HPLC- RP preparativa (Waters Sunfire, C18- ODB, 5µl, 30x100 mm, 5- 100% CH_3CN/H_2O/20 min, 100% de CH_3CN/2 min, CH_3CN y H_2O que contiene TFA al 0.1%, flujo: 40 ml/min) para proporcionar el compuesto del título. MS (LC- MS): 333,0 [M- 100] +; t_R (condiciones de HPLC c): 5.05 min.

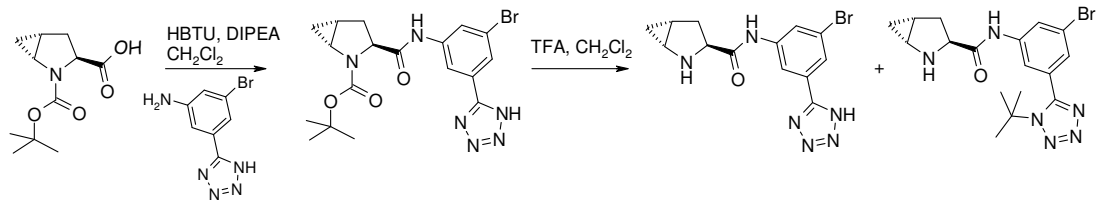
Éster terc- butílo del ácido (2S, 4R) - 2 - (5- carboxi- 3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico

A una mezcla de éster terc- butilo del ácido (2S, 4R) - 2 - (3- cloro- 2- fluoro- 5- metoxicarbonil- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico (140 mg, 0.3 mmol) en THF/MeOH/H_2O 2:1:1 (4 ml) se añadió LiOH (7 mg, 0.3 mmol). La mezcla de reacción se agitó durante 4 h a temperatura ambiente y el solvente se eliminó al vacío para proporcionar el compuesto del título que se usó sin purificación adicional.MS (LC/MS): 319,0 [M- 100] +. t_R (condiciones de HPLC c): 4.40 min.

Ácido 3- cloro- 4- fluoro- 5- {[((2S, 4R)- 4- fluoro- pirrolidina- 2- carbonil)- amino]- metil}- benzoico

A una mezcla de éster terc- butílo del ácido (2S, 4R) - 2 - (5- carboxi- 3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico (146 mg, 0.3 mmol) en CH_2Cl_2 (4 ml) se añadió TFA (1 ml). La mezcla de reacción se agitó durante 1 h a temperatura ambiente y el solvente se eliminó al vacío para proporcionar el compuesto del título que se usó sin purificación adicional.t_R (condiciones de HPLC c): 3.11 min.

Esquema B8: preparación de (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico [3- bromo- 5- (1H- tetrazol- 5- il)- fenil]- amida y (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico [3- bromo- 5- (1- terc- butil- 1H- tetrazol- 5- il)- fenil] - amida



A. Éster terc- butilo del ácido (1R, 3S, 5R) - 3- [3- bromo- 5- (1H- tetrazol- 5- il)- fenilcarbamoil]- 2- aza- biciclo [3.1.0] hexano- 2- carboxílico

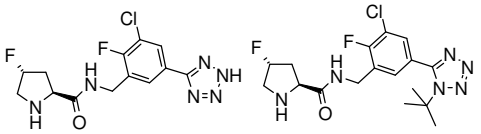
A una solución de éster ter- butilo del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico (250 mg, 1.1 mmol) en CH_2Cl_2 (6 ml) se añadido diclorhidrato 3- bromo- 5- (1H- tetrazol- 5- il)- fenilamina (preparado como se describe en la Parte C, 365 mg, 1.32 mmol), HBTU (626 mg, 1.65 mmoles) y DIPEA (0.576 ml, 3.3 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con CH_2Cl_2 y se lavó sucesivamente con solución acuosa de HCl 1M (30 ml) y una solución acuosa saturada de $NaHCO_3$. La fase orgánica se secó (separador de fases) y se evaporó al vacío. La mezcla crudo se purificó por HPLC preparativa (Nucleosil C18 100- 10, flujo: 40 ml/min, eluyente: 5- 100% CH_3CN/H_2O/20 min, 100% de CH_3CN/2 min, CH_3CN y H_2O que contiene TFA al 0,1%). Después de la combinación de las fracciones purificadas, CH_3CN se eliminó al vacío y la liofilización proporcionó el compuesto deseado. MS (LC/MS): 447,1 [MH] - ; t_R (condiciones de HPLC k): 4.62 min.

B. [3- bromo- 5- (1H- tetrazol- 5- il)- fenil]- amida del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico y (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico [3- bromo- 5- (1- terc- butil- 1H- tetrazol- 5- il)- fenil]- amida

A una solución de éster de terc- butilo (1R, 3S, 5R) - 3 - [3- bromo- 5- (1H- tetrazol- 5- il)- fenilcarbamoil]- 2- aza- biciclo [3.1.0] hexano- 2- carboxílico (200 mg, 0.445 mmol) en CH_2Cl_2 (2 ml) se añadió TFA (0.686 ml, 8.9 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 4 h. Después de completar la mezcla de reacción se diluyó con CH_2Cl_2 y MeOH, y los volátiles se eliminaron al vacío. Se añadió MeOH y la mezcla de reacción se concentró de nuevo al vacío. Esta operación se repitió dos veces para proporcionar una mezcla en una proporción de 2/3 de (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico [3- bromo- 5- (1H- tetrazol- 5- il)- fenil]- amida: MS (LC/MS): 349,2 [M+H]+; t_R

(condiciones de HPLC k): 3.06 min y (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico [3- bromo- 5- (1- terc- butil- 1H- tetrazol- 5- il)- fenil]- amida: MS (LC/MS): 405.3 [M+H]+; t_R (condiciones de HPLC k): 4.46 min.

3- cloro- 2- fluoro- 5- (2H- tetrazol- 5- il)- bencilamida del acido (2S, 4R)- 4- fluoro- pirrolidina- 2- carboxílico y 5 - (1- terc- butil- 1H- tetrazol- 5- il)- 3- cloro- 2- fluoro- bencilamida del ácido (2S, 4R)- 4- fluoro- pirrolidina- 2- carboxílico



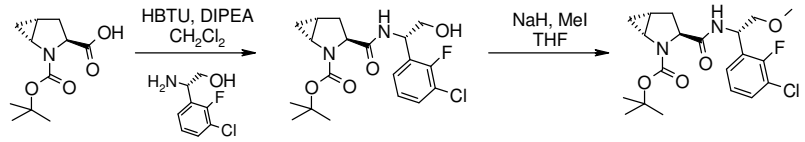
A una solución de una mezcla 1:2 de éster terc- butilo del ácido (2S, 4R)- 2- [5- (1- terc- butilo- 1H- tetrazol- 5- il)- 3- cloro- 2- fluoro- bencilcarbamoil]- 4- fluoro- pirrolidina- 1- carboxílico y éster terc- butilo del ácido (2S, 4R) - 2 - [3- cloro- 2- fluoro- 5- (2H- tetrazol- 5- il)- bencilcarbamoil] ácido- 4- fluoro- pirrolidina- 1- carboxílico (86 mg, 0.19 mmol) en CH_2Cl_2 (3 ml) se añadió TFA (1 ml) y la mezcla de reacción se agitó durante 2 h a temperatura ambiente. El solvente se eliminó aL vacío para proporcionar los compuestos del título que se utilizaron sin separación en la siguiente etapa. 3- cloro- 2- fluoro- 5- (2H- tetrazol- 5- il)- bencilamida del ácido (2S, 4R)- 4- fluoro- pirrolidina- 2- carboxílico: MS (LC- MS): 343,0 [M] + ; t_R (condiciones de HPLC c): 2.47 min y 5 - (1- terc- butil- 1H- tetrazol- 5- il)- 3- cloro- 2 - fluoro- bencilamida del ácido (2S, 4R)- 4- fluoro- pirrolidina- 2- carboxílico: MS (LC- MS): 399.0 [M] +; t_R (condiciones de HPLC c): 3.16 min.

Éster terc- butílo del ácido (2S, 4R) - 2 - [3- cloro- 2- fluoro- 5- (2H- tetrazol- 5- il)- bencilcarbamoil] - 4- fluoro- pirrolidina- 1- carboxílico y éster terc- butílo del ácido(2S, 4R)- 2- [5- (1- terc- butil- 1H- tetrazol- 5- il)- 3- cloro- 2- fluoro- bencilcarbamoil]- 4- fluoro- pirrolidina- 1- carboxílico

A una mezcla de N- Boc- trans- 4- fluoro- L- prolina (107 mg, 0.46 mmol) y HATU (260 mg, 0.69 mmol) en DMF (2 ml) se añadió una mezcla 1:2 de 5 - (1- terc- butil- 1H- tetrazol- 5- il- 3- cloro- 2- fluoro)- bencilamina y 3- cloro- 2- fluoro- 5- (2H- tetrazol- 5- il)- bencilamina (preparación descrita en el Parte C, 220 mg, 0.46 mmoles) y DIPEA (319 l, 1.8 mmol) y la solución resultante se agitó durante la noche a temperatura ambiente. La mezcla de reacción se purificó sin tratamiento acuoso por HPLC- RP preparativa (Waters Sunfire, C18- ODB, 5 µm, 30x100 mm, 5- 100% CH_3CN/H_2O/20 min, 100% de CH_3CN/2 min, CH_3CN y H_2O que contiene TFA al 0.1 %, flujo: 40 ml/min) para proporcionar los compuestos del título

éster terc- butilo del ácido(2S, 4R) - 2 - [3- cloro- 2- fluoro- 5- (2H- tetrazol- 5- il)- bencilcarbamoil]- 4- fluoro - pirrolidina- 1- carboxílico: MS (LC- MS): 343,0 [M- 100]+; t_R (condiciones de HPLC c): 3.27 min y éster terc- butílo del ácido (2S, 4R)- 2- [5- (1- terc- butil- 1H- tetrazol- 5- il)- 3- cloro- 2- fluoro- bencilcarbamoil]- 4- fluoro- pirrolidina- 1- carboxílico: MS (LC- MS): 499,0 [M]+; t_R (condiciones de HPLC c): 4.02 min.

Esquema B9: preparación de éster terc- butilo del ácido (1R,3S,5R)- 3- [(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etilcarbamoil]- 2- aza- biciclo[3.1.0]hexane- 2- carboxílico



A. éster terc- butílo del ácido (1R,3S,5R)- 3- [(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etilcarbamoil]- 2- aza- biciclo[3.1.0]hexane- 2- carboxílico

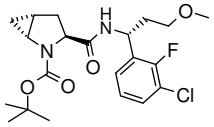
A una mezcla de éster 2- terc- butilo del ácido (1R, 3S, 5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico (750 mg, 3,30 mmol), (2S)- 2- amino- 2- (3- cloro- 2- fluorofenil)etan- 1- ol (746 mg, 3,30 mmol) y HBTU (1,75 g, 4,62 mmol) en CH_2Cl_2 (30 ml) se añadió en atmósfera de nitrógeno DIPEA (2,31 ml, 13,20 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. Se añadieron CH_2Cl_2 y agua, las capas se separaron y la capa acuosa se volvió a extraer con CH_2Cl_2 (x3). Los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron. El material crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:1 a EtOAc) para proporcionar el compuesto deseado como un aceite incoloro. MS (UPLC/MS): 399.3/401.3 [M+H]+, 443.4/445.3 [M + HCOO]- ; t_R (condiciones de HPLC A): 3,28 min.

B. éster terc- butilo del ácido (1R,3S,5R)- 3- [(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etilcarbamoil]- 2- aza- biciclo[3.1.0]hexane- 2- carboxílico

Se añadió éster terc- butilo del ácido (1R,3S,5R)- 3- [(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etilcarbamoil]- 2- aza- biciclo[3.1.0]hexane- 2- carboxílico a una suspensión de NaH (60%en aceite mineral, 25,7 mg, 0,64 mmol) en THF (3 ml) enfriada a 0 °C bajo atmósfera de argón (270 mg, 0,64 mmol). La mezcla de reacción se agitó a 0 °C durante 30 min y se agregó yodometano (0,06 ml, 0,97 mmol). Después de 1 h, la mezcla de reacción se vertió en solución acuosa saturada de $NaHCO_3$. Se añadió CH_2Cl_2, las capas se separaron y la fase acuosa se volvió a extraer con CH_2Cl_2 (x3). Los extractos orgánicos combinados se

secaron (Na_2SO_4), se filtraron y se concentraron. El material crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano para c- hexano/EtOAc 20:80) del compuesto deseado como un aceite incoloro. TLC, R_f (EtOAc) = 0,65; MS (UPLC/MS): 413.4/415.4 [M+H]+, 457.4/459.4 [M+HCOO]- ; t_R (condiciones de HPLC A): 3,67 min.

Éster terc- butilo del ácido (1R,3S,5R)- 3- [(R)- 1- (3- cloro- 2- fluoro- fenil)- 3- metoxi- propilcarbamoil]- 2- aza- biciclo[3.1.0]hexane- 2- carboxílico

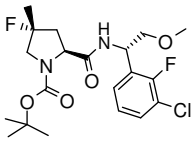


se preparó de acuerdo con el Esquema B9 (Paso B) a partir de éster terc- butilo del ácido. TLC, R_f (EtOAc) = 0,82; MS (UPLC/MS): 427.4/429.4 [M+H]+, 471,4 [M+HCOO]- ; t_R (condiciones de HPLC a): 3,71 min.

éster terc- butilo del ácido (1R,3S,5R)- 3- [(R)- 1- (3- cloro- 2- fluoro- fenil)- 3- hidroxi- propilcarbamoil]- 2- aza- biciclo[3.1.0]hexane- 2- carboxílico

se preparó de acuerdo con el Esquema B9 (Paso A) usando (3R)- 3- amino- 3- (3- cloro- 2- fluorofenil) propan- 1- ol. TLC, R_f (EtOAc) = 0,55; MS (UPLC/MS): 413.4/415.4 [M+H]+, 457,5 [M+HCOO]- ; t_R (condiciones de HPLC a): 3,33 min.

éster terc- butilo del ácido (2S,4R)- 2- [(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etilcarbamoil]- 4- fluoro- 4- metil- pirrolidino- 1- carboxílico

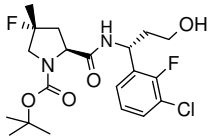


se preparó de acuerdo con el Esquema B9 (Paso B) a partir de éster terc- butilo del ácido (2S,4R)- 2- [(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etilcarbamoil]- 4- fluoro- 4- metil- pirrolidino- 1- carboxílico. TLC, R_f (EtOAc) = 0,90; EM (UPLC- MS): 433.4/435.4 [M+H]+, 477,4 [M+HCOO]- ; t_R (condiciones de HPLC a): 3,73 min.

éster terc- butilo del ácido (2S,4R)- 2- [(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etilcarbamoil]- 4- fluoro- 4- metil- pirrolidino- 1- carboxílico

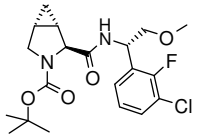
se preparó de acuerdo con el Esquema B9 (Paso A) a partir de éster 1- terc- butilo del ácido (2S, 4R)- 4- fluoro- 4- metil- pirrolidina- 1,2- dicarboxílico (preparado como se ha descrito en el Esquema B18). TLC, R_f (EtOAc) = 0,8; EM (UPLC- MS): 419,3 [M+H]+, 463,2 [M+HCOO]- ; t_R (condiciones de HPLC a): 3,35 min.

Éster terc- butilo del ácido (2S,4R)- 2- [(R)- 1- (3- cloro- 2- fluoro- fenil)- 3- hidroxi- propilcarbamoil]- 4- fluoro- 4- metil- pirrolidino- 1- carboxílico



se preparó de acuerdo con el Esquema B9 (Paso A) a partir de éster 1- terc- butilo del ácido (2S,4R)- 4- fluoro- 4- metil- pirrolidina- 1,2- dicarboxílico (preparado como se describe en el Esquema B18) y (R)- 3- amino- 3- (3- cloro- 2- fluoro- fenil)- propan- 1- ol. TLC, R_f (EtOAc) = 0,55; MS (UPLC/MS): 433,3 [M+H]+, 477,3 [M+HCOO]- ; t_R (condiciones de HPLC a): 3,26 min.

Éster terc- butilo del ácido (1S,2S,5R)- 2- [(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etilcarbamoil]- 3- aza- biciclo[3.1.0]hexane- 3- carboxílico

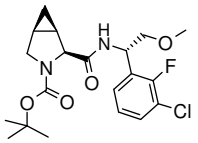


se preparó de acuerdo con el Esquema B9 (Paso B) a partir de éster terc- butilo del ácido. TLC, R_f (EtOAc): 0,65; MS (UPLC/MS): 413.4/415, 4 [M+H]+, 457.4/459, 4 [M+HCOO]- ; t_R(condiciones de HPLC a): 3,67 min.

éster terc- butilo del ácido (1S,2S,5R)- 2- [(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etilcarbamoil]- 3- aza- biciclo[3.1.0]hexane- 3- carboxílico

se preparó de acuerdo con el Esquema B9 (Paso A) a partir de éster 3- terc- butilo del ácido (1S,2S,5R)- 3- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico (Enamina, EN- 400- 12629). TLC, R_f (EtOAc) = 0,65; MS (UPLC/MS): 399.3/401, 3 [M+H]+, 443.4/445, 4 [M+HCOO]- ; t_R (condiciones de HPLC a): 3,28 min.

éster terc- butilo del ácido (1R,2S,5S)- 2- [(S)- 1- (3- Chloro- 2- fluoro- fenil)- 2- metoxi- etilcarbamoil]- 3- aza- biciclo[3.1.0]hexane- 3- carboxílico



se preparó de acuerdo con el Esquema B9 (Paso B) a partir de éster terc- butilo del ácido (1R,2S,5S)- 2- [(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etilcarbamoil]- 3- aza- biciclo[3.1.0]hexane- 3- carboxílico. TLC, R_f (EtOAc): 0,45; MS (UPLC/MS): 413.3/415.3 [M+H]+, 457,3 [M+HCOO]- ; t_R (condiciones de HPLC a): 3,64 min.

éster terc- butilo del ácido (1R,2S,5S)- 2- [(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etilcarbamoil]- 3- aza- biciclo[3.1.0]hexane- 3- carboxílico

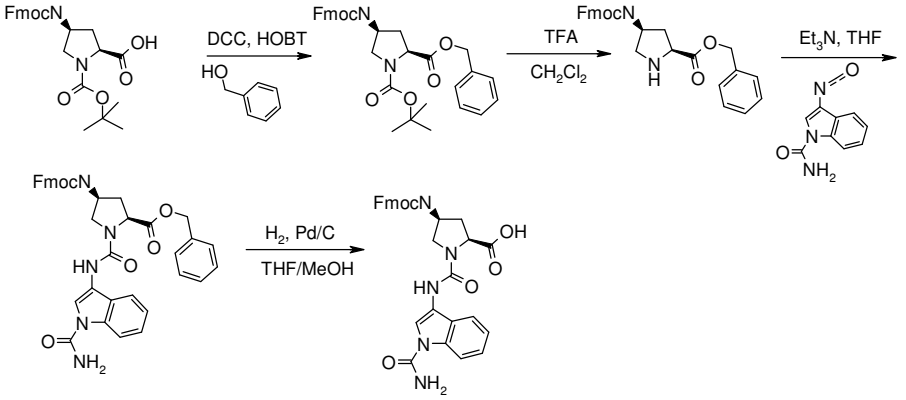
se preparó de acuerdo con el Esquema B9 (Paso A) a partir de éster 3- terc- butilo(1R*,2S*,5S*)- 3- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico racémico. Los diastereoisómeros se separaron mediante HPLC quiral (Chiralpak ADOOCM- EL001, 5x50cm, eluyente: n- heptano/IPA 75/25, flujo: 50ml/min, detección: 220 nm) para proporcionar éster terc- butilo del ácido: t_R (HPLC, Chiralpak (20µm) 046x25cm, n- Heptano/IPA 80:20, flujo: 1ml/min): 7,25 min; TLC, R_f (EtOAc) = 0,58; MS (UPLC/MS) : 399,4 [M+H]+, 443,3 [M+HCOO]- y éster terc- butilo del ácido: t_R (HPLC, Chiralpak (20µm) 046x25cm, n- Heptano/IPA 80:20, flujo: 1ml/min): 8.37min; TLC, R_f (EtOAc) = 0,58; MS (UPLC/MS) : 399,3 [M+H]+, 443,3 [M+HCOO]- . La estereoquímica absoluta de los diastereoisómeros se asigna en función de los resultados de las pruebas para el compuesto final**Ejemplo 212**en el ensayo biológico.

éster3- terc- butilo del ácido (1R*,2S*,5S*)- 3- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico

A una solución del ácido (1R*,2S*,5S*)- 3- aza- biciclo[3.1.0]hexano- 2- carboxílico racémico (10 g, 79 mmoles) (ABCR [22255- 16- 19]) en una mezcla de THF (84 ml) y agua (42 ml) se añadió una solución de NaOH (4,18 g, 105 mmol) en agua (42 ml, 10% w/v) y una solución de Boc_2O (27,4 ml, 118 mmol) en THF (84 ml) y agua (42 ml). La mezcla bifásica resultante se agitó a temperatura ambiente durante la noche. La mezcla se concentró al vacío y la capa acuosa resultante se extrajo EtOAc (x5), después se acidificó a pH 2- 3 por adición de HCl 1N, saturada con NaCl y se extrajo con $CHCl_3$/EtOH 2:1 (x3). Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron para proporcionar el material deseado que se usó sin purificación adicional en la siguiente etapa. MS (UPLC/MS): 226,2 [M-

H]- , 1H- RMN (400 MHz, DMSO): δ (ppm) 12,4 (m, 1H), 4,19 (m, 1H), 3,46 (m , 1H), 3,38 (m, 1H), 1,88 (m, 1H), 1,64 (m, 1H), 1,35 (1, 9H), 0,65 (m, 1H), 0,54 (m, 1H).

Esquema B10: preparación de ácido (2S, 4S)- 4- (9H- fluoren- 9- ilmetoxicarbonilamino)- 1- (R- carbamoil)pirrolidina- 2- carboxílico



A. Éster 2- bencilo del ácido (2S,4S)- 4- (9H- fluoren- 9- ilmetoxicarbonilamino)- pirrolidina- 1,2- dicarboxílico - ester 1- terc- butilo

A una suspensión de ácido (2S,4S)- Fmoc- 4- amino- 1- boc- pirrolidina- 2- carboxílico (7,7 g, 17,1 mmol) en CH_2Cl_2 (50 ml) se añadió DCC (4,2 g, 20,5 mmol), DMAP (0,2 g, 1,7 mmol) y alcohol bencílico (1,7 ml, 17,08 mmol). La suspensión blanca resultante se agitó a temperatura ambiente durante una noche bajo atmósfera de nitrógeno. TLC indicó la finalización de la reacción. La mezcla se filtró, y el filtrado se concentró para proporcionar el residuo crudo que se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano a c- hexano/EtOAc 4:1) para proporcionar el compuesto del título. TLC, R_f (c- hexano/EtOAc 03:01) = 0,25; MS (LC/MS): 565,3 [M+Na]+, 443,2 [MH- Boc]+; t_R(condiciones de HPLC a): 4,5 min; 1H- RMN (400 MHz, DMSO): δ (ppm) 7,91 (d, 2H,), 7,70 (d, 2H), 7,53 (d, 1H), 7,45- 7,32 (m, 9H), 5.23 a 5.6 (m, 2H), 4,35- 4,22 (m, 4H), 4,05 (q, 1H), 3,72- 3,65 (m, 1H), 3.11 a 3.6 (m, 1H), 1,86- 1,81 (m, 1H), 1,41 (s, 4H), 1,28 (s, 5H).

B. Ester bencilo del ácido (2S,4S)- 4- (9H- fluoren- 9- ilmetoxicarbonilamino)- pirrolidina- 2- carboxílico

A una solución de éster 2- bencílo del ácido (2S,4S)- 4- (9H- fluoren- 9- ilmetoxicarbonilamino)- pirrolidina- 1,2- dicarboxílico - (7,3 g, 13,49 mmol) en CH_2Cl_2 (45 ml) se le añadió TFA (5,1 ml, 67,5 mmol). La solución se agitó a temperatura ambiente durante la noche. El solvente se concentró y el residuo se co- evaporó tres veces con CH_2Cl_2 para eliminar el exceso de TFA. El residuo crudo se recogió en éter dietílico y el precipitado resultante se

filtró para proporcionar el compuesto del título como un polvo blanco. MS (LC/MS): 443,2 [M-H]+; t_R (condiciones de HPLC a): 3,3 min; 1H- RMN (400 MHz, DMSO): δ (ppm) 9,84 (s, 1H), 9,14 (s, 1H) , 7,90 (d, 2H), 7,68 (d, 2H), 7,62 (d, 1H), 7,45- 7,33 (m, 9H), 5.28- 5.21 (m, 2H), 4,59- 4,54 (m, 1H), 4,41 (d, 2H), 4.26- 4.16 (m, 2H), 3,46- 3,41 (m, 1H), 3.16 a 3.11 (m, 1H), 2,64- 2,58 (m, 1H).

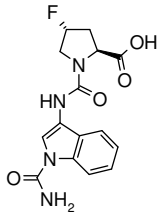
C. Ester bencilo del ácido (2S,4S)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- (9H- fluoren- 9- ilmetoxi carbonilamino)- pirrolidina- 2- carboxílico

A una solución de Ester bencilo del ácido (2S,4S)- 4- (9H- fluoren- 9- ilmetoxicarbonilamino)- 2- pirrolidina- carboxílico (3,03 g, 5,45 mmol) y Et_3N (1,1 ml, 8,2 mmol) en THF seco (60 ml) se añadió una solución de amida del ácido 3- isocianato- indol- 1- carboxílico (1,1 g, 5,4 mmol, preparado como se describe en el Esquema A1) en THF seco (60 ml). La solución resultante se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 20 min. La mezcla se vertió en agua y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron a alto vacío (la temperatura del baño de agua del evaporador rotatorio se mantuvo a temperatura ambiente) para proporcionar el compuesto del título. R_f (c- hexano/EtOAc 1:3) = 0,39; MS (LCMS): 644,2 [M+H]+, 666,2 [M+Na]+; t_R (condiciones de HPLC a): 4,0 min.

D. Ácido (2S,4S)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- (9H- fluoren- 9- ilmetoxi carbonilamino)- 1- (R- carbamoil)pirrolidina- 2- carboxílico

Ester bencilo del ácido (2S,4S)- 4- (9H- fluoren- 9- ilmetoxicarbonilamino)- 1- (R-carbamoil)pirrolidina- 2- carboxílico (2,83 g, 4,4 mmol) se disolvió en una mezcla de MeOH/THF (1:1) (60 ml). Se retiró aire del matraz y se reemplazó con nitrógeno tres veces. A continuación, Pd/C al 10% (425 mg) se añadió a la solución que se desgasificó una vez más y se vuelvió a llenar con nitrógeno tres veces. La mezcla se colocó bajo una atmósfera de hidrógeno, y se agitó a temperatura ambiente durante 2 h. El catalizador se eliminó a través de una almohadilla de Celite y se lavó con THF. El filtrado se concentró, el residuo se recogió en éter dietílico y el precipitado resultante se filtró para proporcionar el compuesto del título. MS (LC/MS): 554,2 [M+H]+, 552,1 [M- H]- ; t_R(condiciones de HPLC a): 3,5 min.

Ácido (2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carboxílico



A. Éster 1- terc- butilo del éster 2- bencílico del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico

A una suspensión de N- Boc- trans- 4- fluoro- L- prolina (4,5 g, 19,29 mmol) en CH_2Cl_2 (68 ml) se añadieron DCC (4,78 g, 23,15 mmol), DMAP (0,236 g, 1,93 mmol) y alcohol bencílico (2 ml, 19,29 mmol). La suspensión blanca resultante se agitó a temperatura ambiente durante 48 h y se filtró. El filtrado se concentró para proporcionar un aceite incoloro que se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano a c-hexano/EtOAc 4- 1) para proporcionar el compuesto deseado. TLC, R_f (c- hexano/EtOAc 3:1) = 0,3; MS: 346.0 [M+Na]+; t_R (condiciones de HPLC a): 3,85 min.

B. Ester bencilo del ácido del ácido (2S,4R)- 4- fluoro- pirrolidina- 2- carboxílico

Ester 2- bencílico del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico - ester 1-terc- butilo (3,16 g, 9,76 mmol) se disolvió en CH_2Cl_2 (50 ml), se añadió TFA (7,47 ml, 98 mmol) y la solución se agitó a temperatura ambiente durante 16 h. La solución se concentró a alto vacío para proporcionar la sal de TFA deseada en forma de un aceite marrón que se usó sin purificación adicional en la siguiente etapa. MS (LC/MS): 224,1 [M+H]+.

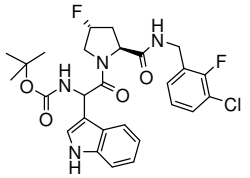
C. Ester bencilo del ácido (2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carboxílico

A una solución de sal de TFA del ester bencilo del ácido (2S,4R)- 4- fluoro- pirrolidina-2- carboxílico (4,45 g, 13,2 mmoles), amida del ácido 3- isocianato- indol- 1- carboxílico (2,65 g, 13,2 mmol) (preparado como se describe en el Esquema A1) y THF (66 ml) se añadió trietilamina (5,51 ml, 39,6 mmol). La solución resultante se agitó a temperatura ambiente bajo una atmósfera de nitrógeno durante 1 h hasta la finalización de la reacción. La mezcla se vertió en agua y se extrajo con EtOAc. La capa orgánica se lavó con una solución acuosa saturada de $NaHCO_3$, se secó sobre Na_2SO_4, se filtró y se concentró. El material crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 9:1 a EtOAc puro) para proporcionar el compuesto deseado. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0,40; MS: 425.2 [M+H]+; t_R (condiciones de HPLC a): 3,6 min.

D. Ácido (2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carboxílico

A una solución de ester bencilo del ácido (2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carboxílico (2,5 g, 5,89 mmol) en THF (40 ml) se añadió Pd/C al 10% (500 mg). Se retiró aire del matraz a alto vacío y se sustituyó con nitrógeno, esta operación se repitió tres veces y finalmente se retiró nitrógeno y se reemplazó con hidrógeno. La mezcla se agitó bajo una atmósfera de hidrógeno durante 16 h. El hidrógeno se eliminó al vacío y se sustituyó con nitrógeno y el catalizador se eliminó mediante filtración a través de una almohadilla de Celite y se lavó con THF. Los solventes se concentraron para proporcionar el producto del título. MS (LC/MS): 335,0 [M+H]+, 691,2 [2M+Na]+, 333,1 [M-H]- ; t_R (condiciones de HPLC a): 2,22 min.

<u>Éster terc- butilo del ácido{1- (1- acetil- 1H- indol- 3- il)- 2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- carbámico</u>



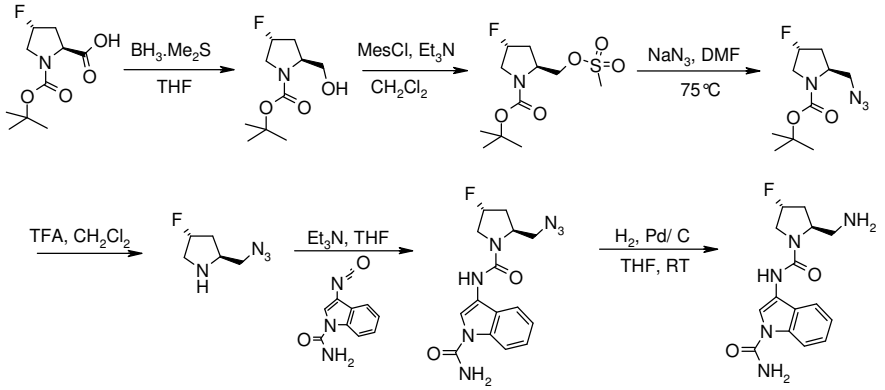
A una solución de 3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 4- fluoro- pirrolidina- 2- carboxílico. Sal de TFA (600 mg, 1,54 mmol), N- Boc- 2- (indol- 3- il)- DL- glicina (538 mg, 1,85 mmol) y HBTU (878 mg, 2,32 mmol) en DMF (5,14 ml) se añadió DIPEA (809 µl, 4,63 mmol) y la mezcla de reacción se agitó a 23 °C durante 24 h. La mezcla se diluyó con EtOAc y se lavó sucesivamente con HCl 1 N y $NaHCO_3$ acuoso al 5%. La capa orgánica se secó (Na_2SO_4), se filtró y se concentró. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (ciclohexano/EtOAc gradiente de 100:0 a 1:1) para proporcionar dos fracciones P1 y P2 que contienediastereosiomero cada uno. P1: TLC, R_f (c- hexano/EtOAc 1:1) = 0,25; MS (LC/MS): 545,2 [M- H]- ; t_R (condiciones de HPLC b): 4,89 min. P2: TLC, R_f (c- hexano/EtOAc 1:1) = 0,15; MS (LC/MS): 545,2 [M- H]- ; t_R (condiciones de HPLC b): 4,96 min.

(2S,4R)- 4- fluoro- pirrolidina- 2- carboxílico ácido 3- cloro- 2- fluoro- bencilamida

El compuesto del título se preparó como una sal de TFA de acuerdo con el Esquema D5 (etapas A y B) a partir de 3- cloro- 2- fluoro- bencilamina y éster terc- butilo del ácido (2S,4R)-

4- fluoro- pirrolidina- 1,2- dicarboxílico. MS (LC- MS): 274,9 [M+H]+; t_R (condiciones de HPLC b): 2,23 min.

Esquema B11: Preparación de amida del ácido 3- [((2S,4R)- 2- aminometil- 4- fluoro- pirrolidina- 1- carbonil)- amino]- indol- 1- carboxílico



A. Éster terc- butilo del ácido (2S,4R)- 4- fluoro- 2- hidroximetil- pirrolidina- 1- carboxílico

A una solución de éster 1- terc- butilo del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico (3 g, 12,9 mmol) en THF seco (130 ml) bajo nitrógeno a- 10 °C se agregó una solución de complejo de borano- sulfuro de dimetilo (2N en THF, 14,1 ml, 28,3 mmol)por goteo durante 45 min y la solución resultante se dejó calentar a temperatura ambiente y se agitó durante la noche bajo atmósfera de nitrógeno. La reacción se apagó mediante la adición cuidadosa de metanol (30 ml). La mezcla se co- evaporó con metanol (2x140 ml), a continuación, se añadieron CH_2Cl_2 y una solución acuosa saturada de $NaHCO_3$. Las capas se separaron y la fase acuosa se extrajo con CH_2Cl_2 (x2), se secó sobre Na_2SO_4, se filtró y se concentró para proporcionar el material deseado. TLC, R_f (EtOAc) = 0,70; 1H- RMN (400 MHz, DMSO): δ (ppm) 5,23 (d, 1H), 4,78 (bs, 1H), 3,85 (m, 1H), 3,71 (m, 1H), 3,55 (m, 1H), 3,48 (m, 1H), 3.7- 3.3 (m, 1H), 2,17 (m, 2H), 1,42 (s, 9H).

B. Éster terc- butilo del ácido (2S,4R)- 4- fluoro- 2- metanosulfoniloximetil- pirrolidina- 1- carboxílico

Éster terc- butilo del ácido (2S,4R)- 4- fluoro- 2- hidroximetil- pirrolidina- 1- carboxílico (2,87 g, 13,1 mmol) se disolvió en 45 ml de CH_2Cl_2. La mezcla se enfrió a 0 °C, y se agregó cloruro de metanosulfonilo (2,55 ml, 32,8 mmol) y trietilamina (4,56 ml, 32,8 mmol). La mezcla se dejó calentar a temperatura ambiente y se agitó durante 1,5 h. La mezcla se apagó con una solución acuosa saturada de $NaHCO_3$, se extrajo dos veces con CH_2Cl_2, se secó sobre

Na_2SO_4 y se concentró. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano a c- hexano/EtOAC 3:7) para proporcionar el material deseado. TLC, R_f (c- hexano/EtOAc 1:1) = 0,4; MS: 320.0 [M+Na]+, 198,1 [MH-Boc]+, 617,2 [2M+Na]+.

C. Éster terc- butilo del ácido (2S,4R)- 2- Azidometil- 4- fluoro- pirrolidina- 1- carboxílico

Una mezcla de éster terc- butilo del ácido (2S,4R)- 4- fluoro- 2- metanosulfoniloximetil- pirrolidina- 1- carboxílico (3,3 g, 11,1 mmol) y NaN_3 (721 mg, 11,1 mmol) en DMF (50 ml) se agitó a 75 °C bajo nitrógeno durante la noche. La mezcla se diluyó con agua y se extrajo con EtOAc (x3). Los extractos orgánicos combinados se lavaron con agua (x3), se secaron sobre Na_2SO_4, y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 100/0 a 0/100) para proporcionar el material deseado. 1H- RMN (400 MHz, DMSO): δ (ppm) 5,25 (d, 1H), 4,03 (m, 1H), 3,92- 3,70 (m, 2H), 3.5- 3.25 (m, 2H), 2,27 (m, 1H), 2.2- 1.8 (m, 1H), 1,43 (s, 9H).

D. (2S,4R)- 2- Azidometil- 4- fluoro- pirrolidina

A una solución de éster terc- butilo del ácido (2S,4R)- 2- azidometil- 4- fluoro- pirrolidina- 1- carboxílico (600 mg, 2,45 mmol) en CH_2Cl_2 (2,5 ml) se añadió TFA (1,88 ml, 24,6 mmol) y la solución se agitó a temperatura ambiente durante 2 h. CH_2Cl_2 se concentró y el producto crudo se secó a alto vacío para proporcionar el material deseado que se usó sin purificación adicional en la siguiente etapa.

E. Amida del ácido 3- [((2S,4R)- 2- Azidometil- 4- fluoro- pirrolidina- 1- carbonil)- amino]- indol- 1- carboxílico

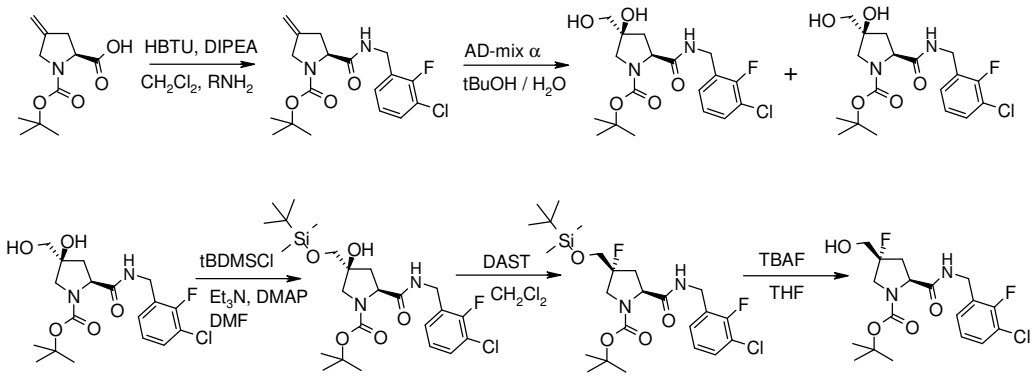
A una solución de (2S,4R)- 2- azidometil- 4- fluoro- pirrolidina (2,46 mmoles) y Et_3N (1,7 ml, 12,3 mmol) en THF (8 ml) se añadió una solución de amida de ácido 3- isocianato- indol- 1- carboxílico (543 mg, 2,70 mmol) en THF (4 ml) y la solución resultante se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 20 min. La mezcla se vertió en agua y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano a c- hexano/EtOAc 1:4 a 100% EtOAc) para

proporcionar el material deseado. TLC, R_f (EtOAc) = 0,7; MS (LC- MS): 346,1 [M+H]+, 368,0 [M+Na]+, 344,0 [M- H]- ; t_R (condiciones de HPLC f): 1,61 min.

F. Amida del ácido 3- [((2S,4R)- 2- aminometil- 4- fluoro- pirrolidina- 1- carbonil)- amino]- indol- 1- carboxílico

Amida del ácido 3- [((2S,4R)- 2- Azidometil- 4- fluoro- pirrolidina- 1- carbonil)- amino]- indol- 1- carboxílico (500 mg, 2,84 mmol) se suspendió en THF (5 ml). Se retiró aire del matraz y se reemplazó con nitrógeno tres veces. Pd/C al 10% (100 mg) se añadió a la solución que se desgasificó de nuevo, se colocó bajo una atmósfera de hidrógeno, y se agitó a temperatura ambiente durante 1,5 h. El catalizador se eliminó a través de una almohadilla de Celite y se lavó con THF y MeOH para proporcionar el material deseado que se usó en la siguiente etapa sin purificación adicional. MS (LC- MS): 320,2 [M+H]+, 639,2 [2M+H]+, 661,3 [2M+Na]+, 318,1 [M- H]- ; t_R (condiciones de HPLC f): 0+1.02+ 1.61 min.

Esquema B12: preparación de éster terc- butilo del ácido (2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- hidroximetil- pirrolidina- 1- carboxílico



A. Ester terc- butilo del ácido (S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- metileno- pirrolidina- 1- carboxílico

A una solución de N- Boc- 4- metilen- L- prolina (5,3 g, 22,6 mmol) en CH_2Cl_2 (25 ml) se agregó una solución de 3- cloro- 2- fluorobencilamina (3,61 g, 22,6 mmol) en CH_2Cl_2 (25 ml) seguido de HBTU (10,3 g, 27,1 mmol) y DIPEA (5,81 ml, 33,9 mmol) y la solución resultante se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 2 h. La mezcla se vertió en HCl 1 N y se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se neutralizaron con una solución acuosa saturada de $NaHCO_3$, se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano a c- hexano/EtOAc c- hexano/EtOAc

85:15 a 50:50) para proporcionar el material deseado. TLC, R_f (EtOAc) = 0,75; MS (LC- MS): 391.0/393.1 [M+Na]+, 313.0/315.0 [MH- tBu]+, 413.0/415.0 [M+HCOO]- ; t_R (condiciones de HPLC f): 2,12 min.

B. Éster terc- butilo del ácido (2S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- 4- hidroximetil- pirrolidina- 1- carboxílico y éster terc- butilo del ácido (2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- 4- hidroximetil- pirrolidina- 1- carboxílico

Un matraz se cargó con t- butanol (13 ml), agua (13 ml), y AD- mix- □ (3,8 g). La mezcla se agitó a temperatura ambiente hasta que las dos fases fueron claras, y después se enfrió a 0 °C. Se añadió éster terc- butilo del ácido (S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- metileno- pirrolidina- 1- carboxílico inmediatamente (1 g, 2,71 mmol), y la suspensión heterogénea se agitó vigorosamente desde 0 °C a temperatura ambiente durante la noche. La reacción se apagó a 0 °C por adición de sulfito de sodio (4 g) y después se calentó a temperatura ambiente y se agitó durante 45 min. La mezcla de reacción se extrajo con CH_2Cl_2 (3x). Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron para proporcionar una mezcla de diastereoisomeros en una proporción de 2:1. La mezcla cruda se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (1- 1 c-hexano/EtOAc a 100% de EtOAc, y luego a partir de CH_2Cl_2 a CH_2Cl_2/MeOH 8:2) para proporcionar éster terc- butilo del ácido (2S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- 4- hidroximetil- pirrolidina- 1- carboxílico (isómero principal): TLC, R_f (EtOAc) = 0,3; MS (LC- MS): 403,1/405,1 [M+H]+, 425.0/427.1 [M+Na]+, 827.2/829.2 [2M+Na]+, 347.0/349.0 [MH- tBu]+, 401.0/403.0 [M- H]- , 447.1/449.0 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,71 min y éster terc- butilo del ácido (2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- 4- hidroximetil- pirrolidina- 1- carboxílico (isómero menor): TLC, R_f (EtOAc) = 0,2; MS (LC- MS): 425.0/427.1 [M+Na]+, 827.2/829.2 [2M+Na]+, 347.0/349.0 [MH- tBu]+, 447.1/449.0 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,66 min.

C. éster terc- butilo del ácido (2S,4S)- 4- (terc- butil- dimetil- silaniloximetil)- 2- (3- cloro- 2- fluoro- bencil carbamoil)- éster 4- hidroxi- pirrolidina- 1- carboxílico

A una solución de éster terc- butilo del ácido (2S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- 4- hidroximetil- pirrolidina- 1- carboxílico (200 mg, 0,5 mmol) en DMF (2 ml) se añadió cloruro de terc- butildimetilsilil (75 mg, 0,5 mmol), trietilamina (69 µl, 0,5 mmol) y DMAP (6 mg, 0,05 mmol). La mezcla se agitó a temperatura ambiente bajo nitrógeno durante la noche. Se añadieron de nuevo cloruro de terc- butildimetilsilil (75 mg, 0,5

mmoles), y trietilamina (69 µl, 0,5 mmol) y la mezcla se agitó adicionalmente a temperatura ambiente durante 2,5 h. La mezcla se vertió en una solución acuosa saturada de $NaHCO_3$, y se extrajo con EtOAc (x 3). Las capas orgánicas combinadas se lavaron con agua, se secaron (Na_2SO_4), se filtraron y se concentraron. La mezcla cruda se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (eluyente:EtOAc) para proporcionar el material deseado. TLC, R_f (c- hexano/EtOAc 1:1) = 0,50; MS (LC- MS): 518.2/520.2 [M+H]+, 540.2/542.2 [M+Na]+, 462.0/464.0 [MH- tBu]+, 516.0/518.2 [M- H]- , t_R (condiciones de HPLC f): 2,72 min.

D. Éster terc- butilo del ácido (2S,4R)- 4- (terc- butil- dimetil- silaniloximetil)- 2- (3- cloro- 2- fluoro- bencil carbamoil)- 4- fluoro- pirrolidina- 1- carboxílico

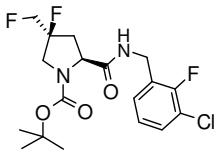
A una solución de éster terc- butilo del ácido (2S,4S)- 4- (terc- butil- dimetil- silaniloximetil)- 2- (3- cloro- 2- fluoro- bencil carbamoil)- 4- hidroxi- pirrolidina- 1- carboxílico (200 mg, 0,35 mmol) en CH_2Cl_2 (10 ml) bajo atmósfera de N_2 a- 78 º C se añadió DAST (92 µl, 0,7 mmol). La mezcla de reacción se dejó alcanzar la temperatura ambiente y se agitó adicionalmente durante 1.5 h, después se vertió en una solución acuosa saturada de $NaHCO_3$ y se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron para proporcionar el material deseado que se usó sin purificación adicional en la siguiente etapa. TLC, R_f (c- hexano/EtOAc 1:1) = 0,75; MS (LC/MS): 541.2/543.1 [M+Na]+, 463.1/465.1 [MH- tBu]+, 419.0/421.1 [MH- Boc]+;t_R(condiciones de HPLC f): 2,81 min.

E. Éster terc- butilo del ácido (2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- hidroximetil- pirrolidina- 1- carboxílico

Una solución de éster terc- butilo del ácido (2S,4S)- 4- (terc- butil- dimetil- silaniloximetil)- 2- (3- cloro- 2- fluoro- bencil carbamoil)- 4- hidroxi- pirrolidina- 1- carboxílico (180 mg, 0,34 mmol) en THF (1,5 ml) y TBAF (680 µl, 0,680 mmol, solución 1 M en THF) se agitó a temperatura ambiente bajo una atmósfera de nitrógeno durante 30 min. Después de la terminación de la reacción, la mezcla se vertió en agua y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se lavaron con agua, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El material crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (gradiente de c- hexano/EtOAc 1:1 a EtOAc) para proporcionar el material deseado. TLC, R_f (EtOAc) = 0,45; MS (LC- MS): 427,0 [M+Na]+, 349,0 [MH-

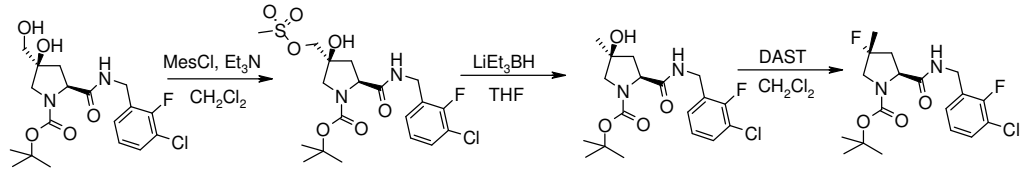
tBu]+, 305,0 [MH- Boc]+, 403.1/405.1 [M- H]- , 449,2/451,1 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,91 min.

Éster terc- butilo del ácido (2S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- fluorometil- pirrolidina- 1- carboxílico



A una solución de éster terc- butilo del ácido (2S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- hidroximetil- pirrolidina- 1- carboxílico (80 mg, 0,19 mmol) (preparado usando el mismo protocolo descrito en el Esquema B12 para éster terc- butilo del ácido (2S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- hidroximetil- pirrolidina- 1- carboxílico) en CH_2Cl_2 (5 ml) a- 78 °C bajo atmósfera de nitrógeno, se añadió DAST (50 µl, 0,375 mmol) y se dejó que la solución alcanzara la temperatura ambiente y se agitó durante 2 h. La mezcla de reacción se vertió en una solución acuosa saturada de $NaHCO_3$ y se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc gradiente2:1- 1:3) para proporcionar el material deseado. TLC, R_f (EtOAc) = 0,72; MS (LC- MS): 429.1/431.0 [M+Na]+, 351.0/353.0 [MH- tBu]- , 451.1/453.1 [M+HCOO]- ; t_R (condiciones de HPLC f): 2,14 min.

Esquema B13: preparación de éster terc- butilo del ácido (2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil- pirrolidina- 1- carboxílico



A. Éster terc- butilo del ácido (2S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- 4- metanosulfoniloxi- metil- pirrolidina- 1- carboxílico

A una solución de éster terc- butilo del ácido (2S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- 4- hidroximetil- pirrolidina- 1- carboxílico (3,53 g, 8,76 mmoles) (preparado como se describe en el Esquema B12) y Et_3N (1,46 ml, 10,5 mmol) en CH_2Cl_2 (90 ml) a 0 °C bajo atmósfera de nitrógeno, se añadió cloruro de metanosulfonilo (819 µl, 10,52 mmol) por goteo. La solución resultante se agitó a 0 º C durante 1,5 h y se apagó con una

solución acuosa saturada de $NaHCO_3$, se extrajo dos veces con CH_2Cl_2, se secó (Na_2SO_4), se filtró y se concentró. El material crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano a c- hexano/EtOAc 4:6) para proporcionar el material deseado. TLC, R_f (EtOAc) = 0,7, MS (UPLC/MS): 481.3/483.3 [M+H]+, 381.2/383.2 [MH- Boc]+, 425.2/427.2 [MH- tBu]+, 479.3/481.3 [M- H]- , 525.3/527.3 [M+HCOO]- ; t_R (condiciones de HPLC f): 2,04 min.

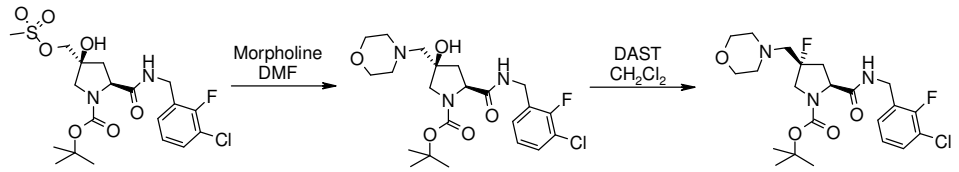
B. Éster terc- butilo del ácido (2S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- 4- metil- pirrolidina- 1- carboxílico

éster terc- butilo del ácido (2S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- 4- metanosulfoniloxi- metil- pirrolidina- 1- carboxílico (1 g, 2,08 mmol) se disolvió en THF (21 ml) bajo atmósfera de nitrógeno antes de la adición de trietilborohidruro de litio (1 M en THF, 20,8 ml, 20,8 mmol). La solución se agitó a temperatura ambiente durante 15 min, después se vertió en agua fría y se extrajo con EtOAc (x2). Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El material crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:1) para proporcionar el material deseado. TLC, R_f (EtOAc) = 0,7; MS (UPLC/MS): 387.3/389.3 [M+H]+, 409.3/411.3 [M+Na]+, 331.2/333.2 [MH- tBu]+, 287.2/289.2 [MH- Boc]+, 795.5/797.6 [2M+Na]+, 385.3/387.2 [M- H]- , 431.3/433.3 [M+HCOO]- .

C. Éster terc- butilo(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil- pirrolidina- 1- carboxílico

A una solución de éster terc- butilo del ácido (2S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- 4- metil- pirrolidina- 1- carboxílico (865 mg, 2,1 mmol) en CH_2Cl_2 (60 ml) bajo nitrógeno a- 78 º C se añadió DAST (550 µl, 4,16 mmol) y se dejó que la solución alcanzará lentamentela temperatura ambiente y se agitó durante 1 h. La mezcla de reacción se vertió en solución acuosa fría saturada de $NaHCO_3$ y se extrajo con CH_2Cl_2 (2 x). Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron para proporcionar el material deseado que se usó en la siguiente etapa sin purificación adicional. TLC, R_f (EtOAc) = 0,75; MS (UPLC/MS): 389.3/391.3 [M+H]+, 411.3/413.2 [M+Na]+, 333.2/335. [MH- tBu]+, 289.2/291.2 [MH- Boc]+, 387.2/389.4 [M- H]- , 433./435.2 [M+HCOO]- ; t_R (condiciones de HPLC f): 2,2 min.

Esquema B14: preparación de éster terc- butilo del ácido (2S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- morfolin- 4- ilmetilpirrolidino- 1- carboxílico



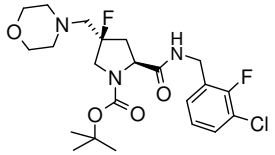
A. Éster terc- butilo del ácido (2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- 4- morfolin- 4- ilmetil- pirrolidino- 1- carboxílico

A una solución de éster terc- butilo del ácido (2S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- 4- metanosulfoniloxi- metil- pirrolidina- 1- carboxílico (200 mg, 0,416 mmol) (preparado como se B13 esquema descrito) en DMF (10 ml) se añadió morfolina (181 ml, 2,079 mmol) y la solución se agitó durante 16 horas a 80 °C. La mezcla de reacción se diluyó con EtOAc, se lavó con una solución acuosa saturada de $NaHCO_3$ (3 veces). Las capas orgánicas se secaron (Na_2SO_4), se filtraron y se concentraron. El material crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (CH_2Cl_2/MeOH 8:2) para proporcionar el material deseado. MS (LC/MS): 472.1/474.1 [M+H]+, 470.0/472.1 [M- H]- , t_R(condiciones de HPLC f): 1,58 min; 19F RMN (100 MHz, DMSO- d6) δ (ppm):- 120.

B. Éster terc- butilo del ácido (2S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- morfolin- 4- ilmetil- pirrolidina- 1- carboxílico

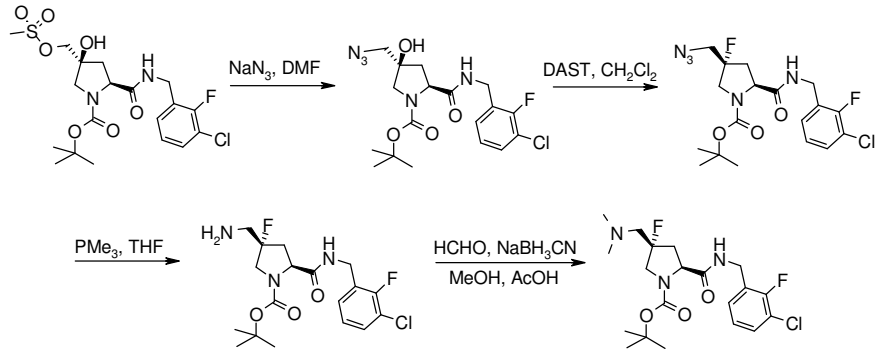
A una solución de éster terc- butilo del ácido (2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- 4- morfolin- 4- ilmetil- pirrolidino- 1- carboxílico (85 mg, 0,18 mmol) en CH_2Cl_2 (10 ml) bajo atmósfera de N_2 a - 78 º C se añadió DAST (47 µl, 0,359 mmol). Se dejó que la mezcla de reacción alcanzará la temperatura ambiente y se agitó adicionalmente durante 1,5 h, después se vertió en una solución acuosa saturada de $NaHCO_3$ y se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El material crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (CH_2Cl_2/MeOH 8:2) para proporcionar el material deseado. MS (LC/MS): 474.1/476.2 [M+H]+, 472,1 [M- H]- ;t_R(condiciones de HPLC f): 1,59 min.

Éster terc- butilo del ácido (2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- morfolin- 4- ilmetil- pirrolidino- 1- carboxílico



se obtuvo utilizando los mismos protocolos como se describe en el Esquema B14 para la preparación de éster terc- butilo del ácido (2S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- morfolin- 4- ilmetilpirrolidino- 1- carboxílicoa partir de éster terc- butilo del ácido (2S,4R)- 2- (3- cloro- 2- fluoro- bencil- carbamoil)- 4- hidroxi- 4- metanosulfoniloxi- pirrolidina- 1- carboxílico (preparado a partir de éster terc- butilo del ácido (2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- 4- hidroximetil- pirrolidina- 1- carboxílico en forma de esquema descrito B13). MS (LC/MS): 474.1/476.2 [M+H]+, 472,1 [M- H]- ; t_R (condiciones de HPLC f): 1,62 min.

Esquema B15: Éster terc- butilo del ácido (2S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- dimetilaminometil- 4- fluoro- pirrolidino- 1- carboxílico



A. Éster terc- butilo del ácido (2S,4S)- 4- azidometil- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- pirrolidina- 1- carboxílico

A una solución de éster terc- butilo del ácido (2S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- 4- metanosulfoniloxi- metil- pirrolidina- 1- carboxílico(580 mg, 1,21 mmol) (preparado como se describe en el esquema B13) en DMF (20 ml) se añadió azida de sodio (392 ml, 6,03 mmol) y la solución se agitó durante 16 horas a 80 °C. La mezcla de reacción se diluyó con EtOAc, se lavó con una solución acuosa saturada de $NaHCO_3$ (3 veces). Las capas orgánicas se secaron (Na_2SO_4), se filtraron y se concentraron. El material crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:1) para proporcionar el material deseado. MS (LC/MS): 430.1/432.1 [M+H]+, 374,1 [MH- tBu]+, 332 [MH- Boc]+; t_R (condiciones de HPLC f): 2,22 min.

B. Éster terc- butilo del ácido (2S,4R)- 4- azidometil- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico

A una solución de éster terc- butilo del ácido (2S,4S)- 4- azidometil- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- pirrolidina- 1- carboxílico (430 mg, 1,0 mmol) en CH_2Cl_2 (25 ml) bajo atmósfera de N_2 a - 78 º C se añadió DAST (266 µl, 2,01 mmol). La mezcla de reacción se dejó calentar hasta temperatura ambiente y se agitó adicionalmente durante 1,5 h. La mezcla de reacción se vertió en una solución acuosa saturada de $NaHCO_3$ y se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El material crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:1) para proporcionar el material deseado. MS (LC/MS): 474.1/476.2 [M+H]+, 472,1 [M- H]- , tr (condiciones de HPLC f): 2,23 min, 19F RMN (100 MHz, DMSO- d6) δ (ppm):- 120,- 150.

C. Éster terc- butilo del ácido (2S,4S)- 4- aminometil- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico

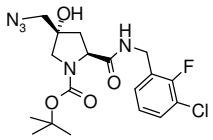
A una solución de éster terc- butilo del ácido (2S,4R)- 4- azidometil- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico (380 mg, 0,884 mmol) en THF (25 ml) bajo atmósfera de N_2 a temperatura ambiente se añadió 1M PMe_3 en THF (1,06 ml, 1,06 mmol). La mezcla de reacción se agitó durante 16 h, después se apagó con agua y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El material crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (CH_2Cl_2/MeOH 8:2) para proporcionar el material deseado. MS (LC/MS): 404/406 [M+H]+, 402 [M- H]- ; t_R (condiciones de HPLC f): 1,57 min, 19F RMN (100 MHz, DMSO- d_6) δ (ppm):- 120,- 154.

D. Éster terc- butilo del ácido (2S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- dimetilaminometil- 4- fluoro- pirrolidino- 1- carboxílico

A una solución de éster terc- butilo del ácido (2S,4S)- 4- aminometil- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico (245 mg, 0,607 mmol) en MeOH (2 ml) se añadió formaldehído (836 µl, 6,07 mmol), cianoborohidruro de sodio (126 mg, 2,0 mmol) y ácido acético (69,5 µl, 1,21 mmol). La mezcla de reacción se agitó durante 16 h a temperatura ambiente y después se concentró. El material crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (CH_2Cl_2/MeOH 8:2) para

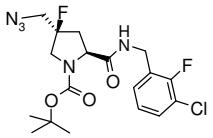
proporcionar el material deseado. MS (LC/MS): 432.1/434.1 [M+H]+, 430,1 [M- H]- , t_R(condiciones de HPLC f): 1,62 min, 19F RMN (100 MHz, DMSO- d_6) δ (ppm):- 121 ,- 149.

Éster terc- butilo del ácido (2S,4R)- 4- Azidometil- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- pirrolidina- 1- carboxílico



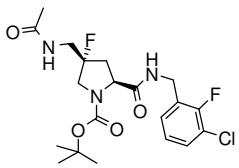
se obtuvo utilizando los mismos protocolos que se describen en el Esquema B15 Paso A para la preparación de éster terc- butilo del ácido (2S,4R)- 4- azidometil- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico a partir de éster terc- butilo del ácido (2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- 4- metanosulfoniloxi- metil- pirrolidina- 1- carboxílico (preparado a partir de éster terc- butilo del ácido (2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- 4- hidroximetil- pirrolidina- 1- carboxílico como se describe en el esquemaB13). MS (UPLC/MS): 450/452 [M+Na]+, 472/474 [M+HCOO]- ; t_R (condiciones de HPLC f): 2,08 min.

Éster terc- butilo del ácido (2S,4S)- 4- Azidometil- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico



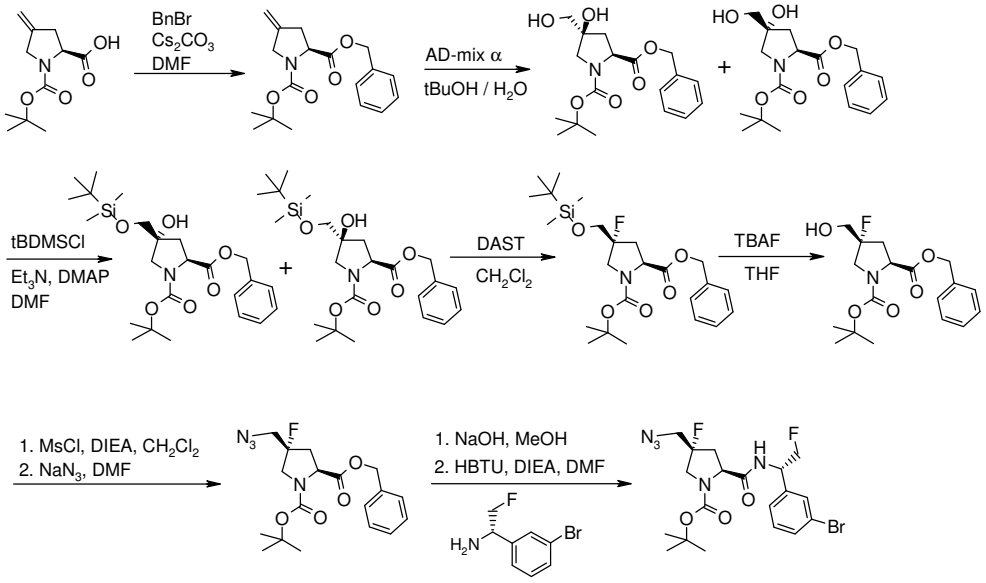
se obtuvo utilizando los mismos protocolos que se describen en el Esquema B15 paso A y B para la preparación de éster terc- butilo del ácido (2S,4R)- 4- azidometil- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico empezando a partir de terc- butilo del ácido (2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- 4- metanosulfoniloxi- metil- pirrolidina- 1- carboxílico (preparado a partir de éster terc- butilo del ácido (2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- 4- hidroximetil- pirrolidina- 1- carboxílico como se describe B13 esquema). MS (LC/MS): 474.1/476.2 [M+H]+, 472,1 [M- H]- , t_R(condiciones de HPLC f): 2,180 min, 19F RMN (100 MHz, DMSO- d_6) δ (ppm):- 120,- 150.

Éster terc- butilo del ácido (2S,4S)- 4- (acetilamino- metil)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidino- 1- carboxílico



A una solución de éster terc- butilo del ácido (2S,4S)- 4- aminometil- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico (179 mg, 0,51 mmol) en MeOH (5 ml) se añadió anhídrido acético (0,52 ml, 5,1 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 horas, después se apagó con NaOH 6N. Después de la extracción con CH_2Cl_2 (3 x 30 ml), las fases orgánicas se unieron y se secaron sobre Na_2SO_4, se filtraron y se concentraron. La purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:1).]. MS (UPLC/MS): 395 [M+H]+; t_R (condiciones de HPLC f): 2,02 min.

Esquema B16: preparación de éster terc- butilo del ácido (2S,4R)- 4- azidometil- 2- [(S)- 1- (3- bromo- fenil)- 2- fluoro- etilcarbamoil]- 4- fluoro- pirrolidino- 1- carboxílico



A. Éster 1- terc- butilo del ácido 2- bencílico (S)- 4- metileno- pirrolidina- 1,2- dicarboxílico

A ácido (S)- 1- (terc- butoxicarbonil)- 4- metilenopirrolidino- 2- carboxílico (4 g, 17,60 mmol) disuelto en DMF (100 ml) a 0 °C se añadió bromuro de bencilo (2,51 ml, 21,12 mmol) y carbonato de cesio (6,31 g, 19,36 mmol). La solución se agitó 16 h a temperatura ambiente y después se concentró.La purificación mediante cromatografía en columna ultrarrápida sobre gel

de sílice (c- hexano/EtOAc 1:1). MS (UPLC/MS): 218 [MH- tBu]+, t_R (condiciones de HPLC f): 2,44 min.

B. Éster 2- bencilo del ácido (2S,4S)- 4- hidroxi- 4- hidroximetil- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butiloy éster 2- bencilo del ácido (2S,4S)- 4- hidroxi- 4- hidroximetil- pirrolidina- 1- dicarboxílico- éster 1- terc- butilo

Una solución de mezcla AD- alfa (30 g, 21,43 mmol) en t- BuOH (120 ml) y agua (120 ml) se agitó hasta que ambas fases fueron claras y después se enfrió a 0 °C.Se añadió éster2- bencilo del ácido (S)- 4- metileno- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo (6,48 g, 20,42 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 16 h. La mezcla de reacción se apagó a 0 °C por adición de sulfito de sodio (14,5 g) y después se dejó que alcanzara la temperatura ambiente y se agitó durante 1 h. Después de la extracción con CH_2Cl_2 (3 x 100 ml), las fases orgánicas se unieron, se secaron con Na_2SO_4, se filtraron y se concentraron. La purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:1) dio los compuestos deseados como una mezcla inseparable. MS (UPLC/MS): 352 [M+H]+, t_R (condiciones de HPLC f): 1,50 min.

C. Éster 2- bencilo (2S,4R)- 4- (terc- butil- dimetil- silaniloximetil)- 4- hidroxi- pirrolidina- 1,2- dicarboxílico éster 1- terc- butiloy éster 2- bencilo(2S,4S)- 4 (terc- butil- dimetil- silaniloximetil)- 4- hidroxi- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo

A una solución de éster 2- bencilo del ácido (2S,4S)- 4- hidroxi- 4- hidroximetil- pirrolidina- 1,2- dicarboxílico- éster- 1- terc- butilo y éster 2- bencilo del ácido (2S,4S)- 4- hidroxi- 4- hidroximetil- pirrolidina- 1,2- dicarboxílico- éster- 1- terc- butilo (5,46 g, 15,54 mmol) en DMF (80 ml) se añadió terc- butilo de dimetilclorosilano (2,45 g, 16,32 mmol), trietilamina (2,16 ml, 15,54 mmol) y DMAP (0,19 g, 1,55 mmol). La solución se agitó durante 16 h a temperatura ambiente, luego se lavó con $NaHCO_3$ saturado (2 x 100 ml). La capa orgánica se secó con Na_2SO_4, se filtró y se concentró. La purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 9:1) dioéster 2- bencilo del ácido (2S,4R)- 4- (terc- butil- dimetil- silaniloximetil)- 4- hidroxi- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo: MS (UPLC/MS): 466 [M+H]+]+, 510 [M+HCOO]- ; t_R (condiciones de HPLC f): 2,83 min y éster 2- bencilo(2S,4S)- 4- (terc- butil- dimetil- silaniloximetil)- 4- hidroxi- pirrolidina- 1,2- dicarboxílico- éster1- terc- butilo: MS (UPLC/MS): 466 [M+H]+, 510 [M+HCOO]- ; t_R (condiciones de HPLC f): 2,95 min.

D. Éster 2- bencilo del ácido (2S,4R)- 4- (terc- butil- dimetil- silaniloximetil)- 4- fluoro- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo

A una solución de éster 2- bencilo del ácido (2S,4S)- 4- (terc- butil- dimetil- silaniloximetil)- 4- hidroxi- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo (5,20 g, 11,17 mmol) en CH_2Cl_2 (100 ml) a - 78 º C se añadió DAST (2,21 ml, 16,75 mmol). La solución se agitó durante 16 horas a temperatura ambiente, luego se lavó con $NaHCO_3$ saturado (2 x 100 ml). La capa orgánica se secó con Na_2SO_4, se filtró y se concentró. Purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 9:1). MS (UPLC/MS): 468 [M+H]+, 512 [M+HCOO]- ; t_R (condiciones de HPLC f): 3,00 min.

E. Éster 2- bencilo del ácido (2S,4R)- 4- fluoro- 4- hidroximetil- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo

A una solución de éster 2- bencilo del ácido (2S,4R)- 4- (terc- butil- dimetil- silaniloximetil)- 4- fluoro- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo (4,10 g, 8,77 mmol) en THF (80 ml) a temperatura ambiente se añadió TBAF 1M en THF (17,53 ml, 17,53 mmol). La reacción se agitó a temperatura ambiente durante 30 min y después se vertió en agua y se extrajo con EtOAc. La capa orgánica se secó con Na_2SO_4, se filtró y se concentró. Purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 03:02). MS (UPLC/MS): 354 [M+H]+, 398 [M+HCOO]- ; t_R (condiciones de HPLC f): 2,07 min.

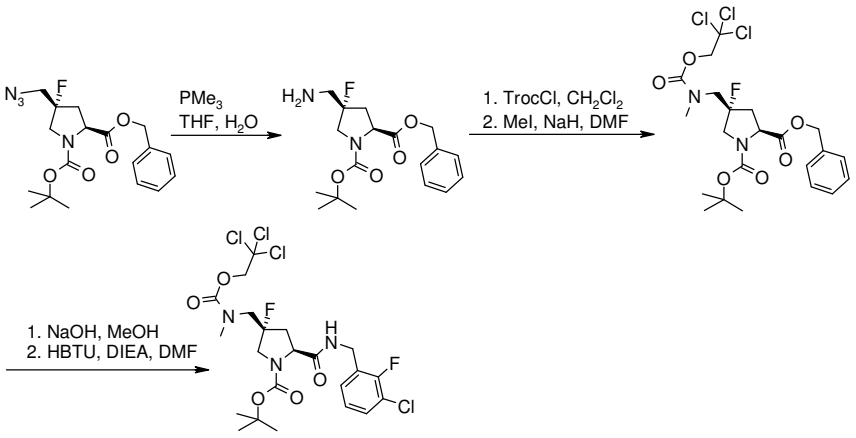
F. Éster 2- bencilo del ácido (2S,4R)- 4- azidometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico

A una solución de éster 2- bencilo del ácido (2S,4R)- 4- fluoro- 4- hidroximetil- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo (1,76 g, 4,98 mmol) en CH_2Cl_2 (30 ml) y unas gotas de NEt_3 se agitó a temperatura ambiente durante 10 min y después se agregó cloruro de metanosulfonilo (0,39 ml, 5,03 mmol). La reacción se agitó a temperatura ambiente durante 30 min y después se vertió en agua y se extrajo con EtOAc. La capa orgánica se secó con Na_2SO_4, se filtró y se concentró. El residuo (2,25 g, 4,21 mmol) se disolvió en DMF (50 ml) y se añadió azida de sodio (1,69 g, 26,1 mmol). La solución se agitó durante 16 horas a 80 °C y después se enfrió a temperatura ambiente, se vertió en agua y se extrajo con EtOAc. La capa orgánica se secó con Na_2SO_4, se filtró y se concentró. Purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:1). MS (UPLC/MS): 379 [M+H]+; t_R (condiciones de HPLC f): 2,44 min.

G. Éster terc- butilo del ácido (2S,4R)- 4- Azidometil- 2- [(S)- 1- (3- bromo- fenil)- 2- fluoro- etilcarbamoil]- 4- fluoro- pirrolidino- 1- carboxílico

A una solución de éster 2- bencilo del ácido (2S,4R)- 4- azidometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo (500 mg, 1,32 mmol) en metanol (20 ml), se añadió hidróxido de sodio 1M (2,64 ml, 2,64 mmol). La solución se agitó durante 2 horas a temperatura ambiente, luego se diluyó con agua, el metanol se eliminó a presión reducida. La capa acuosa se lavó con Et_2O (2 x 100 ml). La capa acuosa se acidificó hasta pH 3 con HCl 2N y se extrajo con EtOAc (2 x 100 ml), se secó con Na_2SO_4, se filtró y se concentró. Al residuo (100 mg, 0,34 mmoles), (S)- 1- (3- bromo- fenil)- 2- fluoro- etilamina (descrito en la Parte C) (83 mg, 0,38 mmol) y HBTU (197 mg, 0,52 mmol) en DMF (5 ml) se añadió DIPEA (0,12 ml, 0,69 mmol). La mezcla de reacción se agitó durante 16 h a temperatura ambiente, luego se vertió en agua y se extrajo con EtOAc. La capa orgánica se secó con Na_2SO_4, se filtró y se concentró. Purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (c-hexano/EtOAc 1:1). MS (UPLC/MS): 488 [M+H]+, 532 [M+HCOO]- ; t_R (condiciones de HPLC f): 2,32 min.

Esquema B17: preparación de éster 2- bencilo del ácido (2S,4S)- 4- fluoro- 4- {[metil- (2,2,2- tricloro- etoxicarbonil)- amino]- metil}- pirrolidino- 1,2- dicarboxílico- éster 1- terc- butilo



A. Éster 2- bencilo del ácido (2S,4S)- 4- aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo

Una solución de éster 2- bencilo del ácido (2S,4R)- 4- azidometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo (preparado como se describe en el Esquema B16) (1 g, 2,64 mmol), trimetilfosfina en THF (3,17 ml, 3,17 mmol) y agua (0,10 ml, 5,29 mmol) en THF

(40 ml) se agitó durante 16 h a temperatura ambiente. La mezcla de reacción se apagó con agua, se extrajo con EtOAc, se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. Purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (CH_2Cl_2/MeOH 9:1). MS (UPLC/MS): 353 [M+H]+, 411 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,62 min.

B. éster terc- butilo del ácido (2S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- {[metil- (2,2,2- tricloro- etoxicarbonil)- amino]- metil}- pirrolidino- 1- carboxílico

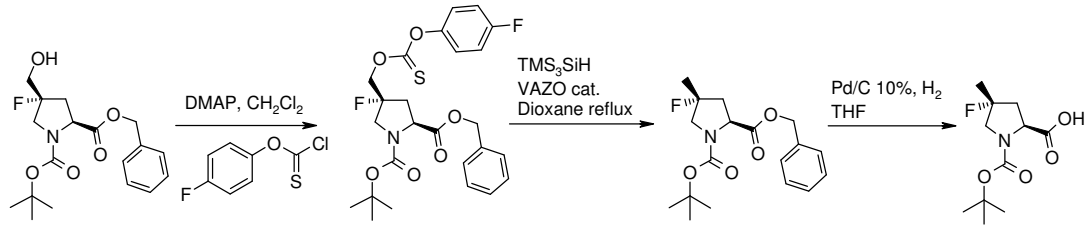
A una solución de éster 2- bencilo del ácido (2S,4S)- 4- aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo (100 mg, 0,28 mmol) en CH_2Cl_2 (10 ml) se añadió Troc- Cl (0,05 ml, 0,34 mmol). La mezcla de reacción se agitó durante 16 h a temperatura ambiente. La mezcla de reacción se apagó con agua, se extrajo con EtOAc, se lavó con salmuera, se secó sobre Na_2SO_4, se filtró, se concentró y se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:1). A una solución de éster2- bencilo del ácido (2S,4S)- 4- fluoro- 4- [(2,2,2- tricloro- etoxicarbonilamino)- metil]- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butil (50 mg, 0,09 mmol) y yoduro de metilo (0,02 ml, 0,28 mmol) en DMF (5 ml) a 0 º C se añadió hidruro de sodio (2,50 mg, 0,10 mmol) en porciones. La mezcla de reacción se agitó 90 min a 0 °C y 16 h a temperatura ambiente. La mezcla de reacción se apagó con agua, se extrajo con EtOAc, se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. Purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:1). MS (UPLC/MS): 541/543 [M+H]+, 586/587 [M+HCOO]- ; t_R (condiciones de HPLC f): 2,66 min.

C. Éster 2- bencilo del ácido (2S,4S)- 4- fluoro- 4- {[metil- (2,2,2- tricloro- etoxicarbonil)- amino]- metil}- pirrolidino- 1,2- dicarboxílico- éster 1- terc- butilo

A una solución de éster de terc- butilo del ácido (2S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- {[metil- (2,2,2- tricloro- etoxicarbonil)- amino]- metil}- pirrolidino- 1- carboxilic (110 mg, 0,20 mmol) en metanol (5 ml), se añadió hidróxido de sodio a 1 M(0,40 ml, 0,40 mmol). La solución se agitó durante 2 h a temperatura ambiente, luego se diluyó con agua, el metanol se eliminó bajo presión reducida. La capa acuosa se lavó con Et_2O (2 x 25 ml). La capa acuosa se acidificó hasta pH 3 con HCl 2N y se extrajo con EtOAc (2 x 25 ml), se secó con Na_2SO_4, se filtró y se concentró. Al residuo (80 mg, 0,17 mmol), (3- cloro- 2- fluorofenil) metanamina (33,9 mg, 0,21 mmol) y HBTU (101 mg, 0,26 mmol) disuelto en DMF (5 ml) se añadió DIPEA (0,06 ml, 0,35 mmol). La mezcla de reacción se agitó durante 16 h a

temperatura ambiente. La mezcla de reacción se apagó con agua, se extrajo con EtOAc, se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró.Purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:1). MS (UPLC/MS): 592/594 [M+H]+, 636/638 [M+HCOO]- ; t_R (condiciones de HPLC f): 2,49 min.

Esquema B18: preparación de éster 1- terc- butilo del ácido (R)- 4- fluoro- 4- metil- pirrolidina- 1,2- dicarboxílico



A. Éster 2- bencilo del ácido (2S,4R)- 4- fluoro- 4- (4- fluoro- fenoxitiocarboniloximetil)- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo

A una solución de éster 2- bencilo del ácido (2S,4R)- 4- fluoro- 4- hidroximetil- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo (síntesis descrita en el Esquema B16) (300 mg, 0,85 mmol) en CH_2Cl_2 (10 ml) se añadió formiato de cloro 4- fluorofeniltiono (0,18 ml, 1,27 mmol) y DMAP (311 mg, 2,55 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 días y luego se diluyó con CH_2Cl_2 (40 ml), se lavó con HCl acuoso 0,5 (50 ml), agua (50 ml) y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró.Purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 3:01) dio el compuesto deseado. MS (UPLC/MS): 508 [M+H]+; t_R (condiciones de HPLC f): 2,73 min.

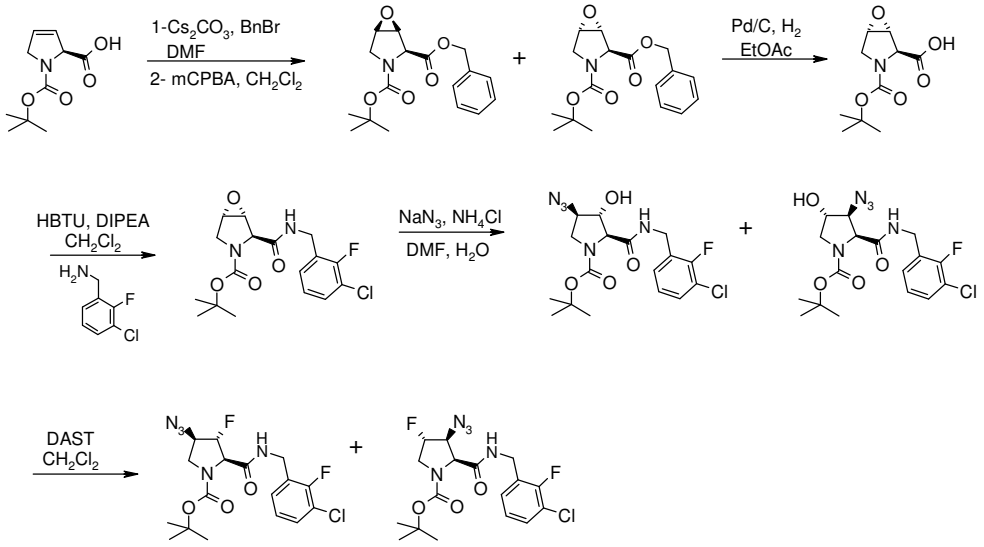
B. éster 2- bencilo del ácido (2S,4R)- 4- fluoro- 4- metil- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo

A una solución de éster 2- bencilo del ácido (2S,4R)- 4- fluoro- 4- (4- fluoro- fenoxitiocarboniloximetil)- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo (290 mg, 0,57 mmol) en dioxano (5 ml) se añadieron VAZO (69 mg, 0,28 mmoles) y tris(trimetilsilil)silano (0,24 ml, 0,77 mmol). La mezcla de reacción se calentó a reflujo durante 30 min y después se agitó durante 16 h a temperatura ambiente y se concentró. Purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 4:1). MS (UPLC/MS): 338 [M+H]+; t_R (condiciones de HPLC f): 2,38 min.

C. Éster 1- terc- butilo del ácido (2S,4R)- 4- fluoro- 4- metil- pirrolidina- 1,2- dicarboxílico

Una solución que contiene éster 2- bencilo del ácido (2S,4R)- 4- fluoro- 4- metil- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo (700 mg, 2,075 mmol) y Pd/C al 10% (221 mg, 2,075 mmol) en THF (6 ml) se colocó bajo una atmósfera de nitrógeno y se agitó durante 5 h. El catalizador se eliminó a través de una almohadilla de celita y se lavó con MeOH. Los solventes se eliminaron al vacío para proporcionar el material deseado como un aceite incoloro que se usó sin purificación adicional en la siguiente etapa. MS (UPLC/MS): 246,2 [M- H]- , 292,2 [M+HCOO-]- , 493,4 [2M- H]- .

<u>EsquemaB19: preparación de 3- cloro- 2- fluoro- bencilamida del ácido (2R,3R,4R)- 4- azido- 3- fluoro- pirrolidina- 2- carboxílico y3- cloro- 2- fluoro- bencilamidadel ácido (2S,3S,4S)- 3- azido- 4- fluoro- pirrolidina- 2- carboxílico</u>



A.Éster 2- bencilo del ácido (S)- 2,5- dihidro- pirrol- 1,2- dicarboxílico- éster 1- terc- butilo

A una solución de ácido (S)- 1- (terc- butoxicarbonil)- 2,5- dihidro- 1H- pirrol- 2- carboxílico (10 g, 46,9 mmol) en DMF (249 ml) enfriada a 0 º C se añadieron carbonato de cesio (16,8 g, 51,6 mmol) y después bromuro de bencilo (6,69 ml, 56,3 mmol) y la mezcla se dejó calentar a temperatura ambiente durante una noche. La mezcla de reacción se apagó con agua (500 ml) y se extrajo con acetato de etilo (3 x 200 ml). Las capas orgánicas se combinaron y se lavaron con salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano a c- hexano/EtOAc 4:1) para proporcionar el material deseado. TLC, R_f (c- hexano/EtOAc 4:1) = 0,25; MS (UPLC): 326 [M+Na]+, 204 [MH- Boc]+; t_R (condiciones de HPLC f): 2,35 min.

B. Éster 2- bencilo del ácido (1R,2S,5S)- 6- oxa- 3- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico- 3- terc- butilo y éster 2- bencilo del ácido (1S,2S,5R)- 6- oxa- 3- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico- éster 3- terc- butilo

A una solución de éster 2- bencilo del ácido (S)- 2,5- dihidro- pirrol- 1,2- dicarboxílico- éster 1- terc- butilo (6,14 g, 20,2 mmol) se añadió ácido 3- cloroperbenzoico (6,99 g, 40,5 mmol) y 4,4 'tiobis(6- terc- butil- m cresol) (0,726 g, 2,02 mmol). La mezcla se sometió a reflujo bajo atmósfera de nitrógeno durante la noche,luego, se añadió un lote adicional de ácido 3- cloroperbenzoico (6,99 g, 40,5 mmol) y 4,4'tiobis (6- terc- butil- m cresol) (0,726 g, 2,02 mmol). Se continuó el reflujo durante 24 h. La mezcla de reacción se diluyó con CH_2Cl_2, se lavó con solución acuosa de metabisulfito de sodio (5%), $NaHCO_3$ acuoso saturado, salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. Los epóxidos diastereoméricos en una proporción de 65/35 (determinado por RMN en la mezcla cruda) se separaron mediante cromatografía en columna ultrarrápida (c- hexano a c- hexano/EtOAc 4:1) para proporcionar éster 2- bencilo del ácido (1R,2S,5S)- 6- oxa- 3- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico- éster 3- terc- butilo: TLC, R_f (c- hexano/EtOAc 4:1) = 0,20; EM (LC/MS): 220 [MH- Boc]+, 342 [M+Na]+; t_R (condiciones de HPLC f): 2,14 min y éster 2- bencilo (1S,2S,5R)- 6- oxa- 3- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico- éster 3- terc- butilo: TLC, R_f (c- hexano/EtOAc 4:1) = 0,15; MS (LC/MS): 220 [MH- Boc]+, 342 [M+Na]+; t_R (condiciones de HPLC f): 2,03 min.

C. éster 3- terc- butilo del ácido (1R,2S,5S)- 6- oxa- 3- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico

Una solución de éster 2- bencilo del ácido (1R,2S,5S)- 6- oxa- 3- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico- éster 3- terc- butilo(2,62 g, 8,21 mmol) en acetato de etilo (32 ml) se hidrogenó bajo atmósfera de H_2 con hidróxido de paladio sobre carbono (1,15 g, 8,21 mmol) durante 1 noche. La mezcla de reacción se filtró sobre un filtro de fibra de vidrio, se apagó con una solución de Na_2CO_3 acuoso saturado y se extrajo dos veces con EtOAc. La capa acuosa se acidificó con HCl 1 N a pH = 2 y se extrajo 4 veces con acetato de etilo, se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró para proporcionar el material deseado que se usó en la siguiente etapa sin purificación adicional. MS (UPLC): 230 [M+H]+, 228 [M- H]- .

D. Éster terc- butilo del ácido (1R,2S,5S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 6- oxa- 3- aza- biciclo[3.1.0]hexano- 3- carboxílico

A una mezcla de éster 3- terc- butilo del ácido (1R,2S,5S)- 6- oxa- 3- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico (1,55 g, 6,79 mmol), (3- cloro- 2- fluoro)bencilamina (1,63 g, 10,19 mmol) y HBTU (3,86 g, 10,2 mmol) en CH_2Cl_2 (17 ml) se añadió diisopropiletilamina (1,78 ml, 10,19 mmol). La solución resultante se agitó durante la noche a temperatura ambiente bajo atmósfera de nitrógeno después se vertió en una solución acuosa saturada de $NaHCO_3$ y se extrajo con CH_2Cl_2 (x3). Las capas orgánicas se combinaron, se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano a c- hexano/EtOAc 1:1). TLC, R_f (EtOAc) = 0,65; MS (UPLC): 371 [M+H]+, 271 [MH- Boc]+; t_R (condiciones de HPLC f): 2,04 min.

E. Éster terc- butilo del ácido (2S,3R,4R)- 4- Azido- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- hidroxi- pirrolidina- 1- carboxílicoy Éster terc- butilo del ácido (2S,3S,4S)- 3- Azido- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- pirrolidina- 1- carboxílico

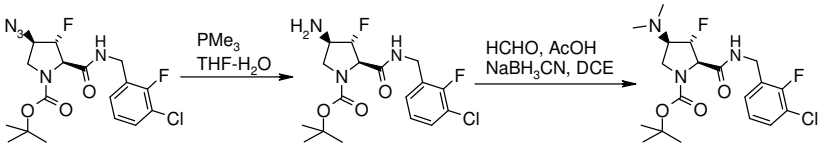
Una solución de éster terc- butilo del ácido (1R,2S,5S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 6- oxa- 3- aza- biciclo[3.1.0]hexano- 3- carboxílico(2,3 g, 5,95 mmol), azida de sodio (2,32 g, 35,7 mmol) y NH_4Cl (0,637 g, 11,9 mmol) en DMF (23 ml) con H_2O (3,22 ml, 179 mmol) se calentó a 100 °C durante 1 h. La mezcla de reacción se vertió en hielo, se extrajo con CH_2Cl_2, se lavó con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano a c- hexano/EtOAc 1:01) para proporcionar una mezcla de regioisómeros inseparableséster tert- butilo del ácido (2S,3R,4R)- 4- azido- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- hidroxi- pirrolidina- 1- carboxílico y éster terc- butilo del ácido (2S,3S,4S)- 3- azido- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- pirrolidina- 1- carboxílico en una proporción de 3:2 (estereoquímica absoluta se asignó mediante RMN). TLC, R_f (c- hexano/EtOAc 1:1) = 0,3; MS (UPLC): 414 [M+H]+, 315 [MH- Boc]+, 412 [M- H]- ; t_R (condiciones de HPLC f): 2,06 min.

F. éster terc- butilo del ácido (2R,3R,4R)- 4- Azido- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- fluoro- pirrolidina- 1- carboxílico y éster tert- butilo del ácido

(2S,3S,4S)- 3- Azido- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico

A una solución de éster tert- butilo del ácido (2S,3R,4R)- 4- azido- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- hidroxi- pirrolidina- 1- carboxílico y éstertert- butilo del ácido (2S,3S,4S)- 3- azido- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- pirrolidina- 1- carboxílico(proporción de 3/2, 1,14 g, 2,75 mmol) en CH_2Cl_2 (55 ml) se añadió DAST (1,456 ml, 11,02 mmol) a - 78 °C y la mezcla de reacción se agitó durante la noche a temperatura ambiente. La mezcla de reacción se apagó cuidadosamente con una solución acuosa saturada de $NaHCO_3$, se extrajo con CH_2Cl_2, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano a c- hexano/EtOAc 9:01) para proporcionar una mezcla de los dos regioisómeros, que se separaron mediante HPLC preparativa (C18 Sunfire Prep- ODB, 5 micras, 30X100 mm, 30% de CH3CN/H2O 1,5 min, 30- 100% en CH_3CN/H_2O 58,5 min, CH_3CN/H_2O que contienen 0,1% de TFA, flujo: 20 ml/min) para proporcionar después de la liofilización de las fracciones purificadas: éster terc- butilo del ácido (2R,3R,4R)- 4- azido- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- fluoro- pirrolidina- 1- carboxílico; TLC, R_f (c- hexano/EtOAc 4:1) = 0,23; MS (LC/MS): 416 [M+H]+, 316 [MH- Boc]+; 414 [M- H]- , t_R (condiciones de HPLC h): 3,11 min y éster terc- butilo del ácido (2S,3S,4S)- 3- azido- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico; R_f (c- hexano/EtOAc 4:1) = 0,13; MS (LC/MS): 416 [M+H]+, 316 [MH- Boc]+; 414 [M- H]- ; t_R (condiciones de HPLC h): 3,02 min.

<u>Esquema B20: preparación de éster terc- butilo del ácido (2R,3S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- dimetilamino- 3- fluoro- pirrolidina- 1- carboxílico</u>



A. éster terc- butilo del ácido (2R,3S,4R)- 4- amino- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- fluoro- pirrolidina- 1- carboxílico

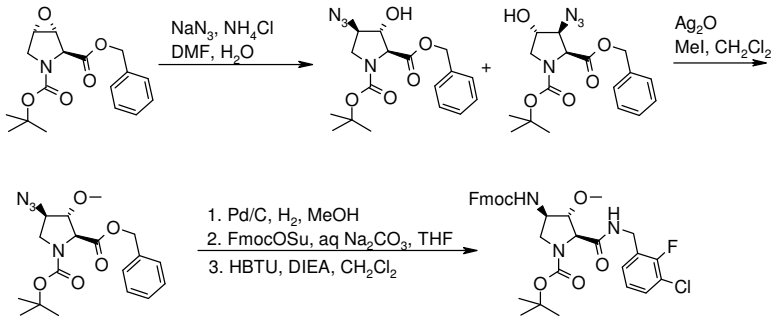
Una solución de éster terc- butilo del ácido (2R,3R,4R)- 4- azido- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- fluoro- pirrolidina- 1- carboxílico (descrito en el Esquema B19) (485 mg, 1,16 mmol), trimetilfosfina en THF (2,33 ml, 2,33 mmol) y agua (0,04 ml, 2,33 mmol) en THF (20 ml) se agitó durante 16 h a temperatura ambiente. La mezcla de reacción se apagó con agua y se extrajo dos veces con EtOAc. La fase orgánica se lavó con salmuera, se

secó sobreNa_2SO_4, se filtró y se concentró.Purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (CH_2Cl_2/MeOH 95:5). MS (UPLC/MS): 390/392 [M+H]+, 434/436 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,64 min.

B. Éster terc- butilo del ácido (2R,3S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- dimetilamino- 3- fluoro- pirrolidina- 1- carboxílico

A una solución de éster terc- butilo del ácido (2R,3S,4R)- 4- amino- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- fluoro- pirrolidina- 1- carboxílico (190 mg, 0,48 mmol) en MeOH (2 ml) se agregó formaldehído (134 µl, 4,87 mmol). La mezcla de reacción se agitó 30 min a temperatura ambiente antes de la adición de cianoborohidruro de sodio (101 mg, 1,60 mmol) y ácido acético (56 µl, 0,97 mmol). Después de agitar durante 30 min, la solución se concentró. Purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (c-hexano/EtOAc 1:01) dio el compuesto deseado. MS (UPLC/MS): 418/420 [M+H]+, 462/464 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,61 min.

Esquema B21: preparación de éster 9H- fluoren- 9- ilmetil del ácido [(3R,4S,5S)- 1- terc-Butilcarbamoil- 5- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- metoxi- pirrolidin- 3- il]-carbámico



A. éster terc- butilo del ácido (2S,3R,4R)- 4- Azido- 2- bencilcarbamoil- 3- hidroxi- pirrolidina- 1- carboxílico y éster terc- butilo del ácido (2S,3S,4S)- 3- azido- 2- bencilcarbamoil- 4- hidroxi- pirrolidina- 1- carboxílico

Una solución de éster 2- bencilo del ácido (1R,2S,5S)- 6- oxa- 3- aza-biciclo[3.1.0]hexano- 2,3- dicarboxílico- éster 3- terc- butilo (descrito en el Esquema B19) (5,43 g, 11,90 mmol), azida de sodio (4,64 g, 71,4 mmol) y NH_4Cl (1,27 g, 23,80 mmol) en DMF (74 ml) con H_2O (6,43 ml, 357 mmol) se calentó a 100 °C durante 1 h. La mezcla de reacción se vertió en hielo, se extrajo con CH_2Cl_2 (3 x 250 ml), se lavó con agua y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró.Purificación mediante cromatografía en columna

ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:1) dio los compuestos deseados como una mezcla inseparable. MS (UPLC/MS): 307 [MH- tBu]+, 407 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,04 min.

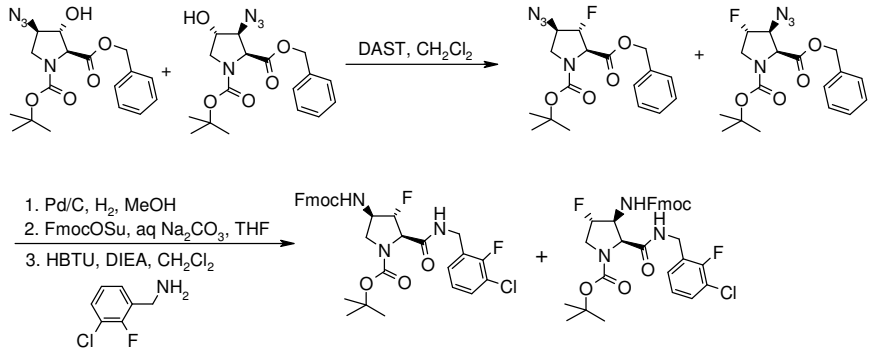
B. Éster 2- bencilo del ácido (2S,3R,4R)- 4- azido- 3- metoxi- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo

Una solución de éster terc- butilo del ácido (2S,3R,4R)- 4- azido- 2- bencilcarbamoil- 3- hidroxi- pirrolidina- 1- carboxílico y éster terc- butilo del ácido (2S,3S,4S)- 3- azido- 2- bencilcarbamoil- 4- hidroxi- pirrolidina- 1- carboxílico (517 mg, 1,42 mmol) en CH_2Cl_2 (10 ml), óxido de plata (1,32 g, 5,71 mmol) y yoduro de metilo (0,35 ml, 5,71 mmol) se calentó en un tubo sellado durante 1 semana a 40 °C en la oscuridad. La mezcla de reacción se filtró sobre una almohadilla de celite y se concentró. Purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 4:1) dio sólo éster 2- bencilo del ácido (2S,3R,4R)- 4- azido- 3- metoxi- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo. MS (UPLC/MS): 321 [MH- tBu]+, 421 [M+HCOO]- ; t_R (condiciones de HPLC f): 2,40 min.

C. éster terc- butilo del ácido (2S,3S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- (9H- fluoren- 9- ilmetoxicarbonilamino)- 3- metoxi- pirrolidina- 1- carboxílico

Una solución de éster 2- bencilo del ácido (2S,3R,4R)- 4- azido- 3- metoxi- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo (440 mg, 1,16 mmol) en metanol (3 ml) se hidrogenó con paladio sobre carbono al 10% (124 mg, 1,16 mmoles) durante la noche. La mezcla de reacción se filtró sobre un filtro de fibra de vidrio, se lavó con metanol y se evaporó al vacío. El residuo se disolvió en THF (2 ml) y se agregó una solución de Na_2CO_3 acuoso al 10% (3,09 ml, 1,11 mmol). La mezcla de reacción se enfrió a 0 ºC y después se añadió y se agitó durante 2 h a temperatura ambiente FmocOSu disuelto en THF (7 ml). La mezcla de reacción se concentró a vacío para dejar un residuo que se disolvió en EtOAc (10 ml) y se trató con solución acuosa saturada. Una solución de NH_4Cl. La mezcla se extrajo con EtOAc (3 x 20 ml) y se recogieron las capas orgánicas, se secaron sobre $MgSO_4$, se filtraron y se concentraron. El residuo se disolvió en DMF (3 ml), después se agregaron 3- cloro- 2- fluoro bencilamina (267 mg, 1,67 mmol) y HBTU (526 mg, 1,38 mmol), DIPEA (292 µl, 1,67 mmol). La solución de color naranja resultante se agitó durante la noche a temperatura ambiente. Purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 3:2) proporcionó el compuesto del título. MS (UPLC/MS): 624/626 [M+H]+, 668/670 [M+HCOO]- ; t_R (condiciones de HPLC f): 2,65 min.

Esquema B22: preparación de éster terc- butilo del ácido (2R,3S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- (9H- fluoren- 9- ilmetoxicarbonilamino)- 3- fluoro- pirrolidino- 1- carboxílico y éster terc- butilo del ácido (2S,3S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- (9H- fluoren- 9- ilmetoxicarbonilamino)- 4- fluoro- pirrolidino- 1- carboxílico



A. Éster 2- bencilo del ácido (2R,3R,4R)- 4- azido- 3- fluoro- pirrolidina- 1,2- dicarboxílico- éster1- terc- butilo y éster 2- bencilo del ácido (2S,3S,4S)- 3- azido- 4- fluoro- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo

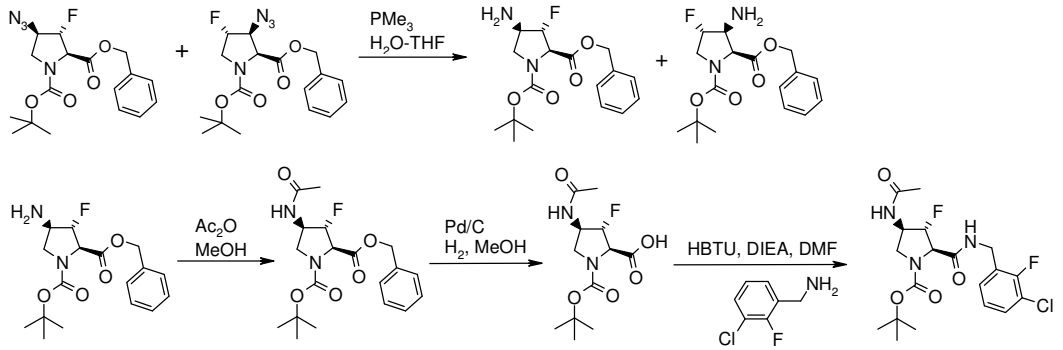
Una solución de éster 2- bencilo del ácido (2S,3R,4R)- 4- azido- 3- hidroxi- pirrolidina- 1,2- dicarboxílico- éster1- terc- butilo y éster 2- bencilo(2S,3S,4S)- 3- azido- 4- hidroxi- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo (descrito en el Esquema B21) (3,95 g, 10 mmol) en CH_2Cl_2 (100 ml) se enfrió bajo argón a - 78 °C luego se añadió DAST (6,62 ml). La mezcla de reacción se agitó durante 16 h a temperatura ambiente, se apagó cuidadosamente con solución saturada acuosa de $NaHCO_3$ (100 ml) y se agitó durante 30 min a 0 °C, se extrajo dos veces con CH_2Cl_2, se secó sobre Na_2SO_4, se filtró y se concentró. Purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:1). MS (UPLC/MS): 365 [M+H]+; t_R (condiciones de HPLC f): 2,40 min.

B. Éster terc- butilo del ácido (2R,3S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- (9H- fluoren- 9- ilmetoxi- carbonilamino)- 3- fluoro- pirrolidina- 1- carboxílico y éster terc- butilo del ácido (2S,3S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- (9H- fluoren- 9- ilmetoxicarbonilamino)- 4- fluoro- pirrolidino- 1- carboxílico

Una solución de éster 2- bencilo del ácido (2R,3R,4R)- 4- azido- 3- fluoro- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo y éster 2- bencilo del ácido (2S,3S,4S)- 3- azido- 4-

fluoro- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo (2,78 g, 7,63 mmol) en metanol (25 ml) se hidrogenó con paladio sobre carbono al 10% (812 mg, 0,76 mmoles) durante la noche. La mezcla de reacción se filtró sobre un filtro de fibra de vidrio, se lavó con metanol y se concentró. Se disolvieron 200 mg (0,084 mmoles) del residuo en THF (2 ml) y una solución acuosa de Na_2CO_3 al 10% (1 ml, 1 mmol) se añadió. La mezcla de reacción se enfrió a 0 º C y despuésse añadióFmocOSu (284 mg, 0,084 mmol) disuelto en THF (7 ml) y se agitó durante 2 h a temperatura ambiente. La mezcla de reacción se concentró al vacío para proporcionar un residuo que se disolvió en EtOAc (10 ml) y se trató con una solución de NH_4Cl acuoso saturado. La mezcla se extrajo con EtOAc (3 x 20 ml) y las capas orgánicasse recogieron, se secaron sobre $MgSO_4$, se filtraron y se concentraron. El residuo se disolvió en DMF (3 ml), después se añadieron 3- cloro- 2 fluoro- bencilamina (192 mg, 1,2 mmol) y HBTU (456 mg, 1,2 mmol), DIPEA (210 µl, 1,2 mmol). La solución resultante se agitó durante la noche a temperatura ambiente. Purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 4:1). MS (UPLC/MS): 612/614 [M+H]+, 656/658 [M+HCOO]- ; t_R (condiciones de HPLC f): 0.75/0.76 min.

Esquema B23: preparación de éster terc- butilo del ácido (2R,3S,4R)- 4- acetilamino- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- fluoro- pirrolidina- 1- carboxílico y éster terc- butilo del ácido (2S,3S,4S)- 3- acetilamino- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico



A. Éster 2- bencilo terc- butilo del ácido (2S,3S,4S)- 3- amino- 4- fluoro- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo y éster 2- bencilo del ácido (2R,3S,4R)- 4- amino- 3- fluoro- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo

Una mezcla de éster terc- butilo del ácido (2R,3R,4R)- 4- azido- 2- bencilcarbamoil- 3- fluoro- pirrolidina- 1- carboxílico y éster terc- butilo del ácido (2S,3S,4S)- 3- azido- 2- bencilcarbamoil- 4- fluoro- pirrolidina- 1- carboxílico (3,52 g, 8,98 mmol) (descrito en el

Esquema B22), trimetilfosfina en THF (17,97 ml, 17,97 mmol) y agua (0,32 ml, 17,97 mmol) en THF (100 ml) se agitó durante 16 h a temperatura ambiente. La mezcla de reacción se apagó con agua y se extrajo dos veces con EtOAc. Las fases orgánicas se unieron, se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron.Purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:1) dio éster 2- bencilo del ácido (2S,3S,4S)- 3- amino- 4- fluoro- pirrolidina- 1,2- dicarboxílico- éster1- terc- butilo: MS (UPLC/MS): 339 [M+H]+; t_R(condiciones de HPLC f): 1,59 min y éster 2- bencilo del ácido (2R,3S,4R)- 4- amino- 3- fluoro- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo: MS (UPLC/MS): 339 [M+H]+; t_R (condiciones de HPLC f): 1,62 min.

B. éster 2- bencilo del ácido (2R,3S,4R)- 4- acetilamino- 3- fluoro- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo

A una solución de éster 2- bencilo del ácido (2S,3S,4S)- 3- amino- 4- fluoro- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo (762 mg, 2,25 mmol) en metanol (20 ml)se añadió acético anhídrido (3,19 ml, 33,8 mmol) bajo atmósfera de argón. La mezcla de reacción se agitó durante 16 h a temperatura ambiente. Después de la concentración, el residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 3:1). MS (UPLC/MS): 381 [M+H]+, 281 [MH- Boc]- ; t_R (condiciones de HPLC f): 2,00 min.

C. Éster 1- terc- butilo del ácido (2R,3S,4R)- 4- acetilamino- 3- fluoro- pirrolidina- 1,2- dicarboxílico

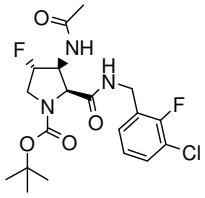
Una solución de éster 2- bencilo del ácido (2R,3S,4R)- 4- acetilamino- 3- fluoro- pirrolidina- 1,2- dicarboxílico- éster1- terc- butilo (315 mg, 0,82 mmol) en metanol (2 ml) se hidrogenó con paladio sobre carbono al 10% (88 mg, 0,82 mmoles) durante la noche. La mezcla de reacción se filtró a través de fibra de vidrio y se concentró. El residuo se utilizó como estaba para la siguiente etapa.

D. Éster terc- butilo del ácido (2R,3S,4R)- 4- acetilamino- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- fluoro- pirrolidina- 1- carboxílico

A una mezcla de éster 1- terc- butilo del ácido (2R,3S,4R)- 4- acetilamino- 3- fluoro- pirrolidina- 1,2- dicarboxílico (245 mg, 0,84 mmol), (3- cloro- 2- fluoro)bencilamina (202 mg, 1,26 mmol) y HBTU (480 mg, 1,26 mmol) en DMF (7,5 ml) se añadió DIPEA (0,22 ml, 1,26 mmol). La solución resultante se agitó durante la noche a temperatura ambiente. La mezcla de reacción se vertió en $NaHCO_3$acuoso saturado y se extrajo con CH_2Cl_2 (3 X 20 ml). Las fases

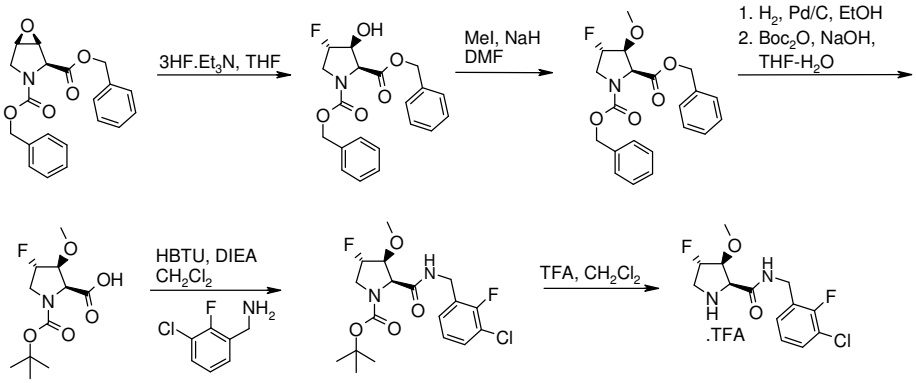
orgánicas se unieron, se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. Purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:1). MS (UPLC/MS): 376 [MH- tBu]+, 476 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,93 min.

Éster terc- butilo del ácido (2S,3S,4S)- 3- acetilamino- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico



El compuesto del título se preparó de una manera similar como se describe anteriormente a partir de éster2- bencilo del ácido (2R,3S,4R)- 4- amino- 3- fluoro- pirrolidina- 1,2- dicarboxílico- éster 1- terc- butilo. MS (UPLC/MS): 432 [M+H]+, 476 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,96 min.

<u>Esquema B24: preparación de3- cloro- 2- fluoro- bencilamida trifluoroacetato del ácido (2S,3S,4S)- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico</u>



A. éster dibencilo del ácido (2S,3S,4S)- 4- fluoro- 3- hidroxi- pirrolidina- 1,2- dicarboxílico

A una solución de éster dibencilo del ácido (1S,2S,5R)- 6- oxa- 3- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico (preparado como se describe en el esquema B19, 4 g, 11,3 mmol) en THF (3 ml) se añadió 3HF.Et_3N (18,5 ml, 113 mmol). La mezcla de reacción se calentó a 130 °C (6x40 minutos) y luego se vertió en una solución saturada de Na_2CO_3 y se agitó durante 30 min. La mezcla se extrajo con EtOAc (2 x 100 ml), las fases orgánicas se unieron, se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c-

hexano/EtOAc 7:03) para proporcionar una mezcla que contiene éster dibencilo del ácido (2S,3S,4S)- 4- fluoro- 3- hidroxi- pirrolidina- 1,2- dicarboxílico como el principal isómero. MS (UPLC): 374 [M+H]+; t_R (condiciones de HPLC f): 2,13 min.

B. dibencilo del ácido (2S,3S,4S)- 4- fluoro- 3- metoxi- pirrolidina- 1,2- dicarboxílico

A una solución de éster dibencilo del ácido (2S,3S,4S)- 4- fluoro- 3- hidroxi- pirrolidina- 1,2- dicarboxílico (531 mg, 1,42 mmoles) se enfrió con un baño de hielo y bajo atmósfera de argón se le añadió NaH (en aceite mineral al 60%, 62 mg, 1,52 mmol). La mezcla de reacción se agitó durante 30 min y después se agregóMeI (0,26 ml, 4,27 mmol). La mezcla de reacción se agitó durante 30 min y después se apagó con agua. Después de la extracción con EtOAc (2 x 25 ml), las fases orgánicas se unieron, se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano a c- hexano/EtOAc 07:03). MS (UPLC): 388 [M+H]+; t_R (condiciones de HPLC f): 2,36 min.

C. Éster 1- terc- butilo del ácido (2S,3S,4S)- 4- fluoro- 3- metoxi- pirrolidina- 1,2- dicarboxílico

A una solución de éster dibencílico del ácido (2S,3S,4S)- 4- fluoro- 3- metoxi- pirrolidina- 1,2- dicarboxílico (430 mg, 1,11 mmol) en MeOH (25 ml) se añadió Pd/C al 10% (100 mg). La reacción se colocó bajo atmósfera de hidrógeno y se agitó durante 2 h, después se filtró a través de fibra de vidrio, se enjuagó con MeOH (25 ml) y agua (25 ml). Después de la concentración, el residuo se liofilizó durante la noche. El polvo obtenido se disolvió en THF/agua 1/1 (20 ml) y después se agregó 1N NaOH acuoso (0,755 ml) y anhídrido de Boc (412 mg, 2,22 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante la noche. Después de la concentración, el residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:1+0,5% de AcOH). MS (UPLC): 264 [M+H]+; t_R (condiciones de HPLC f): 0,65 min.

D. Éster terc- butilo del ácido (2S,3S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 3- metoxi- pirrolidina- 1- carboxílico

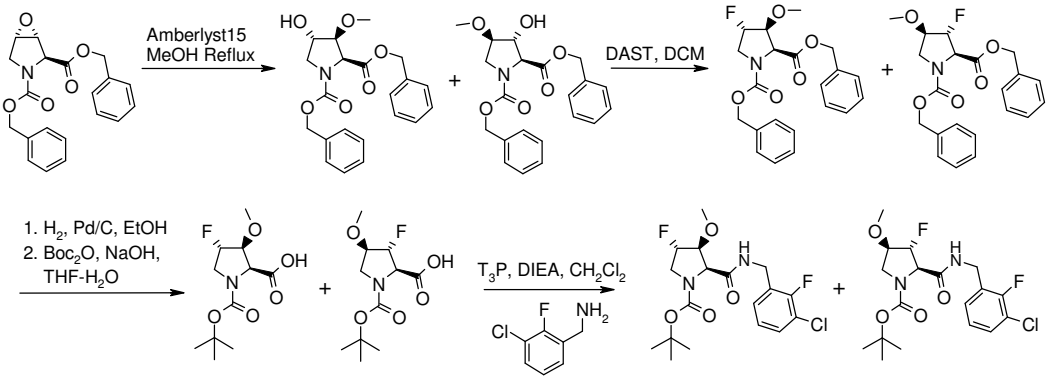
A una solución de éster 1- terc- butilo del ácido (2S,3S,4S)- 4- fluoro- 3- metoxi- pirrolidina- 1,2- dicarboxílico (500 mg, 1,90 mmol) en DMF (20 ml) se añadieron 3- cloro- 2- fluoro- bencilamina (330 mg, 2,1 mmol), HBTU (1,4 g, 3,8 mmol) y DIPEA (1,32 ml, 7,6 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h, después se vertió en

agua (50 ml). Después de la extracción con EtOAc (3 x 30 ml), las fases orgánicas se unieron, se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano a c- hexano/EtOAc 1:1) para proporcionar éster terc- butilo del ácido (2S,3S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 3- metoxi- pirrolidina- 1- carboxílico: R_f, TLC (c- hexano/EtOAc 1:1) = 0,37; MS (UPLC): 405.1/407.2 [M+H]+, 349.1/351.1 [MH- tBu]+, 449.2/451.2 [M+HCOO]- ; t_R (condiciones de HPLC f): 2,12 min. 1H RMN (400 MHz, DMSO- d_6) δ (ppm): 8,59 (m, 1H), 7,48 (m, 1H), 7,37 (m, 1H), 7,20 (m, 1H), 5,20 (d anc, 1H), 4,47- 4,26 (m, 3H), 4,19 (ddd, 1H), 3,81- 3,65 (m, 1H), 3,54- 3,40 (m, 1H), 3,36 (s, 3H), 1,42 y 1,27 (2 s, 9H).

E. 3- cloro- 2- fluoro- bencilamida trifluoroacetato del ácido (2S,3S,4S)- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico

Se agregó TFA (0,86 ml, 11,12 mmol) a una solución de éster terc- butilo del ácido (2S,3S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 3- metoxi- pirrolidina- 1- carboxílico (450 mg, 1,12 mmol) en CH_2Cl_2 (20 ml). La mezcla de reacción se agitó durante una noche y después se concentró. El residuo se trituró con Et_2O (10 ml) para proporcionar un precipitado que se separó por filtración, se lavó con Et_2O (10 ml) después se secó a alto vacío. La estereoquímica absoluta se confirma por rayos- X. t_R(condiciones de HPLC f): 0,40 min; MS (UPLC): 349 [M+HCOO]- , 305 [M+H]+.

<u>Esquema B25: Alternativo para la preparación de éster terc- butilo del ácido (2S,3S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 3- metoxi- pirrolidina- 1- carboxílico</u>



A. Éster dibencilo del ácido (2S,3S,4S)- 4- hidroxi- 3- metoxi- pirrolidina- 1,2- dicarboxílico y éster dibencilo del ácido (2S,3R,4R)- 3- hidroxi- 4- metoxi- pirrolidina- 1, 2- dicarboxílico

A una solución de éster dibencilo del ácido (1R,2S,5S)- 6- oxa- 3- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico (preparado como se describeen el esquemaB19, 30 g, 85 mmol) en MeOH (150 ml) se añadió Amberlyst 15 (30 g). La mezcla de reacción se calentó durante la noche a 65 °C, después se dejó enfriar a temperatura ambiente y se filtró. Amberlyst 15 residuo se lavó con MeOH. Los filtrados combinados se combinaron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano 100% a EtOAc 100%) para proporcionar una mezcla de los 2 regioisómeros como un aceite de color amarillo. R_f, TLC (c- hexano/EtOAc 1:1) = 0,5; MS (UPLC): 386,2 [M+H]+, 430,2 [M+HCOO]- ; t_R (condiciones de HPLC a): 1,93 min.

B. Éster dibencilo del ácido (2S,3S,4S)- 4- fluoro- 3- metoxi- pirrolidina- 1,2- dicarboxílico y éster dibencilo del ácido (2R,3R,4R)- 3- fluoro- 4- metoxi- pirrolidina- 1, 2- dicarboxílico

Una solución de éster dibencilo del ácido (2S,3S,4S)- 4- hidroxi- 3- metoxi- pirrolidina- 1,2- dicarboxílicoy éster dibencilo del ácido (2S,3R,4R)- 3- hidroxi- 4- metoxi- pirrolidina- 1,2- dicarboxílico (17,8 g, 46,2 mmol) en CH_2Cl_2 (250 ml) se enfrió bajo argón a - 78 °C y después se añadió DAST (12,2 ml, 92 mmol) por goteo. Se dejó que la mezcla de reacción alcanzará la temperatura ambiente y se agitó adicionalmente durante 16 h. La mezcla de reacción se diluyó con CH_2Cl_2 y se apagó cuidadosamente con solución saturada acuosade $NaHCO_3$. Las capas se separaron, la capa acuosa se extrajo dos veces con CH_2Cl_2, las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. Purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 100:0 a 0:100) dio una mezcla de los2 regioisómeros como un sólido de color amarillo. MS (UPLC/MS): 388,3 [M+H]+, 405,3 [M+NH4]+; t_R (condiciones de HPLC f): 2,34 min.

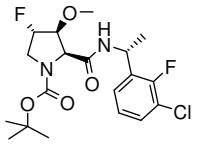
C. éster 1- terc- butilo del ácido (2S,3S,4S)- 4- fluoro- 3- metoxi- pirrolidina- 1,2- dicarboxílicoy 1- terc- butilo del ácido (2R,3R,4R)- 3- fluoro- 4- metoxi- pirrolidina- 1,2- dicarboxílico

se obtuvo en forma de una mezcla utilizando el protocolo descrito en el Esquema B24 paso C. R_f, TLC (EtOAc) = 0,1.

D. Éster terc- butilo del ácido (2S,3S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 3- metoxi- pirrolidina- 1- carboxílico y éster terc- butilo del ácido (2R,3R,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- fluoro- 4- metoxi- pirrolidina- 1- carboxílico.

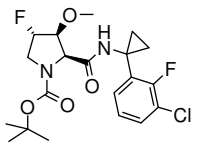
A una solución de éster 1- terc- butilo del ácido (2S,3S,4S)- 4- fluoro- 3- metoxi- pirrolidina- 1,2- dicarboxílico y éster 1- terc- butilo del ácido (2R,3R,4R)- 3- fluoro- 4- metoxi- pirrolidina- 1,2- dicarboxílico (1,55 g, 5,89 mmol) en CH_2Cl_2 (50 ml) se añadieron 3- cloro- 2- fluoro- bencilamina (1,03 g, 6,48 mmol), propilfosfónico anhídrido (50% en EtOAc, 5,20 ml, 8,83 mmol) y DIPEA (3,08 ml, 17,7 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h y se concentró. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 7:3) para proporcionar éster terc- butilo del ácido (2S,3S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 3- metoxi- pirrolidina- 1- carboxílico: R_f, TLC (c- hexano/EtOAc 1:1) = 0,35; MS (UPLC): 405.1/407.2 [M+H]+, 349.1/351.1 [MH- tBu]+, 449.2/451.2 [M+HCOO]- ; t_R (condiciones de HPLC f): 2,12 min y éster tert- butilo del ácido (2R,3R,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- fluoro- 4- metoxi- pirrolidina- 1- carboxílico: R_f, TLC (c- hexano/EtOAc 1:1) = 0,5; MS (UPLC): 405.1/407.2 [M+H]+, 349,0/351,1 [MH- tBu]+, 449.2/451.2 [M+HCOO]- ; t_R (condiciones de HPLC f): 2,20 min.

éster terc- butilo del ácido (2S,3S,4S)- 2- [(R)- 1- (3- cloro- 2- fluoro- fenil)- etilcarbamoil]- 4- fluoro- 3- metoxi- pirrolidino- 1- carboxílico



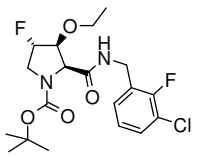
Se preparó de acuerdo con los mismos protocolos descritos en el Esquema B25 usando (R)- 1- (3- cloro- 2- fluoro- fenil)- etilamina en el Paso D. La separación de dos regioisómeros se realizó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 6:4) para proporcionar éster terc- butilo del ácido ((2S,3S,4S)- 2- [(R)- 1- (3- cloro- 2- fluoro- fenil)- etilcarbamoil]- 4- fluoro- 3- metoxi- pirrolidino- 1- carboxílico. MS (UPLC): 405/407 [M+H]+; t_R (condiciones de HPLC f): 2,14 min.

Éster terc- butilo del ácido (2S,3S,4S)- 2- [1- (3- cloro- 2- fluoro- fenil)- ciclopropilcarbamoil]- 4- fluoro- 3- methoxi- pirrolidino- 1- carboxílico



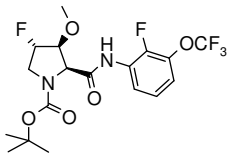
Se preparó de acuerdo con los mismos protocolos descritos en el Esquema B25 usando 1- (3- cloro- 2- fluoro- fenil)- ciclopropilamina en el Paso D. 1- (3- cloro- 2- fluoro- fenil)- ciclopropilamina se preparó como se describe en la Parte C. La separación de dos regioisómeros se realizó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:1) para proporcionar éster terc- butilo del ácido (2S,3S,4S)- 2- [1- (3- cloro- 2- fluoro- fenil)- ciclopropilcarbamoil]- 4- fluoro- 3- metoxi- pirrolidino- 1- carboxílico. MS (UPLC): 431/433 [M+H]+; t_R (condiciones de HPLC f): 2,21 min.

Éster terc- butilo del ácido (2S,3S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- etoxi- 4- fluoro- pirrolidina- 1- carboxílico



Se preparó de acuerdo con los mismos protocolos descritos en el Esquema B25 utilizando EtOH en lugar de MeOH en el paso A. La separación de dos regioisómeros se realizó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 6:4) para proporcionar éster terc- butilo del ácido (2S,3S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- etoxi- 4- fluoro- pirrolidina- 1- carboxílico. MS (UPLC): 419/421 [M+H]+; t_R (condiciones de HPLC f): 2,23 min.

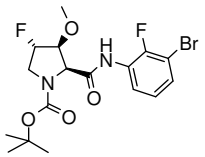
Éster terc- butilo del ácido (2S,3S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- etoxi- 4- fluoro- pirrolidino- 1- carboxílico



A una solución de éster 1- terc- butilo del ácido (2S,3S,4S)- 4- fluoro- 3- metoxi- pirrolidina- 1,2- dicarboxílico y éster 1- terc- butilo del ácido (2R,3R,4R)- 3- fluoro- 4- metoxi- pirrolidina- 1,2- dicarboxílico (preparado como se describe en el Esquema B25, 1,00 g, 3,80 mmol) en CH_2Cl_2 (10 ml) a 0 °C bajo atmósfera de nitrógeno se añadió 1- cloro- N,N,2- trimetilprop- 1- en- 1- amina (609 mg, 4,56 mmol) y la mezcla se agitó a esta temperatura durante 1 h. Luego, se añadió 2- fluoro- 3- (trifluorometoxi)anilina (0,815 mg, 4,18 mmol), seguido de DIPEA (1,327 ml, 7,60 mmol) y la mezcla se agitó a temperatura ambiente durante 1 h. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de

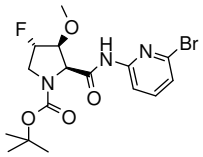
sílice (c- hexano/EtOAc 01:00- 1:1) para proporcionar éster terc- butilo del ácido (2S,3S,4S)- 4- fluoro- 2- (2- fluoro- 3- trifluorometoxi- fenilcarbamoil)- 3- metoxi- pirrolidino- 1- carboxílico. 1H RMN (400 MHz, DMSO- d_6) mezcla 2:1 de rotámeros δ (ppm): 10,15 (m, 1H), 7,87 (m, 1/3H), 7,77 (m, 2/3H), 7,31 (m, 2H), 5.29- 5.11 (m, 1H), 4,76 (d, 1/3H), 4,70 (d, 2/3H), 4,29 (m, 1H), 3,80- 3,53 (m, 2H), 3,39 (m, 3H), 1,39 (s, 3H), 1,31 (s, 6H). MS (UPLC-MS): 441 [M+H]+; t_R (condiciones de HPLC f): 2,14 min.

éster terc- butilo del ácido (2S,3S,4S)- 2- (3- bromo- 2- fluoro- fenilcarbamoil)- 4- fluoro- 3- metoxi- pirrolidina- 1- carboxílico



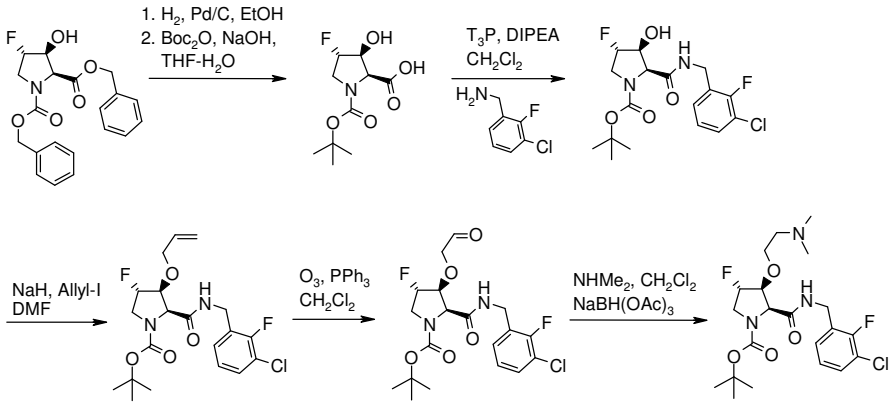
A una solución de éster 1- terc- butilo del ácido (2S,3S,4S)- 4- fluoro- 3- metoxi- pirrolidina- 1,2- dicarboxílico y éster 1- terc- butilo del ácido (2R,3R,4R)- 3- fluoro- 4- metoxi- pirrolidina- 1,2- dicarboxílico (preparado como se describe en el Esquema B25, 100 mg, 0,380 mmol) en CH_2Cl_2 (2,4 ml) a 0 °C bajo atmósfera de nitrógeno se añadió 1- cloro- N,N,2- trimetilprop- 1- en- 1- amina (50,8 mg, 0,38 mmol) y la mezcla se agitó a esta temperatura durante 2 h. A continuación se añadió 3- bromo- 2- fluoroanilina (144 mg, 0,76 mmol), seguido de DIPEA (0,265 ml, 1,52 mmol) y la mezcla se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se concentró y el residuo en bruto se purificó mediante HPLC preparativa (Waters Sunfire C18- ODB, 5µm, 30x100mm, eluyente: 0- 0,5 min 5% de CH_3CN en H_2O, Flujo: 5ml/min, 0,5- 18,5 min 5 a 100% CH3CN/H2O flujo: 40mL/min, 18,5 a 20 min 100% CH_3CN, CH_3CN y H_2O que contiene tanto TFA al 0,1%). Las fracciones purificadas de HPLC se neutralizaron mediante la adición de una solución acuosa saturada de Na_2CO_3, la capa se separó y la capa acuosa se extrajo con CH_2Cl_2 (x2). Los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron. Sólido blanco. R_f, TLC (c- hexano/EtOAc 1:1) = 0,75; MS (UPLC): 435.1/437.1 [M+H]+, 433.1/435.1 [M- H]- ; t_R (condiciones de HPLC f): 2,06 min.

Éster terc- butilo del ácido (2S,3S,4S)- 2- (6- bromo- piridin- 2- ilcarbamoil)- 4- fluoro- 3- metoxi- pirrolidina- 1- carboxílico



Se preparó de acuerdo con los mismos protocolos descritos para la síntesis de éster terc-butilo del ácido (2S,3S,4S)- 2- (3- bromo- 2- fluoro- fenilcarbamoil)- 4- fluoro- 3- metoxi-pirrolidina- 1- carboxílico.Sólido blanco. R_f, TLC (EtOAc) = 0,8; 418.1/420.1 [M+H]+, 416.2/418.1 [M- H]- , t_R(condiciones de HPLC f): 2,0 min.

Esquema B26: Preparación de éster terc- butilo del ácido (2S,3S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- (2- dimetilamino- etoxi)- 4- fluoro- pirrolidino- 1- carboxílico



A. Éster1- terc- butilo del ácido (2S,3S,4S)- 4- fluoro- 3- hidroxi- pirrolidina- 1,2- dicarboxílico

A una solución de éster dibencílico del ácido (2S,3S,4S)- 4- fluoro- 3- hidroxi-pirrolidina- 1,2- dicarboxílico (390 mg, 1,04 mmol) en MeOH (10 ml) se añadió Pd/C al 10% (39 mg). La reacción se colocó bajo atmósfera de hidrógeno y se agitó durante 2 h, después se filtró a través de fibra de vidrio y se enjuagó con agua. Después de la concentración, el residuo se disolvió en NaOH acuoso THF/agua 2/1 (30 ml), (1 N, 2,09 ml, 2,09 mmol) y anhídrido de Boc (456 mg, 2,09 mmol) se añadió y la mezcla de reacción se agitó 16 h a temperatura ambiente. Se eliminó el THF a presión reducida y la capa acuosa se extrajo con Et_2O (x2), se acidificó mediante la adición de $KHSO_4$ (10% en agua) y se extrajo con EtOAc (x2). Los extractos de EtOAc combinados se secaron (Na_2SO_4), se filtraron y se concentraron. El material así obtenido se usó en la siguiente etapa sin purificación adicional.

B. Éster terc- butilo del ácido (2S,3S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 3- hidroxi- pirrolidina- 1- carboxílico

A una solución de éster 1- terc- butilo(2S,3S,4S)- 4- fluoro- 3- hidroxi- pirrolidina- 1,2- dicarboxílico (195 g, 0,782 mmol) en CH_2Cl_2 (10 ml) se añadieron 3- cloro- 2- fluoro- bencilamina (150 mg, 0,94 mmol), anhídrido propilfosfónico (50% en EtOAc, 0,346 ml, 1,17 mmol) y DIPEA (0,41 ml, 2,35 mmol). La mezcla de reacción se agitó 1 h a temperatura ambiente, después se apagó mediante la adición de una solución acuosa saturada de $NaHCO_3$ y se extrajo con CH_2Cl_2 (x2). Los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:1). MS (UPLC): 391.3/393.1 [M+H]+, 435.4/437.4 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,95 min.

C. Éster terc- butilo del ácido (2S,3S,4S)- 3- aliloxi- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico

A una solución de NaH (en aceite mineral al 60%, 8,6 mg, 0,215 mmol) en DMF (5 ml) enfriada con un baño de hielo y bajo atmósfera de argón se le añadió éster terc- butilo del ácido (2S,3S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 3- hidroxi- pirrolidina- 1- carboxílico (70 mg, 0,179 mmol). La mezcla de reacción se agitó durante 20 min antes de la adición de yoduro de alilo (0,025 ml, 0,269 mmol) a 0 °C. La mezcla de reacción se agitó durante 30 min y después se apagó por adición de agua y se extrajo con EtOAc (x2). Los extractos orgánicos se combinaron, se lavaron con salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 3:2). MS (UPLC): 431.4/433.1 [M+H]+, 475.5/577.5 [M+HCOO]- ; t_R (condiciones de HPLC f): 2,29 min.

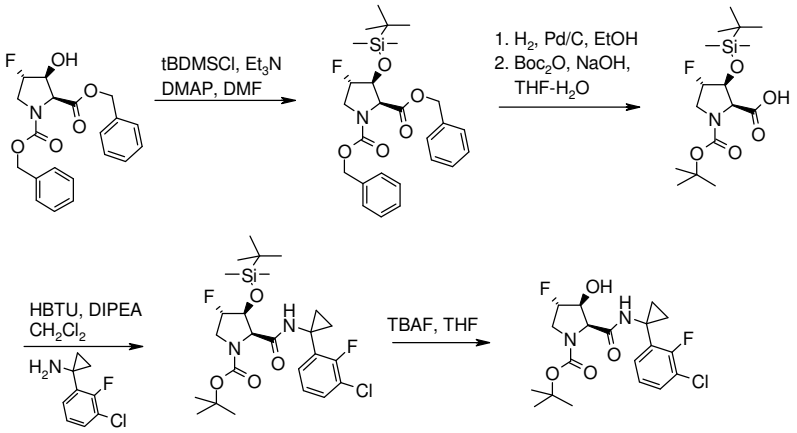
D. Éster terc- butilo del ácido (2S,3S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 3- (2- oxo- etoxi)- pirrolidina- 1- carboxílico

Se burbujeó ozono a través de una solución de éster terc- butilo del ácido (2S,3S,4S)- 3- aliloxi- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico (59 mg , 0,137 mmol) en CH_2Cl_2 (20 ml) a - 78 °C. Cuando la solución se volvió azul, la adición de ozono se detuvo y se hizo pasar nitrógeno a través de la solución hasta que se descargó el color azul. Se añadió trifenilfosfina (35,9 mg, 0,137 mmol) se añadió a la solución ozónido a - 78 °C y la mezcla de reacción se dejó alcanzar lentamente RT. La mezcla de reacción se concentró y el material así obtenido se utilizó sin purificación adicional en la siguiente etapa. MS (UPLC): 433.4/435.4 [M+H]+, 477.4/579.5 [M+HCOO]- .

E. Éster terc- butilo del ácido (2S,3S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- (2- dimetilamino- etoxi)- 4- fluoro- pirrolidino- 1- carboxílico

A una solución del material crudo obtenido en el paso anterior y dimetilamina (2 N en MeOH, 173 µl, 0,347 mmol) en MeOH (3 ml) a 25 °C se añadieron sucesivamente AcOH (100 l) y triacetoxiborohidruro de sodio (73,5 mg , 0,347 mmol). La mezcla de reacción se agitó 2 h y se concentró. El residuo crudo se purificó mediante HPLC preparativa ((Waters Sunfire, C18-ODB, 5 micras, 30x100 mm, 5- 100% CH_3CN/H_2O/20 min, 100% de CH_3CN/2 min, CH3CN y H_2O que contiene 0.1% de TFA, flujo : 40 ml/min) MS (UPLC): 462.4/464.4 [M+H]+, 506.5/508.5 [M+HCOO]- ; t_R (condiciones UPLC m): 0.70 min.

<u>Esquema B27: Preparación de éster terc- butilo del ácido (2S,3S,4S)- 2- [1- (3- cloro- 2- fluoro- fenil)- ciclopropilcarbamoil]- 4- fluoro- 3- hidroxi- pirrolidino- 1- carboxílico</u>



A. Éster dibencilo del ácido (2S,3S,4S)- 3- (terc- butil- dimetil- silaniloxi)- 4- fluoro- pirrolidina- 1,2- dicarboxílico

A una solución de éster dibencilo del ácido (2S,3S,4S)- 4- fluoro- 3- hidroxi- pirrolidina- 1,2- dicarboxílico (1,90 g, 5,09 mmol) en DMF (40 ml) se añadió terc-butildimetilclorosilano (0.844 g, 5,60 mmol), trietilamina (0,709 ml, 5,09 mmol) y DMAP (0,062 g, 0,509 mmol). La mezcla de reacción se agitó 25 °C durante 1 semana. A continuación, se apagó mediante la adición de una solución acuosa saturada de $NaHCO_3$. Las capas se separaron y el extracto orgánico se secó (Na_2SO_4), se filtró y se concentró. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c-hexano/EtOAc 9:1). MS (UPLC): 588,4 [M+H]+, 505,5 [M+NH4]+, 510,4 [M+Na]+; t_R (condiciones de HPLC f): 2,90 min.

B. Éster 1- terc- butilo del ácido (2S,3S,4S)- 3- (terc- butil- dimetil- silaniloxi)- 4- fluoro- pirrolidina- 1,2- dicarboxílico

Se preparó a partir de éster de dibencilo del ácido (2S,3S,4S)- 3- (terc- butil- dimetil- silaniloxi)- 4- fluoro- pirrolidina- 1,2- dicarboxílico de acuerdo con el protocolo descrito en el Esquema B26 paso A. t_R (condiciones UPLC m): 1,21 min.

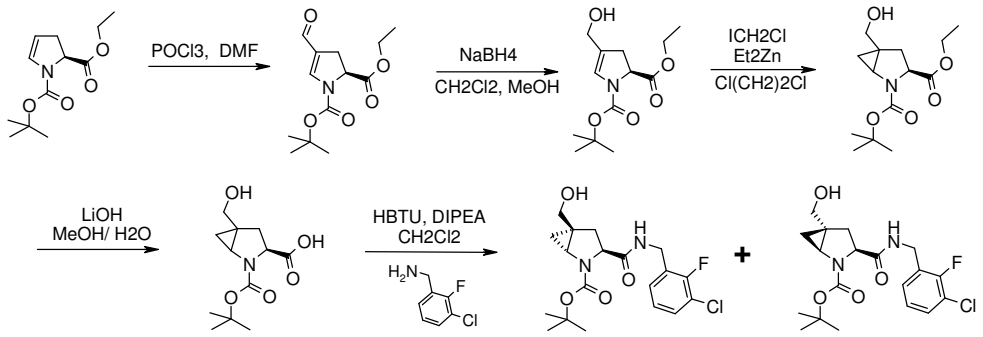
C. (2S,3S,4S)- 3- (terc- butil- dimetil- silaniloxi)- 2- [1- (3- cloro- 2- fluoro- fenil)- ciclopropil carbamoil]- 4- fluoro- pirrolidina- 1- carboxílico éster terc- butilo del ácido

A una solución de éster 1- terc- butilo del ácido (2S,3S,4S)- 3- (terc- butil- dimetil- silaniloxi)- 4- fluoro- pirrolidina- 1,2- dicarboxílico (300 mg, 0,825 mmol), 1- (3- cloro- 2- fluoro- fenil)- ciclopropilamina (preparada como se describe en la Parte C, 272 mg, 0,908 mmol) y HBTU (376 mg, 0,99 mmol) en DMF (10 ml) se añadió DIPEA (0,432 ml , 2,476 mmol) bajo atmósfera de nitrógeno. La mezcla de reacción se agitó 2 horas a 25 °C. A continuación, se apagó mediante la adición de una solución acuosa saturada de $NaHCO_3$ y se extrajo con EtOAc (x2). Los extractos orgánicos combinados fueron se secó (Na_2SO_4), se filtró y se concentró. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc1: 1). MS (UPLC): 531.5/533.5 [M+H]+, 505,5 [M+NH4]+, 510,4 [M+Na]+; t_R (UPLC condiciones m): 1,55 min.

Éster terc- butilo del ácido (2S,3S,4S)- 2- [1- (3- cloro- 2- fluoro- fenil)- ciclopropilcarbamoil]- 4- fluoro- 3- hidroxi- pirrolidino- 1- carboxílico

Se añadió TBAF (1 N en THF, 0,547 ml, 0,547 mmol) a una solución de (2S,3S,4S)- 3- éster tert- butilo del ácido (terc- butil- dimetil- silaniloxi)- 2- [1- (3- cloro- 2- fluoro- fenil)- ciclopropil carbamoil]- 4- fluoro- pirrolidina- 1- carboxílico (242 mg, 0,456 mmol) en THF (10 ml) y la mezcla de reacción se agitó 30 min a 25 °C. A continuación, se vertió en agua, se extrajo con EtOAc (x2), se secó (Na_2SO_4), se filtró y se concentró. El material así obtenido se utilizó sin purificación adicional en la siguiente etapa. MS (UPLC): 417.5/419.5 [M+H]+, 461.5/463.5 [M+HCOO]- ; t_R (condiciones de HPLC f): 2,04 min.

<u>Esquema B28: Preparación de éster terc- butílo del ácido (1R, 3S, 5S) y (1S, 3S, 5R) - 3 - (3- cloro- 2- fluoro- bencilcarbamoil)- 5- hidroximetil- 2- aza- biciclo [3.1.0] hexano- 2- carboxílico</u>



A. Éster 1- terc- butílo del ácido (S)- 4- formil- 2,3- dihidro- pirrol- 1,2- dicarboxílico - éster 2- etilo

Se agregó POCl3 (7,59 ml, 83 mmol) en 25 min a 0 °C bajo atmósfera de N_2 a DMF (6,39 ml, 83 mmol) y la mezcla se agitó a temperatura ambiente durante 20 min. Se agregó CH_2Cl_2 seco (150 ml) a 0 ° C, seguido de una solución de éster 1- terc- butilo del ácido (S) - 2,3- dihidro- pirrol- 1 ,2- dicarboxilato éster 2- etilo (10 g, 41,4 mmoles) en CH_2Cl_2 (50 ml). La mezcla se agitó 30 min a temperatura ambiente hasta la finalización. La mezcla se vertió lentamente en una solución acuosa helada de NaOH 10 N (150 mL) y se extrajo con CH_2Cl_2 (x3). Los extractos orgánicos combinados se lavaron con salmuera (x2), con agua, se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano a c- hexano/EtOAc 09:01) para proporcionar el material deseado como un aceite de color amarillo. R_f, TLC (c- hexano/EtOAc 04:01) = 0,2; EM (UPLC- MS): 270 [M+H]+, 170 [M- Boc] - ; tR (condiciones HPLC f): 1,93 min.

B. Éster 1- terc- butilo del ácido (S)- 4- hidroximetil- 2 ,3- dihidro- pirrol- 1 ,2- dicarboxílico éster - 2- etilo

Se enfrió una solución de éster 1- terc- butilo del ácido (S)- 4- formil- 2 ,3- dihidro- pirrol- 1 ,2- dicarboxílico éster 2- etilo (3,32 g, 12,3 mmol) en CH_2Cl_2 (51,4 ml) a - 78 º C bajo atmósfera de nitrógeno, se agregó $NaBH_4$ sólido (1 g, 24,7 mmol) en porciones manteniendo la temperatura a - 78 ° C. Se agregó MeOH (25,7 ml) por goteo y la mezcla de reacción se dejó llegar a 0 °C y se agitó durante 1h30 a 0 ° C. La reacción se apagó con una solución acuosa saturada de NH_4Cl y se extrajo con CH_2Cl_2 (x3). Las capas orgánicas combinadas se lavaron con salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano a c- hexano/EtOAc 01:01 a EtOAc) para proporcionar el material deseado como un aceite de color

amarillo. R_f, TLC (c- hexano/EtOAc 01:01) = 0,30; EM (UPLC- MS): 272,2 [M+H]+, 316 [M + HCOO] - ; t_R (condiciones HPLC f): 1,74 min.

C. Éster 2- terc- butilo del ácido (1R, 3S, 5S) y (1S, 3S, 5R)- 5- hidroximetil- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico éster 3- etílico

A una solución de éster 1- terc- butilo del ácido (S)- 4- hidroximetil- 2 ,3- dihidro- pirrol- 1 ,2- dicarboxílico éster 2- etilo (1,12 g, 4,13 mmol) en CH_2Cl_2 (115 ml) bajo atmósfera de argón a - 20 °C se agregó lentamente dietilzinc (1 M en hexanos, 8,26 ml, 8,26 mmol) y diyodometano (0,73 ml, 9,08 mmol) y la mezcla de reacción se agitó adicionalmente a - 10 °C durante 2 h. Se añadieron de nuevo dietilzinc (1 M en hexanos, 8,26 ml, 8,26 mmol) y diyodometano (0,73 ml, 9,08 mmol) y la mezcla de reacción se agitó adicionalmente a - 10 °C durante 2 h para completar la reacción. Se agregó lentamente una solución acuosa saturada de NH_4Cl (exotérmica) a - 20 °C seguido de CH_2Cl_2. Las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (x2). A las capas orgánicas combinadas se añadieron algunos cristales de Na_2S y agua (relación de CH_2Cl_2/H_2O 20:1) y la mezcla bifásica se agitó durante 30 min. Se agregó agua, se separaron las capas, se secaron (Na_2SO_4), se filtraron y se concentraron para proporcionar una mezcla de diastereoisómeros. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:01) para proporcionar una mezcla de diastereoisómeros (04:6 (1R, 3S, 5S) / (1S, 3S, 5R)). La estereoquímica absoluta de los diastereoisómeros se determinó por RMN. R_f, TLC (c- hexano/EtOAc 01:01) = 0,25; MS (UPLC- MS): 186,1 [MH- Boc] +, 230,2 [MH- tBu] +, 286,3 [MH + H] +, 308,2 [MH + Na] +, 330,3 [M + HCOO] - ; tR (condiciones HPLC f): 1,75 min.

Alternativamente se preparó éster 2- terc- butilo del ácido (1R, 3S, 5S) y (1S, 3S, 5R)- 5- hidroximetil- 2- aza- biciclo[3.1.0] hexano- 2 ,3- dicarboxílico éster - 3- etilo de acuerdo con el procedimiento siguiente derivado a partir de J. Amer. Chem.. Soc., 1998, 120, 46, 11943.

A una solución de DME seco (198 µl, 1,91 mmol) en CH_2Cl_2 seco (4 ml) bajo atmósfera de argón y enfriada a - 10 º C se agregó dietilzinc (1 M en hexanos, 2,05 ml, 2,05 mmol) seguido por cloroyodometano (330 µl, 4,1 mmol) durante un período de 15- 20 minutos, manteniendo la temperatura interna a - 10 ° C. La solución se agitó durante 10 min adicionales a - 10 °C y una solución de ácido butilborónico y éster diamida del ácido N, N, N ', N'- tetrametil- D- tartárico (346 µl, 1,36 mmol) en CH_2Cl_2 anhidro (1 ml) se agregó durante un período de 5 minutos inmediatamente seguido por la adición de una solución de éster 1- terc- butilo del ácido (S)- 4- hidroximetil- 2 ,3- dihidro- pirrol- 1 ,2- dicarboxílico éster 2- etilo (185 mg, 0,68 mmol) en CH_2Cl_2 seco (1 ml). La mezcla de reacción se agitó a - 10 ° C. La reacción

se apagó con 1 ml de una solución acuosa saturada de NH_4Cl y $KHSO_4$ al 10% (3 ml), se agregó EtOAc, las capas se separaron y la capa acuosa se volvió a extraer con EtOAc (x2). A las capas orgánicas combinadas se agregó una solución que contiene 6 ml de NaOH acuoso 2 N y 1 ml de H_2O_2 acuoso al 30% y la solución bifásica resultante se agitó vigorosamente durante 5 min. Las dos capas se separaron y la capa orgánica se lavó sucesivamente con una solución acuosa saturada de Na_2SO_3, $NaHCO_3$ y salmuera, se secó sobre Na_2SO_4, se filtraron y se concentraron. El material en bruto se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano a c- hexano/EtOAc 6- 4) para proporcionar una mezcla de diastereoisómeros (aproximativamente 70/30 (1R, 3S, 5S) / (1S, 3S, 5R)).

D. Éster 2- terc- butilo del ácido (1R, 3S, 5S) y (1S, 3S, 5R)- 5- hidroximetil- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico

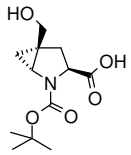
A una mezcla diastereoisomérica de éster 2- terc- butilo del ácido (1R, 3S, 5S) y (1S, 3S, 5R)- 5- hidroximetil- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico éster 3- etílico (relación 04:6, 100 mg, 0,31 mmol) en THF (1,5 ml) y H_2O (0,15 ml) a 0 º C se agregó NaOH (1 M en agua, 0,63 ml, 0,63 mmol). La solución se agitó durante 1 h a temperatura ambiente y se vertió en $KHSO_4$ al 10% (hasta pH 1), se agregó EtOAc y las capas se separaron (x3). Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se utilizó sin purificación adicional en la siguiente paso. EM (HPLC / MS): 256,2 [MH] - , 258,3 [M+H]+, 280,3 [M+Na]+, 200,2 [MH- tBu] +, 515,54 [2M+H]+, 537,4 [2M + Na] +; tR (condiciones HPLC f): 1,28 min.

E. Ester terc- butilo del ácido (1R, 3S, 5S) y (1S, 3S, 5R) - 3 - (3- cloro- 2- fluoro- bencilcarbamoil)- 5- hidroximetil- 2- aza- biciclo [3.1.0] hexano- 2- carboxílico

A una mezcla diastreoisomérica de éster 2- terc- butilo del ácido (1R, 3S, 5S) y (1S, 3S, 5R)- 5- hidroximetil- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico (312 mg, 1,21 mmol), 3- cloro- 2- fluorobencilamina (232 mg, 1,46 mmol), HBTU (690 mg, 1,82 mmol) en CH_2Cl_2 (6 ml) se agregó DIPEA (0,623 ml, 3,64 mmol). La solución resultante se agitó a temperatura ambiente bajo nitrógeno durante la noche. Se añadieron DIPEA (0,21 ml, 1,21 mmol), HBTU (230 mg, 0,6 mmol) y 3- cloro- 2- fluorobencilamina (97 mg, 0,606 mmol) y la mezcla se agitó adicionalmente durante la noche a temperatura ambiente en una atmósfera de N2. La mezcla se vertió en una solución acuosa de HCl 1 N (pH 1) y se extrajo con CH2Cl2 (2x). Las capas orgánicas combinadas se lavaron con salmuera, se secó (Na2SO4), se filtró y se concentró. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice

(C- hexano a c- hexano/EtOAc 40:60) para proporcionar éster terc- butilo del ácido (1S, 3S, 5R) - 3 - (3- cloro- 2- fluoro- bencilcarbamoil) - 5- hidroximetil- 2- aza- biciclo [3.1.0] hexano- 2- carboxilato: TLC, R_f (EtOAc) = 0,55 (teñidos con ninhidrina); EM (UPLC- MS): 399.2/401.2 [M + H] +, 299.2/301.2 [MH- Boc] +, 343.2/345.2 [MH- tBu] +, 443.2/445.3 [M + HCOO] - ; tR (condiciones HPLC f): 1,95 min, y éster terc- butilo de ácido (1R, 3S, 5S) - 3 - (3- cloro- 2- fluoro- bencilcarbamoil)- 5- hidroximetil- 2- aza- biciclo [3.1.0] hexano- 2- carboxilato: TLC, R_f (EtOAc) = 0,45 (teñidos con ninhidrina); EM (UPLC- MS): 399.2/401.2 [M+H]+, 299.2/301.2 [MH- Boc] +, 343.2/345.2 [MH- tBu] +, 443.2/445.3 [M + HCOO] - ; tR (condiciones HPLC f): 1,89 min.

Éster 2- terc- butilo del ácido (1R, 3S, 5S)- 5- hidroximetil- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico

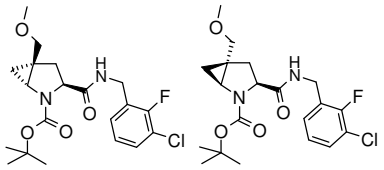


se obtuvo utilizando los mismos protocolos que se describen en el Esquema B28 paso D a partir de éster 2- terc- butilo del ácido (1R, 3S, 5S)- 5- hidroximetil- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico éster 3- etilo. 1H RMN (400 MHz, DMSO- d6) δ (ppm): 12,5 (m, 1H), 4,71 (m, 1H), 3,92 (m, 1H), 3,42- 3,35 (m, 2H), 3,17 (m, 1H), 2,31 (m, 1H), 2,08 (m, 1H), 1,41 y 1,33 (2 s, 9H), 0,79 (m, 1H), 0,67 (m, 1H).

Éster 2- terc- butilo del ácido (1R, 3S, 5S)- 5- hidroximetil- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico éster- 3- acetato

La mezcla de éster 2- terc- butilo del ácido (1R, 3S, 5S) y (1S, 3S, 5R)- 5- hidroximetil- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico éster 3- etilo (360 g) se separó en sus diastereoisómeros mediante columna HPLC quiral preparativa: 8 SMB columnas Chiralpak AD, 20 um, 250 x 30 mm; eluyente: heptano- EtOH 80:20) para proporcionar éster 2- terc- butilo del ácido (1R, 3S, 5S) - 5 hidroximetil- 2- aza- biciclo- [3.1.0] hexano- 2 ,3- dicarboxílico éster - 3- etilo: t_R (Chiralpak AD- prep, 20 uM, 250 x 4,6 mm, n- heptano / EtOH 80/20, tasa de flujo 1 ml / min, detección: UV a 210 nm): 6,94 min y éster 2- terc- butilo del ácido (1S, 3S, 5R)- 5- hidroximetil- 2- aza- biciclo [3.1.0] hexano- 2, 3- dicarboxílico éster - 3- etilo: t_R (Chiralpak AD- prep, 20 uM, 250 x 4,6 mm, n- heptano/EtOH 80/20, tasa de flujo 1 ml / min, detección: UV a 210 nm): 4,20 min.

éster terc- butílo del ácido (1R,3S,5S) and (1S,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 5- metoximetil- 2- aza- biciclo[3.1.0]hexano- 2- carboxílico



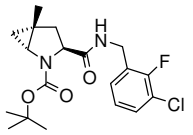
se obtuvieron utilizando los mismos protocolos como se describe en el Esquema B28 pasos D y E para la preparación de éster tert- butilo del ácido (1R, 3S, 5S) y (1S, 3S, 5R) - 3 - (3- cloro- 2- fluoro- bencilcarbamoil) - 5 - hidroximetil- 2- aza- biciclo [3.1.0] hexano- 2- carboxilato a partir de éster 2- terc- butilo del ácido (1R, 3S, 5S) y (1S, 3S, 5R)- 5- metoximetil- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico éster 3- etilo. NaOH se sustituyó por LiOH. H_2O en el paso D. Los diastereoisómeros se separaron mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 01:01 a EtOAc) para proporcionar éster terc- butilo del ácido (1S,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 5- metoximetil- 2- aza- biciclo[3.1.0]hexano- 2- carboxílico como un aceite incoloro: TLC, R_f (c- hexano/EtOAc 01:01) = 0,50; EM (UPLC/MS): 413.3/415.2 [M+H]+, 457.3/459.3 [M + HCOO] - ; tR (condiciones HPLC A): 3,74 min y éster terc- butílo del ácido (1R,3S,5S)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 5- metoximetil- 2- aza- biciclo[3.1.0]hexan- 2- carboxílico como un aceite incoloro: TLC, R_f (c- hexano/EtOAc 01:01) = 0,30; EM (UPLC/MS): 413.2/415.3 [M+H]+, 457.3/459.3 [M + HCOO] - ; tR (a) Condiciones HPLC: 3,57 min.

Éster 2- terc- butilo del ácido (1R, 3S, 5S) y (1S, 3S, 5R)- 5- metoximetil- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico éster- 3- etilo

Éster 2- terc- butilo del ácido (1R, 3S, 5S) y (1S, 3S, 5R)- 5- hidroximetil- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico éster 3- etilo en forma de mezcla de diastereoisómeros (35:65 (1R, 3S, 5S) / (1S, 3S, 5R)) (840 mg, 2,94 mmol) se agregaron lentamente a 0 º C bajo atmósfera de argón a una suspensión de NaH (60% en aceite mineral, 141 mg, 3,53 mmol) en THF (9 ml). La mezcla de reacción se agitó a 0 °C durante 30 min y yodometano (0,28 ml, 4,42 mmol) se agregó lentamente a 0 ° C. La mezcla de reacción se agitó adicionalmente a temperatura ambiente durante la noche. Se añadieron $NaHCO_3$ y CH_2Cl_2 saturada, las capas se separaron y la fase acuosa se volvió a extraer dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron. El material en bruto se purificó mediante cromatografía en columna de gel de sílice (C- hexano a c-

hexano/EtOAc 02:08) para proporcionar el compuesto del título como una mezcla inseparable de diastereoisómeros. TLC, R_f (c- hexano/EtOAc 01:01) = 0,70; EM (UPLC/MS): 300,3 [M+H]+, 599,5 [2M+H]+; t_R (condiciones HPLC A): 3,45 min. La estereoquímica absoluta de los diastereoisómeros se asignó provisionalmente por RMN y con base en los resultados de la prueba para los compuestos finales Ejemplo 214 y Ejemplo 184 en el ensayo biológico.

Éster terc- butilo del ácido (1R, 3S, 5R) - 3 - (3- cloro- 2- fluoro- bencilcarbamoil)- 5- metil- 2- aza- biciclo [3.1.0] hexano- 2- carboxílico

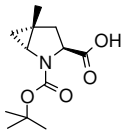


Se agregó trietilborohidruro de litio (1 N en THF, 2,06 ml, 2,06 mmol) a 0 °C a una solución de éster terc- butilo del ácido (1R,3S,5S)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 5- metanosulfoniloximetil- 2- aza- biciclo[3.1.0]hexano- 2- carboxílico (385 mg, 0,67 mmol) en THF (6,8 ml) bajo atmósfera de argón. La solución se agitó durante10 min a 0 ° C, después se vertió en agua fría y se extrajo con EtOAc (x2). Los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano a c- hexano/EtOAc 75:25). TLC, R_f (c- hexano/EtOAc 01:01) = 0,55; EM (UPLC/MS): 383.3/385.3 [M+H]+, 427.5/429.4 [M + HCOO] - ; tR (condiciones HPLC f): 2,24 min.

Éster terc- butílo del ácido (1R,3S,5S)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 5- metanosulfoniloximetil- 2- aza- biciclo[3.1.0]hexano- 2- carboxílico

A una solución de éster terc- butílo del ácido (1R,3S,5S)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 5- hidroximetil- 2- aza- biciclo[3.1.0]hexano- 2- carboxílico (290 mg, 0,72 mmol) y Et_3N (144 l, 1,04 mmol) en CH_2Cl_2 (6,5 ml) a 0 °C bajo atmósfera de nitrógeno se agregó cloruro de metanosulfonilo (81 l, 1,04 mmol) y la mezcla se agitó a temperatura ambiente durante 1 h. Se añadieron de nuevo Et_3N (48 l, 0,35 mmol) y cloruro de metanosulfonilo (27 l, 0,35 mmol) y la mezcla se agitó adicionalmente durante 0,5 h para completar la reacción. Se agregó una solución acuosa saturada de $NaHCO_3$, las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (x2), se secaron (Na_2SO_4), se filtraron y se concentraron. El material así obtenido se usó en la siguiente paso sin purificación adicional. TLC, R_f (EtOAc) = 0,65; EM (UPLC/MS): 477.3/479.3 [M+H]+, 521.3/523.3 [M + HCOO] -

Éster 2- terc- butilo del ácido (1R, 3S, 5R)- 5- metil- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico



A una solución de éster 2- terc- butilo del ácido (1R, 3S, 5R)- 5- metil- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico éster- 3- etilo (185 mg, 0,69 mmol) en MeOH (1,1 ml), THF (1,1 ml) y H_2O (1,1 ml) se agregó KOH (77 mg, 1,37 mmol). La solución se agitó durante 2,5 h a temperatura ambiente, se añadió HCl (0,1 N) (hasta pH 1), se agregó CH_2Cl_2 y se separaron las capas (x2). Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El material (aceite amarillo) así obtenido se utilizó sin purificación adicional en la siguiente paso. 1H RMN (400 MHz, DMSO- d6) δ (ppm): 12,46 (m, 1H), 3,86 (m, 1H), 3,06 (m, 1H), 2,40 (dd, 1H), 1,86 (m, 1H), 1,37 (m, 9H), 1,18 (s, 3H), 0,65 (m, 2H).

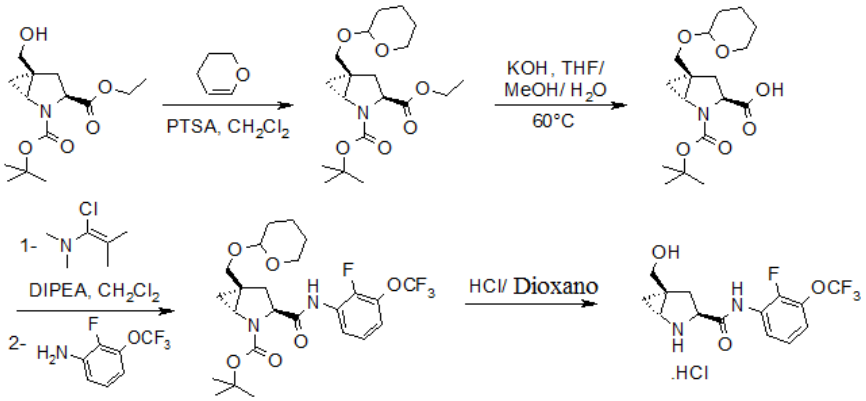
Éster 2- terc- butilo del ácido (1R, 3S, 5R)- 5- metil- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico éster- 3- etílico

A una solución de éster 2- terc- butilo del ácido (1R, 3S, 5S)- 5- metanosulfoniloximetil- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico (100 mg, 0,24 mmol) en DME (2,6 ml) se añadieron sucesivamente Nal (355 mg, 2,37 mmol) y polvo de zinc (155 mg, 2,37 mmol). La mezcla de reacción se sometió a reflujo durante 30 minutos bajo atmósfera de argón, se enfrió a temperatura ambiente y se apagó mediante la adición de una solución acuosa saturada de NH_4Cl (1,6 ml). Se añadieron CH_2Cl_2 (1,6 ml) y algunos cristales de Na_2S y la mezcla bifásica se agitó a temperatura ambiente durante 1 h. Las capas se separaron, los extractos orgánicos se lavaron con salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron bajo presión reducida. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (eluyente: hexano- c a c- hexano / EtOAc). TLC, R_f (c-hexano / EtOAc 2:1) = 0,60; MS (UPLC/MS): 270,3 [M+H]+, 214,2 [MH- tBu] +, 170,2 [MH-Boc] +; 1H RMN (400 MHz, DMSO- d6) δ (ppm): 4,11 (m, 2H), 3,95 (m, 1H), 3,10 (m, 1H), 2,42 (m, 1H), 1,84 (m, 1H), 1,38 (m , 9H), 1,20 (t, 3H), 1,18 (s, 3H), 0,69 (dd, 1H), 0,64 (m, 1H).

Éster 2- terc- butilo del ácido (1R, 3S, 5S)- 5- metanosulfoniloximetil- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico

A una solución de éster 2- terc- butilo del ácido (1R, 3S, 5S)- 5- hidroximetil- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico éster- 3- etil (500 mg, 1,75 mmol) y Et_3N (366 µl, 2,63 mmol) en CH_2Cl_2 (16 ml) se agregó cloruro de metanosulfonilo (205 µl, 2,63 mmol) a 0 °C bajo atmósfera de nitrógeno. La mezcla de reacción se dejó alcanzar lentamente la temperatura ambiente y se agitó durante 1 h. La reacción se apagó mediante la adición de una solución acuosa saturada de $NaHCO_3$, las capas se separaron y la capa acuosa se extrajo dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron. El material así obtenido se utilizó sin purificación adicional en la siguiente paso. Aceite de color amarillo, TLC, R_f (EtOAc) = 0,80.

Esquema B29: Preparación de clorhidrato de (1R, 3S, 5S)- 5- hidroximetil- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico (2- fluoro- 3- trifluorometoxi- fenil)- amida



A. Éster 2- terc- butilo del ácido (1R, 3S, 5S) - 5 - (tetrahidro- piran- 2- iloximetil)- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico éster - 3- etil

Una mezcla de éster 2- terc- butilo del ácido (1R, 3S, 5S)- 5- hidroximetil- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico éster- 3- etil (500 mg, 1,75 mmol), 3,4- dihidro- 2H- pirano (176 l, 1,93 mmol) y $TsOH.H_2O$ (33 mg, 0,17 mmol) en CH_2Cl_2 (6 ml) se agitó durante 3 h a temperatura ambiente. Luego se vertió en una solución acuosa saturada de $NaHCO_3$ y se extrajo con CH_2Cl_2 (x2). Los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano a c- hexano/EtOAc 01:01). Aceite incoloro. TLC, Rf (EtOAc) = 0,85; EM (UPLC/MS): 370,4 [M+H]+, 387,4 [M + H2O] +; tR (condiciones HPLC f): 2,28 min.

B. Éster 2- terc- butilo del ácido (1R, 3S, 5S) - 5- (tetrahidro- piran- 2- iloximetil)- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico

A una solución de éster de 2- terc- butilo del ácido (1R, 3S, 5S) - 5 - (tetrahidro- piran- 2- iloximetil)- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico éster 3- etilo (510 mg, 1,38 mmol) en MeOH (2,3 ml), THF (2,3 ml) y agua (2,3 ml) se agregó KOH (155 mg, 2,76 mmol). La reacción se agitó a 60 °C durante 45 min. Luego se dejó enfriar a temperatura ambiente y se diluyó con EtOAc. Las capas se separaron, la capa acuosa se acidificó mediante la adición de HCl (0,1 N, hasta pH 1) y se extrajo con EtOAc (x2). Los orgánicos se secaron (Na_2SO_4), se filtraron y se concentraron. MS (UPLC/MS): 359,4 [M + NH_4] +, 340,4 [MH] - , 386,4 [M + HCOO] - , 681,5 [2M- H] - ; t_R (condiciones HPLC f): 1,84 min.

C. Éster terc- butílo del ácido (1R,3S,5S)- 3- (2- Fluoro- 3- trifluorometoxi- fenilcarbamoil)- 5- (tetrahidro- piran- 2- iloximetil)- 2- aza- biciclo[3.1.0]hexano- 2- carboxílico

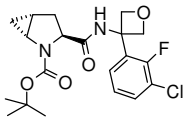
A una solución de éster 2- terc- butilo del ácido (1R, 3S, 5S) - 5 - (tetrahidro- piran- 2- iloximetil)- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico (100 mg, 0,29 mmol) en CH_2Cl_2 seco (1 ml) bajo argón a 0 º C se agregó 1- cloro- N, N ,2- trimetilpropenilamina (58 µl, 0,44 mmol) y la mezcla de reacción se agitó a 0 º C durante 1,5 h. Se agregó 2- fluoro- 3- (trifluorometoxi) anilina (86 mg, 0,44 mmol), seguido de DIPEA (100 µl, 0,59 mmol) y la mezcla se agitó a temperatura ambiente durante la noche. Luego se vertió en agua y se extrajo con CH_2Cl_2 (x2), los extractos orgánicos se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (eluyente: C- hexano a c- hexano/EtOAc 85:15). TLC, Rf (c- hexano/EtOAc 02:01) = 0,45; EM (UPLC/MS): 519,3 [M+H]+, 536,3 [M + NH4] +, 517,4 [MH] - , 563,3 [M- HCOO] - ; tR (condiciones HPLC f): 2,51 min.

D. Clorhidrato de (2- fluoro- 3- trifluorometoxi- fenil)- amida del ácido (1R, 3S, 5S)- 5- hidroximetil- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico

A una solución de éster terc- butílo del ácido (1R,3S,5S)- 3- (2- fluoro- 3- trifluorometoxi- fenilcarbamoil)- 5- (tetrahidro- piran- 2- iloximetil)- 2- aza- biciclo[3.1.0]hexano- 2- carboxílico (105 mg, 0,19 mmol) en dioxano (0,5 ml) se agregó HCl (4 N en dioxano, 481 µl, 1,92 mmol). La mezcla se agitó a temperatura ambiente durante 4 h, el solvente se eliminó a presión reducida y el material así obtenido se utilizó sin purificación

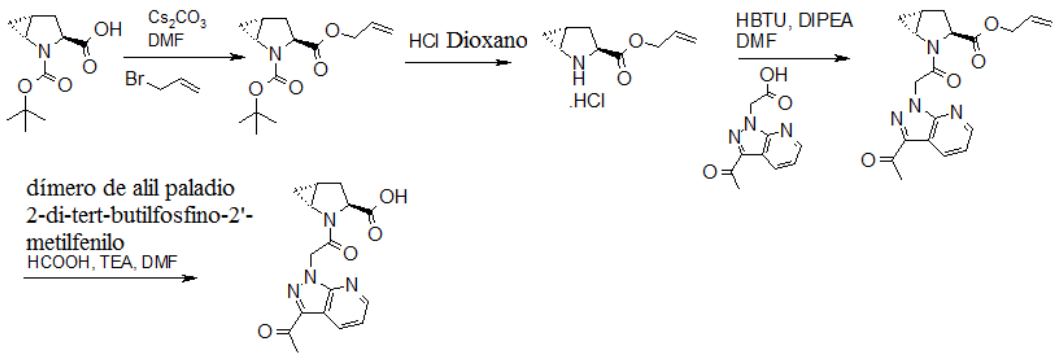
adicional en la siguiente paso. MS (UPLC/MS): 335,2 [M+H]+, 333,2 [MH] - , 379,6 [M + HCOO] - .

Éster tert- butílico del ácido (1R, 3S, 5R) - 3 - [3 - (3- cloro- 2- fluoro- fenil)- oxetan- 3- ilcarbamoil]- 2- aza- biciclo [3.1.0] hexano- 2- carboxílico



A una solución de éster 2- terc- butilo del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico (220 mg, 0,968 mmol), anhídrido propilfosfónico (50% en EtOAc, 0,856 ml, 1,45 mmol) y (3- cloro- 2- fluoro- fenil)- oxetan- 3- ilamina (preparada como se describe en la Parte C, 358 mg, 1,06 mmol) en CH_2Cl_2 (10 ml) se agregó 3 DIPEA (0,507 ml, 2,90 mmol) bajo atmósfera de nitrógeno. La mezcla de reacción se agitó durante 2 h a temperatura ambiente y se concentró. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 03:02). MS (LC/MS): 411.2/413.2 [M+H]+, 455.2/457.2 [M + HCOO] - ; t_R (f) Condiciones HPLC: 2,02 min.

Esquema B30: Preparación del ácido (1R, 3S, 5R) - 2 - [2 - (3- Acetil- pirazolo [3,4- b] piridin- 1- il)- acetil]- 2- azabiciclo [3.1.0] - hexano- 3- carboxílico



A. Éster 3- alilo del ácido (1R, 3S, 5R)- 2- azabiciclo [3.1.0] hexano- 2 ,3- dicarboxílico éster 2- terc- butilo

A una solución de éster 2- terc- butilo del ácido (1R, 3S, 5R)- 2- azabiciclo [3.1.0] hexano- 2 ,3- dicarboxílico (1,5 g, 3,6 mmoles) y Cs_2CO_3 (2,26 g, 6,9 mmol) en DMF (20 ml) se agregó bromuro de alilo (0,6 ml, 3,9 mmol). La mezcla de reacción se agitó durante 40 h a temperatura ambiente. DMF se evaporó. El residuo se disolvió en EtOAc y se lavó con HCl 1 N, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo crudo se purificó mediante

cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano a c- hexano/EtOAc 04:06). MS (LCMS): 167,9 [MH- Boc] +, 290,0 [M+Na]+.

B. Clorhidrato de éster alílico de ácido (1R, 3S, 5R)- 2- azabiciclo[3.1.0]hexano- 3- carboxílico

A éster 3- alilo del ácido (1R, 3S, 5R)- 2- azabiciclo [3.1.0] hexano- 2 ,3- dicarboxílico éster 2- terc- butilo (1,69 g, 6,32 mmol) se agregó HCl 4 N en dioxano (15,8 ml, 63,2 mmol). La mezcla de reacción se agitó durante 6 horas a temperatura ambiente y posteriormente se liofilizó. MS: 168,0 [M+H]+.

C. Éster alílico del ácido (1R, 3S, 5R) - 2 - [2 - (3- Acetil- pirazolo [3,4- b] piridin- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico

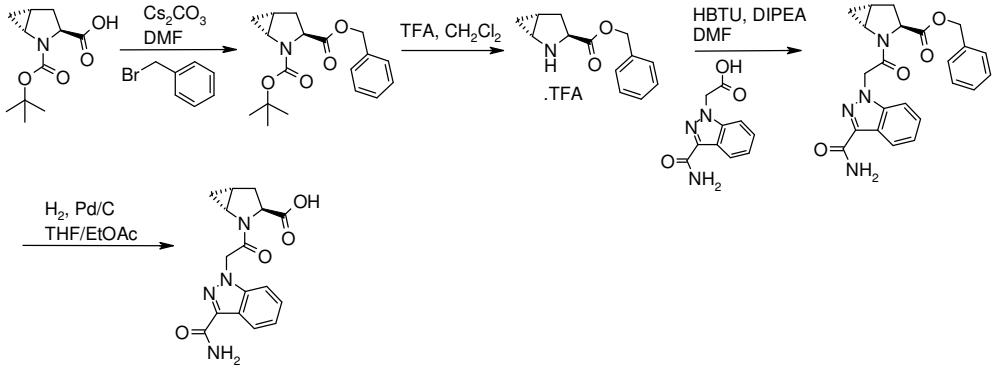
A una solución de clorhidrato de éster 3- alilo del ácido (1R, 3S, 5R)- 2- azabiciclo [3.1.0] hexano- 2 ,3- dicarboxílico (1,03 g, 6,43 mmol), ácido (3- acetil- pirazolo [3, 4- b] piridin- 1- il)- acético (preparado como se describe en la parte A, 1,3 g, 5,93 mmol) y HBTU (2,70 g, 7,12 mmol) en DMF (19,7 ml) se agregó DIPEA (3,11 ml, 17,8 mmol). La mezcla de reacción se agitó durante 16 h a temperatura ambiente. DMF se evaporó. El residuo se vertió en NH_4Cl (solución acuosa saturada) y se extrajo con EtOAc (3 x 50 ml). Las fases orgánicas se combinaron, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano a c- hexano/EtOAc 0:10). R_f, TLC (EtOAc) = 0,6; MS (LCMS): 369,0 [M+H]+, 391,0 [MH + Na] +; t_R (condiciones HPLC k): 2,78 min.

D. Ácido (1R, 3S, 5R) - 2 - [2 - (3- Acetil- pirazolo [3,4- b] piridin- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico

Dímero de cloruro de alil paladio (0,084 g, 0,231 mmol) y 2- di- terc- butilfosfino- 2'- metilbifenilo (0,288 g, 0,923 mmol) se disolvieron en DMF (7,69 ml) bajo atmósfera de argón. La mezcla de reacción se agitó a temperatura ambiente durante 10 min. Después de enfriar la mezcla de reacción a 10 ° C, se agregó ácido fórmico (0,513 ml, 13,38 mmol) seguido por TEA (1,865 ml, 13,38 mmol) y una solución de éster alilo de ácido (1R, 3S, 5R) - 2 - [2 - (3 - acetil- pirazolo [3,4- b] piridin- 1- il) acetil]- 2- azabiciclo [3.1.0] hexano - 3- carboxílico (1 g, 2,3 mmol) en DMF (15,38 ml). La mezcla de reacción se agitó a 10 °C durante 1 h. DMF se evaporó. El residuo se vertió en NH_4Cl (solución acuosa saturada) y se extrajo con EtOAc (3 x 50 ml). Las fases orgánicas se combinaron, se secaron sobre Na_2SO_4, se filtraron y se

concentraron. El residuo se disolvió en MeOH y se filtró sobre un cartucho de PL- tiol. El filtrado se concentró. El residuo crudo se purificó por HPLC preparativa (Waters Sunfire C18-DAB, 5 micras, 30x100mm, flujo: 40 ml / min, eluyente: 5% a 80% de CH_3CN en H_2O en 20 min, CH_3CN y H_2O que contiene 0,1% de TFA) y las fracciones puras se combinaron y liofilizaron. Sólido blanco. MS (LCMS): 328,9 [M+H]+, 351,0 [MH + Na]; tR (condiciones HPLC l): 1,84 min. 1H RMN (400 MHz, DMSO- d6):δ (Ppm) 8,66 (dd, J = 4,52, 1,59 Hz, 1 H), 8,58 (m, J = 6,36 Hz, 1 H), 7,35- 7,50 (m, 1 H), 8,54- 8,61 (m, 1 H), 5,88 (d, J = 16,87 Hz, 1 H), 5,55 (d, J = 17,12 Hz, 1 H), 4.14- 4.24 (m, 1 H), 3,75- 3,83 (m, 1 H), 2,64 (s, 3 H), 2,26- 2,36 (m, 1 H), 2.10- 2.23 (m, 1 H), 1,80- 1,95 (m, 1 H), 0,95- 1,07 (m, 1 H), 0,67- 0,81 (m, 1 H).

Esquema B31: Preparación del ácido (1R, 3S, 5R) - 2 - [2 - (3- carbamoil- indazol- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico



A. Éster 3- bencilo del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico éster 2- terc- butilo

A una solución de éster 2- terc- butilo del ácido (1R, 3S, 5R)- 2- azabiciclo [3.1.0] hexano- 2 ,3- dicarboxílico (2,5 g, 11,0 mmoles) y Cs_2CO_3 (3,94 g, 12,1 mmol) en DMF (50 ml) a 0 º C se agregó por goteo C bromuro de bencilo (2,26 g, 13,2 mmol). La mezcla de reacción se agitó durante la noche a temperatura ambiente. DMF se evaporó. El residuo se disolvió en EtOAc y se lavó con una solución acuosa saturada de $NaHCO_3$, las capas se separaron y la fase acuosa se extrajo con EtOAc (x2). Los extractos orgánicos combinados se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante

cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 100:0 a 0:100) para proporcionar el material deseado como un aceite incoloro. MS (LCMS): 318,2 [M+H]+; tR (condiciones HPLC f): 2,23 min.

B. Trifluoroacetato de éster bencílico del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico

A éster 3- bencilo del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico éster 2- terc- butilo (3,27 g, 9,79 mmol) en CH_2Cl_2 (50 ml) se agregó TFA (7,54 ml, 98 mmol). La mezcla de reacción se agitó durante la noche a temperatura ambiente y posteriormente se concentró bajo presión reducida para proporcionar el material deseado como un aceite de color amarillo. MS (UPLC): 218,1 [M+H]+; t_R (condiciones HPLC f): 1,24 min.

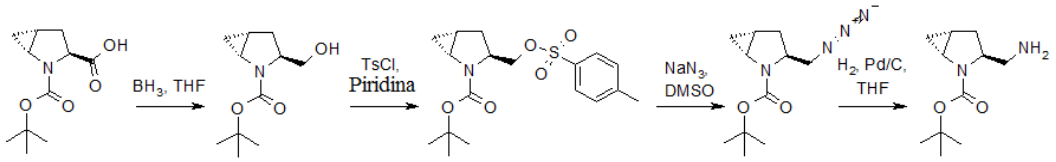
C. Éster bencílico del ácido (1R, 3S, 5R) - 2 - [2 - (3- carbamoil- indazol- 1- il)- acetil] - 2- aza- biciclo [3.1.0] hexano- 3- carboxílico

A una solución de trifluoroacetato de éster bencilo del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- de 3- carboxílico (3,9 g, 9,77 mmol), ácido (3- carbamoil- indazol- 1- il) - acético (preparado como se describe en el Esquema A25, 2,26 g, 9,77 mmol), HBTU (5,56 g, 14,66 mmol) en CH_2Cl_2 (60 ml) se agregó DIPEA (5,12 ml, 29,3 mmol). La mezcla de reacción se agitó durante 48 h a temperatura ambiente. La mezcla de reacción se vertió en agua y se extrajo con CH_2Cl_2 (x3). Los extractos orgánicos combinados se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 10:0 a 0:10). R_f, la TLC (EtOAc) = 0,85; EM (UPLC): 436,3 [M + NH_4] +, 463,2 [M + HCOO] - ; t_R (condiciones HPLC f): 1,82 min.

D. Ácido (1R, 3S, 5R) - 2 - [2 - (3- carbamoil- indazol- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico

Éster bencílico del ácido (1R, 3S, 5R) - 2 - [2 - (3- carbamoil- indazol- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico (3,9 g, 8,85 mmoles) se disolvió en THF (120 ml) y EtOAc (120 ml). El aire se retiró del matraz y se reemplazó con nitrógeno tres veces. Se agregó Pd/C al 10% (390 mg) a la solución que se desgasificó de nuevo, se colocó bajo una atmósfera de hidrógeno, y se agitó a temperatura ambiente durante 4 h. El catalizador se eliminó a través de una almohadilla de Celite y se lavó con EtOAc. Los solventes se eliminaron a presión reducida y la espuma obtenida de este modo se utilizó sin purificación adicional en la siguiente paso. MS (LCMS): 346,2 [M + NH4] +, 327,1 [MH] - ; tR (condiciones HPLC f): 1,12 min.

Esquema B32:Éster terc- butilo del ácido (1R, 3S, 5R)- 3- aminometil- 2- aza- biciclo [3.1.0] hexano- 2- carboxílico



A. Éster terc- butilo del ácido (1R, 3S, 5R)- 3- hidroximetil- 2- aza- biciclo[3.1.0] hexano- 2- carboxilato

A una solución de éster 2- terc- butilo del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico (0,5 g, 2,2 mmol) en THF seco (10 ml) , se enfrió a 0 ° C, se agregó bajo una atmósfera de argón por goteo una solución 1 M de complejo de boro- tetrahidrofurano (4,40 ml, 4,40 mmol). La mezcla de reacción se mantuvo a 0 º C durante 2 h adicionales y después se dejó calentar a temperatura ambiente durante la noche. La reacción se apagó mediante la adición cuidadosa de agua y posteriormente EtOAc. La capa orgánica se lavó posteriormente con soluciones acuosas saturadas de NaCl, $NaHCO_3$, agua y NaCl. La fase orgánica se secó (separador de fases) y se concentró para proporcionar el compuesto del título en forma de un aceite incoloro. MS (LC- MS): 214,0 [M+H]+; t_R (condiciones HPLC k): 2,99 min. El material así obtenido se usó en la siguiente paso sin purificación adicional.

B. Éster terc- butilo del ácido (1R, 3S, 5R) - 3 - (tolueno- 4- sulfoniloximetil)- 2- aza- biciclo [3.1.0] hexano- 2- carboxílico

A una solución helada de éster terc- butílo del ácido (1R, 3S, 5R)- 3- hidroximetil- 2- aza- biciclo [3.1.0] hexano- 2- carboxílico (0,480 g, 2,15 mmol) en piridina (5 ml) se agregó cloruro de 4- toluenosulfonilo (0,490 g, 2,58 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 6 h y después se diluyó con Et_2O. La fase orgánica se lavó con HCl 1N (3x), $NaHCO_3$ acuoso (3x) y NaCl, después se secó (separador de fases) y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (gradiente de eluyente: C- hexano a c- hexano/EtOAc 04:01) para proporcionar el compuesto del título como una cera incolora. TLC, Rf (c- hexano/EtOAc 04:01) = 0,2. MS (LC- MS): 390,0 [M+Na]+, 757,0 [2M+H]+. tR (condiciones HPLC k): 4,07 min.

C. Éster terc- butilo del ácido (1R, 3S, 5R)- 3- Azidometil- 2- aza- biciclo[3.1.0] hexano- 2- carboxílico

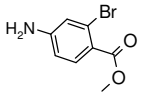
Una mezcla de éster terc- butilo del ácido (1R, 3S, 5R) - 3 - (tolueno- 4- sulfoniloximetil)- 2- aza- biciclo [3.1.0] hexano- 2- carboxilato (0,400 g, 1,08 mmol) y NaN_3 (0,420 g, 6,47 mmol) en DMSO seco (8 ml) se agitó a 65 °C durante la noche. Después de enfriar, la mezcla se diluyó con Et_2O y se lavó con agua (x3) y salmuera (x2). Los orgánicos se secaron (separador de fases) y se concentraron al vacío para proporcionar el compuesto del título en forma de un aceite incoloro. MS (LC- MS): 239,0 [M+H]+; t_R (condiciones HPLC k): 3,78 min. El material así obtenido se usó en la siguiente paso sin purificación adicional.

D. Éster terc- butilo del ácido (1R, 3S, 5R)- 3- aminometil- 2- aza- biciclo [3.1.0] hexano- 2- carboxílico

Éster terc- butílo del ácido (1R, 3S, 5R)- 3- azidometil- 2- aza- biciclo [3.1.0] hexano- 2- carboxílico (195 mg, 0,82 mmol) se suspendió en THF (10 ml). El aire se retiró del matraz y se reemplazó con nitrógeno tres veces. Se agregó Pd/C al 10% (20 mg) a la solución que se desgasificó de nuevo, se colocó bajo una atmósfera de hidrógeno, y se agitó a temperatura ambiente durante la noche. El catalizador se eliminó a través de un filtro de 0,45 micras, y el filtrado se concentró al vacío para proporcionar el compuesto del título. MS (LC- MS): 213,0 [M+H]+; t_R (condiciones HPLC k): 2,51 min. El material así obtenido se usó en la siguiente paso sin purificación adicional.

<u>Parte C: Síntesis de intermedios de anilina y bencilamina:</u>

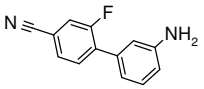
<u>Éster metílico del ácido 4- amino- 2- bromo- benzoico</u>



A una suspensión de éster metílico del ácido 2- bromo- 4- nitro- benzoico [100959- 22- 6] (350 mg, 1,35 mmol) en MeOH (60 ml) se agregó posteriormente polvo de estaño (1,6 g, 13,5 mmol) y 3N HCl acuoso (27,8 ml, 83 mmol). La mezcla se agitó durante la noche a temperatura ambiente. La fase líquida se decantó del exceso de estaño y se neutralizó mediante la adición de una solución acuosa saturada de $NaHCO_3$. Se agregó una cantidad igual de agua en volumen y la fase acuosa se extrajo con EtOAc (3x). Los extractos orgánicos combinados se secaron (separador de fases) y se concentraron al vacío. El residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (eluyente: EtOAc/c- hexano 1:4) para

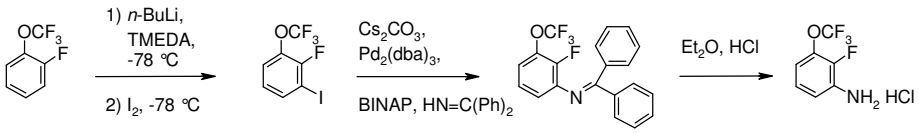
proporcionar el compuesto del título en forma de sólido de color amarillo. MS (LC/MS): 230 [M+H]+; t_R (condiciones HPLC B): 2,89 min.

3'- amino- 2- fluoro- bifenil- 4- carbonitrilo



Se suspendieron ácido 3- aminofenilborónico (200 mg, 1,29 mmol), 3- fluoro- 4- yodobenzonitrilo (319 mg, 1,29 mmol), TBACl (35,9 mg, 0,129 mmol) y Pd $(PPh_3)_4$ (74,6 mg, 0,064 mmoles) en una mezcla de tolueno (4 ml) y K_2CO_3 1 M en agua (4 ml). La mezcla bifásica se agitó vigorosamente bajo atmósfera de argón a 90 º C durante 20 h. La capa orgánica se separó y la fase acuosa se extrajo con tolueno (x2). Las capas orgánicas se combinaron, se lavaron con agua, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna (c- hexano/EtOAc 3:1) para proporcionar el material deseado. MS (LC/MS) [M+H]+ = 213; tR (HPLC, Waters Atlantis, 2.1x30mm, flujo de 0.6mL/min, CH_3CN/H_2O 5 a 95% en 2,5 min, 95% CH_3CN $_2$ min, 95 a 5% CH_3CN, H_2O y CH_3CN ambos contienen 0,1% de HCOOH): 2,84 min.

Clorhidrato de 2- fluoro- 3- (trifluorometoxi)anilina



A. 2- fluoro- 1- yodo- 3- (Trifluorometoxi)benceno

A una solución de 1- fluoro- 2- (trifluorometoxi) benceno [2106- 18- 5] (20,0 g, 111 mmol) en THF seco (200 ml), se enfrió a - 78 ° C, se agregó por goteo n- BuLi (solución 2,5 M en n- hexano, 65 ml, 160 mmol) y, posteriormente TMEDA (60 ml). La mezcla de reacción se agitó durante 60 min adicionales a - 78 º C, seguido por adición de una solución de yodo (30,2 g, 120 mmol) en THF seco (50 ml). La mezcla resultante se agitó durante 1 h y después se apagó mediante la adición de una solución acuosa saturada de NH_4Cl (20 ml). La capa orgánica se lavó con HCl 1 N, agua y salmuera, y se secó sobre $MgSO_4$. Los volátiles se eliminaron al vacío para proporcionar el compuesto del título en forma de aceite de color amarillo. El producto se usó en la siguiente paso de reacción sin purificación adicional. MS (LC/MS): 306,0 [M+H]+.

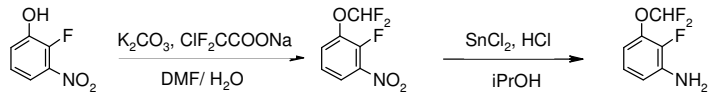
B. benzhidrilideno- (2- fluoro- 3- trifluorometoxi- fenil)- amina

A una solución de 2- fluoro- 1- yodo- 3- (trifluorometoxi) benceno (25 g, 81 mmol) en tolueno seco (200 ml) se agregó Cs_2CO_3 (38,7 g, 120 mmol), Pd_2 (dba) $_3$ (7,42 g, 8,1 mmoles), BINAP (10,8 g, 16,2 mmol) y amina de benzhidrilideno (19,6 g, 108 mmol). La mezcla de reacción se calentó a reflujo durante 8 h con agitación y después se enfrió a temperatura ambiente. La capa orgánica se lavó con agua y salmuera y después se secó sobre $MgSO_4$. Después de la eliminación del solvente al vacío, el residuo se purificó mediante cromatografía en columna sobre gel de sílice (gradiente de solvente de | n- hexano para n- hexano/EtOAc 20:01) para proporcionar el compuesto del título como un aceite de color amarillo pálido. 1H RMN ($CDCl_3$, 400 MHz):δ 7.72 (S, 1H, ArH,), 7,70 (s, 1H, ArH), 7,45- 7,42 (m, 1H, ArH,), 7,37- 7,33 (m, 2H, ArH), 7.25 a 7.17 (m, 3H, ArH), 7,06 (s , 1H, ArH), 7,05 (s, 1H, ArH,), 6,84 (t, 1H, J = 8 Hz, ArH), 6,78 (t, 1H, J = 8 Hz, ArH), 6,67- 6,64 (m, 1H, ArH).

C. Clorhidrato de 2- fluoro- 3- (trifluorometoxi) anilina

A una mezcla de benzhidriliden- (2- fluoro- 3- trifluorometoxi- fenil)- amina (7,5 g, 20 mmol) en Et_2O (40 ml) se agregó HCl acuoso 3 N (10 ml). La mezcla de reacción se agitó durante 4 h a temperatura ambiente, seguido de la adición de agua. La capa acuosa se extrajo con Et_2O (2x10 ml), las capas orgánicas combinadas se lavaron con salmuera y después se secaron sobre $MgSO_4$. Después de la eliminación del solvente al vacío, el residuo se purificó por HPLC preparativa (fase estacionaria: Gimini 300x50 mm, tamaño de partícula 10 µ m; solvente: A H_2O + B CH_3CN, presión: 60- 70 bar). El producto se extrajo con Et_2O como la base libre a partir de las fracciones combinadas. Se burbujeó gas HCl a través de la fase orgánica, y el solvente se eliminó al vacío para proporcionar el compuesto del título. La recristalización a partir de EtOH / éter diisopropílico proporcionó un sólido blanco. 1H RMN (D2O, 400 MHz): δ 7,40- 7,35 (m, 1H, ArH), 7,32- 7,27 (m, 1H, ArH), 7.27- 7.19 (m, 1H, ArH). HRMS: 196.03801 [M] + (Calculado 196.03800 para $C_7H_5F_4NO$) Anal. Calc. para $C_7H_5F_4NO$: C, 36,31, H, 2,61, N, 6,05, Cl, 15,31, F, 32,82 Encontrado: C, 35,78, H, 2,63, N, 6,14, Cl, 15,69, F, 31,99.

3- difluorometoxi- 2- fluoro- fenilamina



A. 1- difluorometoxi- 2- fluoro- 3- nitro- benceno

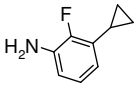
A una mezcla de 2- cloro- 2 ,2- difluoroacetato de sodio (7,14 g, 46,8 moles) y carbonato de potasio (3,50 g, 25,3 mmol) en DMF (10 ml) y agua (2,5 ml) a 110 °C se agregó

una solución de 2- fluoro- 3- nitrofenol (2 g, 12,65 mmol) en DMF (10 ml) y la mezcla se agitó a 110 º C durante 6 h. Después de enfriar, la mezcla se apagó con agua y se extrajo con EtOAc. Después, la capa orgánica se lavó con agua, salmuera y se secó sobre Na_2SO_4, se filtró y se concentró. El material en bruto se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano a c- hexano/EtOAc 01:01). 1H RMN (400 MHz, DMSO- d6) δ (ppm): 7,79 (td, 1H), 7,45 (t, 1H), 5,15 (m, 1H), 7,44 (m, 1H). tR (f) Condiciones HPLC: 2,09 min.

B. 3- difluorometoxi- 2- fluoro- fenilamina

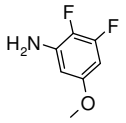
A una mezcla de 1- difluorometoxi- 2- fluoro- 3- nitro- benceno (2,16 g, 10,43 mmol) y cloruro de estaño (II) (6,92 g, 36,5 mmol) en 2- propanol (100 ml) se agregó cuidadosamente HCl (37%, 10,28 ml, 125 mmol) y la mezcla se agitó durante 30 min a 110 ° C. La mezcla de reacción se enfrió a temperatura ambiente, se diluyó con agua y el pH se ajustó a 10 por adición de NaOH 2N. La mezcla se extrajo con EtOAc y la capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró para proporcionar el compuesto del título. 1H RMN (400 MHz, DMSO- d6) δ (ppm): 7,06 (t, 1H), 6,95 (m, 1H), 6,87 (m, 1H), 6,55 (td, 1H), 5,04 (bs, 2H). tR (f) Condiciones HPLC: 1,93 min.

3- Ciclopropil- 2- fluoro- fenilamina



A una solución de 3- bromo- 2- fluoroanilina (200 mg, 1,05 mmol), ácido ciclopropilborónico (118 mg, 1,37 mmol), fosfato de potasio (782 mg, 3,68 mmoles), y triciclohexilfosfina (29,5 mg, 0,105 mmol) en tolueno (2,4 ml) y agua (120 l) se agregó Pd (OAc) $_2$ (11,8 mg, 0,05 mmol). La mezcla de reacción se desgasificó mediante la repetición alterna la aplicación de vacío y presión positiva de nitrógeno (3x), y después se calentó a 100 °C bajo nitrógeno durante la noche. La mezcla se enfrió a temperatura ambiente, se diluyó con agua, y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano a c- hexano/EtOAc 93- 7). TLC, R_f (c- hexano / EtOAc 2:1) = 0,7; EM (UPLC/MS): 152,0 [M+H]+.

2,3- difluoro- 5- metoxi- bencilamina



A. Éster metílico del ácido 2,3- difluoro- 5- metoxi- benzoico

A una solución de ácido 2,3- difluoro- 5- hidroxi- benzoico [749230- 51- 1] (1,00 g, 5,74 mmol; Melford Laboratories Ltd) en DMF (20 ml) se le añadió K_2CO_3 (1,99 g, 14,4 mmol) y MeI (0,79 ml, 12,6 mmol), seguido de agitación a temperatura ambiente durante una noche. La mezcla de reacción se diluyó con EtOAc, los extractos orgánicos se lavaron con una solución acuosa saturada de NH_4Cl (50 ml) y una solución acuosa saturada de $NaHCO_3$, se secaron (separador de fases) y se evaporaron bajo presión reducida. El residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 03:01) para proporcionar el compuesto del título en forma de un aceite incoloro. TLC, Rf (c-hexano/EtOAc 03:01) = 0,37; MS (LC/MS): 203,0 [M+H]+; tR (condiciones HPLC C): 4,72 min.

B. (2,3- difluoro- 5- metoxi- fenil)- metanol

A una solución de éster metílico del ácido 2,3- difluoro- 5- metoxi- benzoico (925 mg, 4,58 mmol) en THF (25 ml), enfriada a 0 ° C, se agregó una solución de $LiBH_4$ (199 mg, 9,15 mmol) en THF (5 ml). La mezcla de reacción se agitó a temperatura ambiente durante toda la noche. Se agregó una alícuota adicional de $LiBH_4$ (4 equiv) y se continuó la agitación a temperatura ambiente durante 6 h, y posteriormente a 60 °C durante la noche. La mezcla se diluyó con EtOAc, los extractos orgánicos se lavaron con solución acuosa de NaOH 1N (50 ml), se secaron (separador de fases) y se evaporaron al vacío para proporcionar el compuesto del título como un sólido blanco. TLC R_f (c- hexano/EtOAc 01:01) = 0,57; MS (LC/MS): 198,0 [M+Na]+; t_R (condiciones HPLC C): 3,74 min.

C. 1- Azidometil- 2 ,3- difluoro- 5- metoxi- benceno

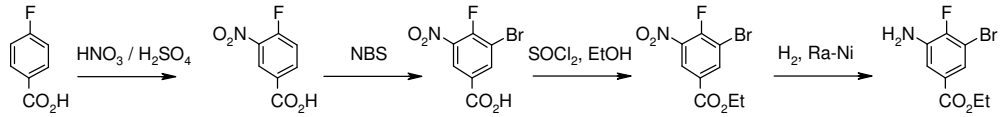
A una solución de (2,3- difluoro- 5- metoxi- fenil)- metanol (715 mg, 4,11 mmol) en tolueno (10 ml) se agregó DPPA (1,04 ml, 4,93 mmol) y DBU (0,805 ml, 5,34 mmol), seguido de agitación a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con EtOAc, los extractos orgánicos se lavaron con salmuera diluida (20 ml), se secaron (separador de fases) y se evaporaron al vacío. El residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 09:01) para proporcionar el compuesto del título en forma

de un aceite incoloro. TLC R_f (c- hexano/EtOAc 03:01) = 0,55; MS (LC/MS): 208,0 [M + NH4] +; t_R (condiciones HPLC C): 5,46 min.

D. 2,3- difluoro- 5- metoxi- bencilamina

A una solución de 1- azidometil- 2 ,3- difluoro- 5- metoxi- benceno (710 mg, 3,57 mmol) en EtOH (20 ml) se agregó Pd/C al 10% (70 mg) y la mezcla de reacción se agitó a temperatura ambiente durante la noche bajo una atmósfera de H_2. La mezcla de reacción se filtró a través de Celite, seguido por el lavado con EtOH y CH_2Cl_2. Los filtrados combinados se evaporaron al vacío y el residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (CH2Cl2/acetona 09:01, luego CH_2Cl_2/MeOH 9:1) para proporcionar el compuesto del título como un aceite amarillento. TLC R_f (CH_2Cl_2/MeOH 9:1) = 0,32; MS (LC/MS): 174,0 [M+H]+; tR (condiciones HPLC C): 2,30 min.

<u>Éster etílo del ácido 3- amino- 5- bromo- 4- fluoro- benzoico</u>



A. - 3- nitro- benzoico ácido 4- fluoro

Se agregó por goteo conc. HNO_3 (79 ml) a una solución de ácido 4- fluoro- benzoico (70 g, 0,5 mol) en conc. H_2SO_4 (500 ml) a 0°C. La mezcla se agitó durante 4 h a temperatura ambiente y después se vertió en agua helada (3,0 L). El precipitado se separó por filtración, se lavó dos veces con agua (0,5 L) y se secó para proporcionar el compuesto del título como un sólido blanco. 1H- RMN (300 MHz, CDCl3): δ (ppm) 11,0 (s, br, 1H), 8,86 (m, 1H), 8,42 (m, 1H), 7,47 (m, 1H).

B. Ácido 3- bromo- 4- fluoro- 5- nitro- benzoico

NBS (47.9 g, 0,268 moles) se agregó en porciones a una solución de ácido 4- fluoro- 3- nitro- benzoico (41.5 g, 0,224 mol) en conc. H_2SO_4 (0,35 L). La mezcla de reacción se agitó durante 5 horas a 65 º C y después se vertió en hielo- agua (1,5 L). El precipitado se separó por filtración, se lavó dos veces con agua (300 ml) y se secó para proporcionar el compuesto del título como un sólido blanco. 1H- RMN (300 MHz, CDCl3): δ (ppm) 10,7 (s, br, 1H), 8,76 (m, 1H), 8,62 (m, 1H).

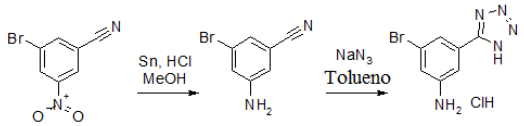
C. Éster Etílico del ácido 3- Bromo- 4- fluoro- 5- nitro- benzoico

Se agregó por goteo $SOCl_2$ (33,7 g, 0,283 mol) a una solución de ácido 3- bromo- 4- fluoro- 5- nitro- benzoico (37.4 g, 0,142 mol) en EtOH (300 ml). La mezcla de reacción se sometió a reflujo durante la noche, se enfrió a temperatura ambiente y posteriormente se concentró a presión reducida. El residuo se disolvió en EtOAc (300 ml), se lavó dos veces con agua (50 ml), se secó (Na_2SO_4) y se concentró para proporcionar el compuesto del título como sólido de color amarillo. 1H- RMN (300 MHz, $CDCl_3$): δ (ppm) 8,65 (m, 1H), 8,53 (m, 1H), 4,46 (m, 2H), 1,45 (m, 3H).

D. Éster etílico del ácido 3- amino- 5- bromo- 4- fluoro- benzoico

Una mezcla de éster etílico del ácido 3- bromo- 4- fluoro- 5- nitro- benzoico (ácido 20 g, 2,2 mol) y 3g de Raney- Ni en EtOH (250 ml) se hidrogenó a temperatura ambiente (1 atm) durante la noche. La mezcla de reacción se filtró, el filtrado se concentró a presión reducida y el residuo se lavó con éter de petróleo para proporcionar el compuesto del título como un sólido blanco. (400 MHz, DMSO- d6): δ (ppm) 7,38 (dd, 1H), 7,26 (dd, 1H), 5,81 (s, 2H), 4,26 (q, 2H), 1,29 (t, 3H).

<u>Diclorhidrato de 3- bromo- 5- (1H- tetrazol- 5- il)- fenilamina</u>



A. 3- Amino- 5- bromo- benzonitrilo

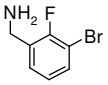
A una solución de 3- bromo- 5- nitrobenzonitrilo (1 g, 4,4 mmol) en MeOH (50 ml) se le añadió estaño (5,23 g, 44 mmol) y HCl 3 N (44 ml, 132 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h, se filtró y se lavó con MeOH. El filtrado se concentró al vacío, y la fase acuosa restante se basificó a pH = 12 por adición de NaOH 4N. La capa acuosa se extrajo dos veces con EtOAc (100 ml), se secaron las fases orgánicas combinadas (Na_2SO_4) y se evaporaron al vacío para proporcionar el compuesto del título como un sólido amarillento. MS (LC/MS): 197,0 [M+H]+; t_R (condiciones HPLC C): 4,30 min.

B. **Clorhidrato de 3- bromo- 5- (1H- tetrazol- 5- il)- fenilamina**

A una solución de 3- amino- 5- bromo- benzonitrilo (200 mg, 1,02 mmol) en tolueno (2 ml) se agregó HCl 6 N (0,220 ml, 1,32 mmol), trietilamina (0,184 ml, 1,32 mmol) y azida de sodio (86,0 mg, 1,32 mmol). La mezcla de reacción se agitó a 100 º C durante 30 min en un

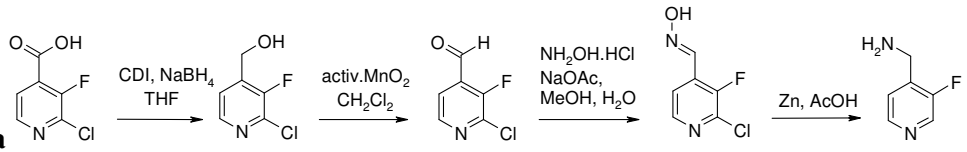
aparato de microondas (Personal Chemistry, Biotage), y después de enfriar a temperatura ambiente se diluyó luego con CH_2Cl_2/MeOH (4:1) y se lavó con 10 ml de agua. La fase orgánica se descartó, y la fase acuosa se acidificó a pH = 1 mediante la adición de HCl 12N. La capa acuosa fue liofilizada durante la noche para proporcionar el compuesto del título como un sólido amarillento. MS (LC/MS): 239,3 [M+H]+; tR (condiciones HPLC C): 3,23 min.

Clorhidrato 3- Bromo- 2- fluoro- bencilamina



Una mezcla de 3- bromo- 2- fluoro- benzonitrilo (1,0 g, 5,0 mmol) y Raney- Ni en EtOH (NH_3 al 4%) (30 ml) se agitó bajo una atmósfera de hidrógeno (1 atm) a temperatura ambiente durante 6,5 h. La mezcla de reacción se filtró a través de Celite, se enjuagó con CH_2Cl_2, y el filtrado se concentró a presión reducida. La mezcla en bruto se recogió en HCl acuoso 1 M, la capa orgánica se separó, y la fase acuosa fue liofilizada durante la noche para proporcionar el compuesto del título como un sólido blanco.MS (LC/MS): 206,0 [M+H]+; tR (condiciones HPLC C): 2,21 min.

C- (3- fluoro- piridin- 4- il)- metilamina



A. (2- Cloro- 3- fluoro- piridin- 4- il)- metanol

Se agregó carbonildiimidazol (1,80 g, 11,1 mmol) a una solución de ácido 2- cloro- 3- fluoro- isonicotínico (1,3 g, 7,41 mmol) en THF (21,2 ml). La mezcla de reacción se agitó a temperatura ambiente durante la noche y después se agregó a una solución de $NaBH_4$ fría (0 º C) (1,40 g, 37 mmol) en agua (52,9 ml). La mezcla se agitó durante 10 min a 0 ° C, y luego se agregó cuidadosamente HCl 1 M para interrumpir la reacción (precaución: hay liberación de H2). Los volátiles se eliminaron mediante evaporación rotatoria y el residuo se disolvió en $NaHCO_3$ acuoso saturado. La mezcla se extrajo repetidamente con CH_2Cl_2, se secaron los extractos orgánicos combinados (separador de fases) y se concentraron al vacío. La purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (gradiente de eluyente: c-hexano/EtOAc 04:01- 02:01) proporcionó el compuesto del título como un sólido blanco. TLC, Rf (c- hexano/EtOAc 01:01) = 0,37; MS (LC/MS): 162,0 [M+H]+; tR (condiciones HPLC B): 1,60 min.

B. 2- Cloro- 3- fluoro- piridina- 4- carbaldehído

Una mezcla de (2- cloro- 3- fluoro- piridin- 4- il)- metanol (0,9 g, 5,76 mmol) y MnO_2 activado (5,76 g, 66,2 mmol) en CH_2Cl_2 se agitó a temperatura ambiente durante la noche. El sólido se separó por filtración y se lavó con CH_2Cl_2, y el filtrado se concentró bajo presión ligeramente reducida para proporcionar el compuesto del título como un líquido incoloro. MS (LC/MS): 191,0 [M + MeOH] +; tR (condiciones HPLC B): 2,02 min.

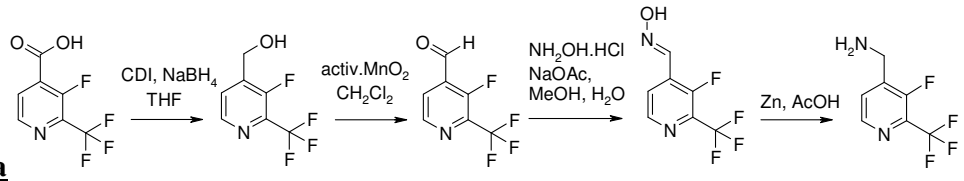
C. Oxima del 2- Cloro- 3- fluoro- piridina- 4- carbaldehído

A una solución de 2- cloro- 3- fluoro- piridina- 4- carbaldehído (1,20 g, 5,64 mmol) en MeOH (48 ml) y agua (8 ml) se añadieron hidrocloruro de hidroxilamina (0,59 g, 8,46 mmol) y acetato de amonio (1,30 g, 16,9 mmoles), y se continuó agitando a temperatura ambiente durante una noche. La mezcla de reacción se concentró al vacío, y el residuo se suspendió en CH_2Cl_2/MeOH 9:1. El precipitado se separó por filtración, se lavó con CH_2Cl_2 y se secó para proporcionar el compuesto del título como un sólido blanco. MS (LC/MS): 175,0 [M+H]+; tR (condiciones HPLC B): 2,78 min.

D. C- (3- fluoro- piridin- 4- il)- metilamina

Se agregó polvo de cinc (2,52 g, 38,6 mmol) a temperatura ambiente a una solución de oxima del 2- cloro- 3- fluoro- piridina- 4- carbaldehído (1,34 g, 6,29 mmol) en ácido acético (30 ml). La mezcla de reacción se agitó a temperatura ambiente durante 2 h, después se concentró al vacío. El residuo oleoso de color se particionó entre CH_2Cl_2 y HCl 1N. Las capas se separaron y la fase acuosa se extrajo dos veces con CH_2Cl_2. El pH de la capa acuosa se ajustó a pH = 9 con NaOH 1 N, y la suspensión blanca resultante se extrajo repetidamente con CH_2Cl_2. Los extractos orgánicos combinados se secaron (separador de fases) y se concentraron a vacío para proporcionar el compuesto del título como un aceite de color amarillo. MS (LC/MS): 127,0 [M+H]+; tR (condiciones HPLC C): 0,50 min.

C- (3- fluoro- 2- trifluorometil- piridin- 4- il)- metilamina



A. (3- fluoro- 2- trifluorometil- piridin- 4- il)- metanol

Se agregó carbonildiimidazol (1,16 g, 7,17 mmol) a una solución de Ácido 3- fluoro- 2- trifluorometil- isonicotínico (1,00 g, 4,78 mmol) en THF (13,7 ml). La mezcla de reacción se agitó a temperatura ambiente durante la noche y después se agregó a una solución fría (0 º C) solución de $NaBH_4$ (0,905 g, 23,9 mmol) en agua (34,2 ml). La mezcla se agitó durante 10 min a 0 ° C, y luego HCl 1 M se agregó cuidadosamente (precaución: hay liberación de H_2). Los volátiles se eliminaron bajo presión reducida, y el residuo se disolvió en $NaHCO_3$ acuoso saturado. La mezcla se extrajo repetidamente con CH_2Cl_2, se secaron los extractos orgánicos combinados (separador de fases) y se concentraron al vacío. La purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (gradiente de eluyente: c-hexano/EtOAc 1:01 a 0:1) proporcionó el compuesto del título como un aceite de color amarillo. TLC, Rf (c- hexano/EtOAc 01:01) = 0,27; MS (LC/MS): 196,0 [M+H]+; tR (condiciones HPLC B): 2,62 min.

B. 3- fluoro- 2- trifluorometil- piridina- 4- carbaldehído

Una mezcla de (3- fluoro- 2- trifluorometil- piridin- 4- il)- metanol (0,620 g, 3,18 mmol) y MnO_2 activado (3,20 g, 36,5 mmol) en CH_2Cl_2 se agitó a temperatura ambiente durante la noche. El sólido se separó por filtración, se lavó con CH_2Cl_2, y el filtrado se concentró a presión ligeramente reducida para proporcionar el compuesto del título como un líquido amarillo. MS (LC/MS): 212,0 [M + NH4] +, 226,0 [M + MeOH] +. tR (condiciones HPLC C): 3,26 min.

C. Oxima del 3- fluoro- 2- trifluorometil- piridina- 4- carbaldehído

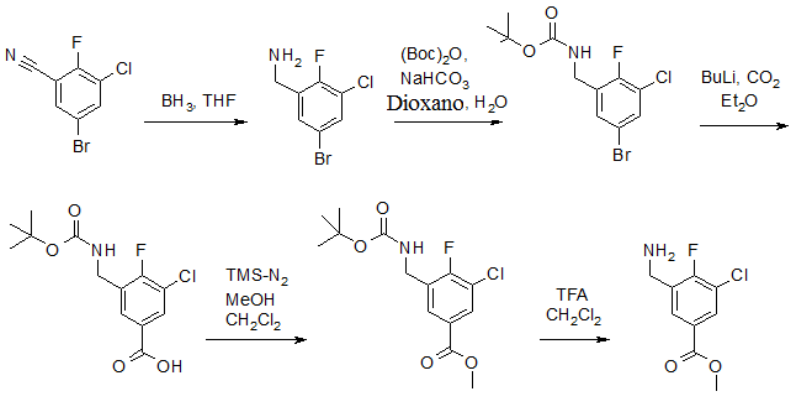
A una solución de 3- fluoro- 2- trifluorometil- piridina- 4- carbaldehído (0,495 g, 2,05 mmol) en MeOH (17,6 ml) y agua (2,9 ml) se agregó hidrocloruro de hidroxilamina (0,214 g, 3,08 mmol) y acetato de amonio (0,474 g, 6,15 mmoles), y la mezcla resultante se agitó a temperatura ambiente durante la noche. Los volátiles se eliminaron al vacío, y el residuo se suspendió en CH_2Cl_2/MeOH 9:1.El precipitado se separó por filtración, se lavó con CH_2Cl_2 y se secó para proporcionar el compuesto del título como un sólido blanco. MS (LC/MS): 209,0 [M+H]+; tR (condiciones HPLC C): 4,28 min.

D. C- (3- fluoro- 2- trifluorometil- piridin- 4- il)- metilamina

Se agregó polvo de cinc (0,63 g, 9,62 mmol) a temperatura ambiente a una solución de oxima del 3- fluoro- 2- trifluorometil- piridina- 4- carbaldehído (0,460 g, 1,57 mmol) en ácido acético (8 ml). La mezcla de reacción se agitó a temperatura ambiente durante 3 h, después se

filtró a través de un filtro de 0,45 micras, y el filtrado se concentró al vacío. El residuo oleoso de color se particionó entre CH_2Cl_2 y HCl 1 N, las capas se separaron y la fase acuosa se extrajo dos veces con CH_2Cl_2. El pH de la capa acuosa se ajustó a pH = 9 mediante la adición de una solución acuosa saturada de $NaHCO_3$, y la suspensión blanca resultante se extrajo cuatro veces con CH_2Cl_2. Los extractos orgánicos combinados se secaron (separador de fases) y se concentraron al vacío para proporcionar el compuesto del título como un aceite de color amarillo. MS (LC/MS): 195,0 [M+H]+; tR (condiciones HPLC C): 2,47 min.

<u>Éster metílico del ácido 3- aminometil- 5- cloro- 4- fluoro- benzoico</u>



A. 5- bromo- 3- cloro- 2- fluoro- bencilamina

A una solución de 5- bromo- 3- cloro- 2- fluorobenzonitrilo (13,2 g, 56,3 mmol) en THF (200 ml) se agregó bajo una atmósfera de argón una solución 1 M de complejo de boro-tetrahidrofurano (70,4 ml, 70,4 mmol) por goteo durante 30 min. La mezcla de reacción se calentó a 65 ° C durante 1,5 h. Después de enfriar a temperatura ambiente, una solución de HCl 2 N (70,4 ml, 141 mmol) se agregó por goteo durante 30 min. La mezcla de reacción se calentó de nuevo a 65 °C durante 1 h y posteriormente se enfrió a temperatura ambiente. Los volátiles se evaporaron y el residuo se recogió en solución acuosa de HCl 1 M, seguido por extracción con EtOAc (3x150 ml). Los extractos orgánicos combinados se lavaron con solución acuosa 1 M de HCl. Las fases ácidas combinadas se basificaron a pH = 12 por adición de solución acuosa de NaOH 4 M y después se extrajeron con EtOAc (3x150 ml). Los orgánicos se secaron (Na_2SO_4), se filtraron y se evaporaron al vacío para proporcionar el compuesto del título como un aceite amarillento. MS (LC/MS): 238,0 [M+H]+; tR (condiciones HPLC C): 3,25 min. El material así obtenido se utilizó directamente en la siguiente paso sin purificación adicional.

B. Éster terc- butílo del ácido (5- bromo- 3- cloro- 2- fluoro- bencil)- carbámico

A una solución de 5- bromo- 3- cloro- 2- fluoro- bencilamina (10,6 g, 44,3 mmol) en dioxano/H_2O 03:01 (280 ml) se agregó Boc_2O (10,3 ml, 44,3 mmol) y $NaHCO_3$ (11,2 g, 133 mmol) . La mezcla de reacción se agitó a temperatura ambiente durante 60 h. Luego los volátiles se retiraron bajo presión reducida, el residuo se recogió en agua, y la capa acuosa se extrajo dos veces con EtOAc (200 ml). Los orgánicos se secaron (Na_2SO_4), se filtraron y se evaporaron al vacío para proporcionar el compuesto del título como un sólido blanco. MS (LC/MS): 284,0 [M+H]+; tR (condiciones HPLC C): 5,98 min. El material así obtenido se utilizó directamente en la siguiente paso sin purificación adicional.

C. Ácido 3 - (terc- butoxicarbonilamino- metil)- 5- cloro- 4- fluoro- benzoico

A una solución de éster terc- butilo del ácido (5- bromo- 3- cloro- 2- fluoro- bencil)- carbamato (8 g, 23,6 mmol) en Et_2O (300 ml), se enfrió a - 78 ° C, se agregó bajo una atmósfera de argón n - BuLi (1,6 M en hexano; 37,5 ml, 60,1 mmol) por goteo durante 30 min. La mezcla de reacción se agitó a - 78 °C durante 15 min, luego se burbujeó gas de CO_2 a través de la mezcla durante 1 min. Después de agitar durante 15 min, una solución saturada de NH_4Cl (50 ml) por goteo durante 15 min, y la mezcla de reacción se dejó calentar hasta temperatura ambiente. La fase acuosa se basificó a pH = 12 por adición de una solución acuosa de NaOH 4 M y después se lavó con EtOAc (100 ml). La capa acuosa se acidificó a pH = 1 por adición de una solución acuosa de HCl 4M y se extrajo con EtOAc (3x200 ml). Los extractos orgánicos combinados se secaron (Na_2SO_4) y se concentraron al vacío para proporcionar el compuesto del título como un sólido de color blanco. MS (LC/MS): 302,0 [MH] - ; tR (condiciones HPLC C): 4,79 min.

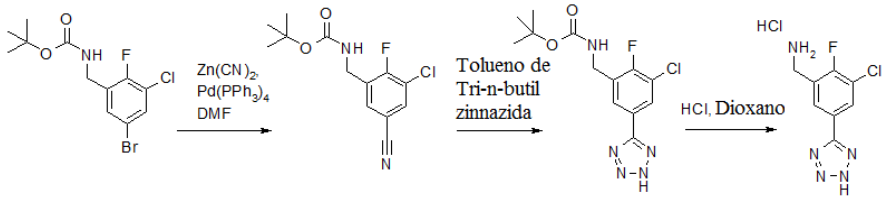
D. Éster metílico del ácido 3 - (terc- butoxicarbonilamino- metil)- 5- cloro- 4- fluoro- benzoico

A una solución de ácido 3- (terc- butoxicarbonilamino- metil)- 5- cloro- 4- fluoro- benzoico (4,00 g, 13,2 mmol) en CH_2Cl_2 (100 ml) se agregó MeOH (6,94 ml, 171 mmol) y, posteriormente, trimetilsilildiazometano (8,56 ml, 17,1 mmol) de una manera por goteo durante 15 min. Se continuó la agitación a temperatura ambiente durante 4,5 h. Luego los volátiles se evaporaron bajo presión reducida para proporcionar el compuesto del título como un aceite incoloro, que se utilizó directamente en la siguiente paso sin purificación adicional. TLC Rf (c-hexano/EtOAc 06:01) = 0,40; tR (condiciones HPLC C): 5,56 min.

E. Éster metílico del ácido 3- aminometil- 5- cloro- 4- fluoro- benzoico

A una solución de éster metílico del ácido 3 - (terc- butoxicarbonilamino- metil)- 5- cloro- 4- fluoro- benzoico (4,25 g, 13,4 mmol) en CH_2Cl_2 (70 ml) se agregó TFA (10,3 ml, 134 mmol), y se continuó agitando a temperatura ambiente durante la noche. Luego se agregó metanol a la mezcla de reacción, y los volátiles se eliminaron al vacío. El residuo se recogió en metanol y se concentró de nuevo a presión reducida para proporcionar el compuesto del título como un sólido de color beige. MS (LC/MS): 218,0 [M+H]+; tR (condiciones HPLC C): 3,10 min. El material así obtenido se usó en la siguiente paso de reacción sin purificación adicional.

3- cloro- 2- fluoro- 5- (2H- tetrazol- 5- il)- bencilamina



A. Éster de terc- butilo del ácido (3- Cloro- 5- ciano- 2- fluoro- bencil)- carbámico

A una solución de éster terc- butilo del ácido (5- bromo- 3- cloro- 2- fluoro- bencil)- carbamato (3 g, 8,86 mmol) en DMF (45 ml) se agregó cianuro de cinc (1,04 g, 8,86 mmol) y Pd (Ph_3P) 4 (1,02 g, 0,886 mmol). La mezcla de reacción se agitó a 120 º C durante 15 min en un aparato de microondas (Personal Chemistry, Biotage). Después de enfriar a temperatura ambiente, la mezcla se filtró a través de Celite y se lavó con EtOAc. El filtrado se lavó con una solución de NH_4Cl acuoso saturado (4x75 ml), se secó (Na_2SO_4) y se evaporó al vacío. La purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (gradiente de eluyente: c- hexano/EtOAc 09:01- 03:01) proporcionó el compuesto del título como un sólido blanco. TLC Rf (c- hexano/EtOAc 03:01) = 0,35; tR (condiciones HPLC C): 5,28 min.

B. Éster terc- butilo del ácido [3- cloro- 2- fluoro- 5- (2H- tetrazol- 5- il)- bencil]- carbámico

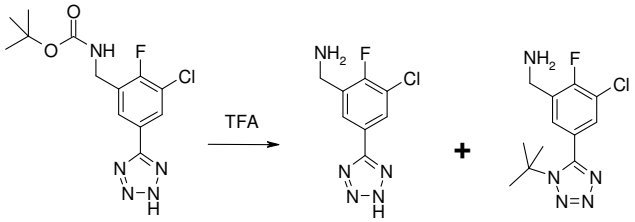
A una solución de éster terc- butílo del ácido (3- cloro- 5- ciano- 2- fluoro- bencil)- carbámico (1,30 g, 4,57 mmol) en tolueno (35 ml) se agregó tri- n- butil- tinazida (6,26 ml, 22,8 mmol). La mezcla de reacción se agitó a 135 º C durante 90 min en un horno de microondas (Personal Chemistry, Biotage). Después de enfriar a temperatura ambiente, la mezcla se diluyó con EtOAc y se lavó con una solución de NH_4Cl acuoso saturado (3x100 ml). Después de lavar la fase orgánica con 70 ml de una solución acuosa de NaOH 1M y la separación de las fases, se obtuvieron tres capas: la fase orgánica superior se descartó, la capa aceitosa media se aisló y se

diluyó con EtOAc. La fase acuosa se acidificó con solución acuosa de HCl 4 M, se extrajo dos veces con EtOAc (50 ml). Todos los compuestos orgánicos se combinaron, se secaron (separador de fases) y se evaporaron al vacío para proporcionar el compuesto del título. Sólido amarillento. MS (LC/MS): 328,0 [M+H]+, 349,9 [M+Na]+, 271,9 [MH- tBu] +; tR (condiciones HPLC C): 4,74 min. El material así obtenido se usó en la siguiente paso de reacción sin purificación adicional.

C. Clorhidrato de 3- cloro- 2- fluoro- 5- (2H- tetrazol- 5- il)- bencilamina

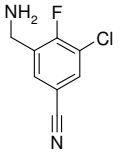
A una solución de éster terc- butilo del ácido [3- cloro- 2- fluoro- 5- (2H- tetrazol- 5- il)- bencil]- carbamato (1,06 g, 3,23 mmol) en dioxano (20 ml) se agregó una solución de HCl 4 M en dioxano (8,09 ml, 32,3 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 72 h y luego se liofilizó durante la noche para proporcionar el compuesto del título como un sólido blanco. MS (LC/MS): 228,0 [M+H]+; tR (condiciones HPLC C): 2,68 min.

5 - (1- terc- butil- 1H- tetrazol- 5- il)- 3- cloro- 2- fluoro- bencilamina



A una solución de éster terc- butilo del ácido [3- cloro- 2- fluoro- 5- (2H- tetrazol- 5- il)- bencil] - carbamato (0,15 g, 0,46 mmol) en CH_2Cl_2 (4 ml) se agregó TFA (1,5 ml). La mezcla de reacción se agitó a temperatura ambiente durante 2 h y el solvente se eliminó al vacío para proporcionar el compuesto del título como una mezcla 2:1 de 5 - (1- terc- butil- 1H- tetrazol- 5- il)- 3- cloro - 2- fluoro- bencilamina y 3- cloro- 2- fluoro- 5- (2H- tetrazol- 5- il)- bencilamina, que se utilizó en los pasos siguientes sin separación. MS (LC/MS): 228,0 y 284,0 [M+H]+. t_R (condiciones HPLC C): 2,16 y 2,99 min.

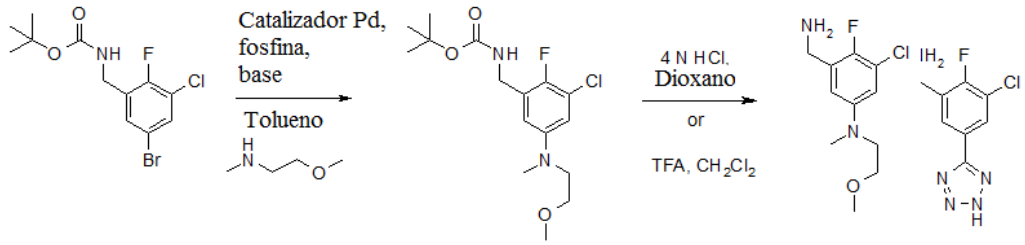
3- aminometil- 5- cloro- 4- fluoro- benzonitrilo



A una solución de éster terc- butilo del ácido (3- cloro- 5- ciano- 2- fluoro- bencil)- carbamato (645 mg, 2,27 mmol) en CH_2Cl_2 (15 ml) se agregó TFA (1,75 ml, 22,7 moles), y se

continuó agitando a temperatura ambiente durante la noche. Los volátiles se eliminaron a presión reducida, se agregó agua y la mezcla se lavó con EtOAc. La capa acuosa se basificó a pH = 12 por adición de solución de NaOH 4M y se extrajo dos veces con EtOAc. Los extractos orgánicos combinados se secaron (separador de fases) y se evaporaron para proporcionar el compuesto del título como un sólido de color beige. MS (LC/MS): 185,0 [M+H]+; tR (condiciones HPLC C): 2,62 min.

Esquema C1: Preparación de (3- aminometil- 5- cloro- 4- fluoro- fenil) - (2- metoxi- etil)- metil- amina



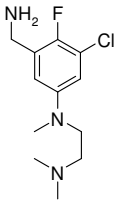
A. Éster terc- butilo del ácido {3- cloro- 2- fluoro- 5- [(2- metoxi- etil)- metil- amino]- bencil}- carbámico

Una suspensión de éster terc- butilo del ácido (5- bromo- 3- cloro- 2- fluoro- bencil)- carbámico (250 mg, 0,7 mmol), N- metoxietil- metilamina (99 mg, 1,1 mmol), terc- butóxido sódico (142 mg, 1,5 mmoles) y di- µ- bromobis- (tri- terc- butilfosfino) dipaladio (I) [CAS 185812- 86- 6] (29 mg, 0,04 mmol) en tolueno (5 ml) se selló en un horno de microondas vial y se calentó durante 30 min a 140 °C (Emrys Optimizer, química personal). La mezcla de reacción se apagó mediante la adición de $NaHCO_3$ acuoso saturado, se extrajo con EtOAc, se secó (Na_2SO_4) y se evaporó al vacío. El producto crudo se purificó por HPLC preparativa RP- (Waters Sunfire, C18- ODB, 5 micras, 30x100 mm, 5- 100% CH_3CN/H_2O/20 min, CH_3CN al 100%/ 2 min, CH_3CN y H_2O que contiene TFA al 0.1%, flujo: 40 ml / min) para proporcionar el compuesto del título después de la liofilización. MS (LC/MS): 347,0 [M] +. tR (condiciones HPLC C): 5,23 min.

B. (3- aminometil- 5- cloro- 4- fluoro- fenil) - (2- metoxi- etil)- metil- amina

A una mezcla de éster terc- butilo del ácido {3- cloro- 2- fluoro- 5- [(2- metoxi- etil)- metil- amino]- bencil}- carbámico (60 mg, 0,17 mmol) en MeOH (2 ml) se agregó una solución de HCl 4N en dioxano (2 ml). La mezcla de reacción se agitó durante 1 h a temperatura ambiente y el solvente se eliminó al vacío para proporcionar el compuesto del título. MS (LC/MS): 247,0 [M] +. tR (condiciones HPLC C): 3,15 min.

N- (3- aminometil- 5- cloro- 4- fluoro- fenil)- N, N ', N'- trimetil- etano- 1 ,2- diamina

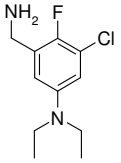


se preparó de acuerdo con el Esquema C1 (paso B) a partir de éster terc- butilo del ácido {3- cloro- 5- [(2- dimetilamino- etil)- metil- amino]- 2- fluoro- bencil}- carbámico y HCl 4 N en dioxano . MS (LC- MS): 260,0 [M] +

Éster terc- butilo del ácido {3- cloro- 5- [(2- dimetilamino- etil)- metil- amino]- 2- fluoro- bencil}- carbámico

se preparó de acuerdo con el Esquema C1 (paso A) a partir de éster terc- butilo del ácido (5- bromo- 3- cloro- 2- fluoro- bencil)- carbámico (300 mg, 0,89 mmol), N, N, N '- trimetil- etilendiamina (136 mg, 1,3 mmol), terc- butóxido sódico (170 mg, 1,8 mmoles) y di- µ bromobis- (tri- terc- butilfosfino) dipaladio (I) [CAS 185812- 86- 6] (34 mg, 0.04 sodio mmol). MS (LC- MS): 360,3 [M] +; tR (condiciones HPLC C): 4,15 min.

(3- aminometil- 5- cloro- 4- fluoro- fenil)- dietil- amina

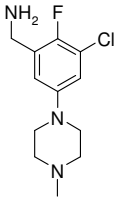


se preparó de acuerdo con el Esquema C1 (paso B) a partir de éster terc- butilo del ácido (3- cloro- 5- dietilamino- 2- fluoro- bencil)- carbámico y TFA en CH_2Cl_2. MS (LC- MS): 231,0 [M] +; t_R (condiciones HPLC C): 2,29 min.

Éster terc- butilo del ácido (3- Cloro- 5- dietilamino- 2- fluoro- bencil)- carbámico

se preparó de acuerdo con el Esquema C1 (paso A) a partir de éster terc- butilo del ácido (5- bromo- 3- cloro- 2- fluoro- bencil)- carbámico (300 mg, 0,89 mmol), dietilamina (0,14 ml, 1,3 mmol), terc- butóxido sódico (170 mg, 1,8 mmoles) y di- µ- bromobis- (tri- terc- butilfosfino) dipaladio (I) [CAS 185812- 86- 6] (34 mg, 0,04 mmol). MS (LC- MS): 331,2 [M] +; tR (condiciones HPLC C): 4,08 min.

3- cloro- 2- fluoro- 5- (4- metil- piperazin- 1- il)- bencilamina

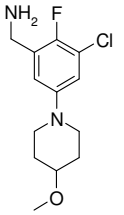


se preparó de acuerdo con el Esquema C1 (paso B) a partir de éster terc- butilo del ácido [3- cloro- 2- fluoro- 5- (4- metil- piperazin- 1- il)- bencil]- carbámico y HCl 4 N en dioxano. MS (LC- MS): 258,0 [M] +; tR (condiciones HPLC f): 0,74 min.

Éster terc- butilo del ácido [3- cloro- 2- fluoro- 5- (4- metil- piperazin- 1- il)- bencil]- carbámico

se preparó de acuerdo con el Esquema C1 (paso A) a partir de éster terc- butilo del ácido (5- bromo- 3- cloro- 2- fluoro- bencil)- carbámico (200 mg, 0,59 mmoles), 1- metilpiperazina (71 mg, 0,71 mmol), carbonato de cesio (269 mg, 0,83 mmol), acetato de paladio (II) (6,6 mg, 0,03 mmol) y 4,5- bis (difenilfosfino) - 9,9- dimetilxanteno (24 mg, 0,04 mmol). MS (LC- MS): 358,0 [M] +; tR (condiciones HPLC C): 3,98 min.

3- cloro- 2- fluoro- 5- (4- metoxi- piperidin- 1- il)- bencilamina

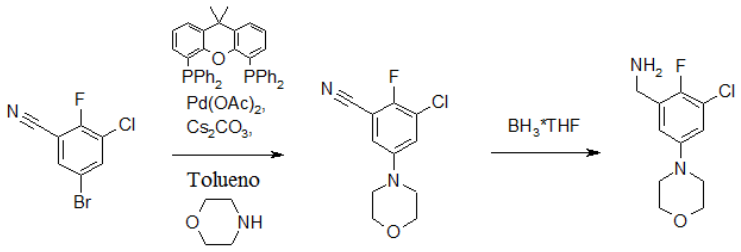


se preparó de acuerdo con el Esquema C1 (paso B) a partir de éster terc- butilo del ácido [3- cloro- 2- fluoro- 5- (4- metil- piperazin- 1- il)- bencil]- carbámico y HCl 4 N en dioxano. MS (LC- MS): 273,0 [M] +; tR (condiciones HPLC C): 2,97 min.

Éster terc- butilo del ácido [3- cloro- 2- fluoro- 5- (4- metoxi- piperidin- 1- il)- bencil]- carbámico

se preparó de acuerdo con el Esquema C1 (paso A) a partir de éster terc- butilo del ácido (5- bromo- 3- cloro- 2- fluoro- bencil)- carbámico (250 mg, 0,74 mmoles), 1- metoxipiperidina (102 mg, 0,89 mmol), carbonato de cesio (337 mg, 1,0 mmol), acetato de paladio (II) (8,3 mg, 0,04 mmol) y 4,5- bis (difenilfosfino) - 9,9- dimetilxanteno (30 mg, 0,05 mmol). MS (LC- MS): 373,0 [M] +; tR (condiciones HPLC C): 4,68 min.

3- cloro- 2- fluoro- 5- morfolin- 4- il- bencilamina



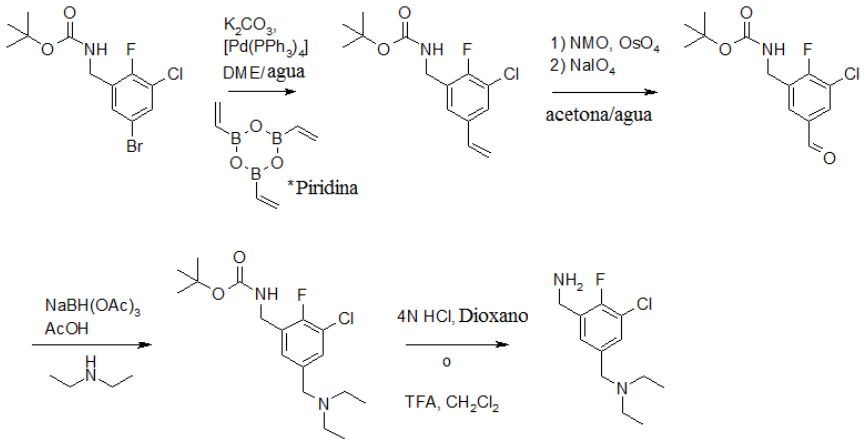
A. 3- Cloro- 2- fluoro- 5- morfolin- 4- il- benzonitrilo

Una suspensión de 5- bromo- 3- cloro- 2- fluoro- benzonitrilo (200 mg, 0,85 mmol), morfolina (74 mg, 0,85 mmol), carbonato de cesio (389 mg, 1,2 mmol), acetato de paladio (II) (10 mg, 0,04 mmol) y 4,5- bis (difenilfosfino) - 9,9- dimetilxanteno (35 mg, 0,06 mmol) en tolueno (5 ml) se selló en un vial de microondas y se calentó durante 30 min a 140 °C (Emrys Optimizer; química personal). La mezcla de reacción se apagó mediante la adición de $NaHCO_3$ acuoso saturado, se extrajo con EtOAc, se secó (Na_2SO_4) y el solvente se eliminó al vacío para proporcionar el compuesto del título que se utilizó sin purificación adicional en la siguiente paso.TLC Rf (hexano / EtOAc 1:1) = 0,60; tR (condiciones HPLC c): 5,28 min.

B. 3- Cloro- 2- fluoro- 5- morfolin- 4- il- bencilamina

A una solución de 3- cloro- 2- fluoro- 5- morfolin- 4- il- benzonitrilo (215 mg, 0,85 mmol) en THF (2 ml) se agregó por goteo una solución de BH_3- THF. La mezcla de reacción se calentó a reflujo durante varias horas, se enfrió a temperatura ambiente y se apagó cuidadosamente mediante la adición de metanol. El solvente se eliminó al vacío y el producto crudo se purificó por HPLC RP- preparativa (Waters Sunfire, C18- ODB, 5 micras, 30x100 mm, 5- 100% CH_3CN/H_2O/20 min, CH_3CN al 100%/ 2 min, CH_3CN y H_2O que contiene 0.1% TFA, flujo: 40 ml / min) para proporcionar el compuesto del título . MS (LC/MS): 244,9 [M] +; tR (condiciones HPLC C): 3,02 min.

Esquema C2: preparación de (3- aminometil- 5- cloro- 4- fluoro- bencil)- dietil- amina



A. Éster terc- butilo del ácido (3- Cloro- 2- fluoro- 5- vinil- bencil)- carbámico

A una solución de éster terc- butílo del ácido (5- bromo- 3- cloro- 2- fluoro- bencil)- carbámico (6 g, 17,7 mmol) en DME (100 ml) se agregó Pd $(Ph_3)_4$ (1,0 g, 0,9 mmol) bajo atmósfera de argón y la mezcla se agitó durante 30 min a temperatura ambiente. Después de la adición de complejo anhídrido vinil borónico- piridina (4,3 g, 17,7 mmol), agua (25 ml) y K_2CO_3 (2,45 g, 17,7 mmol), la reacción se calentó a reflujo durante 7 h. La mezcla de reacción se concentró al vacío hasta la mitad del volumen, se apagó mediante la adición de $NaHCO_3$ acuoso saturado y se extrajo EtOAc. Después del secado (Na_2SO_4), el solvente se eliminó al vacío y el residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (eluyente: hexano / EtOAc 09:01- 04:01) para proporcionar el compuesto del título en forma de un aceite incoloro. 1H- RMN (500 MHz, DMSO): δ (ppm) 7,62 (d, 1H), 7,45 (m, 1H,- NH), 7,35 (d, 1H), 6,68 (dd, 1H), 5,82 (d, 1H), 5,32 (d, 1H), 4,18 (d, 2H), 1,39 (s, 9H).

B. Éster terc- butilo del ácido (3- cloro- 2- fluoro- 5- formil- bencil)- carbámico

A una solución de éster terc- butílo del ácido (3- cloro- 2- fluoro- 5- vinil- bencil)- carbámico (2,7 g, 9,5 mmol) en acetona (20 ml) se agregó monohidrato de N- metilmorfolina- N- óxido (1,5 g, 11 mmol) y una solución de osmiumtetraoxido acuoso al 4% (3,7 ml, 0,5 mmol). La reacción se agitó durante 1 h, se agregó una solución acuosa saturada de $Na_2S_2O_3$ y se continuó la agitación durante una hora. Después de la extracción con EtOAc y la eliminación del solvente al vacío, el residuo se disolvió en acetona / agua (3:1, 40 ml) y se agregó $NaIO_4$ (4,0 g, 19 mmol). Después de agitar durante 2 h a temperatura ambiente, la mezcla de reacción se filtró, se lavó con EtOAc, se extrajo con EtOAc, se secó (Na_2SO_4) y el solvente se eliminó al vacío para proporcionar el compuesto del título que se utilizó sin purificación adicional. tR (condiciones HPLC C): 5,22 min.

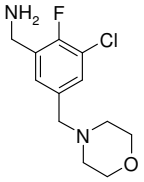
C. Éster terc- butilo del ácido (3- Cloro- 5- dietilaminometil- 2- fluoro- bencil) carbámico

Una solución de éster terc- butilo del ácido (3- cloro- 2- fluoro- 5- formil- bencil)- carbámico (200 mg, 0,7 mmol), dietilamina (51 mg, 0,7 mmol) y ácido acético (0,06 ml) en THF (ml) se agitó durante 30 min a temperatura ambiente. Después de la adición de triacetoxiborohidruro de sodio (368 mg, 1,7 mmol), la reacción se agitó durante la noche, se apagó mediante la adición de $NaHCO_3$ acuoso saturado y se extrajo con EtOAc. El solvente se eliminó al vacío y el residuo se purificó por HPLC RP- preparativa (Waters Sunfire, C18- ODB, 5 micras, 30x100 mm, 5- 100% CH_3CN/H_2O/20 min, CH_3CN al 100% / 2 min, CH_3CN y H_2O que contiene 0,1% TFA, flujo: 40 ml / min) para proporcionar el compuesto del título. MS (LC- MS): 345,0 [M] +; tR (condiciones HPLC C): 4,09 min.

D. (3- aminometil- 5- cloro- 4- fluoro- bencil)- dietil- amina

A una mezcla de éster terc- butilo del ácido (3- cloro- 5- dietilaminometil- 2- fluoro- bencil)- carbámico (115 mg, 0,33 mmol) en MeOH (1 ml) se agregó una solución de HCl 4N en dioxano (3 ml). La mezcla de reacción se agitó durante 2 h a temperatura ambiente y el solvente se eliminó al vacío para proporcionar el compuesto del título.MS (LC/MS): 245,0 [M] +; tR (condiciones HPLC C): 2,13 min.

3- cloro- 2- fluoro- 5- morfolin- 4- ilmetil- bencilamina

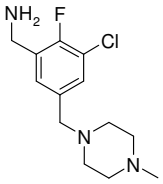


se preparó de acuerdo con el Esquema C2 (paso D) a partir de éster terc- butilo del ácido (3- cloro- 2- fluoro- 5- morfolin- 4- ilmetil- bencil)- carbámico (231 mg, 0,64 mmol) y HCl 4 N en dioxano. MS (LC- MS): 259,0 [M] +.

Éster terc- butilo del ácido (3- cloro- 2- fluoro- 5- morfolin- 4- ilmetil- bencil)- carbámico

se preparó de acuerdo con el Esquema C2 (paso C) a partir de éster terc- butilo del ácido (3- cloro- 2- fluoro- 5- formil- bencil)- carbámico (220 mg, 0,65 mmol), morfolina (57 mg, 0,65 mmol), ácido acético (0,056 ml, 0,9 mmol) y triacetoxiborohidruro de sodio (344 mg, 1,6 mmol) en THF (8 ml). TLC, Rf (EtOAc) = 0,44; MS (LC- MS): 359,0 [M] +.

3- cloro- 2- fluoro- 5- (4- metil- piperazin- 1- ilmetil)- bencilamina

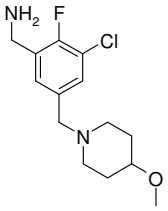


se preparó de acuerdo con el Esquema C2 (paso D) a partir de éster terc- butílo del ácido [3- cloro- 2- fluoro- 5- (4- metil- piperazin- 1- ilmetil)- bencil]- carbámico (225 mg, 0,61 mmol) y HCl 4 N en dioxano. MS (LC- MS): 272,0 [M] +; tR (condiciones HPLC C): 2,07 min.

Éster terc- butilo del ácido [3- cloro- 2- fluoro- 5- (4- metil- piperazin- 1- ilmetil)- bencil]- carbámico

se preparó de acuerdo con el Esquema C2 (paso C) a partir de éster terc- butílo del ácido (3- cloro- 2- fluoro- 5- formil- bencil)- carbámico (200 mg, 0,59 mmoles), 1- metilpiperazina (59 mg, 0,59 mmol), ácido acético (0,053 ml, 0,89 mmol) y triacetoxiborohidruro de sodio (313 mg, 1,5 mmol) en THF (8 ml). MS (LC- MS): 372,0 [M] +; tR (condiciones HPLC C): 3,64 min.

3- cloro- 2- fluoro- 5- (4- metoxi- piperidin- 1- ilmetil)- bencilamina

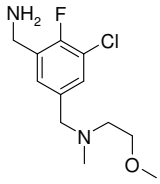


se preparó de acuerdo con el Esquema C2 (paso D) a partir de éster terc- butílo del ácido [3- cloro- 2- fluoro- 5- (4- metoxi- piperidin- 1- ilmetil)- bencil]- carbámico (225 mg, 0,61 mmol) y HCl 4 N en dioxano. MS (LC- MS): 287,0 [M] +; tR (condiciones HPLC C): 2,34 min.

Éster terc- butilo del ácido [3- cloro- 2- fluoro- 5- (4- metoxi- piperidin- 1- ilmetil)- bencil]- carbámico

se preparó de acuerdo con el Esquema C2 (paso C) a partir de éster terc- butilo del ácido (3- cloro- 2- fluoro- 5- formil- bencil)- carbámico (200 mg, 0,59 mmoles), 1- metoxipiperidina (68 mg, 0,59 mmol), ácido acético (0,051 ml, 0,89 mmol) y triacetoxiborohidruro de sodio (313 mg, 1,5 mmol) en THF (8 ml). MS (LC- MS): 387,0 [M] +

(3- aminometil- 5- cloro- 4- fluoro- bencil) - (2- metoxi- etil)- metil- amina

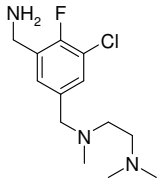


se preparó de acuerdo con el Esquema C2 (paso D) a partir de éster terc- butilo del ácido (3- cloro- 2- fluoro- 5- {[(2- metoxi- etil)- metil- amino]- metil}- bencil)- carbámico (222 mg, 0,47 mmol) y HCl 4 N en dioxano. MS (LC- MS): 261,0 [M] +.

Éster terc- butilo del ácido (3- cloro- 2- fluoro- 5- {[(2- metoxi- etil)- metil- amino]- metil}- bencil)- carbámico

se preparó de acuerdo con el Esquema C2 (paso C) a partir de éster terc- butilo del ácido (3- cloro- 2- fluoro- 5- formil- bencil)- carbámico (200 mg, 0,59 mmol), N- metoxietil- metilamina (74 mg, 0,83 mmoles), ácido acético (0,06 ml, 1,0 mmol) y triacetoxiborohidruro de sodio (368 mg, 1,7 mmol) en THF (8 ml). MS (LC- MS): 362,3 [M+H]+; tR (condiciones HPLC C): 4,04 min.

N- (3- aminometil- 5- cloro- 4- fluoro- bencil)- N, N ', N'- trimetil- etano- 1 ,2- diamina

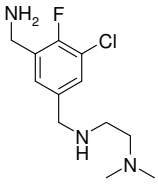


se preparó de acuerdo con el Esquema C2 (paso D) a partir de éster terc- butilo del ácido (3- cloro- 5- {[(2- dimetilamino- etil)- metil- amino]- metil}- 2- fluoro- bencil)- carbámico (228 mg, 0,51 mmol) y HCl 4 N en dioxano. MS (LC- MS): 274,0 [M] +.

Éster terc- butil- carbámico del ácido (3- Cloro- 5- {[(2- dimetilamino- etil)- metil- amino]- metil}- 2- fluoro- bencil)

se preparó de acuerdo con el Esquema C2 (paso C) a partir de éster terc- butilo del ácido (3- cloro- 2- fluoro- 5- formil- bencil)- carbámico (200 mg, 0,59 mmol), N, N, N '- trimetil- etilendiamina (71 mg, 0,70 mmol), ácido acético (0,06 ml, 1,0 mmol) y triacetoxiborohidruro de sodio (368 mg, 1,7 mmol) en THF (8 ml). MS (LC- MS): 374,0 [M] +; tR (condiciones HPLC C): 3,53 min.

N- (3- aminometil- 5- cloro- 4- fluoro- bencil)- N ', N'- dimetil- etano- 1 ,2- diamina

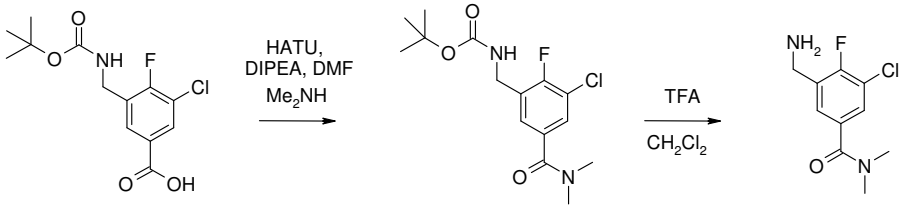


se preparó de acuerdo con el Esquema C2 (paso D) a partir de éster terc- butilo del ácido (3- cloro- 5- {[(2- dimetilamino- etil)- metil- amino]- metil}- 2- fluoro- bencil)- carbámico (165 mg, 0,46 mmol) y HCl 4 N en dioxano (3 ml). MS (LC- MS): 260,0 [M] +.

Éster terc- butílo del ácido {3- cloro- 5- [(2- dimetilamino- etilamino)- metil]- 2- fluoro- bencil}- carbámico

se preparó de acuerdo con el Esquema C2 (paso C) a partir de éster terc- butilo del ácido(3- cloro- 2- fluoro- 5- formil- bencil)- carbámico (200 mg, 0,70 mmol), N, N- dimetil- etilendiamina (67 mg, 0,77 mmol), ácido acético (0,06 ml, 1,0 mmol) y triacetoxiborohidruro de sodio (368 mg, 1,7 mmol) en THF (8 ml). MS (LC- MS): 360,3 [M+H]+; tR (condiciones HPLC C): 3,49 min.

Esquema C3: preparación de 3- aminometil- 5- cloro- 4- fluoro- N, N- dimetil- benzamida



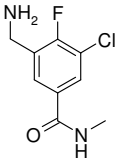
A. Éster terc- butilo del ácido (3- Cloro- 5- dimetilcarbamoil- 2- fluoro- bencil)- carbámico

Una mezcla de ácido 3 - (terc- butoxicarbonilamino- metil)- 5- cloro- 4- fluoro- benzoico (100 mg, 0,3 mmol), HATU (188 mg, 0,5 mmol), dimetilamina (0,2 ml, 2 M en THF) y DIPEA (0,23 ml, 1,3 mmol) en DMF (2 ml) se agitó durante 16 h a temperatura ambiente. El producto crudo se purificó sin tratamiento acuoso por HPLC- RP preparativa (Waters Sunfire, C18- ODB, 5 micras, 30x100 mm, 5- 100% CH_3CN/H_2O/20 min, CH_3CN al 100%/ 2 min, CH_3CN y H_2O que contiene TFA al 0.1%, flujo: 40 ml / min) para proporcionar el compuesto del título. MS (LC- MS): 275,0 [M- 55] +; tR (condiciones HPLC C): 4,68 min.

B. 3- aminometil- 5- cloro- 4- fluoro- N, N- dimetil- benzamida

A una mezcla de éster terc- butílo del ácido (3- cloro- 5- dimetilcarbamoil- 2- fluoro- bencil)- carbámico (115 mg, 0,33 mmol) en CH_2Cl_2 (4 ml) se agregó TFA (1 ml). La mezcla de reacción se agitó durante 1 h a temperatura ambiente y el solvente se eliminó al vacío para proporcionar el compuesto del título. MS (LC/MS): 231,0 [M] +. tR (condiciones HPLC C): 2,59 min.

3- aminometil- 5- cloro- 4- fluoro- N- metil- benzamida

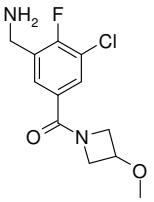


se preparó de acuerdo con el Esquema C3 (paso B) a partir de éster terc- butílo del ácido (3- cloro- 2- fluoro- 5- metilcarbamoil- bencil)- carbámico (99 mg, 0,3 mmol) y TFA (0,5 ml) en CH_2Cl_2. MS (LC- MS): 217,0 [M] +; tR (condiciones HPLC C): 2,39 min.

Éster terc- butilo del ácido (3- cloro- 2- fluoro- 5- metilcarbamoil- bencil) - carbámico

se preparó de acuerdo con el Esquema C3 (paso A) a partir del ácido 3 - (terc- butoxicarbonilamino- metil)- 5- cloro- 4- fluoro- benzoico (125 mg, 0,41 mmol), HATU (235 mg, 0,6 mmol), metilamina (0,25 ml, 2 M en THF) y DIPEA (0,29 ml, 1,6 mmol) en DMF (2 ml). MS (LC- MS): 633,0 [2M] +; tR (condiciones HPLC C): 4,55 min.

(3- aminometil- 5- cloro- 4- fluoro- fenil) - (3- metoxi- azetidin- 1- il)- metanona

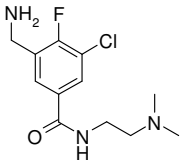


se preparó de acuerdo con el Esquema C3 (paso B) a partir de [3- cloro- 2- fluoro- 5- (3- metoxi- azetidina- 1- carbonil)- bencil]- éster terc- butílo del ácido carbámico (99 mg, 0,3 mmol) y TFA (0,5 ml) en CH2Cl2. MS (LC- MS): 273,0 [M] +; tR (condiciones HPLC C): 2,73 min.

Éster terc- butilo del ácido [3- cloro- 2- fluoro- 5- bencil- (3- metoxi- azetidina- 1- carbonil)]- carbámico

se preparó de acuerdo con el Esquema C3 (paso A) a partir del ácido 3 - (terc-butoxicarbonilamino- metil)- 5- cloro- 4- fluoro- benzoico (116 mg, 0,38 mmol), HATU (218 mg, 0,46 mmol), 3 - metoxi- azetidina (57 mg, 0,57 mmol) y DIPEA (0,27 ml, 1,5 mmol) en DMF (2 ml). MS (LC- MS): 373,0 [M] +

3- aminometil- 5- cloro- N- (2- dimetilamino- etil)- 4- fluoro- benzamida

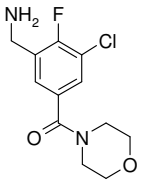


se preparó de acuerdo con el Esquema C3 (paso B) a partir de éster terc- butilo del ácido [3- cloro- 5- (2- dimetilamino- etilcarbamoil)- 2- fluoro- bencil]- carbámico (120 mg, 0,3 mmol) y TFA (1 ml) en CH_2Cl_2. MS (LC- MS): 274,0 [M] +; tR (condiciones HPLC C): 2,17 min.

Éster terc- butilo del ácido [3- cloro- 5- (2- dimetilamino- etilcarbamoil)- 2- fluoro- bencil]- carbámico

se preparó de acuerdo con el Esquema C3 (paso A) a partir del ácido 3 - (terc-butoxicarbonilamino- metil)- 5- cloro- 4- fluoro- benzoico (116 mg, 0,38 mmol), HATU (218 mg, 0,46 mmol), N, N- dimetiletilendiamina (40 mg, 0,46 mmol) y DIPEA (0,2 ml, 1,1 mmol) en DMF (2 ml). MS (LC- MS): 374,2 [M] +; tR (condiciones HPLC C): 3,87 min.

(3- aminometil- 5- cloro- 4- fluoro- fenil)- morfolin- 4- il- metanona

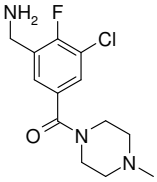


se preparó de acuerdo con el Esquema C3 (paso B) a partir de éster terc- butilo del ácido [3- cloro- 2- fluoro- 5- (morfolina- 4- carbonil)- bencil]- carbámico (72 mg, 0,19 mmol) y TFA (1 ml) en CH_2Cl_2. MS (LC- MS): 273,0 [M] +; tR (condiciones HPLC C): 2,64 min.

Éster terc- butilo del ácido [3- cloro- 2- fluoro- 5- (morfolina- 4- carbonil)- bencil]- carbámico

se preparó de acuerdo con el Esquema C3 (paso A) a partir del ácido 3 - (terc-butoxicarbonilamino- metil)- 5- cloro- 4- fluoro- benzoico (125 mg, 0,41 mmol), HATU (235 mg, 0,62 mmol), morfolina (43 mg, 0,49 mmol) y DIPEA (0,22 ml, 1,2 mmol) en DMF (2 ml). MS (LC- MS): 317,0 [M- 55] +; tR (condiciones HPLC C): 4,65 min.

(3- aminometil- 5- cloro- 4- fluoro- fenil) - (4- metil- piperazin- 1- il)- metanona

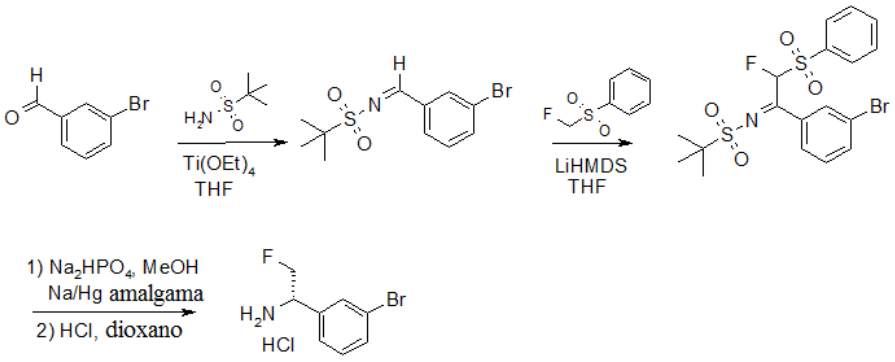


se preparó de acuerdo con el Esquema C3 (paso B) a partir de éster terc- butílo del ácido [3- cloro- 2- fluoro- 5- (4- metil- piperazina- 1- carbonil)- bencil]- carbámico (165 mg, 0,43 mmol) y TFA (2 ml) en CH_2Cl_2. MS (LC- MS): 286,0 [M] +; tR (condiciones HPLC C): 1,47 min.

Éster terc- butilo del ácido [3- cloro- 2- fluoro- 5- (4- metil- piperazina- 1- carbonil)- bencil]- carbámico

se preparó de acuerdo con el Esquema C3 (paso A) a partir del ácido 3 - (terc-butoxicarbonilamino- metil)- 5- cloro- 4- fluoro- benzoico (150 mg, 0,49 mmol), HATU (282 mg, 0,74 mmol), 4 - metilpiperazina (59 mg, 0,59 mmol) y DIPEA (0,26 ml, 1,5 mmol) en DMF (2 ml). MS (LC- MS): 386,0 [M] +; tR (condiciones HPLC C): 3,77 min.

Clorhidrato de (S) - 1 - (3- bromo- fenil)- 2- fluoro- etilamina



A. 1- (3- bromo- fenil)- met- (Z)- ilidenoamida del ácido 2- metil- propano- 2- sulfónico

A una solución de 3- bromo- benzaldehído (1,27 ml, 10,8 mmol) en THF (50 ml) se agregó etóxido de titanio (IV) (0,786 ml, 21,6 mmol) y terc- butilsulfonamida (1,31 g, 10,8 mmoles), y la agitación se continuó durante 16 horas a 65 ° C. Después de enfriar a temperatura ambiente, los volátiles se evaporaron, y el residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 03:01) para proporcionar el compuesto del título. MS (LC/MS): 289 [M+H]+; tR (condiciones HPLC f): 2,35 min.

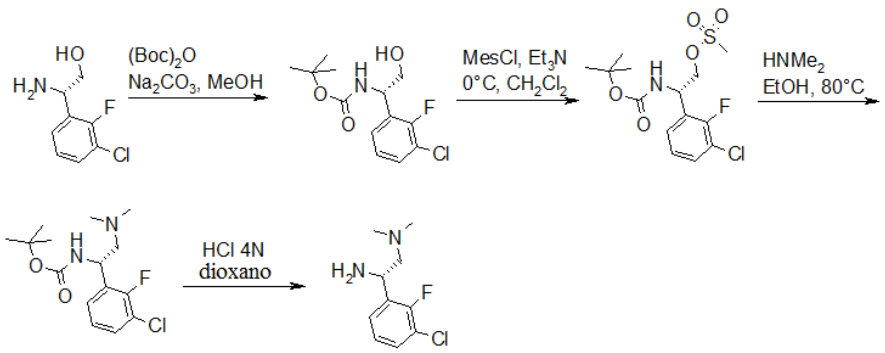
B. [2- bencenosulfonil- 1- (3- bromo- fenil)- 2- fluoro- et- (Z)- ilideno]- amida del ácido 2- metil- propano- 2- sulfónico

A una mezcla de 1 - (3- bromo- fenil)- met- (Z)- ilidenoamida del ácido 2- metil- propano- 2- sulfónico (2,16 g, 7,49 mmol) y (fluorometilsulfonilo)benceno (1,31 g, 7,49 mmol) en THF (50 ml), se enfrió a - 78 ° C, se agregó LiHMDS (1M en THF, 7,87 ml, 7,87 mmol). La mezcla de reacción se agitó durante 40 min a - 78 ° C, seguido de un temple NH_4Cl acuoso saturado (10 ml) a - 78 ° C. La mezcla se extrajo con EtOAc (3x), se secó sobre Na_2SO_4, se filtró y se concentró al vacío. La purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 03:01) proporcionó el compuesto del título. MS (LC/MS): 462/464 [M+H]+; tR (condiciones HPLC f): 2,20 min.

C. Clorhidrato (S) - 1 - (3- bromo- fenil)- 2- fluoro- etilamina

A una mezcla de [2- bencenosulfonil- 1- (3- bromo- fenil)- 2- fluoro- et- (Z)- ilideno]- amida del ácido 2- metil- propano- 2- sulfónico (1,74 g, 3,76 moles) y fosfato de sodio dibásico (4,27 g, 30,1 mmol) en metanol (50 ml), se enfrió a - 20 ° C, se agregó Na / Hg amalgama (6,92 g, 30,1 mmol). La mezcla de reacción se agitó durante 1 h a - 20 ° C, seguido por filtración. Al filtrado se le añadió una solución de HCl 4 N en dioxano (9,41 ml, 37,6 mmol), seguido de agitación durante 30 min a 25 ° C. Después de la evaporación de las sustancias volátiles, se agregó Et_2O al residuo y el precipitado resultante se separó por filtración. El compuesto del título así obtenido se usó en el siguiente paso de reacción sin purificación adicional. MS (LC/MS): 218/220 [M+H]+; tR (condiciones HPLC f): 1,05 min.

Esquema C4: preparación de (S) - 1 - (3- cloro- 2- fluoro- fenil)- N * 2 *, N * 2 *- dimetil- etano- 1 ,2- diamina



A. Éster terc- butilo del ácido [(S) - 1 - (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- carbámico

A una solución de (2S)- 2- amino- 2- (3- cloro- 2- fluorofenil) etan- 1- ol (517 mg, 2,29 mmol) en MeOH (35 ml) se agregó (Boc) $_2$O (0,54 ml, 2,31 mmol) y carbonato de sodio (970 mg, 9,15 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante la noche. Los volátiles orgánicos se eliminaron y el material en bruto se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano a c- hexano/EtOAc 01:01). TLC, Rf (c- hexano/EtOAc 01:01): 0,55; EM (UPLC/MS): 290.2/292.2 [M+H]+, 334.2/336.3 [M + HCOO] - ; tR (condiciones HPLC A): 3,36 min.

B. Éster (S)- 2- terc- butoxicarbonilamino- 2- (3- cloro- 2- fluoro- fenil)- etílico del ácido metanosulfónico

A una solución de éster terc- butilo del ácido [(S) - 1 - (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- carbámico (550 mg, 1,9 mmol) y trietilamina (0,29 ml, 2,09 mmol) en CH_2Cl_2 (5,5 ml) se enfrió a - 10 º C se agregó bajo atmósfera de nitrógeno, cloruro de mesilo (0,16 ml, 2,09 mmol) y la mezcla de reacción se agitó a 0 º C durante 1,5 h. La mezcla de reacción se apagó con hielo y agua y después se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se lavaron con agua, se secaron (Na_2SO_4), se filtraron y se concentraron. El material bruto se usó sin purificación en el siguiente paso. MS (UPLC/MS): 412.3/414.3 [M + HCOO] - ; tR (condiciones HPLC A): 3,66 min.

C. Éster terc- butilo del ácido [(S) - 1 - (3- cloro- 2- fluoro- fenil)- 2- dimetilamino- etil]- carbámico

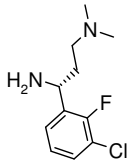
Una solución de éster (S)- 2- terc- butoxicarbonilamino- 2- (3- cloro- 2- fluoro- fenil)- etílico del ácido metanosulfónico (690 mg, 1,88 mmol) en dimetilamina al 33% en EtOH (5,6 M, 7,5 ml , 42 mmol) se calentó a 80 °C durante 2 h en un tubo sellado. La mezcla de reacción se concentró y el material bruto se purificó mediante cromatografía en columna ultrarrápida

sobre gel de sílice (c- hexano/EtOAc 01:01 a EtOAc) para proporcionar un aceite de color amarillo pálido. TLC, Rf (EtOAc): 0,60; EM (UPLC/MS): 317.3/319.3 [M+H]+; tR (condiciones HPLC A): 3,19 min.

D. (S) - 1 - (3- cloro- 2- fluoro- fenil)- N * 2 *, N * 2 *- dimetil- etano- 1 ,2- diamina

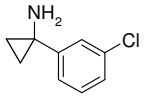
A una solución de éster terc- butilo del ácido [(S) - 1 - (3- cloro- 2- fluoro- fenil)- 2- dimetilamino- etil]- carbámico (315 mg, 0,99 mmol) en dioxano (6 ml) fue añadió HCl 4 N en dioxano (9,94 ml, 39,8 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h y se concentró para proporcionar el material deseado en forma de una sal de HCl que se usó sin purificación adicional en el siguiente paso. MS (UPLC/MS): 217.2/219.2 [M+H]+; 1H RMN (400 MHz, DMSO- d6) δ (ppm): 9,17 (bs, 2H), 7,75 (m, 2H), 7,40 (t, 1H), 5,16 (m, 1H), 3,85 (m, 1H), 3,60 (m, 1H), 2,87 (s, 3H).

(R) - 1 - (3- cloro- 2- fluoro- fenil)- N * 3 *, N * 3 *- dimetil- propano- 1 ,3- diamina



se preparó usando procedimientos similares a los descritos para la síntesis del ácido (3- acetil- pirrolo [2,3- c] piridin- 1- il)- acético en el Esquema C4 a partir de (R)- 3- amino- 3- (3 - cloro- 2- fluoro- fenil)- propan- 1- ol. 1H- RMN (400 MHz, DMSO): δ (ppm): 8,89 (m, 2H), 7,73 (m, 2H), 7,39 (t, 1H), 4,69 (m, 1H), 3,13 (m, 1H), 2,98 (m, 1H), 2,73 (s, 6H), 2,47 (m, 1H), 2,34 (, 1H).

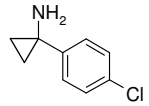
1 - (3- cloro- fenil)- ciclopropilamina



A una solución de 3- clorobenzonitrilo (1 g, 7,27 mmol) y titanio (IV) isopropóxido (2.34 ml, 8 mmol) en Et_2O (35 ml) a - 78 º C se agregó cloruro de etil magnesio en THF (5,71 ml, 15,99 mmol). La solución se agitó durante 10 min a - 78 °C y después a 25 °C durante 1 h. Se agregó $BF_3.Et_2O$ (1,82 ml, 14,54 mmol) y la solución se agitó durante 1 h a 25 º C. La mezcla de reacción se apagó con HCl 1 N (22 ml) se agregó Et_2O (100 ml). Luego se agregó NaOH acuoso al 10%. (70 ml) y las capas se separaron. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo crudo se purificó por HPLC preparativa (Waters SunFire

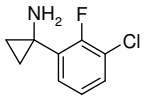
C18- ODB, 5 micras, 19x50 mm, CH_3CN 5%/H_2O 2,5 min, 5- 100% CH_3CN/H_2O en 10 min, CH_3CN/H_2O que contiene HCOOH al 0,1% flujo: 20 ml / min) para proporcionar, después de la liofilización de las fracciones purificadas el compuesto del título. MS (UPLC- MS): 170 [M+H]+, 168 [MH] - ; tR (condiciones HPLC f): 1,22 min.

1 - (4- cloro- fenil)- ciclopropilamina



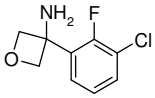
se preparó usando el mismo procedimiento como el de la preparación de 1 - (3- cloro- fenil)- ciclopropilamina a partir de 4- clorobenzonitrilo. MS (UPLC- MS): 170 [M+H]+, 168 [MH]; tR (condiciones HPLC f): 1,21 min.

1 - (3- cloro- 2- fluoro- fenil)- ciclopropilamina



se preparó usando el mismo procedimiento que para la preparación de 1 - (3- cloro- fenil)- ciclopropilamina a partir de 3- cloro- 2- fluroro- benzonitrilo. MS (UPLC- MS): 186/188 [M+H]+; tR (condiciones HPLC f): 1,13 min.

Clorhidrato de 3 - (3- cloro- 2- fluoro- fenil)- oxetan- 3- ilamina



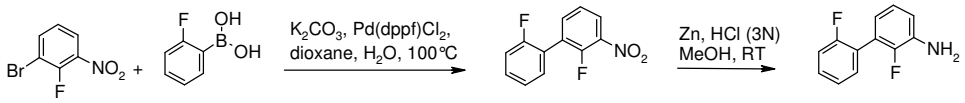
Una solución de [3 - (3- cloro- 2- fluoro- fenil)- oxetan- 3- il]- amida del ácido 2- metil- propano- 2- sulfínico (940 mg, 2,46 mmoles) y ácido clorhídrico (4 N en dioxano, 0,922 ml, 3,69 mmol) en MeOH (5 ml) se agitó 30 min a 0 °C y se concentró. El material así obtenido se utilizó sin purificación adicional en el siguiente paso. MS (UPLC- MS): 202/204 [M+H]+; t_R (condiciones HPLC f): 0,86 min.

[3 - (3- cloro- 2- fluoro- fenil)- oxetan- 3- il]- amida del ácido 2- metil- propano- 2- sulfínico

A una solución de 1- bromo- 3- cloro- 2- fluorobenceno (896 mg, 4,28 mmol) en THF (100 ml) se agregó a - 78 º C bajo atmósfera de nitrógeno, n- butil- litio (1,6 N en hexanos, 2,67 ml, 4,28 mmoles). La mezcla de reacción se agitó durante 1 h a - 78 °C y una solución de 2-

metil- N- (oxetan- 3- ilideno) propano- 2- sulfinamida (500 mg, 2,85 mmol) en THF (17,5 ml) se agregó por goteo. La mezcla de reacción se agitó durante 1 h adicional a - 78 º C y después se dejó llegar a temperatura ambiente y se apagó mediante la adición lenta de una solución acuosa saturada de NH_4Cl, se extrajo con EtOAc (x2). Los extractos orgánicos combinados se lavaron con agua y salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron. El material así obtenido se utilizó sin purificación adicional en el siguiente paso. MS (UPLC- MS): 306.1/308.1 [M+H]+; tR (condiciones HPLC f): 1,85 min.

Esquema C5: Preparación de 2,2 '- difluoro- bifenil- 3- ilamina



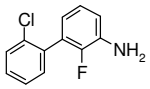
A. 2,2 '- difluoro- 3- nitro- bifenil

A una solución de 1- bromo- 2- fluoro- 3- nitrobenceno [58534- 94- 4] (150 mg, 0,68 mmol) y ácido 2- fluorofenilborónico [09.03.1193] (191 mg, 1,36 mmol) en dioxano (4 ml) y agua (1 ml) se agregó carbonato de potasio (236 mg, 1,70 mmol) y aducto Pd (dppf) $Cl_2.CH_2Cl_2$ (55,7 mg, 0,068 mmol). La solución se calentó durante 30 min a 100 °C bajo irradiación de microondas. La mezcla de reacción se diluyó con CH_2Cl_2 y la solución resultante se lavó sucesivamente con solución acuosa saturada de $NaHCO_3$, solución de HCl 1N y salmuera, después se secó (separador de fases) y se concentró a presión reducida. El residuo se purificó por HPLC preparativa (Waters Sunfire, C18- ODB, 5 micras, 30x100 mm, flujo: 40 ml / min, eluyente: 20- 100% CH_3CN/H_2O/20 min, CH_3CN al 100% / 2 min, CH_3CN y H_2O que contiene TFA al 0,1%) para proporcionar después de la liofilización de las fracciones purificadas el compuesto de título. MS (LC- MS): 236 [M+H]+; tR (condiciones HPLC k): 3,81 min.

B. 2,2 '- difluoro- bifenil- 3- ilamina

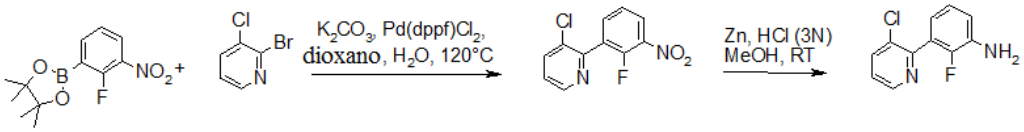
A una suspensión de 2,2 '- difluoro- 3- nitro- bifenilo (100 mg, 0,36 mmol) en metanol (5 ml) se agregó una solución de 3N HCl acuoso (7,23 ml, 21,7 mmol) y Zn en polvo (426 mg, 6,51 mmol). La mezcla se agitó durate 4 h a temperatura ambiente. La mezcla de reacción se concentró y se neutralizó con una solución de $NaHCO_3$ acuoso saturado, después se diluyó con un volumen igual de agua y se extrajo (x3) con CH_2Cl_2. Los extractos orgánicos combinados se secaron (separador de fases) y se concentraron al vacío para proporcionar el compuesto de título. MS (LC- MS): 206 [M+H]+; tR (condiciones HPLC k): 3,30 min.

2'- cloro- 2- fluoro- bifenil- 3- ilamina



se preparó mediante el uso de los mismos procedimientos que los descritos para la preparación de 2,2 '- difluoro- bifenil- 3- ilamina en el Esquema C5, a partir del ácido 2- clorofenilborónico [1679- 18- 1]. MS (LC- MS): 222 [M+H]+; t_R (condiciones HPLC k): 3,42 min.

Esquema C6: Preparación de 3 - (3- cloro- piridin- 2- il)- 2- fluoro- fenilamina



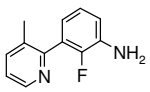
A. 3- Cloro- 2- (2- fluoro- 3- nitro- fenil)- piridina

A una solución de 2- bromo- 3- cloropiridina [96424- 68- 9] (144 mg, 0,75 mmol) y éster pinacol del ácido 2- fluoro- 3- nitrofenilborónico [1189042- 70- 3] (200 mg, 0,75 mmol) en dioxano (4 ml) y agua (1 ml) se agregó carbonato de potasio (259 mg, 1,87 mmol) y aducto Pd (dppf) $Cl_2.CH_2Cl_2$ (61,2 mg, 0,075 mmol). La solución se calentó durante 60 min a 120 °C bajo irradiación de microondas. La mezcla de reacción se diluyó con EtOAc y la solución resultante se lavó sucesivamente con solución acuosa saturada de $NaHCO_3$ y salmuera, después se secó (separador de fases) y se concentró a presión reducida. El residuo se purificó mediante cromatografía instantánea sobre gel de sílice (c- hexano/EtOAc 04:01) para proporcionar el compuesto del título. MS (LC- MS): 253 [M+H]+; tR (condiciones HPLC k): 3,45 min.

B. 3 - (3- cloro- piridin- 2- il)- 2- fluoro- fenilamina

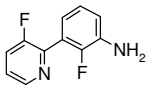
se preparó mediante el mismo procedimiento como se describe para la preparación de 2,2 '- difluoro- bifenil- 3- ilamina en el Esquema C5 el paso B. MS (LC- MS): 223 [M+H]+; tR (condiciones HPLC k): 2,63 min.

2- fluoro- 3- (3- metil- piridin- 2- il)- fenilamina



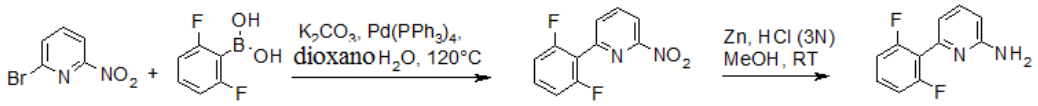
se preparó mediante el uso de los mismos procedimientos descritos para la preparación de 3 - (3- cloro- piridin- 2- il)- 2- fluoro- fenilamina en el Esquema C6, comenzando a partir de 2- bromo- 3- metilpiridina [3430- 17 - 9].MS (LC- MS): 203 [M+H]+; tR (condiciones HPLC k): 1,36 min.

2- fluoro- 3- (3- fluoro- piridin- 2- il)- fenilamina



se preparó mediante el uso de los mismos procedimientos descritos para la preparación de 3 - (3- cloro- piridin- 2- il)- 2- fluoro- fenilamina en el Esquema C6, a partir de 2- bromo- 3- fluoropiridina [40273- 45 - 8] y ácido 2- fluoro- 3- nitrofenilborónico [1150114- 29- 6]. MS (LC- MS): 207 [M+H]+; tR (condiciones HPLC k): 2,39 min.

6 - (2,6- difluoro- fenil)- piridin- 2- ilamina



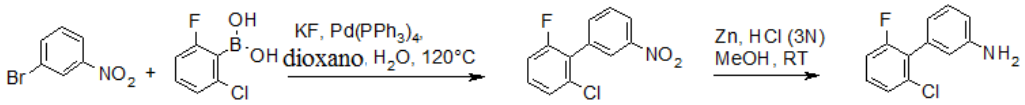
A. 2 - (2,6- difluoro- fenil)- 6- nitro- piridina

A una solución de 2- bromo- 6- nitropiridina [21203- 78- 1] (200 mg, 0,99 mmol) y ácido 2,6- difluorofenilborónico [162101- 25- 9] (311 mg, 1,97 mmol) en dioxano (4 ml) y agua (1 ml) se agregó carbonato de potasio (340 mg, 2,46 mmol) y Pd $(PPh_3)_4$ (114 mg, 0,099 mmol). La solución se calentó durante 60 min a 120 °C bajo irradiación de microondas. Se agregó más 2,6- difluorofenilborónico (622 mg, 3,94 mmoles) a la mezcla seguido de calentamiento a 120 °C durante 120 minutos bajo irradiación de microondas. La mezcla de reacción se diluyó con EtOAc y la solución resultante se lavó sucesivamente con solución acuosa saturada de $NaHCO_3$ y salmuera, los orgánicos se secaron entonces (separador de fases) y se concentraron a presión reducida. El residuo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 09:01) para proporcionar el compuesto del título. MS (LC- MS): 237 [M+H]+, 259 [M+Na]+; tR (condiciones HPLC k): 3,44 min.

B. 6 - (2,6- difluoro- fenil)- piridin- 2- ilamina

se preparó mediante el mismo procedimiento como se describe para la preparación de 2,2 '- difluoro- bifenil- 3- ilamina en el Esquema C5 el paso B. MS (LC- MS): 207 [M+H]+; tR (condiciones HPLC k): 2,39 min.

2'- cloro- 6'- fluorobifenil- 3- amina



A. 2- cloro- 6- fluoro- 3'- nitro- 1, 1'- bifenilo

A una solución de 1- bromo- 3- nitrobenceno [585- 79- 5] (400 mg, 1,98 mmol) y ácido 2- cloro- 6- fluorofenilborónico [313545- 32- 3] (414 mg, 2,37 mmol) en dioxano (12 ml) y agua (3 ml) se agregó fluoruro de potasio (460 mg, 7,92 mmol) y Pd $(PPh_3)_4$ (229 mg, 0,20 mmol). La solución se calentó durante 60 min a 120 °C bajo irradiación de microondas. Se agregó más ácido 2- cloro- 6- fluorofenilborónico (414 mg, 2,37 mmol) a la mezcla seguido de calentamiento a 120 °C durante 45 min bajo irradiación de microondas. La mezcla de reacción se diluyó con EtOAc y la solución resultante se lavó sucesivamente con solución acuosa saturada de $NaHCO_3$ y salmuera, los orgánicos se secaron entonces (separador de fases) y se concentraron a presión reducida. El residuo se purificó por HPLC preparativa (Waters Sunfire, C18- ODB, 5 micras, 30x100 mm, flujo: 50 ml / min, eluyente: 20- 100% CH_3CN/H_2O/20 min, CH_3CN al 100% / 2 min, CH_3CN y H_2O que contiene TFA al 0,1%) para proporcionar el compuesto del título. t_R (condiciones HPLC C): 5,42 min.

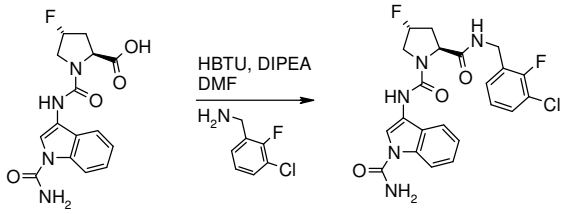
B. 2'- Cloro- 6'- fluorobifenil- 3- amina

se preparó mediante el mismo procedimiento como se describe para la preparación de 2,2 '- difluoro- bifenil- 3- ilamina en el Esquema C5 el paso B. MS (LC- MS): 222 [M+H]+; t_R (c) Condiciones HPLC: 3,58 min.

Parte D: Síntesis de ejemplos 1- 773

Los datos 1H RMN y HRMS para compuestos seleccionados se pueden encontrar al final de la Parte D.

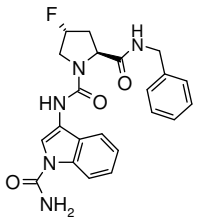
Esquema D1: protocolo general descrito para la preparación del Ejemplo 1: 1 - [(1- carbamoil- 1H- indol- 3- il)- amida] 2 - (3- cloro- 2- fluoro - bencilamida) del ácido (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico

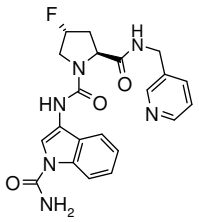
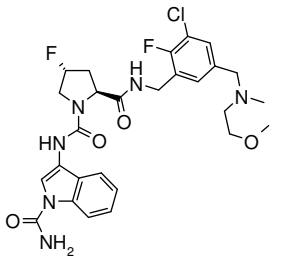
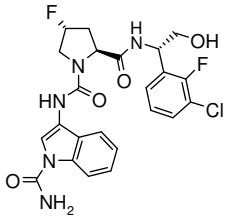
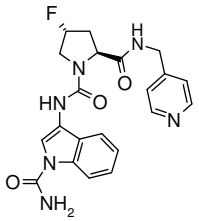
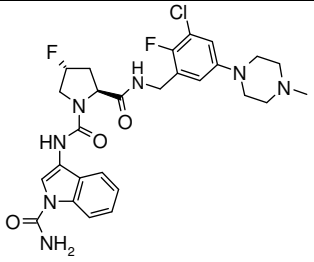


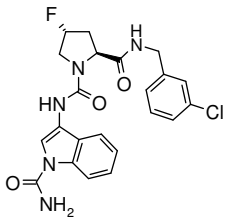
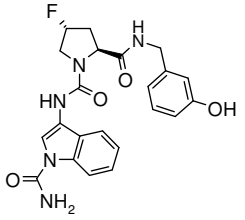
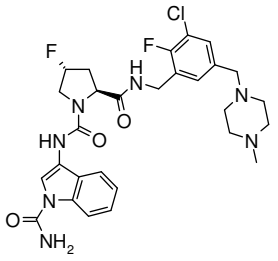
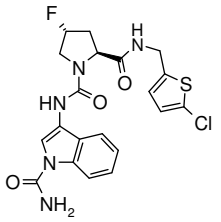
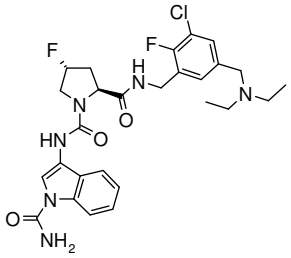
Ácido (2S, 4R) - 1 - (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carboxílico (80 mg, 0,24 mmol, preparado como se describe en la Parte B), 3- cloro- 2- fluorobencilamina (76 mg, 0,48 mmol) y HBTU (136 mg, 0,36 mmol) se disolvieron en DMF (7,98 ml). Se agregó DIPEA (125 µl, 0,718 mmol) y la mezcla de reacción se agitó a 25 °C durante 1 h. La mezcla de reacción bruta se diluyó con EtOAc y se lavó sucesivamente con HCl 1 N y $NaHCO_3$ (5% en agua). La capa orgánica se secó (Na_2SO_4), se filtró y se concentró. El material en bruto se purificó por HPLC preparativa (Waters Sunfire C18- ODB, 5 um, 19x50mm, flujo: 20 ml / min, gradiente: 0- 2,5 min CH_3CN al 20%, 02.05 a 12.05 min 20 a 100% de CH_3CN, 12,5- 15 min 100% de CH_3CN, H_2O y CH_3CN que contiene HCOOH al 0,1%) las fracciones puras se combinaron, se extrajeron con EtOAc y se concentraron. El residuo finalmente se recogió en Et_2O y el compuesto deseado se obtuvo después de la filtración. MS: 475,9 [M+H]+, 498 [M+Na]+; tR (condiciones HPLC B): 3,64 min.

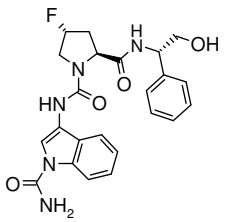
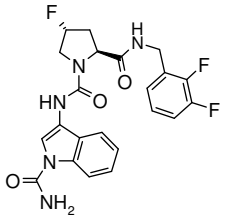
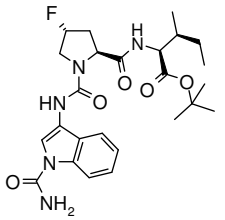
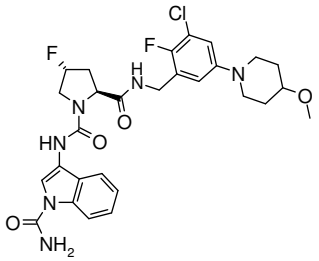
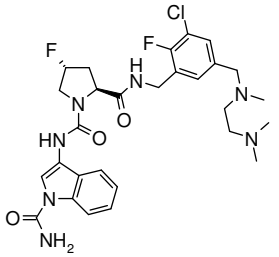
Los ejemplos a continuación se prepararon de acuerdo con los procedimientos generales descritos en el Esquema D1 para el **Ejemplo 1** *utilizando precursores de síntesis comercialmente disponibles, si no se indica lo contrario (ver notas al final de la tabla 1):*

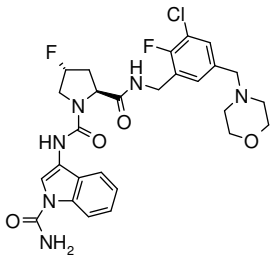
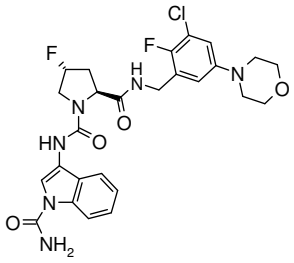
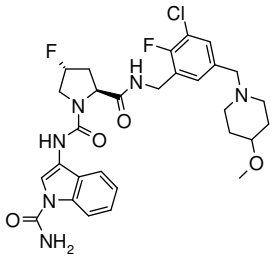
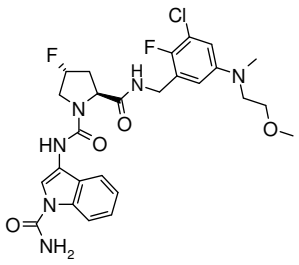
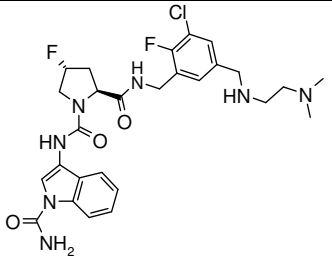
Tabla 1:

Ejemplo	Estructura	Nombre	Caracterización (Notas de pie de tabla), TLC, R_f (eluyente); MS (LC/MS); t_R (condiciones de HPLC)
2		2- bencilamida 1 - [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico	424 [M+H]+; t_R (b): 3,15 min.

3		1 - [(1- carbamoil- 1H- indol- 3- il)- amida] 2 - [(piridin- 3- ilmetil)- amida] del ácido (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico	425.0 [M+H]+, 423,1 [M- H] - ; t_R (a): 1.05 min.
4		1 - [(1- carbamoil- 1H- indol- 3- il)- amida] 2 - (3- cloro- 2- fluoro- 5- {[(2- metoxi- etil)- metil- amino]- metil}- bencilamida) del ácido (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico	(1 [C2]) 577,3 [M] +; t_R (c): 3.67 min.
5		ácido 1 - [(1- carbamoil- 1H- indol- 3- il)- amida] 2 - {[(S) - 1 - (3 - cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida} del ácido (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico	506,4 [M+H], 504,3 [M- H] - ; t_R (a): 2.87 min.
6		1 - [(1- carbamoil- 1H- indol- 3- il)- amida] 2 - [(piridin- 4- ilmetil)- amida] del ácido (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico.	425.2 [M+H]+, 447.1 [M+Na]+, 871.3 [2M+Na]+, 423.1 [MH] - , 380 [M- $CONH_2$] - ; t_R (a): 1,27 min.
7		1- [3- cloro- 2- fluoro- 5- (4- metil- piperazin- 1- il)- bencilamida] del ácido (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico	(1 [C1]) 574.2/577.3 [M+H]+; t_R (c): 3,63 min.

8		1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico	458,2 [M+H]+ 456,1 [MH] - ; tR (a): 3,05 min; tR (b): 3,34 min.
9		1 - [(1- carbamoil- 1H- indol- 3- il)- amida] 2 - (3- hidroxi- bencilamida) del ácido (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico	440 [M+H]+; t_R (b): 2,66 min.
10		1- [(1- carbamoil- 1H- indol- 3- il)- amida]2- [cloro- 2- fluoro- 5- (4- metil- piperazin- 1- ilmetil)- bencilamida] del ácido (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico	(1 [C2]) 588 [M+H]+; tR (c): 3.31 min.
11		(2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico del ácido [- Amida del ácido 1- [(1- carbamoil- 1H- indol- 3- il)] – amida] 2- [(5- cloro- tiofen- 2- ilmetil)- amida]	463,9 [M+H]+; t_R (b): 3,55 min.
12		1 - [(1- carbamoil- 1H- indol- 3- il)- amida] 2 - (3- cloro- 5- dietilamino- metil- 2- fluoro- bencil- amida) del ácido (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico	(1 [C2]) 561,3 [M] +; t_R (c): 3.72 min.

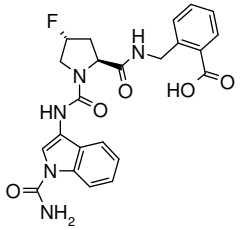
13		1 - [(1- carbamoil- 1H- indol- 3- il)- amida] 2 - [((S)- 2- hidroxi- 1 - fenil- etil)- amida] del ácido (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico	454,3 [M+H]+, 452,3 [M- H] - ; t_R (a): 2.63 min.
14		1 - [- (1- carbamoil- 1H- indol- 3- il)amida] 2 - (2,3- difluoro- bencilamida) del ácido (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico ácido	460,1 [M+H]+; 415 [M- $CONH_2$] - ; t_R (a): 2,95 min.
15		Éster terc- butilo del ácido (2S, 3S)- 2- {[(2S, 4R)- 1- (1- cabarmoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbanil]- amino}- 3- metil- pentanoicoo.	R_f (EtOAc) = 0,7; 504.3 [M+H]+, 526.3 [M+Na]+, 448.1 [MH- tBu] +, 502.2 [MH] - , 459.2 [M- $CONH_2$] - ; t_R (a): 3.42 min.
16		1- [- (1- carbamoil- 1H- indol- 3- il)] - 2 - [3- cloro- 2- fluoro- 5- (4- metoxi- piperidin- 1- il)- bencilamida] del ácido (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico	(1[C1]) 589.3/592.3 [M+H]+, t_R (c): 3,76 min.
17		1 - [(1- carbamoil- 1H- indol- 3- il)- amida] 2 - (3- cloro- 5- {[(2 - dimetilamino- etil)- metil- amino]- metil}- 2- fluoro- bencilamida) del ácido (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2-	(1[C2]) 590.2 [M]+; t_R (c): 3.25 min.

		dicarboxílico.	
18		1 - [(1- carbamoil- 1H- indol- 3- il)- amida] 2 - (3- cloro- 2- fluoro- 5- morfolin- 4- ilmetil- bencilamida) del ácido (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico.	(1 [C2]) 575,2 [M] +; t_R (c): 3,57 min.
19		1 - [(1- carbamoil- 1H- indol- 3- il)- amida] 2 - (3- cloro- 2- fluoro- 5- morfolin- 4- il- bencilamida) del ácido (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico	(1) 561.3/564 [M+H]+, tR (c): 4,26 min.
20		1- [(1- carbamoil- 1H- indol- 3- il)] - 2 - [3- cloro- 2- fluoro- 5- (4- metoxi- piperidin- 1- ilmetil)- bencilamida] del ácido (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico	(1 [C2]) 603 [M+H]+; t_R (c): 3,72 min.
21		1 - [(1- carbamoil- 1H- indol- 3- il)- amida] 2 - {3- cloro- 2- fluoro- 5- [(2- metoxi- etil)- metil- amino]- bencilamida} del ácido (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico ácido	(1 [C1]) 563.3/566.3 [M+H]+, t_R (c): 3,99 min.
22		1 - [(1- carbamoil- 1H- indol- 3- il)- amida] 2 - {3- cloro- 5- [(2 - dimetilamino- etilamino)- metil]- 2- fluoro- bencilamida} del ácido (2S,	(1 [C2]) 576.2/579.2 [M+H]+, t_R (c): 3,27 min.

		4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico ácido	

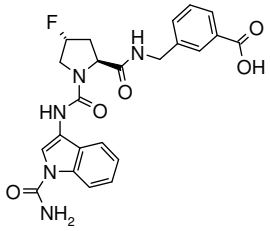
(1) La bencilamina sustituida o derivado de anilina usado en el paso A se preparó como se describe en la Parte C [Esquema].

Ejemplo 23: Ácido 2({[(2S, 4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- metil)- benzoico



A una solución de éster terc- butílo del ácido 2- ({[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- metil)- benzoico (preparado de acuerdo con el Esquema D1 utilizando éster terc- butílo del ácido 2- aminometil- benzoico) (76 mg, 0.145 mm) en CH_2Cl_2 (1 ml) se añadió TFA (168 µl, 2.18 mmol) y la solución resultante se agitó a temperatura ambiente durante la noche. La mezcla cruda se concentró para proporcionar un sólido que se suspendió en Et_2O y se filtró para proporcionar el material deseado. MS (LC-MS): 468,1 [M+H]+, 490.1 [M+Na]+, 957,2 [2M+Na]+, 466,1 [MH] - , 423,1 [M- CONH2] - , t_R (condiciones de HPLC a): 2.64 min.

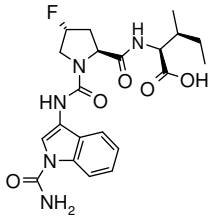
Ejemplo 24: Ácido 2- ({[(2S,4R)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 3- carbonil]- amino}- metil)- benzoico



A una solución de éster terc- butílo del ácido 3- ({[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- metil)- benzoico (preparado de acuerdo con el Esquema D1 utilizando éster terc- butílo del ácido 3- aminometil- benzoico) (21 mg, 0.04 mmol) en CH_2Cl_2 (0.5 ml) se añadió TFA (31 µl, 0.4 mmol) y la solución se agitó a temperatura ambiente durante 24 h. El solvente se concentró y el residuo crudo se purificó por HPLC preparativa (C18- ODB, 5 m, 19x50 mm, aguas, eluyente: CH_3CN/H_2O + 0,1%

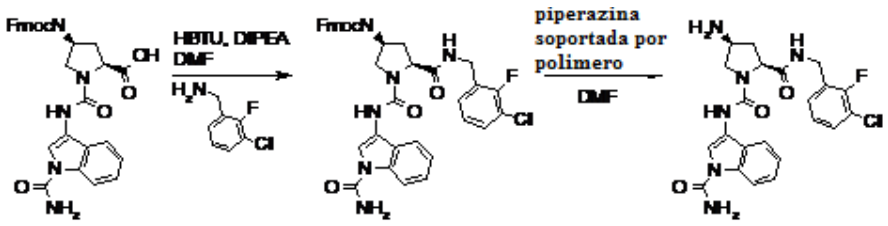
HCOOH, flujo: 20 ml/min, método estándar al 20%) para proporcionar después liofilización de las fracciones purificadas el material deseado. MS (LC- MS): 468 [M+H]+, 490 [M+Na]+, 466 [MH] - , 423,0 [M- $CONH_2$] - ; t_R (condiciones de HPLC a): 2.57 min.

Ejemplo 25: Ácido (2S,3S)- 2- {[(2S,4R)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- 3- metil- pentanoico



A una suspensión de éster terc- butílo del ácido (2S,3S)- 2- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- 3- metil- pentanoico Ejemplo 15(64 mg, 0.127 mmol) en CH_2Cl_2 (1 ml) se le añadió TFA (97µl, 1.27 mmol) y la solución resultante se agitó a temperatura ambiente durante 20 h. TFA (1.27 mmoles) se añadió de nuevo para asegurar la terminación de la reacción. CH_2Cl_2 se concentró y el residuo crudo se purificó mediante HPLC preparativa (C18- ODB, 5 m, 19x50 mm, aguas, eluyente: CH_3CN/H_2O + HCOOH al 0,1%, flujo: 20 ml/min, método estándar de 20%) para proporcionar después de liofilización de las fracciones purificadas el material deseado que se disolvió en CH_3CN y se purificó de nuevo el cartucho de trimetilaminopropilo (Mega Bond Elut- SAX, 1 g, a partir de Varian, acondicionado con 20 ml de CH_3CN). La columna se eluyó con CH_3CN y el compuesto fue finalmente liberado con 10 ml de HCl 0.1 N en CH_3CN, la concentración dio lugar a un residuo que se recogió en Et_2O y se separa por filtración para proporcionar el material deseado. MS (LC- MS): 448.1 [M+H]+, 446 [MH] - ; t_R (condiciones de HPLC a): 2,67 min.

<u>Esquema D2: protocolo general descrito para la preparación del Ejemplo 26: 1 - [(1- carbamoil- 1H- indol- 3- il)- amida] 2 - (3- cloro- 2- fluoro- bencilo) del ácido (2S, 4S)- 4- amino- pirrolidina- 1 ,2- dicarboxílico</u>



A. 1 - [(1- carbamoil- 1H- indol- 3- il)- amida] 2 - (3- cloro- 2- fluoro- bencilamida) del ácido (2S, 4S) - 4 - (9H- fluoren- 9- ilmetoxicarbonilamino)- pirrolidina- 1 ,2- dicarboxílico

Ácido (2S,4S)- 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 4- (9H- fluoren- 9- ilmetoxicarbonilamino)- pirrolidina- 2- carboxílico (400 mg, 0,723 mmol, preparado como se describe en el Esquema B10), 3- cloro- 2- fluorobencilamina (230 mg, 1.45 mmol) y HBTU (411 mg, 1.08 mmol) se disolvieron en DMF (2.5 ml). Se añadió DIPEA (0.378 ml, 2.18 mmol) y la mezcla de reacción se agitó a 25 °C durante 16 h. La mezcla de reacción se diluyó en EtOAc y se lavó sucesivamente con HCl 1 N y $NaHCO_3$ (5% en agua). Los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron a sequedad. El residuo crudo se purificó mediante HPLC preparativa (Waters Sunfire C18- ODB, 5 um, 30x100mm, 20% de CH_3CN/2 min, 20- 100% CH_3CN/H_2O/18 min, 100% de CH_3CN/2 min, CH_3CN y H_2O que contiene TFA al 0,1 %, flujo: 40 ml/min)para proporcionar el compuesto deseado. MS (LC/MS): 695 [M+H]+, 717 [M+Na]+; t_R (condiciones de HPLC b): 5.16 min.

Protocolo alternativo:

Ácido (2S,4S)- 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 4- (9H- fluoren- 9- ilmetoxicarbonilamino)- pirrolidina- 2- carboxílico (40 mg, 0.072 mmol, preparado como se describe en el Esquema B10) y amina (0.08 mmol) se disolvieron en NMP (0.7 ml). Se añadió DIPEA (0.025 ml, 0.143 mmol) y HBTU (40.6 mg, 0.107 mmol) y la mezcla de reacción se agitó a 25 °C durante 90 min. La mezcla de reacción se diluyó con MeOH (1 ml) y se filtró sobre una membrana de PTFE (0.45 um). El filtrado resultante se purificó mediante HPLC preparativa (Waters Sunfire C18- ODB, 5 um, 30x150mm, 45% CH_3CN/3.0 min, 45- 70% CH_3CN/H_2O/12 min, 70- 95% de CH^3CN/2 min, CH_3CN y H_2O que contiene TFA al 0,1%, flujo: 50 ml/min) para proporcionar el compuesto deseado.

Protocolo Alternativo 2:

Ácido (2S, 4S)- 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 4- (9H- fluoren- 9- ilmetoxicarbonilamino)- pirrolidina- 2- carboxílico (70 mg, 0.126 mmol, preparado como se describe en el Esquema B10), amina (0.253 mmol) y HBTU (100 mg, 0.264 mmol) se disolvieron en DMF (2 ml). Se añadió DIPEA (0.066 ml, 0.379 mmol) y la mezcla de reacción se agitó a 25 °C durante 90 min. La mezcla de reacción se diluyó con MeOH (2 ml), se filtró sobre una membrana de PTFE (0,45 um) y se lavó con MeOH. El filtrado resultante se purificó mediante HPLC preparativa (Waters Sunfire C18- ODB, 5 µm, 30x150mm, 20% CH_3CN/1.5

min, 20- 88% de CH_3CN/9 min, 88- 100% de CH_3CN/3 min, H_2O que contiene TFA al 0.1%, flujo: 50 ml/min) para proporcionar el compuesto deseado.

B. 1 - [(1- carbamoil- 1H- indol- 3- il)] 2 - (3- cloro- 2- fluoro- bencilamida) del ácido (2S, 4S)- 4- amino- pirrolidina- 1 ,2- dicarboxílico

A una solución de 1 - [(1- carbamoil- 1H- indol- 3- il)- amida] 2 - (3- cloro- 2- fluoro- bencilamida) del ácido (2S, 4S) - 4 - (9H- fluoren- 9- ilmetoxicarbonilamino)- pirrolidina- 1 ,2- dicarboxílico (209 mg, 0.3 mmol) en DMF (15 ml) se añadió polímero de piperazina unido (AldrichCAS 526290, carga = 1,5 mmol/g, 2 g, 3.01 mmol) y la mezcla de reacción se agitó a 25 °C durante 16 h. La mezcla de reacción se filtró, el polímero se lavó con CH_2Cl_2 y el filtrado se concentró a sequedad. El residuo crudo se purificó mediante HPLC preparativa (Waters Sunfire C18- ODB, 5 µm, 30x100mm, 20% de CH_3CN/2 min, 20- 100% CH_3CN/H_2O/18 min, 100% de CH_3CN/2 min, CH_3CN y H_2O que contiene HCOOH al 0.1, flujo: 40 ml/min) para proporcionar el compuesto del título como una sal de formiato. MS (LC/MS): 473 [M+H]+; t_R (condiciones de HPLC b): 2.52 min.

Protocolo alternativo:

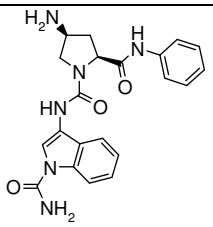
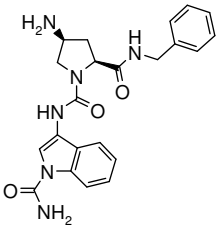
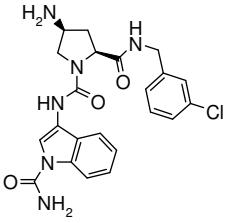
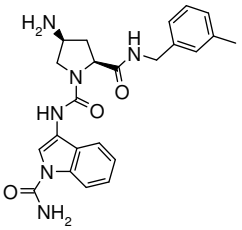
Alternativamente el residuo crudo se puede purificar mediante liberación de trinquete utilizando una columna de ácido- 1g silicaPrep Tosic (SPE- R60530B- 06S de Silicycle). Se acondicionó la columna con MeOH (10 ml), y se añadió el residuo crudo se disolvió en MeOH. La columna se lavó MeOH (10 ml) y el compuesto fue liberado por elución con amoniaco 2 M en MeOH (10 ml).

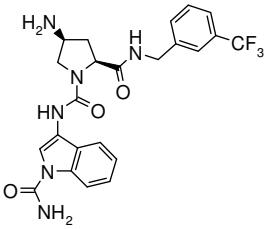
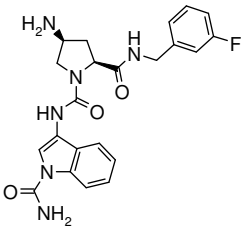
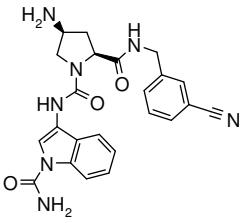
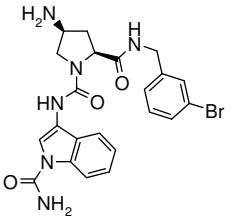
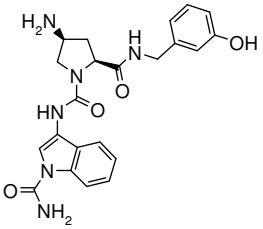
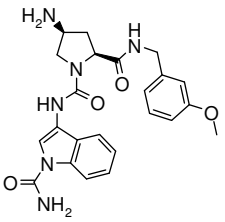
Alternativa protocolo 2:

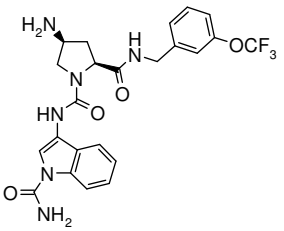
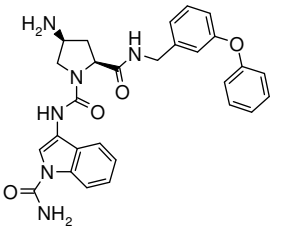
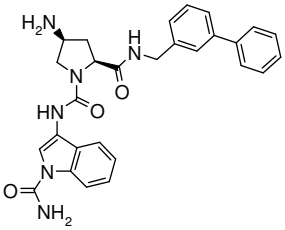
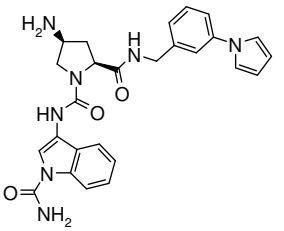
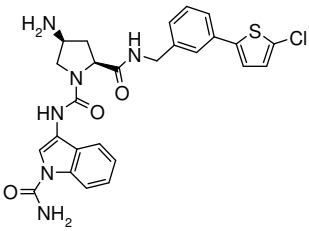
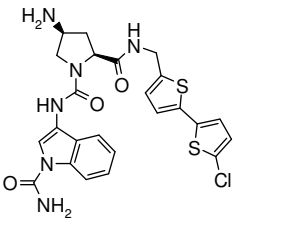
A las soluciones de 1 - [(1- carbamoil- 1H- indol- 3- il)- amida]amidas del ácido (2S, 4S) - 4 - (9H- fluoren- 9- ilmetoxicarbonilamino)- pirrolidina- 1 ,2- dicarboxílico en DMF (2.0 ml) se añadió polímero de piperazina unido (Aldrich CAS 526290, carga = 1.5 mmol/g, 2 g, 3.01 mmoles), los recipientes de reacción se lavó con argón y las mezclas de reacción se agitaron a 25 °C durante 48 h. Las soluciones resultantes se vertieron en cartuchos que contienen 500 mg de ácido silicaPrep Tosic (SPE- R60530B- 06S de Silicycle), acondicionado con MeOH (10 ml). Las columnas se lavaron con MeOH (20 ml) y los compuestos fueron luego liberados por elución con amoniaco 2 M en MeOH (10 ml).

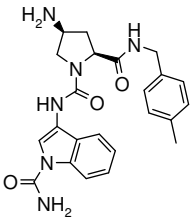
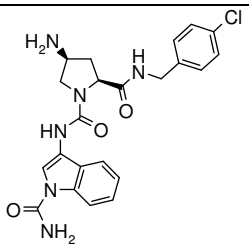
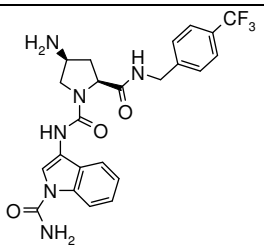
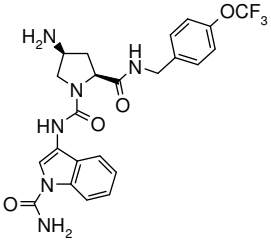
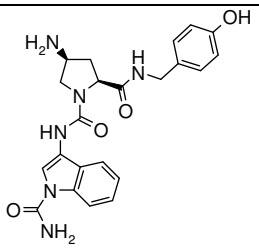
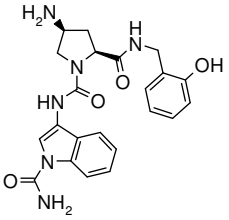
Los ejemplos siguientes se prepararon de acuerdo con el procedimiento general descrito para el **Ejemplo 26** *Esquema D2, usando diversas aminas en el paso A:*

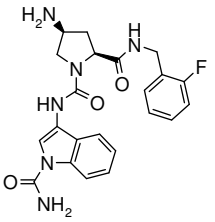
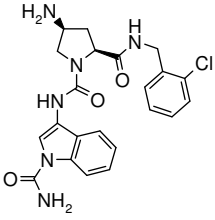
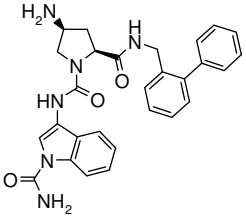
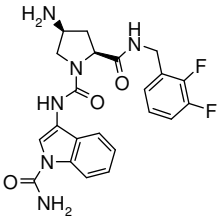
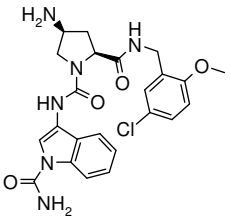
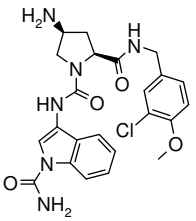
Tabla 2:

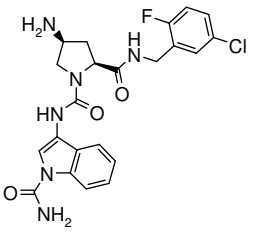
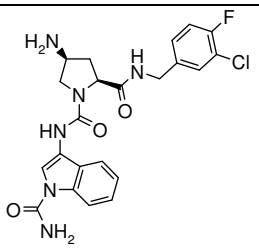
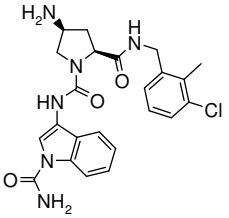
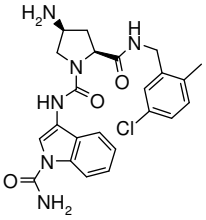
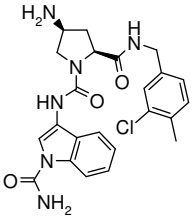
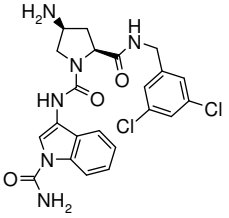
Ejemplo	**Estructura**	**Nombre**	Caracterización (Notas de pie de tabla), TLC, R_f (eluyente); MS (LC/MS); t_R (HPLC conditions)
27		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- fenilamida del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(1)407 [M+H]+; t_R (d): 0.6 min.
28		2- bencilamida 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(2)421.3 [M+H]+; t_R (d): 0.62 min.
29		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- bencilamida) del ácido (2S, 4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico como una sal de formiato	(1)454/456.1 [M+H]+, 932.2 [2M+Na]+, 453.1 [M- H]- ; t_R (d): 2.51 min.
30		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- metil- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(1) 435 [M+H]+; t_R (b): 2.62 min.

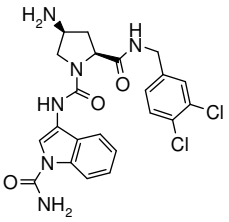
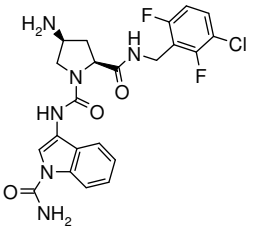
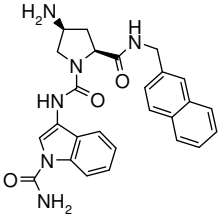
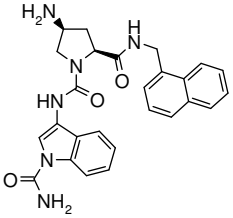
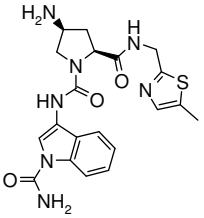
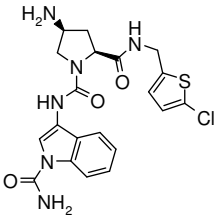
31		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- trifluorometil- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(1)489 [M+H]+; t_R (b): 2.95 min.
32		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- fluoro- bencilamida) del ácido (2S, 4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(2) 439.1 [M+H]+; t_R (d): 0.75 min.
33		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- Ciano- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(1) 446 [M+H]+; t_R (b) : 2.09 min.
34		2- (3- bromo- bencilamida) 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(1) 499/501 [M+H]+; t_R (b) : 2.78 min.
35		(2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico acid 1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- hidroxi- bencilamida)	(2)437.1 [M+H]+; t_R (d): 0.52 min.
36		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- metoxi- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(1) 451 [M+H]+; t_R (b) : 2.36.

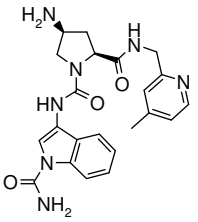
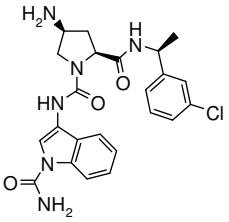
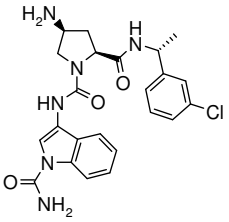
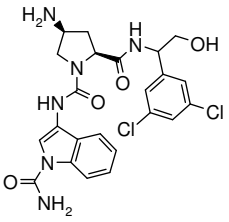
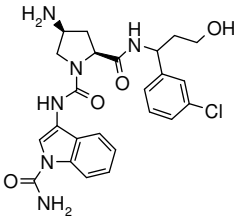
37		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- trifluorometoxi- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(2) 505.1 [M+H]+; t_R (d): 0.90 min.
38		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- fenoxi- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(2) 513.2 [M+H]+; t_R (d): 0.95 min.
39		2- [(bifenil- 3- ilmetil)- amida] 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S, 4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico como una sal de formiato	(1) 497.2 [M+H]+, 495.2 [M- H]- ; t_R (a): 2.8 min.
40		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- pirrol- 1- il- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(2) 486.2 [M+H]+; t_R (d): 0.87 min.
41		(2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico acid 1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [3- (5- cloro- tiofen- 2- il)- bencilamida]	(1)R_f (MeOH) = 0.25; 537.1/539.2 [M+H]+, 536/538 [M- H]- ; t_R (a): 2.92 min.
42		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5'- cloro- [2,2']bitiofenil- 5- ilmetil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(1)R_f (MeOH) = 0.28; 543.1/545 [M+H]+, 541/543.2 [M- H]- ; t_R (a): 2.90 min.

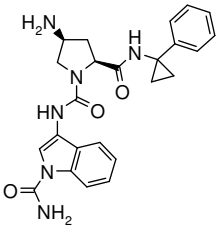
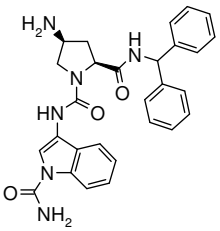
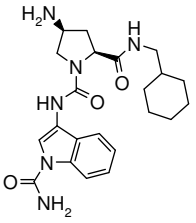
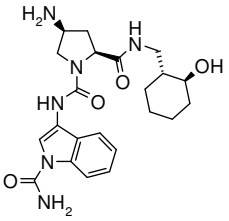
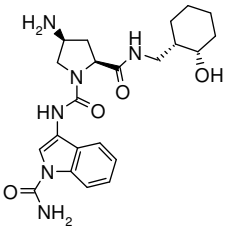
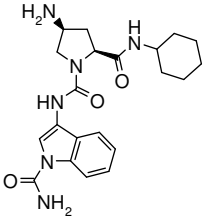
43		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (4- metil- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3)435.2 [M+H]+; t_R (d): 0.87 min.
44		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (4- cloro- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(2) 455 [M+H]+; t_R (d): 0.82 min.
45		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (4- trifluorometil- bencilamida) del ácido (2S, 4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(2)489.1 [M+H]+; t_R (d): 0.88 min.
46		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (4- trifluorometoxi- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(2)505.1 [M+H]+; t_R (d): 0.91 min.
47		(1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (4- hidroxi- bencilamida) del ácido 2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(2) 437.1 [M+H]+; t_R (d): 0.52 min.
48		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (2- hidroxi- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3)437.1 [M+H]+; t_R (d): 0.72 min.

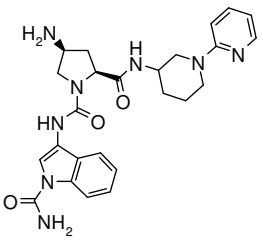
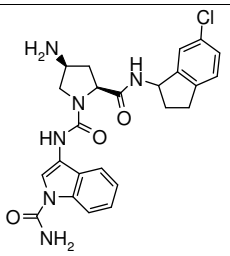
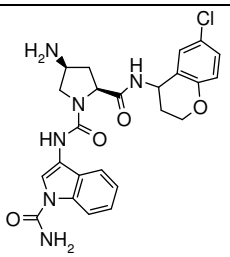
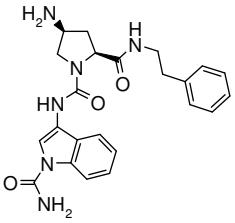
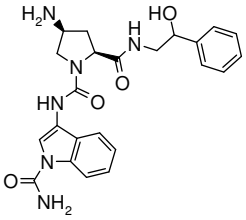
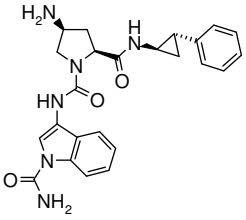
49		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (2- fluoro- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(1) 439.3 [M+H]+; t_R (b) : 2.12 min.
50		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (2- cloro- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3)455.1 [M+H]+; t_R (d): 0.88 min.
51		2- [(bifenil- 2- ilmetil)- amida] 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3)497.1 [M+H]+; t_R (d): 1.02 min.
52		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (2,3- difluoro- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(1) 457.2 [M+H]+; t_R (b): 2.24 min.
53		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (5- cloro- 2- metoxi- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(1) 485 [M+H]+; t_R (b) : 2.80 min.
54		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 4- metoxi- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(1) 485 [M+H]+; t_R (b): 2.67 min.

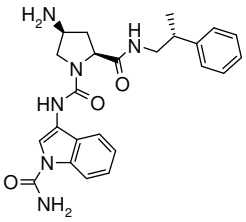
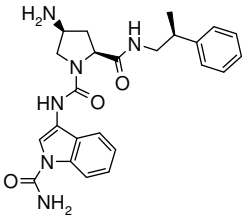
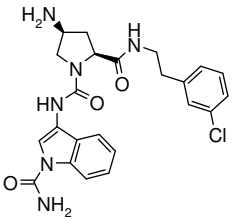
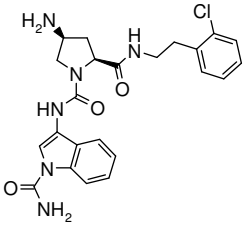
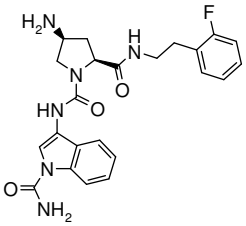
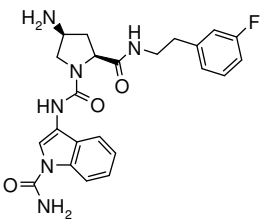
55		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (5- cloro- 2- fluoro- bencilamida) Del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(1)473 [M+H]+; t_R (b): 2.68 min.
56		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 4- fluoro- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(1)473 [M+H]+; t_R (b): 2.77 min.
57		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- metil- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(1) 469 [M+H]+; t_R (b): 2.82 min.
58		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (5- cloro- 2- metil- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(1) 469 [M+H]+; t_R (b): 2.84 min.
59		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 4- metil- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(1) 469 [M+H]+; t_R (b) : 2.93 min.
60		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3,5- dicloro- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3)489.1 [M+H]+; t_R (d): 0.96 min.

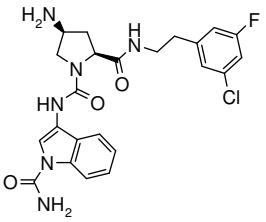
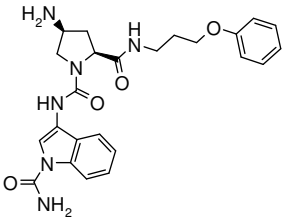
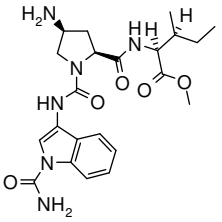
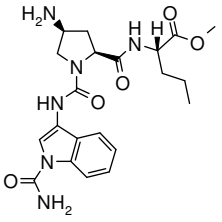
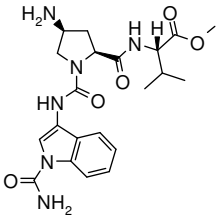
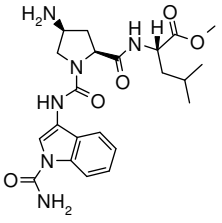
61		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3,4- dicloro- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3)489.1 [M+H]+; t_R (d): 0.96 min.
62		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2,6- difluoro- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3)491.1 [M+H]+; t_R (d): 0.88 min.
63		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(naftalen- 2- ilmetil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3)471.2 [M+H]+; t_R (d): 0.95 min.
64		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(naftalen- 1- ilmetil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3)471.2 [M+H]+; t_R (d): 0.94 min.
65		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- metil- tiazol- 2- ilmetil)- amida] del ácido (2S, 4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3,4)442.1 [M+H]+; t_R (d): 0.60 min.
66		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- cloro- tiofen- 2- ilmetil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(1) 461 [M+H]; t_R (b) : 2.37 min.

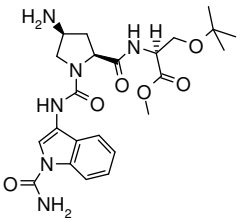
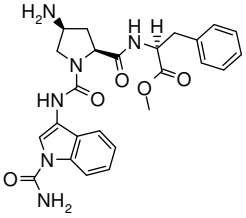
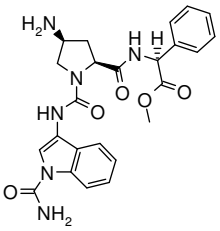
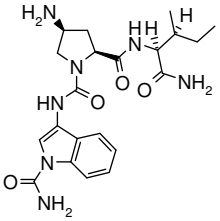
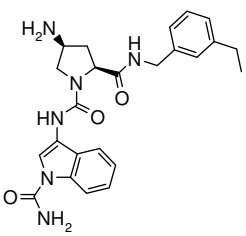
67		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(4- metil- piridin- 2- ilmetil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3,4) 436.2 [M+H]+; t_R (e): 1.13 min.
68		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- fenil)- etil]- amida} del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico como una sal de formiato	(1)469/471 [M+H]+, 424/426 [M-$CONH_2$]- ; t_R (a): 2.57 min.
69		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(R)- 1- (3- cloro- fenil)- etil]- amida} del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico acid como una sal de formiato	(1)469/471 [M+H]+, 424/426 [M-$CONH_2$]- ; t_R (a): 2.59 min.
70		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[1- (3,5- dicloro- fenil)- 2- hidroxi- etil]- amida} del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(1) mixture of 2 diastereosiomers. 519 [M+H]+; t_R (b): 2.72/2.76 min.
71		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[1- (3- cloro- fenil)- 3- hidroxi- propil]- amida} del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3)499.1 [M+H]+; t_R (d): 0.82 min.

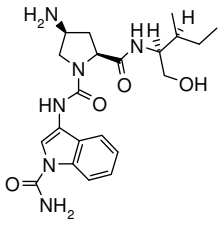
72		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(1- fenil- ciclopropil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(2)447.1 [M+H]+; t_R (d): 0.77 min.
73		2- benzhydril- amida 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico como una sal de formiato	(1)497.2 [M+H]+, 495.2 [M- H]- ; t_R (a): 2.80 min.
74		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- ciclohexilmetil- amida del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(2) 427.1 [M+H]+, t_R (d): 0.83 min.
75		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [((1R*,2S*)- 2- hidroxi- ciclohexilmetil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(2)mixture of trans diastereoisomers: 443.2 [M+H]+, 465.2 [M+Na]+, 441.2 [M- H]- ; t_R (a): 1.84/1.36 min.
76		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [((1S,2S)- 2- hidroxi- ciclohexilmetil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3)443.2 [M+H]+; t_R (d): 0.70 min.
77		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- ciclohexilamida del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(2) 413.1 [M+H]+, t_R (d): 0.75 min.

78		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3,4,5,6- tetrahidro- 2H- [1,2']bipiridinil- 3- il)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(2) Mixture of diastereoisomers 491.2 [M+H]+,t_R(e): 1.12/1.19 min.
79		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(6- cloro- indan- 1- il)- amida] del ácido (2S, 4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3)481.1 [M+H]+; t_R (d): 0.94 min.
80		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(6- cloro- croman- 4- il)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3)497.1 [M+H]+; t_R (d): 0.92 min.
81		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (fenetil- amida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(2) 435.1 [M+H]+, t_R (d): 0.77 min.
82		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(2- hidroxi- 2- fenil- etil)- amida] del ácido (2S, 4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3)451.2 [M+H]+; t_R (d): 0.71 min.
83		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [((1R,2S)- 2- fenil- ciclopropil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3)447.2 [M+H]+; t_R (d): 0.90 min.

84		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [((R)- 2- fenil- propil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3)449.2 [M+H]+; t_R (d): 0.90 min.
85		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [((S)- 2- fenil- propil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3)449.2 [M+H]+; t_R (d): 0.90 min.
86		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[2- (3- cloro- fenil)- etil]- amida} del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3) 469.1 [M+H]+; t_R (d): 0.91 min.
87		1- [(1- carbamoil- 1Hindol- 3- il)- amida] 2- {[2- (2- cloro- fenil)- etil]- amida} del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3)469.1 [M+H]+; t_R (d): 0.91 min.
88		1- [(1- carbamoil- 1Hindol- 3- il)- amida] 2- {[2- (2- fluoro- fenil)- etil]- amida} del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3)453.1 [M+H]+; t_R (d): 0.86 min.
89		1- [(1- carbamoil- 1Hindol- 3- il)- amida] 2- {[2- (3- fluoro- fenil)- etil]- amida} del ácido (2S, 4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3)453.1 [M+H]+; t_R (d): 0.86 min.

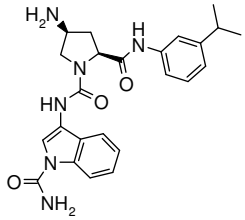
90		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[2- (3- cloro- 5- fluoro- fenil)- etil]- amida} del ácido (2S, 4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(3)473.1 [M+H]+; t_R (d): 0.90 min.
91		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(2- fenoxi- etil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(2) 451.1 [M+H]+, t_R (d): 0.78 min.
92		Éster metilo del ácido (2S,3S)- 2- {[(2S,4S)- 4- Amino- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- 3- metil- pentanoico	(2)459.1 [M+H]+, t_R (d): 0.79 min.
93		Ester metilo del ácido (S)- 2- {[(2S,4S)- 4- Amino- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- pentanoico	(3)445.2 [M+H]+; t_R (d): 0.80 min.
94		Ester metilo del ácido (R)- 2- {[(2S,4S)- 4- Amino- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- 3- metil- butirico	(3)445.2 [M+H]+; t_R (d): 0.76 min.
95		Éster metilo del ácido (S)- 2- {[(2S,4S)- 4- Amino- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- 4- metil-	(3)459.2 [M+H]+; t_R (d): 0.87 min.

		pentanoico	
96		Éster metilo del ácido (S)- 2- {[(2S,4S)- 4- Amino- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- 3- tert- butoxi- propionico	(3)489.2 [M+H]+; t_R (d): 0.87 min.
97		Éster metilo del ácido (S)- 2- {[(2S,4S)- 4- Amino- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- 3- fenil- propionico	(3)493.2 [M+H]+; t_R (d): 0.88 min.
98		Éster metilo del ácido (S)- {[(2S,4S)- 4- Amino- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- fenil- acetic	(3)479.1 [M+H]+; t_R (d): 0.84 min.
99		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [((1S,2S)- 1- carbamoil- 2- metil- butil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(2)444.1 [M+H]+, t_R (d): 0.61 min.
100		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- etil- bencilamida) del ácido (2S, 4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(2)449.1 [M+H]+; t_R (d): 0.86 min.

101		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [((1S,2S)- 1- hidroximetil- 2- metil- butil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico	(2) 431.1 [M+H]+, t_R (d): 0.69 min.

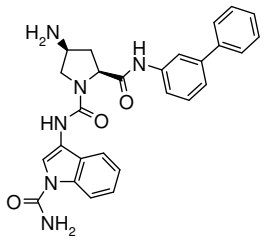
(1) Compuesto preparado según el procedimiento general descrito para el**Ejemplo 26**Esquema D2; (2) Compuesto preparado según el protocolo alternativo descrito para la etapa A y el uso de gel de sílice derivatizado piperazina (SPE- R60530B- 06S de Silicycle) en el paso B; (3) Compuesto preparado utilizando los protocolos alternativos 2, tanto para la etapa A y B; (4) En el paso B agitación se continuó a 60 °C durante 30 h adicionales.

Ejemplo 102: (2S, 4S)- 4- amino- pirrolidina- 1 ,2- dicarboxílico ácido 1 - [(1- carbamoil- 1H- indol- 3- il)- amida] 2 - [(3- isopropil- fenil) - amida]



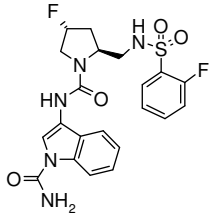
Se preparó de acuerdo con el procedimiento general descrito en el Esquema D2 utilizando 5 equivalentes de 3- isopropilanilina en el paso A y gel de sílice derivatizado piperazina (Silicycle, carga = 0.9 mmo /g, cat Número: SPE- R60030B) en el paso B. MS (LC/MS): 449,2 [M+H]+, 920,3 [2M+Na]+, 447,3 [MH] - ; t_R (a) Condiciones de HPLC: 2,74 min.

Ejemplo 103: 2- bifenil- 3- ilamida 1 - [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S, 4S)- 4- amino- pirrolidina- 1 ,2- dicarboxílico



Se preparó de acuerdo con los procedimientos generales descritos en el Esquema D2 usando 10 equivalentes de bifenil- 3- ilamina en el paso A. MS (LC/MS): 483,3 [M+H]+, 481,2 [MH] - ; t_R (condiciones de HPLC a): 2.83 min.

Esquema D3: protocolo general descrito para la preparación del Ejemplo 104: amida de ácido 3- ({(2S,4R)- 4- Fluoro- 2- [(2- fluoro- bencenosulfonilamino)- metil]- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico

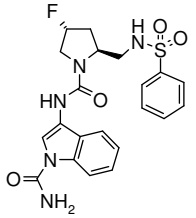
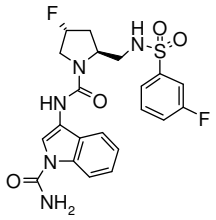
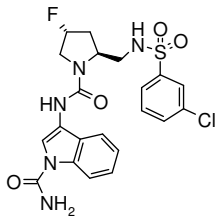
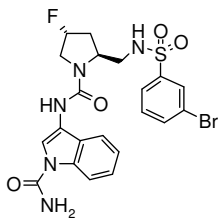
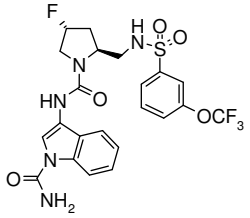


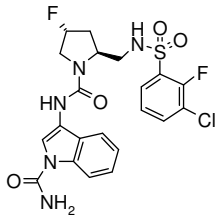
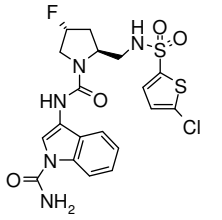
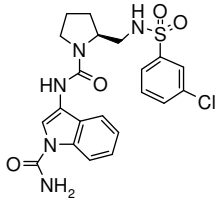
A una mezcla de 3 - [((2S, 4R)- 2- aminometil- 4- fluoro- pirrolidina- 1- carbonil)- amino]- amida de ácido indol- 1- carboxílico (52 mg, 0.163 mmol) (preparado como se describe Esquema B11) y cloruro de 2- fluorobencenosulfonilo (24 µl, 0,179 mmol) en CH_2Cl_2 (0.5 ml), se añadió trietilamina (25µ l, 0.179 mmol) y la suspensión resultante se agitó a temperatura ambiente bajo nitrógeno durante la noche. La mezcla se vertió en agua y se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó medainte HPLC preparativa (Waters Sunfire, C18-ODB, 5 µm, 19x50 mm, eluyente: 20% a 100% de CH_3CN en H_2O en 15 min, CH_3CN y H_2O que contiene HCOOH al 0,1%, flujo: 20 ml/min) para proporcionar después de la liofilización de las fracciones purificadas el material deseado. R_f, la TLC (EtOAc) = 0,55; MS (LC- MS): 478,1 [M+H]+, 500 [M+Na]+, 516 [M + K] +, 977,2 [2M+Na]+, 476 [MH] - , t_R (f) Condiciones de HPLC: 1,73 min.

*Los ejemplos siguientes se prepararon de acuerdo con el procedimiento descrito en el Esquema D3 para***Ejemplo 104,** *utilizando diversos cloruros de sulfonilo:*

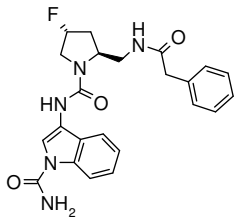
Tabla 3:

Ejemplo	Estructura	**Nombre**	Caracterización TLC, R_f (eluyente); MS (LC/MS); t_R(condiciones

			HPLC)
105		Amida del ácido 3-{[(2S,4R)- 2-(Bencenosulfonilamino-metil)- 4- fluoro- pirrolidina-1- carbonil]- amino}- indol-1- carboxílico	R_f (EtOAc) = 0.65; 460 [M+H]+, 482 [M+Na]+, 919 [2M+H]+, 941 [2M+Na]+, 458.2 [M- H]- ; t_R (f): 1.71 min.
106		Amida del ácido 3-({(2S,4R)- 4- Fluoro- 2- [(3-fluoro-bencenosulfonilamino)-metil]- pirrolidina- 1-carbonil}- amino)- indol- 1-carboxílico	R_f (EtOAc) = 0.7; 478 [M+H]+, 476 [M- H]- ; t_R (f): 1.79 min.
107		Amida del ácido 3-({(2S,4R)- 4- Fluoro- 2- [(3-cloro-bencenosulfonilamino)-metil]- pirrolidina- 1-carbonil}- amino)- indol- 1-carboxílico	R_f (EtOAc) = 0.7; 494/496 [M+H]+, 516.1/518.2 [M+Na]+, 492/494 [M- H]- ; t_R (f): 1.99 min.
108		Amida del ácido 3-({(2S,4R)- 4- Fluoro- 2- [(3-bromo-bencenosulfonilamino)-metil]- pirrolidina- 1-carbonil}- amino)- indol- 1-carboxílico	R_f (EtOAc) = 0.70; 537.9/539.9 [M+H]+, 559.9/561.8 [M+Na]+, 356/538 [M- H]- ; t_R (f): 1.89 min.
109		3- ({(2S,4R)- 4- Fluoro- 2-[(3- trifluorometoxi-bencenosulfonilamino)-metil]- pirrolidina- 1-	R_f (EtOAc) = 0.75; 544.2 [M+H]+, 566 [M+Na]+, 542 [M-H]- ; t_R (f): 2.08

		carbonil}- amino)- indol- 1- carboxílico acid amida	min.
110		Amida del ácido 3- ({(2S,4R)- 2- [(3- Cloro- 2- fluoro- bencenosulfonilamino)- metil]- 4- fluoro- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico	512/514 [M+H]+, 534.1/536 [M+Na]+, 510/512 [M- H]- ; t_R (f): 1.92 min.
111		Amida del ácido 3- ({(2S,4R)- 2- [(5- Cloro- tiofeno- 2- sulfonilamino)- metil]- 4- fluoro- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico	R_f (EtOAc) = 0.7; 500/502 [M+H]+, 522/524 [M+Na]+, 498/500 [M- $CONH_2$]- ; t_R (f): 1.88 min.
112		Ámida del ácido 3- ({(S)- 2- [(3- Cloro- bencenosulfonilamino)- metil]- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico	476.0 [M+H]+, 474.1 [M- H]- ; t_R (a): 3.34 min.

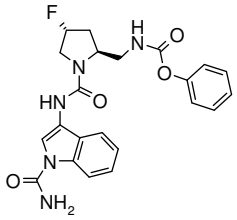
Ejemplo 113: Amida del ácido 3 - {[(2S, 4R)- 4- fluoro- 2- (fenilacetilamino- metil)- pirrolidina- 1- carbonil]- amino}- indol- 1- carboxílico



A una mezcla de amida del ácido 3 - [((2S, 4R)- 2- aminometil- 4- fluoro- pirrolidina- 1- carbonil)- amino]- indol- 1- carboxílico (50 mg, 0.16 mmol, preparado como se describe en Esquema B11) y cloruro de fenilacetilo (23 µl, 0.17 mmol) en CH_2Cl_2 (0.5 ml), se añadió trietilamina (24 µl, 0.17 mmol) y la suspensión resultante se agitó a temperatura ambiente bajo

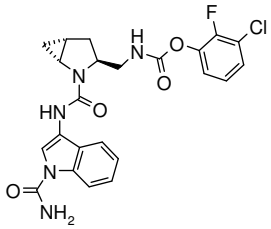
N_2 durante la noche. La mezcla se vertió en agua y se extrajo con CH_2Cl_2 (x2). Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se purificó mediante HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 19x50 mm, eluyente: 20% a 100% CH_3CN en H_2O en 15 min, CH_3CN y H_2O que contiene HCOOH al 0,1%, flujo: 20 ml/min) para proporcionar después de la liofilización de las fracciones purificadas el material deseado. R_f, la TLC (EtOAc) = 0.1; MS (LC- MS): 438.1 [M+H]+, 897,2 [2M+Na]+, 393,1 [M- $CONH_2$] - ; t_R (condiciones de HPLC f): 1.70 min.

Ejemplo 114: Éster fenilo del ácido [(2S, 4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidin- 2- ilmetil]- carbamicoo



A una mezcla de amida del ácido 3 - [((2S, 4R)- 2- aminometil- 4- fluoro- pirrolidina- 1- carbonil)- amino]- indol- 1- carboxílico (50 mg, 0.157 mmol, preparado como se describe en Esquema B11) y cloroformiato de fenilo (22 µl, 0.17 mmol) en CH_2Cl_2 (0.5 ml), se añadió trietilamina (24µ l, 0.17 mmol) y la suspensión resultante se agitó a temperatura ambiente bajo nitrógeno durante la noche. La mezcla se vertió en agua y se extrajo con CH_2Cl_2 (x2). Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se purificó mediante HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 19x50 mm, eluyente: 20% a 100% de CH_3CN en H_2O en 15 min, CH_3CN y H_2O que contiene HCOOH al 0,1%, flujo: 20 ml/min) para proporcionar después de la liofilización de las fracciones purificadas el material deseado. R_f, la TLC (EtOAc) = 0,45; MS (LC- MS): 440 [M+H]+, 901,3 [2M+Na]+; t_R (condiciones de HPLC f): 1,77 min.

Ejemplo 115: Éster 3- cloro - 2- fluoro- fenilo del ácido [(1R, 3S, 5R) - 2 - (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 2- aza- biciclo [3.1.0] hex- 3- ilmetil]- carbamicoo



A una solución de éster [(1R, 3S, 5R) - 1 - (2- aza- biciclo [3.1.0] hex- 3- il) metil]- carbamato de 3- cloro- 2- fluoro- fenil, trifluoroacetato (60.0 mg, 0.211 mmol) y Et_3N (88 µl, 0.62 mmol) en THF (5 ml) se añadió amida del ácido 3- isocianato- indol- 1- carboxílico (43.0 mg, 0.211 mmol; preparado como se describe en el Esquema A1). La solución se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 3 días. Se purificó mediante HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 30x100 mm, eluyente: 5- 100% CH_3CN/H_2O/20 min, 100% de CH_3CN/2 min, CH_3CN y H_2O que contiene TFA al 0.1%, flujo: 40 ml/min) proporcionó después de la liofilización de las fracciones purificadas por HPLC el compuesto del título. MS (LC/MS): 486,0 [M+H]+; t_R (condiciones de HPLC k): 3.57 min.

Éster terc- butílo del ácido (1R, 3S, 5R) - 3 - [(3- cloro- 2- fluoro- fenoxicarbonilamino)- metil]- 2- aza- iciclo [3.1.0] hexano- 2- carboxílico

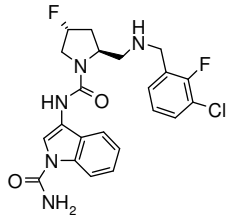
A una solución de 3- cloro- 2- fluorofenol (180 mg, 1.20 mmol) en CH_2Cl_2 seco (10 ml), se enfrió a 0 ºC, se añadió trifosgeno (120 mg, 0.4 mmol) seguido de la adición por goteo de una solución de DIPEA (210µl, 1.20 mmol) en CH_2Cl_2 (5 ml). La mezcla se dejó calentar a temperatura ambiente y se continuó agitando durante 1 h. La mezcla de reacción se añadió a continuación por goteo a una solución de éster terc- butilo del ácido (1R, 3S, 5R)- 3- aminometil- 2- aza- biciclo [3.1.0] hexano- 2- carboxílico de terc- butilo (170 mg, 0.80 mmol)(Preparado como se describe en la Parte B)y DIPEA (168 µl, 0.96 mmol) en CH_2Cl_2 (10 ml) a temperatura ambiente. Después de agitar durante 2 h, la reacción se apagó mediante la adición de metanol (2 ml) y agua con agitación vigorosa. La mezcla se extrajo con CH_2Cl_2 (2x), los extractos orgánicos combinados se lavaron con salmuera, se secaron (separador de fases) y se concentraron bajo presión reducida. La purificación mediante cromatografía en columna ultrarrápida sobre gel de sílice (gradiente de eluyente: c- hexano/EtOAc 9:1 a c- hexano/EtOAc 1:1) proporcionó el compuesto del título en forma de una cera incolora. MS (LC/MS): 385,0 [M+H]+; t_R (condiciones de HPLC k): 4.03 min.

Trifluoroacetato éster [(1R, 3S, 5R) - 1 - (2- aza- biciclo [3.1.0] hex- 3- il) metil]- carbamato de 3- cloro- 2- fluoro- fenilo

A una solución de éster terc- butílo del ácido (1R,3S,5R)- 3- [(3- cloro- 2- fluoro- fenoxicarbonilamino)- metil]- 2- aza- iciclo[3.1.0]hexano- 2- carboxílico (130 mg, 0.34 mmol) en CH_2Cl_2 (4 ml) se añadió TFA (2 ml, 26 mmol) y la solución se agitó a temperatura ambiente durante 2 h. Luego se añadió metanol y los volátiles se eliminaron bajo presión reducida. El residuo se recogió en MeOH y se concentró al vacío para proporcionar el compuesto del título

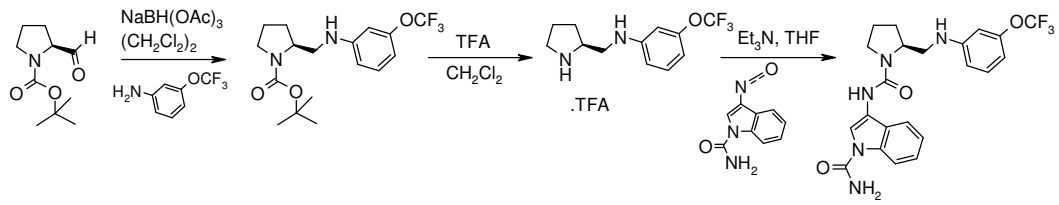
crudo en forma de una cera incolora. MS (LC/MS): 285,0 [M+H]+; t_R (condiciones de HPLC k): 2.66 min. El material así obtenido se utilizó directamente en la siguiente etapa sin purificación adicional.

Ejemplo 116: Amida de ácido 3- ({(2S,4R)- 2- [(3- Cloro- 2- fluoro- bencilamino)- metil]- 4- fluoro- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico



Amida de ácido 3 - [((2S, 4R)- 2- aminometil- 4- fluoro- pirrolidina- 1- carbonil)- amino]- indol- 1- carboxílico (50 mg, 0.157 mmol) y 3- cloro- 2- fluorobenzaldehído (25 mg, 0.157 mmol, preparado como se describe en el Esquema B11) se mezclaron en dicloroetano (1 ml), se añadió triacetoxiborohidruro de sodio (46.5 mg, 0.22 mmol) y la mezcla se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 2 días. 3- cloro- 2- fluorobenzaldehído (25 mg, 0.157 mmol) y se añadió triacetoxiborohidruro (46.5 mg, 0.219 mmol) para completar la reacción. La mezcla de reacción se vertió en una solución acuosa saturada de $NaHCO_3$ y se extrajo con CH_2Cl_2. Los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y concentraron. El residuo crudo se diluyó en MeOH se purificó por SiliaPrep Tosic Ácido- 1g (SPE- R60530B- 06S de Silicycle), la columna se lavó con 10 ml de MeOH y el compuesto liberado con 10 ml de amoniaco 2 M en MeOH para proporcionar, después de la concentración 20% a 100% CH_3CN en H_2O en 15 min, CH_3CN y H_2O que contiene HCOOH al 0,1%, flujo: material que se purificó adicionalmente por HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 19x50 mm, eluyente deseada 20 ml/min) para proporcionar después de la liofilización de las fracciones purificadas el material deseado en forma de una sal de ácido fórmico. MS (LC- MS): 462.1/464 [M+H]+, 460/462 [MH] - ; tR (condiciones HPLC f): 1,54 min.

Ejemplo 117: Amida de ácido 3- ({(S)- 2- [(3- Trifluorometoxi- fenilamino)- metil]- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico



A. Éster terc- butilo del ácido (S) - 2 [(3- trifluorometoxi- fenilamino)- metil]- pirrolidina- 1- carboxílico

N- (terc- butoxicarbonil)- L- prolinal (200 mg, 1.00 mmol) y 3- trifluorometoxi- fenilamina (186.8 mg, 1.05 mmol) se mezclaron en 1,2- dicloroetano (10 ml) y se trató con triacetoxiborohidruro de sodio (314 mg, 1.41 mmol). La mezcla se agitó a temperatura ambiente bajo nitrógeno durante la noche, después se apagó mediante la adición de agua, se extrajo con CH_2Cl_2, se secó sobre Na_2SO_4, se filtró y se concentró. El aceite crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano para c- hexano/EtOAc 1:1) para proporcionar el material deseado. MS (LC/MS): 361.1 [M+H]+.

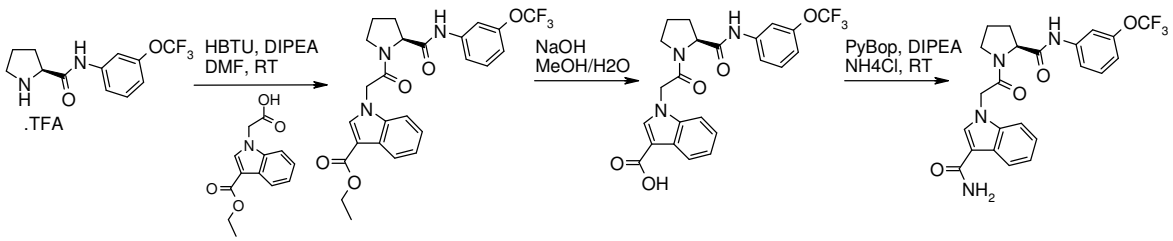
B. (S)- 1- pirrolidin- 2- ilmetil- (3- trifluorometoxi- fenil)- amina

Una solución de éster terc- butílo del ácido (S) - 2 - [(3- trifluorometoxi- fenilamino)- metil]- pirrolidina- 1- carboxílico (100 mg, 0.277 mmol) y TFA (1 MLL) en CH_2Cl_2 (2 ml) se agitó a temperatura ambiente durante 2 h. El solvente se concentró y el residuo se co- evaporó dos veces con CH_2Cl_2 y se secó al vacío durante la noche para proporcionar el compuesto del título crudo en forma de una sal de TFA. MS: 261.1 [MH- Boc] +, t_R (condiciones de HPLC a): 2.61 min.

C. Amida de ácido 3- ({(S)- 2- [(3- Trifluorometoxi- fenilamino)- metil]- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico

A una solución de (S)- 1- pirrolidin- 2- ilmetil- (3- trifluorometoxi- fenil)- amina (49 mg, 0.131 mmol) y Et_3N (55 µl, 0.393 mmol) en THF (1.5 ml) se añadió una solución de 3- isocianato- 1- metil- 1H- indol (26 mg, 0.393 mmol, preparado como se describe en el Esquema A1) en THF (1.5 ml). La solución resultante se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 1 h. La mezcla se vertió en agua y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se purificó mediante HPLC preparativa (Waters C18- ODB, 5 µm, 19x50 mm, eluyente: CH_3CN/H_2O +HCOOH al 0.1%, flujo: 20 ml/min) para proporcionar, después de liofilización de la fracción purificada del compuesto del título. TLC, R_f (c- hexano/EtOAc 1:2) = 0.23; MS (LC/MS): 462,1 [M+H]+, 484,1 [M+Na]+; t_R (condiciones de HPLC a): 3,75 min.

Ejemplo 118: Amida del ácido 1- {2- Oxo- 2- [(S)- 2- (3- trifluorometoxi- fenilcarbamoil)- pirrolidin- 1- il]- etil}- 1H- indol- 3- carboxílico



A. Éster etílo del ácido 1- {2- Oxo- 2- [(S)- 2- (3- trifluorometoxi- fenilcarbamoil)- pirrolidin- 1- il]- etil}- 1H- indol- 3- carboxílico

El compuesto del título se preparó de acuerdo con el procedimiento general descrito en el Esquema D6 usando Éster etílo del ácido 1- carboximetil- 1H- indol- 3- carboxílico (preparado como se describe en la Parte a) y DMF como solvente. TLC, R_f (EtOAc) = 0,56; MS (LC/MS): 526 [M+Na]+, 502 [MH] - ; t_R (condiciones de HPLC a): 3,90 min.

B. ácido 1- {2- Oxo- 2- [(S)- 2- (3- trifluorometoxi- fenilcarbamoil)- pirrolidin- 1- il]- etil}- 1H- indol- 3- carboxílico

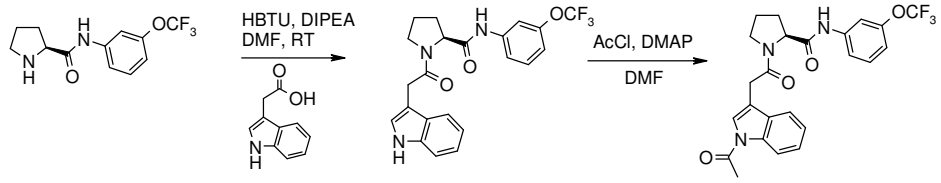
A una solución de Éster etílo del ácido 1- {2- oxo- 2- [(S)- 2- (3- trifluorometoxi- fenilcarbamoil)- pirrolidin- 1- il]- etil}- 1H- indol- 3- carboxílico (314 mg, 0.62 mmol) en MeOH (12 ml) y agua (1.2 ml) se añadió NaOH 1 N (1.87 ml, 1.87 mmol) y la mezcla se calentó a 80 °C durante 6 h. MeOH se concentró, se añadió HCl 1 N y el residuo se extrajo con EtOAc. Los extractos orgánicos se secaron con Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante HPLC preparativa (Interchrom C18- ODB, 10 m, 28x250 mm, 20% de CH_3CN en H_2O 2,5 min, luego 20% a 100% CH_3CN en H_2O en 32.5 min, CH_3CN y H_2O que contiene HCOOH al 0,1%; flujo: 40 ml/min) para proporcionar, después de liofilización de las fracciones purificadas el compuesto deseado. TLC, R_f (EtOAc) = 0,05; MS (LC/MS): 498,1 [M+Na]+, 474,1 [MH] - ; t_R (condiciones de HPLC a): 3.48 min.

C. Ejemplo 118: Amida de ácido 1- {2- Oxo- 2- [(S)- 2- (3- trifluorometoxi- fenilcarbamoil)- pirrolidin- 1- il]- etil}- 1H- indol- 3- carboxílico

Ácido 1- {2- Oxo- 2- [(S)- 2- (3- trifluorometoxi- fenilcarbamoil)- pirrolidin- 1- il]- etil}- 1H- indol- 3- carboxílico (11 mg, 0.023 mmoles), se trató con PyBOP (12 mg, 0.023 mmol), HOBt (3.54 mg, 0.023 mmol), DIPEA (16 µl, 0.092 mmol), y NH_4Cl (1 mg, 0.069 mmoles) en DMF (1 ml) y la mezcla de reacción se agitó a temperatura ambiente en una

atmósfera de nitrógeno durante 3 h, después se vertió en una solución acuosa saturada de $NaHCO_3$, se añadió EtOAc (20 ml) y las capas se separaron. La capa acuosa se extrajo de nuevo dos veces con EtOAc y los extractos orgánicos combinados se secaron (Na_2SO_4), se filtró y se concentró. El residuo crudo se purificó mediante HPLC preparativa (Waters SunFire C18- ODB, 5 µm, 19x50 mm, 20% de CH_3CN/H_2O 2.5 min, 20- 100% de CH_3CN/H_2O en 10 min, CH_3CN/H_2O que contiene HCOOH al 0,1%, flujo: 20 ml/min) para proporcionar, después de liofilización de las fracciones purificadas el compuesto deseado. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0,17; MS (LC/MS): 473,2 [MH] - ; t_R (a) Condiciones de HPLC: 3,24 min.

Ejemplo 119 (S) - 1 - [2 - (1- Acetil- 1H- indol- 3- il)- acetil]- pirrolidina- 2- carboxílico (3- trifluorometoxi- fenil)- amida



A. (3- trifluorometoxi- fenil)- amida del ácido (S) - 1 - (2- 1H- indol- 3- il- acetil)- pirrolidina- 2- carboxílico

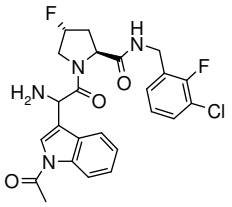
El compuesto del título se preparó de acuerdo con el procedimiento general descrito en el Esquema D6 usando ácido (1H- indol- 3- il)- acético utilizando DMF como solvente. TLC, R_f (c- hexano/EtOAc 1:1) = 0,14; MS (LC/MS): 432,3 [M+H]+, 454,1 [M+Na]+; t_R (HPLCconditions a): 3,68 min.

B. Ejemplo 119: (S) - 1 - [2 - (1- Acetil- 1H- indol- 3- il)- acetil]- pirrolidina- 2- carboxílico (3- trifluorometoxi- fenil)- amida

A una solución de (3- trifluorometoxi- fenil)- amida del ácido (S) - 1 - (2- 1H- indol- 3- il- acetil)- pirrolidina- 2- carboxílico (100 mg, 0.232 mmol) en DMF (1.5 ml) bajo atmósfera de nitrógeno se añadió cloruro de acetilo (148 µl, 2,09 mmol) seguido de DMAP (85 mg, 0,7 mmol) y la mezcla de reacción se calentó a 80 °C durante 18 h. Después de la terminación de la reacción, la mezcla se vertió en ácido cítrico (solución al 10%), y se extrajo tres veces con EtOAc. Las capas orgánicas combinadas se lavaron dos veces con agua, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El material crudo se purificó mediante HPLC preparativa (Waters SunFire C18- ODB, 5 µm, 19x50 mm, 20% de CH_3CN/H_2O 2,5 min, 20- 100% CH_3CN/H_2O en 10 min, CH_3CN/H_2O que contiene HCOOH al 0,1% de flujo: 20 ml/min) para proporcionar, después de liofilización de las fracciones purificadas el compuesto

deseado. TLC, R_f (c- hexano/EtOAC 3:7) = 0,16; MS (LC/MS): 474,1 [M+H]+, 496 [M+Na]+, 472 [MH] - ; tR (condiciones de HPLC a): 3.80 min.

Ejemplo 120: (2S, 4R) - 1 - [2 - (1- Acetil- 1H- indol- 3- il)- 2- amino- acetil]- 4- fluoro- pirrolidina- 2- carboxílico 3- cloro- 2 - fluoro- bencilamida



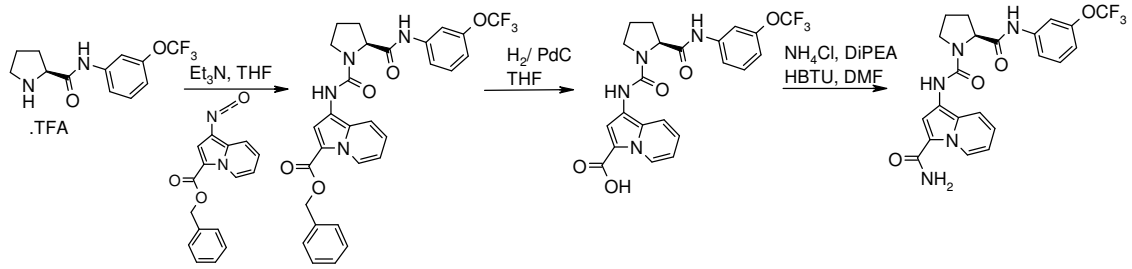
Una solución de éster terc- butílo del ácido {1- (1- acetil- 1H- indol- 3- il)- 2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- carbamico (102 mg, 0.173 mmol) y TFA (66.7 µl, 0.866 mmol) en CH_2Cl_2 (0.58 ml) se agitó a 23 °C durante la noche. Se añadió de nuevo TFA (66.7 µl, 0.866 mmol) y la mezcla de reacción se agitó a 23 °C durante 4 h más para completar la reacción. Los solventes se eliminaron al vacío y el residuo crudo se purificó mediante HPLC preparativa (Waters SunFire C18ODB, µm, 19x50, eluyente: 5% de CH_3CN/95% H_2O a 100% de CH_3CN en 17 min, CH_3CN y H_2O que contiene TFA al 0.1%, flujo de 20 ml/min) para proporcionar después de liofilización de las fracciones purificadas el material deseado. MS (LC- MS): 487.1 [MH] - ; t_R (condiciones de HPLC b): 3.19 min.

<u>Éster terc- butílo del ácido {1- (1- Acetil- 1H- indol- 3-</u> il)**<u>- 2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- carbamico</u>**

A una solución de éster terc- butilo del ácido [2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 1- (1H- indol- 3- il)- 2- oxo- etil]- carbamico se añadió diastereosiomero P2 (preparado como se describe en la Parte B) (150 mg, 0.274 mmol) en THF seco (1.37 ml) en atmósfera de argón y a 0 °C, tBuOK (40 mg, 0.356 mmol). La mezcla de reacción se agitó 5 min a 0 ºC y después se añadió cloruro de acetilo (25,3 µl, 0.356 mmol) y la mezcla de reacción se dejó calentar hasta 23 °C y se agitó durante la noche. La mezcla se apagó mediante la adición de una solución acuosa saturada de $NaHCO_3$ y se extrajo con EtOAc (x3). Las capas orgánicas se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c-hexano/EtOAc gradiente de 100:0 a 0:100) para proporcionar el material deseado. TLC, R_f

(EtOAc) = 0,65; MS (LC- MS): 587,2 [MH] - , 611 [M+Na]+; t_R (condiciones de HPLC b): 5.18 min.

Esquema D4: preparación del Ejemplo 121: 1 - [(3- carbamoil- indolizin- 1- il)] 2 - [(3- trifluorometoxi- fenil)- amida] del ácido (S)- pirrolidina- 1 ,2- dicarboxílico



A. Éster bencilo del ácido 1- {[(S)- 2- (3- Trifluorometoxi- fenilcarbamoil)- pirrolidina- 1- carbonil]- amino}- indolizina- 3- carboxílico

A una solución del (3- trifluorometoxi- fenil)- amida del ácido (S)- pirrolidina- 2- carboxílico sal de TFA (328 mg, 0.845 mmol) y trietilamina (353 µl, 2,54 mmol) en THF (10 ml) se añadió éster bencilo del ácido 1- isocianato- indolizina- 3- carboxílico (247 mg, 0.845 mmol, preparado como se describe en el Esquema A6). La mezcla resultante se agitó a temperatura ambiente bajo nitrógeno durante el fin de semana y después se vertió en HCl 1 N y se extrajo con EtOAc (x3). Los extractos orgánicos combinados se lavaron con una solución acuosa saturada de $NaHCO_3$, se secaron (Na_2SO_4), se filtraron y se concentraron. La mezcla crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (1:1 a c-hexano/EtOAc c- hexano/EtOAc 3:7) para proporcionar el compuesto deseado. TLC, R_f (c-hexano/EtOAc 1:1) = 0.3; MS (LC/MS): 567,3 [M+H]+ 565,2 [MH] - ; t_R (condiciones de HPLC a): 4.16 min.

B. Ácido 1- {[(S)- 2- (3- Trifluorometoxi- fenilcarbamoil)- pirrolidina- 1- carbonil]- amino}- indolizina- 3- carboxílico

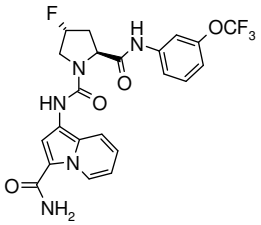
A éster bencilo del ácido 1- {[(S)- 2- (3- Trifluorometoxi- fenilcarbamoil)- pirrolidina- 1- carbonil]- amino}- indolizina- 3- carboxílico (100 mg, 0.177 mmol) disuelto en THF (3 ml) se añadió Pd/C al 10% (20 mg). El aire se retiró del matraz al vacío y se reemplazó con nitrógeno tres veces, finalmente el nitrógeno se retiró y se sustituyó con hidrógeno y la mezcla se agitó a temperatura ambiente durante 5 h. El hidrógeno se eliminó y se sustituyó por nitrógeno, el catalizador se eliminó por filtración a través de una almohadilla de Celite y se lavó

con THF. Los solventes se concentraron para proporcionar una mezcla que contiene el compuesto deseado contaminado con 20% del análogo descarboxilado. La mezcla se utilizó sin purificación adicional en la siguiente etapa. LC/ MS: 475 [MH] - ; t_R (condiciones de HPLC a): 3,41 min.

C. Ejemplo 121: (3- carbamoil- indolizin- 1- il)] 2 - [(3- trifluorometoxi- fenil)- amida] del ácido (S)- pirrolidina- 1 ,2- dicarboxílico

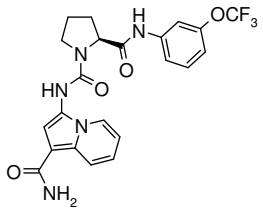
A una solución del ácido que contiene 20% del análogo descarboxilado (65 mg, 0.136 mmoles), NH_4Cl (8.80 mg, 0.164 mmol) y HBTU (78 mg, 0.205 mmol) en DMF (2.5 ml) se añadió DIPEA (49 µl, 0.287 mmol) y la solución resultante se agitó a temperatura ambiente bajo nitrógeno durante la noche. Después de la terminación de la reacción, la mezcla se vertió en HCl 1 N y se extrajo con EtOAc (x3). Los extractos orgánicos combinados se lavaron con agua (x2), se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se purificó medainte HPLC preparativa (Waters SunFire C18- ODB, 5 µm, 19x50 mm, 20% de CH_3CN/H_2O 2.5 min, 20- 100% de CH_3CN/H_2O en 10 min, CH_3CN/H_2O que contiene HCOOH al 0.1%, flujo: 20 ml/min) para proporcionar después de la liofilización de las fracciones purificadas el compuesto deseado en forma de un polvo. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0,4; MS (LC/MS): 476 [M+H]+, 498,1 [M+Na]+, 474,1 [MH] - ; t_R (condiciones de HPLC a): 3.30 min.

Ejemplo 122: 1 - [(3- carbamoil- indolizin- 1- il)]- amida]2- [(3- trifluorometoxi- fenil)- amida del ácido (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico



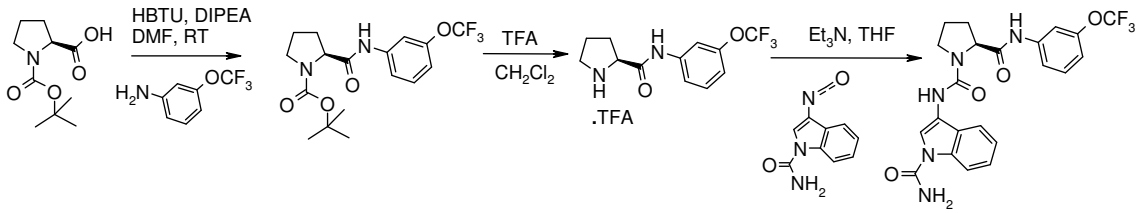
El compuesto del título se preparó de acuerdo con el mismo procedimiento como se describe en el Esquema D4 a partir de 1 - [(3- carbamoil- indolizin- 1- il)- amida] 2 - [(3- trifluoro metoxi- fenil)- amida] del ácido (S)- pirrolidina- 1 ,2- dicarboxílico. MS: 494 [M+H]+, 492,1 [MH] - ; tR (Condiciones de HPLC a): 187 min.

Ejemplo 123: 1 - [- amida del ácido (1- carbamoil- indolizin- 3- il)] 2 - [(3- trifluorometoxi- fenil)- amida] del ácido (S)- pirrolidina- 1 ,2- dicarboxílico



El compuesto del título se preparó a partir de éster bencilo del ácido 3- isocianato- indolizina- 1- carboxílico (preparado como se describe en el Esquema A7) utilizando el protocolo descrito en el Esquema D4. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0,4; MS (LC/MS): 476 [M+H]+, 498,1 [M+Na]+, 474,1 [MH] - ; t_R (condiciones de HPLC a): 3.13 min.

<u>Esquema D5: protocolo general descrito para la preparación del Ejemplo 124: 1 - [(1- carbamoil- 1H- indol- 3- il)- amida] 2 - [(3 - trifluorometoxi- fenil)- amida] del ácido (S)- pirrolidina- 1 ,2- dicarboxílico</u>



A. Éster tetc- butilo del ácido (S) - 2 (3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 1- carboxílico

A una mezcla de Boc- L- prolina (5 g, 23.23 mmol), 3 - (trifluorometoxi) anilina (3.73 ml, 27.88 mmol) y HBTU (13.2 g, 34.8 mmol) en DMF (60 ml) se añadió DIPEA (7.95 ml, 46.5 mmol) y la solución de color amarillo resultante se agitó a temperatura ambiente en atmósfera de nitrógeno. El solvente se concentró al vacío y el residuo se disolvió en EtOAc y se lavó con HCl 1N. Las capas orgánicas reunidas se neutralizaron por adición de una solución acuosa saturada de $NaHCO_3$. Las capas se separaron y la fase acuosa se extrajo de nuevo dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 3:1- 2:1) para proporcionar el compuesto deseado. TLC, R_f (c- hexano/EtOAc 1:1) = 0,57; MS (LC/MS): 397,1 [M+Na]+, 275,2 [MH- Boc]+, 373,3 [MH] - ; t_R (condiciones de HPLC a) 3.81 min.

Diclorometano también se puede utilizar en lugar de DMF.

B. (3- trifluorometoxi- fenil)- amida del ácido (S)- pirrolidina- 2- carboxílico

A una solución de éster terc- butílo del ácido (S) - 2 - (3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 1- carboxílico (8.52 g, 22.6 mmol) en CH_2Cl_2 (50 ml) se añadió TFA (8.65 ml, 113 mmol) y la solución se agitó a temperatura ambiente durante 12 h. La mezcla de reacción cruda se concentró al vacío, se añadió Et_2O y el precipitado blanco se separó mediante filtración para proporcionar el compuesto deseado en forma de una sal de TFA. MS (LC/MS): 275,2 [M+H]+, 273,3 [MH] - ; t_R (condiciones de HPLC a) 2.47 min.

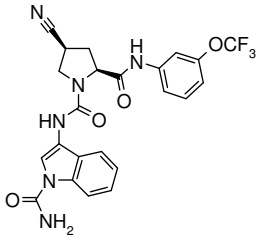
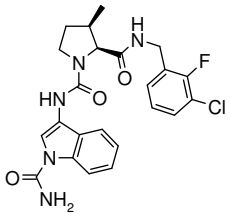
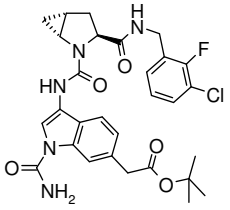
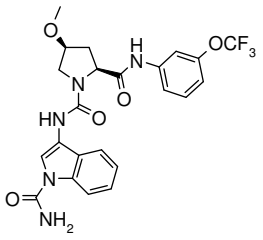
C. Ejemplo 124: 1 - [(1- carbamoil- 1H- indol- 3- il)- amida] 2 - [(3- trifluorometoxi- fenil)- amida] del ácido (S)- pirrolidina- 1 ,2- dicarboxílico

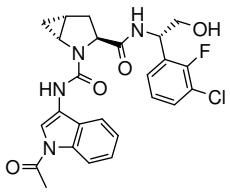
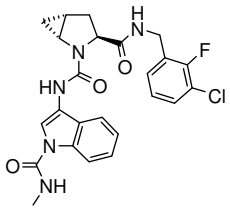
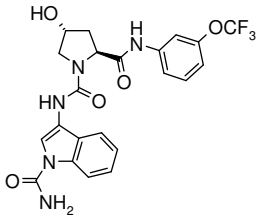
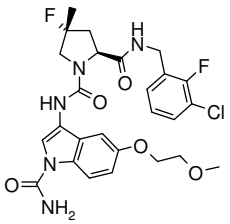
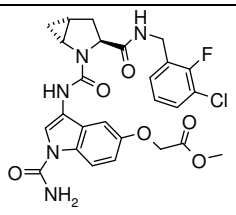
A una solución de trifluoroacetato de (3- trifluorometoxi- fenil)- amida del ácido (S)- pirrolidina- 2- carboxílico (328 mg, 0.845 mmol) y Et_3N (353 µl, 2.53 mmol) en THF (7.5 ml) se añadió una suspensión de amida de ácido 3- isocianato- indol- 1- carboxílico (170 mg, 0.845 mmol, preparado como se describe en el Esquema A1) en THF (7.5 ml). La solución resultante se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 1 h, se vertió en agua y la mezcla se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se purificó mediante HPLC preparativa (Waters SunFire C18- ODB, 5 µm, 19x50 mm, 20% de CH_3CN/H_2O 2.5 min, 20- 100% de CH3CN/H_2O en 10 min, CH3CN/H_2O que contiene HCOOH al 0.1%, flujo: 20 ml/min) para proporcionar después de liofilización de las fracciones purificadas medainte HPLC el compuesto del título. TLC, R_f (c- hexano/EtOAc 1:2) = 0,11; MS (LC/MS): 476,2 [M+H]+, 973,2 [2M+Na]+.

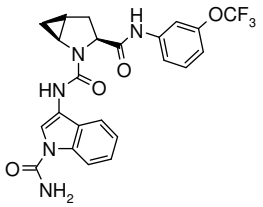
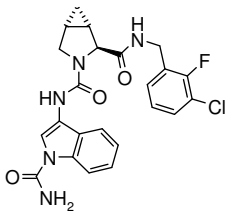
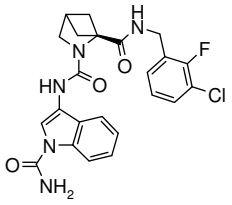
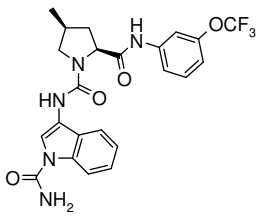
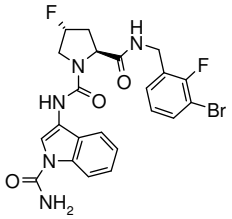
Los ejemplos siguientes se prepararon de acuerdo a los procedimientos generales descritos en el Esquema D5 para la preparación del **Ejemplo 124** *a partir de precursores de sintesìs disponibles en el mercado, si no se indica lo contrario (ver notas al final del cuadro 4):*

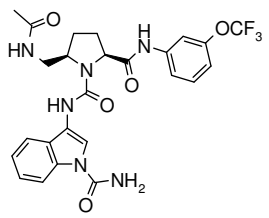
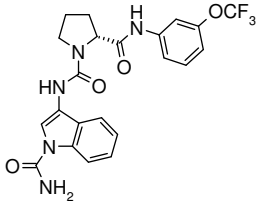
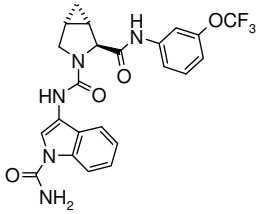
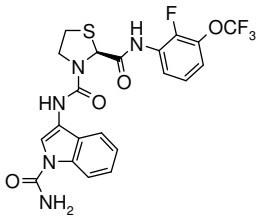
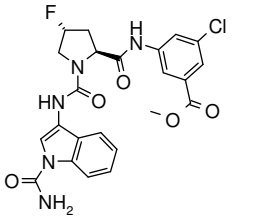
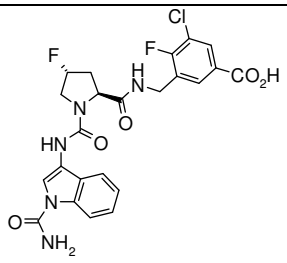
Tabla 4:

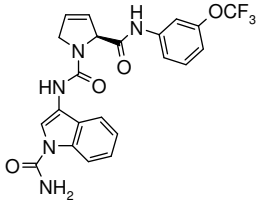
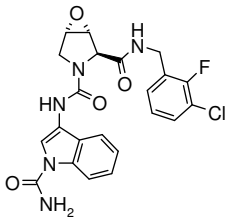
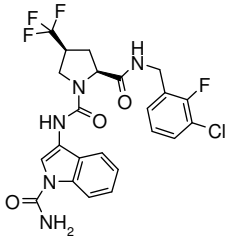
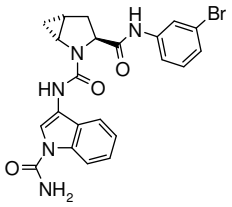
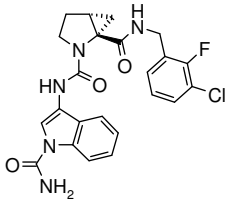
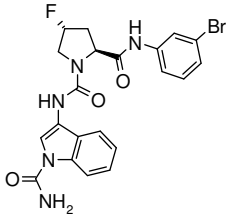
Ejemplo	**Estructura**	**Nombre**	Caracterización (Notas de pie de tabla), TLC, R_f

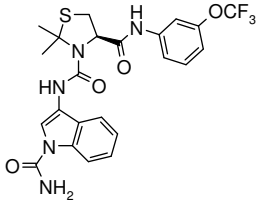
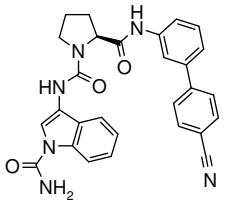
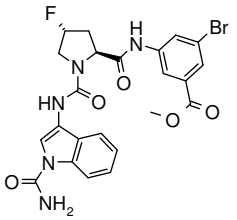
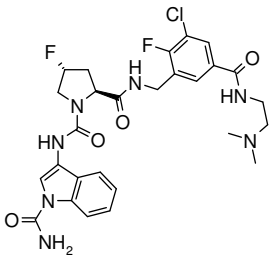
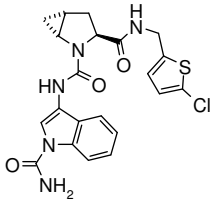
			(eluyente); MS (LC/MS); t_R (condiciones HPLC); 19F NMR (100 MHz, solvente) δ (ppm):
125		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- Ciano- pirrolidina- 1,2 dicarboxílico	501.1 [M+H]+; t_R (b): 4.07 min.
126		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R)- 3- metil- pirrolidina- 1,2- dicarboxílico	(7) R_f (EtOAc) = 0.5; 472.1/474.2 [M+H]+, 427/429 [M- $CONH_2$]- ; t_R (a): 3.24 min.
127		Éster terc- butilo del ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 6- il)- acetico	(9)R_f (EtOAc) = 0.44; 584.4/586.4 [M+H]+, 582.7/584.4 [M- H]- , 539.4/541.4 [M- $CONH_2$]- , 628.4/630.4 [M+HCOO]- ; t_R (f): 2.20 min.
128		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- metoxi- pirrolidina- 1,2- dicarboxílico	506.2 [M+H]+, 504.1 [M- H]- ; t_R (a): 3.43 min.

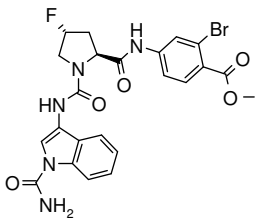
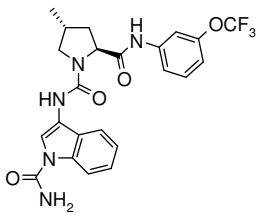
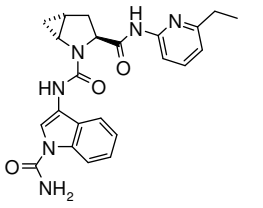
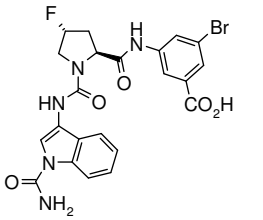
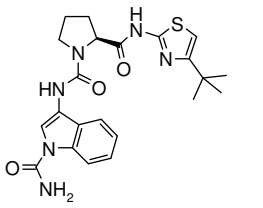
129		2- [(1- acetil- 1H- indol- 3- il)- amida] 3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2hidroxi- etil]- amida} del ácido (1R,3S,5R)- 2- Azabiciclo[3.1.0]hexano- 2,3- dicarboxílico	(5, 8[B9],9[A1]) R_f (EtOAc) = 0.45; 499.4/501.3 [M+H]+, 521.3/523.4 [M+Na]+, 543.3/545.4 [M+HCOO]- , 497.5/499.8 [M- H]- ; t_R (a): 1.95 min.
130		3- (3- cloro- 2- fluoro- bencilamida) 2- [(1- metilcarbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- Azabiciclo[3.1.0]hexano- 2,3- dicarboxílico	(9[A2]) R_f (EtOAc) = 0.3; 484.4 [M+H]+, 484.4 [M+HCOO]- ; t_R (a): 3.34 min.
131		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- Hidroxi- pirrolidina- 1,2- dicarboxílico	492.1 [M+H]+, 490.1 [M- H]- ; t_R (a): 3.08 min.
132		1- {[1- carbamoil- 5- (2- metoxi- etoxi)- 1H- indol- 3- il]- amida} 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- 4- metil- pirrolidina- 1,2- dicarboxílico	(8[B13],9)R_f(EtOAc) = 0.35; 550.5/552.4 [M+H]+, 572.3/574.5 [M+Na]+, 548.4/550.4 [M- H]- , 594.4/596.4 [M+HCOO]- ; t_R (f): 1.82 min.
133		Éster metilo del ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza-	(9)R_f (EtOAc) = 0.2; 558.1/560.2 [M+H]+, 580/582.1 [M+Na]+, 513.1/515 [M-

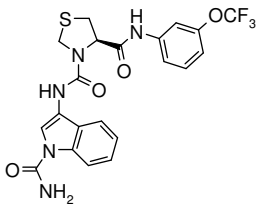
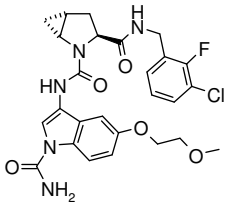
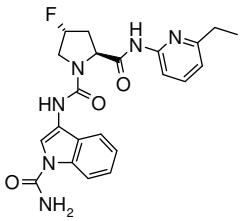
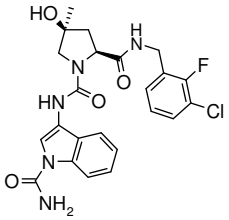
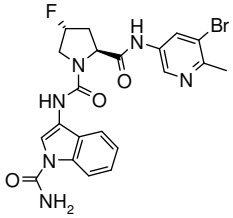
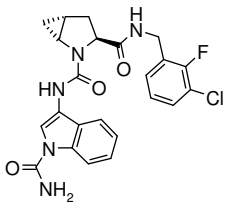
		biciclo[3.1.0]hexano- 2-carbonil]- amino}- 1H- indol-5- iloxi)- acetico	$CONH_2$]- ; t_R (f): 1.87 min.
134		2- [(1- carbamoil- 1H- indol-3- il)- amida] 3- [(3-trifluorometoxi- fenil)- amida] del ácido (1S,3S,5S)- 2- Aza-biciclo[3.1.0]hexano- 2,3-dicarboxílico	R_f (c- hexano/EtOAc 1:2) = 0.15, 488.2 [M+H]+, 486.1 [M-H]- ; t_R (a): 3.59 min.
135		3- [(1- carbamoil- 1H- indol-3- il)- amida] 2- (3- cloro- 2-fluoro- bencilamida) del ácido (1S,2S,5R)- 3- Aza-biciclo[3.1.0]hexano- 2,3-dicarboxílico	470 [M+H]+, 425 [M-$CONH_2$]- ; t_R (f): 1.84 min.
136		2- [(1- carbamoil- 1H- indol-3- il)- amida] 1- (3- cloro- 2-fluoro- bencilamida) del ácido 2- Aza- biciclo[2.1.1]hexano-1,2- dicarboxílico	(1) Sólido blanco. R_f (EtOAc) = 0.2; 470/473 [M]+; t_R (c): 4.51 min.
137		1- [(1- carbamoil- 1H- indol-3- il)- amida] 2- [(3-trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- metil-pirrolidina- 1,2- dicarboxílico	(8[B2]) R_f (c-hexano/EtOAc 1:3) = 0.44; 487.9 [M- H]- , 446.0 [M- $CONH_2$]- ; t_R (c): 4.51 min.
138		2- (3- bromo- 2- fluoro-bencilamida) 1- [(1-carbamoil- 1H- indol- 3- il)-amida] del ácido (2S,4R)- 4-Fluoro- pirrolidina- 1,2-dicarboxílico	(1,6) 522.0 [M+H]+; t_R (c): 4.38 min.

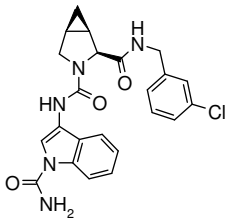
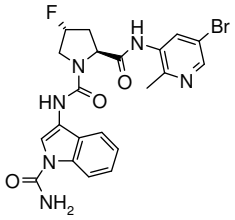
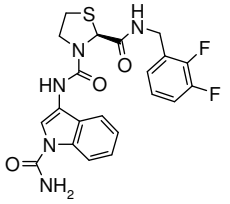
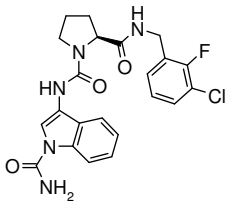
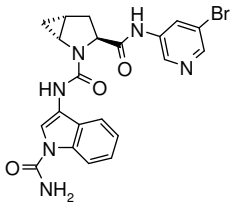
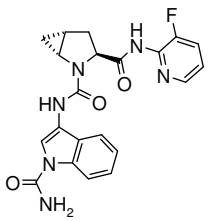
139		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del (2S,5R)- 5- (Acetilamino- metil)- pirrolidina- 1,2- dicarboxílico	(8[B4]) 547 [M+H]+; t_R (b): 4.05 min.
140		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del (R)- Pirrolidina- 1,2- dicarboxílico	476.1 [M+H]+, 498.1 [M+Na]+, 474.1 [M-H]- ; t_R(a): 3.47 min.
141		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (1S*,2S*,5R*)- 3- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	488.2 [M+H]+, 510.1 [M+Na]+; t_R (a): 3.52 min
142		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(2- fluoro- 3- trifluorometoxi- fenil)- amida] del ácido (S)- Tazolidina- 2,3- dicarboxílico	(1,6) Sólido blanco. 510 [M+H]+; t_R (b) 4.36 min.
143		Éster metilo del ácido 3- Cloro- 5- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- benzoico	(1) 500 [M+H]+; t_R (b): 3.96 min.
144		Ácido 3- ({[(2S,4R)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- metil)- 5- cloro- 4-	(8) 520.0 [M]+; t_R (c): 3.05 min

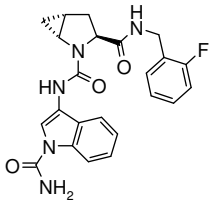
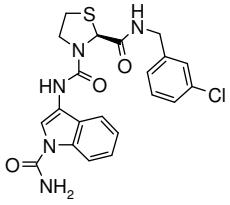
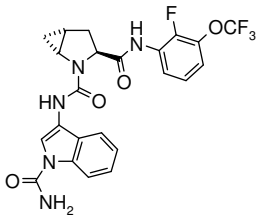
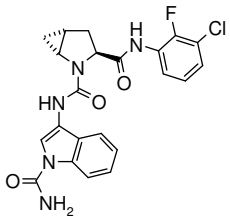
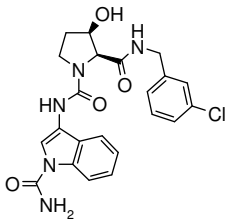
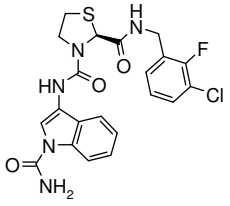
		fluoro- benzoico	
145		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- 2,5- Dihidro- pirrole- 1,2- dicarboxílico	474.1 [M+H]+, 969.2 [2MH+Na]+, 472.1 [M- H]- ; t_R (a): 3.38 min.
146		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,2S,5S)- 6- Oxa- 3- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(8[B19]) 472 [M+H]+; t_R (f): 1.76 min; 19F NMR (CD_3OD): - 124.
147		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Trifluorometil- pirrolidina- 1,2- dicarboxílico	(1) Off- Sólido blanco. R_f (EtOAc) = 0.30; 526.0 [M+H]+; t_R (c): 4.88 min.
148		3- [(3- bromo- fenil)- amida] 2- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(1)481.9/483.0 [M+H]+, 481.9/482.8 [M- H]- , 436.9/438.9 [M- $CONH_2$]- ; t_R (b) 4.20 min.
149		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 1- (3- cloro- 2- fluoro- bencilamida) del ácido (1S,5R)- 2- Aza- biciclo[3.1.0]hexano- 1,2- dicarboxílico	(1) Sólido blanco.R_f (EtOAc) = 0.43; 470 [M+H]+; t_R (c): 4.49 min.
150		2- [(3- bromo- fenil)- amida] 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- Fluoro-	(1) 487/489 [M+H]+; t_R (b): 3.64 min.

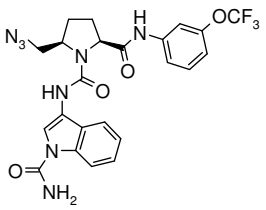
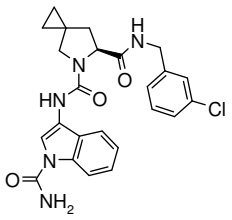
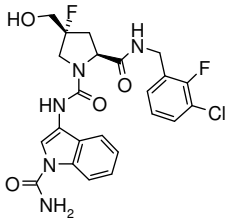
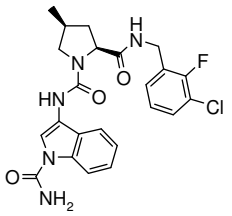
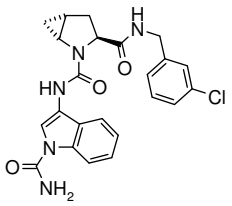
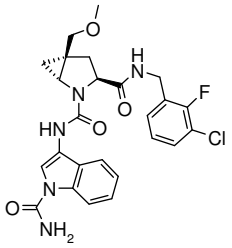
		pirrolidina- 1,2- dicarboxílico	
151		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 4- [(3- trifluorometoxi- fenil)- amida] del ácido (R)- 2,2- dimetil- tiazolidina- 3,4- dicarboxílico	R_f (c- hexano/EtOAc 1:3) = 0.51; 522.1 [M+H]+, 520.2 [M-H]- ; t_R (c): 5.39 min.
152		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(4'- Ciano- bifenil- 3- il)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico	493 [M+H]+; t_R (j) 2.90 min.
153		Éster metilo del ácido 3- Bromo- 5- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- benzoico	R_f (EtOAc) = 0.75; 546.1/548.1 [M+H]+, 568.1/570 [M+Na]+, 544/546 [M- H]- , 500/502 [M- $CONH_2$]- ; t_R (a): 3.33 min.
154		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [3- cloro- 5- (2- dimetilamino- etilcarba- moil)- 2- fluoro- bencilamida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(3,6[C3]) 590.2 [M]+; t_R (c): 3.59 min.
155		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(5- cloro- tiofen- 2- ilmetil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	458 [M+H]+, 456 [M-H]- , 413 [M- $CONH_2$]; t_R (f): 1.99 min.

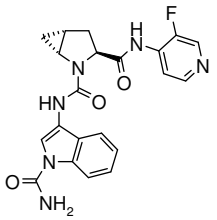
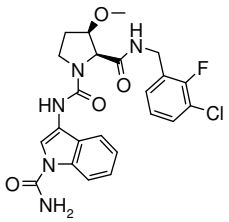
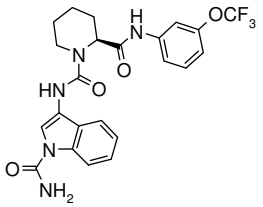
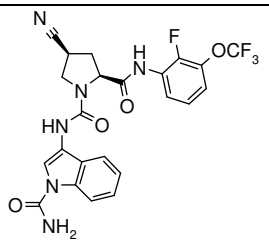
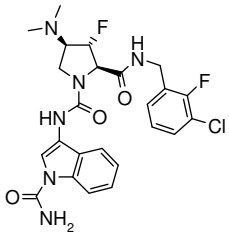
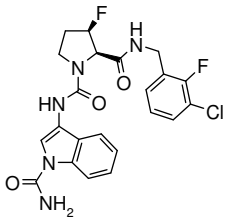
156		Éster metilo del ácido 2- Bromo- 4- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- benzoico	(1) 546/548 [M+H]+; t_R (b): 3.55 min.
157		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- metil- pirrolidina- 1,2- dicarboxílico	(8[B2]) R_f (c- hexano/EtOAc 1:3) = 0.44; 489.1 [M- H], 445.0 [M- $CONH_2$]- ; t_R (c): 4.65 min.
158		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(6- etil- piridin- 2- il)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	433.1 [M+H]+ 432.1 [M- H]- ; t_R (a): 2.49 min.
159		Ácido 3- Bromo- 5- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- benzoico	(8[B7]) R_f (CH_2Cl_2/MeOH 4:1) = 0.23; 532.0/534.0 [M+H]+, 554.0/556.0 [M+Na]+, 530.2/532.2 [M- H]- , 486.9/489.0 [M- $CONH_2$]- ; t_R (a): 2.98 min.
160		2- [(4- tert- butil- tiazol- 2- il)- amida] 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico	R_f (c- hexano/EtOAc 1:2)= 0.32; 455.2 [M+H]+, 909.2 [2M+H]+, 453.1 [M- H]- ; t_R (H a): 3.5 min.

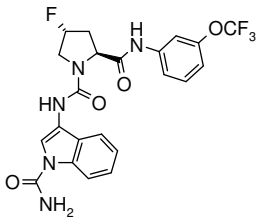
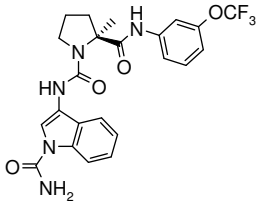
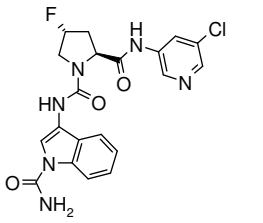
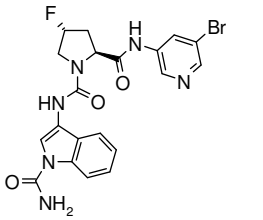
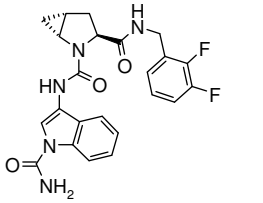
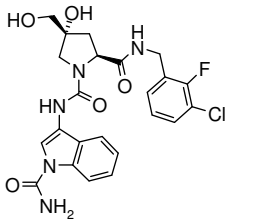
161		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 4- [(3- trifluorometoxi- fenil)- amida] del ácido (R)- Tazolidina- 3,4- dicarboxílico	R_f (c- hexano/EtOAc 1:3) = 0.42; 494.0 [M+H]+, 492.1 [M- H]- ; t_R (c): 5.03 min.
162		2- {[1- carbamoil- 5- (2- metoxi- etoxi)- 1H- indol- 3- il]- amida} 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(9)R_f (EtOAc) = 0.3; 544.2/546.1 [M+H]+, 566/568.1 [M+Na]+, 542 [M- H]- , 499.1 [M- $CONH_2$]- ; t_R (f): 1.85 min.
163		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(6- etil- piridin- 2- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	439.1 [M+H]+, 899.2 [2M+Na]+, 437.0 [M- H]- ; t_R (a): 2.32 min.
164		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Hidroxi- 4- metil- pirrolidina- 1,2- dicarboxílico	(8[B13])R_f (EtOAc) = 0.21; 488.2/490.1 [M+H]+, 486.1/488.1 [M- H]- ; t_R (f): 1.75 min.
165		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- bromo- 4- metil- piridin- 3- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(4)R_f (EtOAc) = 0.38; 503/505 [M+H]+; t_R (c): 3.70 min
166		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	470 [M+H]+; t_R (b): 3.87 min.

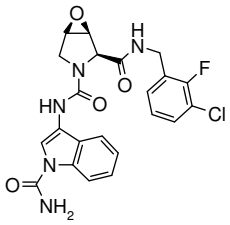
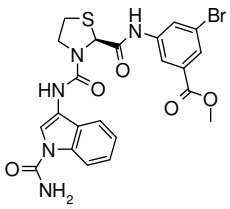
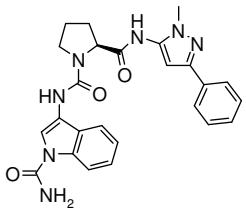
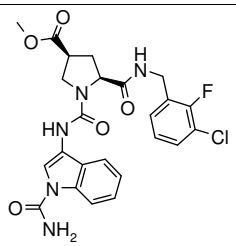
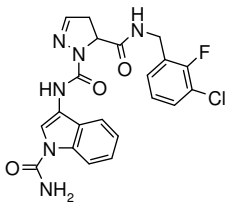
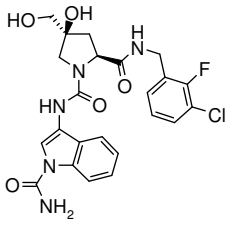
167		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- bencilamida) del ácido (1R*,2S*,5S*)- 3- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	452.0 [M+H]+, 407.0 [M- $CONH_2$]- ; t_R (a): 3.16 min.
168		2- [(5- bromo- 2- metil- piridin- 3- il)- amida] 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	505.0 [M+H]+; t_R (c): 3.67 min.
169		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (2,3- difluoro- bencilamida) del ácido (S)- tazolidina- 2,3- dicarboxílico	460.1 [M+H]+, 941.2 [2M+Na]+, 415.0 [M- $CONH_2$]- ; t_R (a): 3.11 min.
170		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- Pirrolidina- 1,2- dicarboxílico	458.0 [M+H]+, t_R (b): 3.70 min.
171		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(5- bromo- piridin- 3- il)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(4) Sólido blanco.R_f (EtOAc) = 0.48; 483/485 [M+H]+; t_R (c): 4.08 min.
172		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(3- fluoro- piridin- 2- il)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(4) Off- Sólido blanco.R_f (CH_2Cl_2/MeOH 95/5) = 0.21; 423 [M+H]+; t_R (c): 3.59 min.

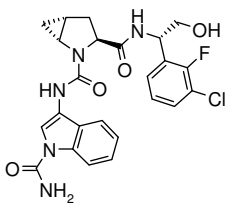
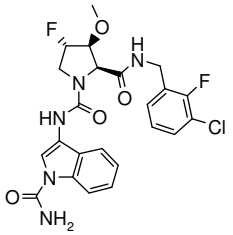
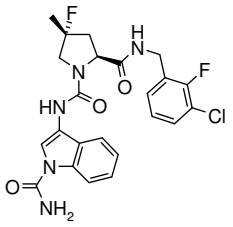
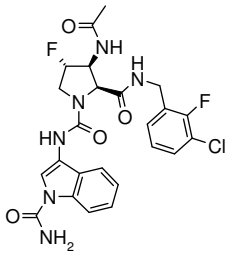
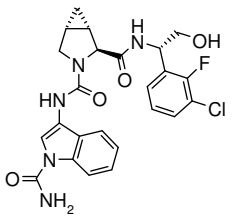
173		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- (2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Azabiciclo[3.1.0]hexano- 2,3- dicarboxílico	R_f (EtOAc) = 0.5;436.4/438.5 [M+H]+, 871.7/873.7 [2M+H]+, 480.4/482.4 [M+HCOO]- ; t_R (f): 1.77 min.
174		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- bencilamida) del ácido (S)- tazolidina- 2,3- dicarboxílico	458 [M+H]+; t_R (a): 3.17 min.
175		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(2- fluoro- 3- trifluorometoxi- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(1,6) Sólido blanco. 506 [M+H]+; t_R (b) 4.47 min.
176		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(3- cloro- 2- fluoro- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(1) Sólido blanco. 456 [M+H]+; t_R (b): 4.14 min.
177		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- bencilamida) del ácido (2S,3R)- 3- Hidroxi- pirrolidina- 1,2- dicarboxílico	(1) Sólido blanco.456 [M+H]+; t_R (b): 2.84 min.
178		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- tazolidina- 2,3- dicarboxílico	475.9 [M+H]+, 498 [M+Na]+; t_R (b): 3.89 min.

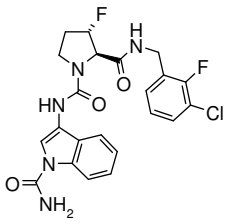
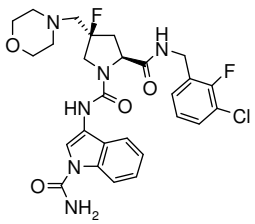
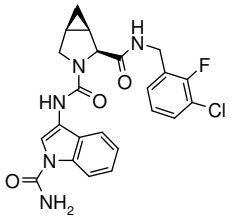
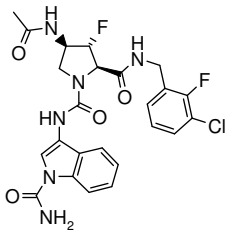
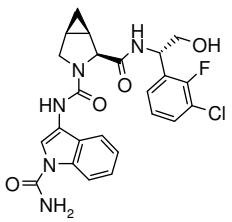
179		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,5R)- 5- Azidometil- pirrolidina- 1,2- dicarboxílico	(8[B3]) 531.1 [M+H]+; t_R (b): 4.85 min.
180		5- [(1- carbamoil- 1H- indol- 3- il)- amida] 6- (3- cloro- bencilamida) del ácido (S)- 5- Aza- spiro[2.4]heptano- 5,6- dicarboxílico	466.1 [M+H]+, 421.1 [M- $CONH_2$]- ; t_R (a): 3.26 min.
181		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- 4- hidroximetil- pirrolidina- 1,2- dicarboxílico	(8[B12])R_f (EtOAc) = 0.15; 506.2/508.1 [M+H]+, 528.1/530.2 [M+Na]+, 504.1/506 [M- H]- ; t_R (f): 1.69 min.
182		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- metil- pirrolidina- 1,2- dicarboxílico	(1, 8[B2])R_f (EtOAc) = 0.51; 472.0 [M+H]+; t_R (c): 4.62 min.
183		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- (3- cloro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	452/454 [M+H]+; t_R (a): 3.16 min; t_R (b): 3.78 min.
184		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5S)- 5- metoximetil- 2- aza- biciclo[3.1.0]hexano- 2,3-	(5,8) Rf (EtOAc) = 0.20; 514.4/516.4 [M+H]+, 512.3 [M-H]- ; t_R (a): 3.27 min.

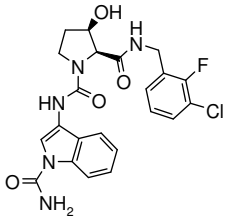
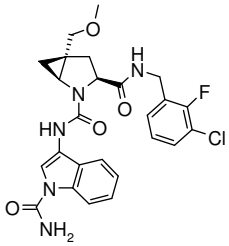
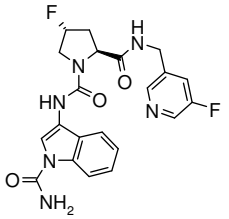
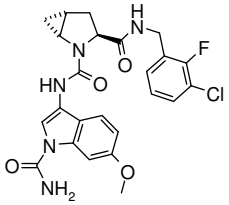
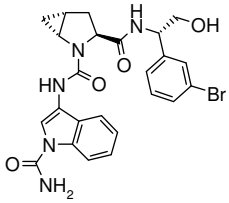
		dicarboxílico	
185		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(3- fluoro- piridin- 4- il)- amida] del ácido(1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(4) R_f (EtOAc) = 0.23; 423 [M+H]+; t_R (c): 3.4 min.
186		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R)- 3- metoxi- pirrolidina- 1,2- dicarboxílico	(8) Sólido blanco. 488 [M+H]+; t_R (b): 3.61 min.
187		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Piperidina- 1,2- dicarboxílico	R_f (c- hexano/EtOAc 1:2) = 0.21; 490.1 [M+H]+, 1001.2 [2M+Na]+, 488.1 [M-H]- ; t_R (a): 3.75 min.
188		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(2- fluoro- 3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- Ciano- pirrolidina- 1,2- dicarboxílico	(2 at 50°C,3,6) R_f (EtOAc) = 0.45; 519.1 [M+H]+, 541.0 [M+Na]+, 517.2 [M-H]- ; t_R (f): 1.93.
189		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2R,3S,4R)- 4- dimetilamino- 3- fluoro- pirrolidina- 1,2- dicarboxílico	(8[B20]) R_f (CH_2Cl_2/MeOH 95/5) = 0.26; 519 [M+H]+, 563 [M- HCOO]- ; t_R (f): 1.51 min.
190		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2R,3R)- 3- Fluoro- pirrolidina- 1,2- dicarboxílico	(8) Sólido blanco. 476 [M+H]+; t_R (b): 3.66 min.

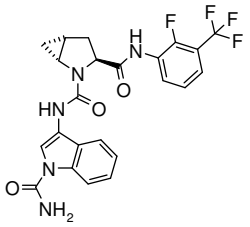
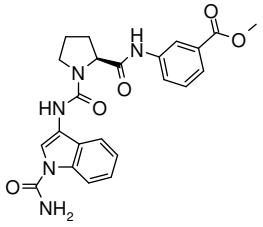
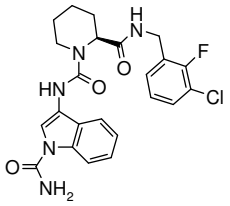
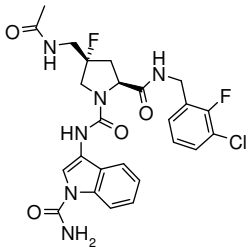
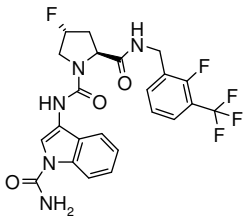
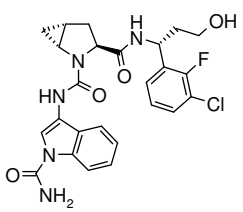
191		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	R_f (c- hexano/EtOAc 1:2) = 0.33; 494.0 [M+H]+, 492.1 [M-H]- ; t_R (a): 3.41 min.
192		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- 2- metil- pirrolidina- 1,2- dicarboxílico	490.1 [M+H]+, 512.2 [M+Na]+; t_R (a): 3.61 min.
193		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- cloro- piridin- 3- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(4)R_f (c- hexano/EtOAc 1:3) = 0.12; 445 [M+H]+; t_R (b): 3.79 min.
194		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- bromo- piridin- 3- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(4) R_f (c- hexano/EtOAc 1:3) = 0.1; 491 [M+H]+; t_R (c): 3.85 min.
195		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- (2,3- difluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	454.1 [M+H]+, 929.3 [2M+Na]+, 409.1 [M-$CONH_2$]- ; t_R (a): 3.09 min.
196		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Hidroxi- 4- hidroximetil- pirrolidina- 1,2- dicarboxílico	(8[B12]) 504 [M+H]+, 502 [M- H]- ; t_R (f): 1.57 min.

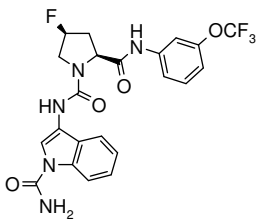
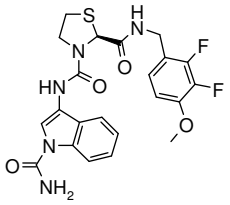
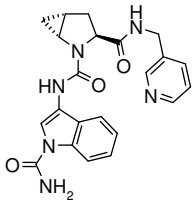
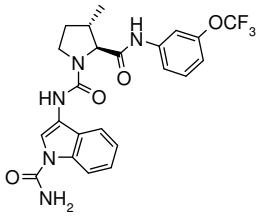
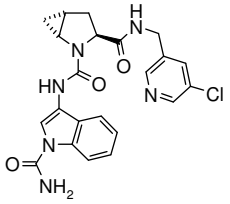
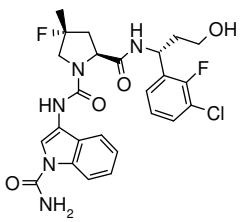
197		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (1S,2S,5R)- 6- Oxa- 3- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(8[B19]) 472 [M+H]+; t_R (f): 1.54 min; 19F NMR (CD_3OD): - 124.
198		Éster metilo del ácido 3- Bromo- 5- {[(S)- 3- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- Tazolidina- 2- carbonil]- amino}- benzoico	(1) 544.2/546.2 [M+H]+; t_R (b): 4.26 min.
199		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(2- metil- 5- fenil- 2H- pirazol- 3- il)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico	R_f (EtOAc) = 0.26; 472.1 [M+H]+, 470.2 [M- H]- ; t_R (a): 3.07 min.
200		Éster metilo del ácido (3S,5S)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- 5- (3- cloro- 2- fluoro- bencilcarbamoil)- pirrolidina- 3- carboxílico	(8) 516 [M+H]+, 540 [M+Na]+; t_R (b): 3.37 min.
201		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 5- (3- cloro- 2- fluoro- bencilamida) del ácido 4,5- dihidro- pirazo- 1,5- dicarboxílico	(8[B5]) R_f (CH_2Cl_2/acetone 1:1) = 0.53; 457.0 [M+H]+; t_R (b) : 3.77 min.
202		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Hidroxi- 4- hidroximetil- pirrolidina- 1,2- dicarboxílico	(8[B12]) 504 [M+H]+, 502 [M- H]- ; t_R (f): 1.60 min.

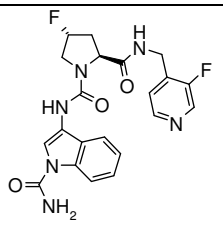
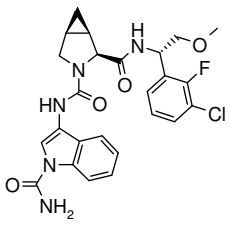
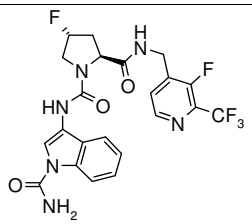
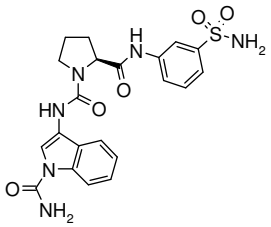
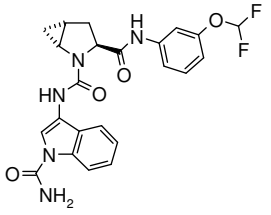
203		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida} del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(5,8[B9]) R_f (CH_2Cl_2/MeOH 95:5) = 0.2; 498.1/500.4 [M- H]- , 543.8 [M+HCOO]- , 500.2 [M+H]+, 522/522.7 [M+Na]+; t_R (a): 1.81 min.
204		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3S,4S)- 4- Fluoro- 3- metoxi- pirrolidina- 1,2- dicarboxílico	(8[B24]) 506 [M+H]+, 550[M+HCOO]- ; t_R (f): 1.87 min.
205		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- 4- metil- pirrolidina- 1,2- dicarboxílico	(8[B13]) TLC, R_f (EtOAc) = 0.45; 490.1/492.1 [M+H]+, 488/490 [M- H]- , 445/447.1 [M- $CONH_2$]- ; t_R (f): 1.89 min.
206		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3S,4S)- 3- Acetilamino- 4- fluoro- pirrolidina- 1,2- dicarboxílico	(8[B23]) R_f (CH_2Cl_2/MeOH 95/5) = 0.26 ; 531 [M+H]+, 533 [M- H]- ; t_R (f): 1.72 min.
207		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S) - 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida} del ácido (1S,2S,5R)- 3- Azabiciclo[3.1.0]hexano- 2,3-	(5,8[B9]) R_f (EtOAc) = 0.25; 500.3 [M+H]+, 544.3/546.4 [M+HCOO]- ; t_R (a): 2.93 min.

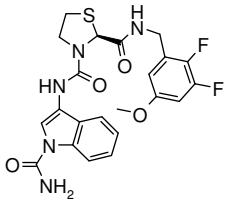
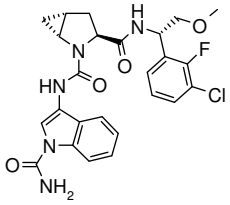
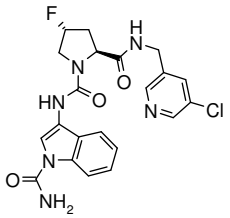
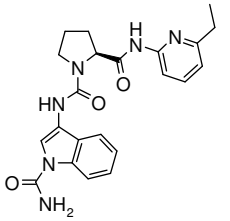
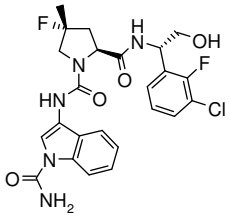
		dicarboxílico	
208		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2R,3S)- 3- Fluoro- pirrolidina- 1,2- dicarboxílico	(8) Sólido blanco. 476 [M+H]+; t_R (b): 3.86 min.
209		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- 4- morfolin- 4- ilmetil- pirrolidina- 1,2- dicarboxílico	(8[B14]) 575 [M+H]+, 502 [M- H]- ; t_R (f): 1.53 min.
210		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,2S,5S)- 3- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	R_f (EtOAc) = 0.45; 470.4/472.4 [M+H]+, 468.3/470.3 [M- H]- , 514.4/516.5 [M+HCOO]- ; t_R (a): 3.21 min.
211		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2R,3S,4R)- 4- Acetilamino- 3- fluoro- pirrolidina- 1,2- dicarboxílico	(8[B23])R_f (EtOAc) = 0.26 ; 531 [M+H]+, 533 [M- H]- ; t_R (f): 1.74 min.
212		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida} del ácido (1R,2S,5S)- 3- Azabiciclo[3.1.0]hexano- 2,3- dicarboxílico	(5,8[B9]) R_f (EtOAc) = 0.3; 520.3 [M+H]+, 564.3/566.3 [M+HCOO]- ; t_R (a): 3.0 min.

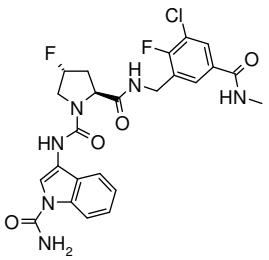
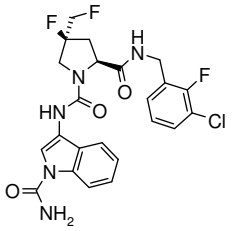
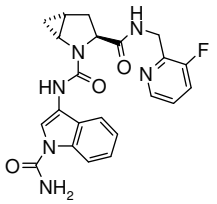
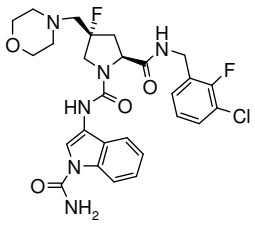
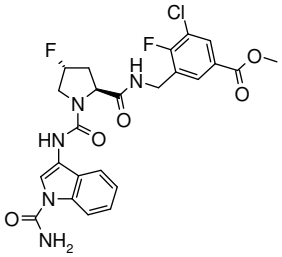
213		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R)- 3- Hidroxi- pirrolidina- 1,2- dicarboxílico	(1) Sólido blanco.474 [M+H]+; t_R (b): 3.11 min.
214		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1S,3S,5R)- 5- Metoximetil- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(5,8) Sólido blanco. Rf (EtOAc) = 0.20; 514.4/516.4 [M+H]+, 512.4 [M- H]- , 558.3/560.3 [M+HCOO]- ; t_R (a): 3.27 min.
215		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- fluoro- piridin- 3- ilmetil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(1) Sólido blanco.443 [M+H]+; t_R (b): 3.15 min.
216		2- [(1- carbamoil- 6- metoxi- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(9[A1])R_f (EtOAc) = 0.45; 500/502.2 [M+H]+, 455.2/457.2 [M- $CONH_2$]- ; t_R (f): 1.90 min.
217		3- {[(S)- 1- (3- bromo- fenil)- 2- hidroxi- etil]- amida} 2- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- Azabiciclo[3.1.0]hexano- 2,3- dicarboxílico	(5)R_f (EtOAc) = 0.25; 526.3/528.3 [M+H]+, 570.4/572.4 [M+HCOO]- ; t_R (a): 3.1 min.

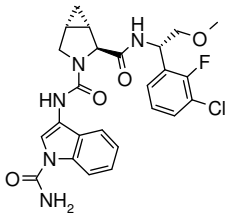
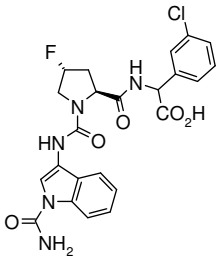
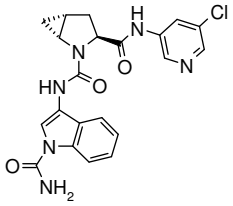
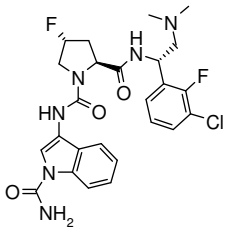
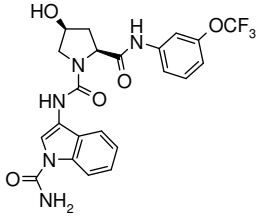
218		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(2- fluoro- 3- trifluorometil- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(1) Sólido blanco. 490 [M+H]+; t_R (b): 4.39 min.
219		Éster metilo del ácido 3- {[(S)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- benzoico	450.1 [M+H]+, 473.0 [M+Na]+, 899.2 [2M+H]+, 448.1 [M-H]- ; t_R (a): 3.03 min.
220		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- Piperidina- 1,2- dicarboxílico	(1) 472 [M+H]+, 494 [M+Na]+; t_R (c): 4.72 min.
221		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- (Acetilamino- metil)- 4- fluoro- pirrolidina- 1,2- dicarboxílico	(8) 531 [M+H]- , 533 [M+H]+; t_R (f): 0.56 min; 19F NMR (DMSO- d_6): - 121, - 150.
222		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (2- fluoro- 3- trifluorometil- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(1) Sólido blanco.510 [M+H]+; t_R (b): 3.88 min.
223		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- {[(R) - 1- (3- cloro- 2- fluoro- fenil)- 3- hidroxi- propil]- amida} del ácido (1R,3S,5R)- 2- Azabiciclo[3.1.0]hexano- 2,3- dicarboxílico	(5,8[B9]) R_f (EtOAc) = 0.1; 514.3/516.3 [M+H]+, 558.3/560.2 [M+HCOO]- ; t_R (a): 3.15 min.

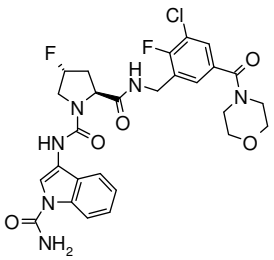
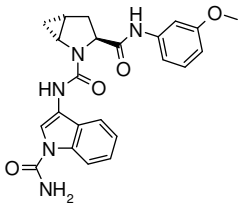
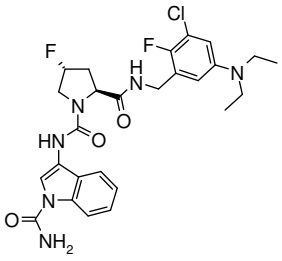
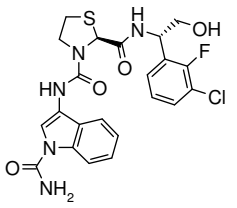
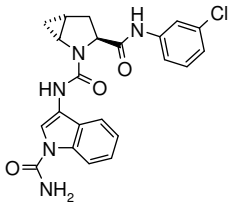
224		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(1)R_f (c- hexano/EtOAc 1:3) = 0.19; 494 [M+H]+; t_R (c): 4.78 min.
225		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (2,3- difluoro- 4- metoxi- bencilamida) del ácido (S)- Tazolidina- 2,3- dicarboxílico	(2,3) Sólido blanco. R_f (c- hexano/EtOAc 1:3) = 0.33; 490.1 [M+H]+; t_R (c): 4.39 min.
226		2- [(1- carbamoil- 1H- indol- 3- il)amida] 3- [(piridin- 3- ilmetil)- amida] del ácido (1R,3S,5R)- 2Azabiciclo[3.1.0]hexano- 2,3- dicarboxílico	(1) 419.3 [M+H]+; t_R (a): 1.83 min.
227		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,3S)- 3- metil- pirrolidina- 1,2- dicarboxílico	490 [M+H]+; t_R (b): 4.51 min.
228		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(5- cloro- piridin- 3- ilmetil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	453 [M+H]+; t_R (a): 2.70 min.
229		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(R)- 1- (3- cloro- 2- fluoro- fenil)- 3- hidroxi- propil]- amida} del ácido (2S,4R)- 4- Fluoro- 4- metil- pirrolidina- 1,2-	(5,8[B9])R_f (EtOAc) = 0.1; 514.3/516.3 [M+H]+, 558.3/560.2 [M+HCOO]- ; t_R (a): 3.15 min.

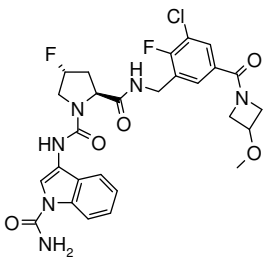
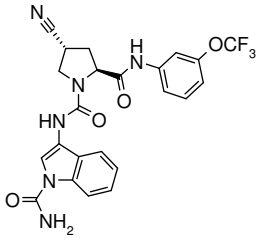
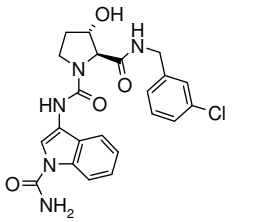
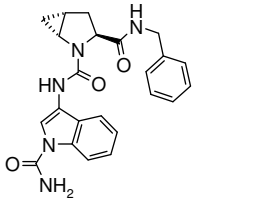
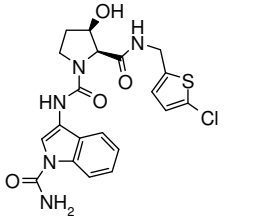
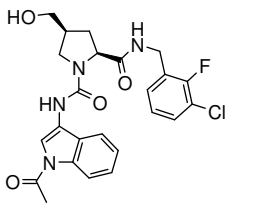
		dicarboxílico	
230		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- fluoro- piridin- 4- ilmetil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(1,6). 443.0 [M+H]+; t_R (c): 3.05 min.
231		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etil]- amida} del ácido (1R,2S,5S)- 3- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(5,8[B9]) polvo blanco. R_f (CH_2CL_2/MeOH 9:1): 0.60; 514.3/516.3 [M+H]+, 558.3/560.3 [M+HCOO]- ; t_R (a): 3.31 min.
232		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- fluoro- 2- trifluorometil- piridin- 4- ilmetil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(1,6). 511.0 [M+H]+; t_R (c): 4.16 min.
233		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- sulfamoil- fenil)- amida] del (S)- Pirrolidina- 1,2- dicarboxílico	471.1 [M+H]+, 963.3 [2M+Na]+; t_R (a): 2.58 min.
234		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(3- difluorometoxi- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(1)470.0 [M+H]+, 468.9 [M- H]- , 425.0 [M- $CONH_2$]- ; t_R (b) 4.05 min. HCO_2

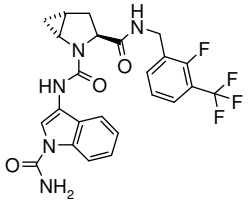
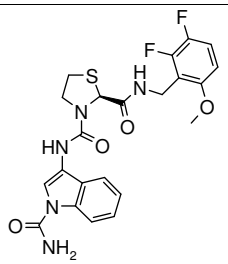
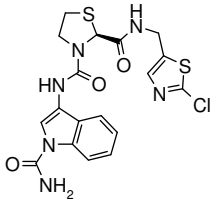
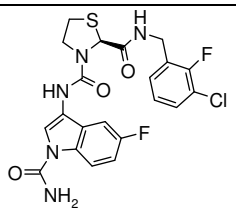
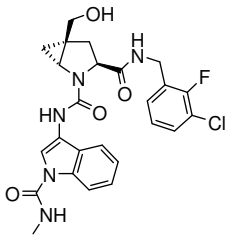
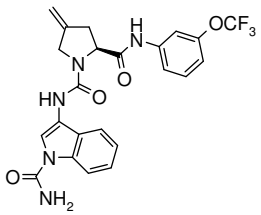
235		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (2,3- difluoro- 5- metoxi- bencilamida) del ácido (S)- Tazolidina- 2,3- dicarboxílico	(2,3,6) Solid. R_f (c-hexano/EtOAc 1:3) = 0.33; 490 [M+H]+; t_R (c): 4.48 min.
236		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etil]- amida} del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(5,8[B9]) polvo blanco. 514.4/516.4 [M+H]+, 531.4/533.4 [M+Na]+, 558.4/560.4 [M+HCOO]- ; t_R (f): 1.97 min.
237		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- cloro- piridin- 3- ilmetil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	459.1/461 [M+H]+; t_R (f): 1.30 min.
238		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(6- etil- piridin- 2- il)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico	R_f (CH_2Cl_2/iPrOH 95:5) = 0.13; 421.1 [M+H]+, 419.2 [M-H]- ; t_R (a): 2.42 min.
239		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S) - 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida} del ácido (2S,4R)- 4- Fluoro- 4- metil- pirrolidina- 1,2- dicarboxílico	(5,8[B9]) R_f (CH_2Cl_2/MeOH 9:1) = 0.3; 500.3/502.4 [M+H]+, 544.2/546.2 [M+HCOO]- ; t_R (a): 3.02 min.

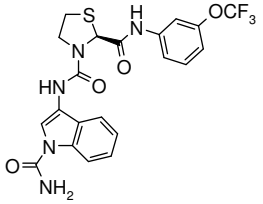
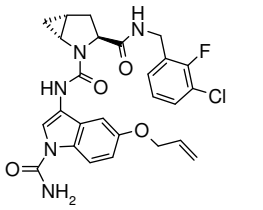
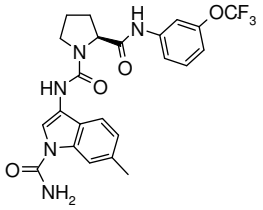
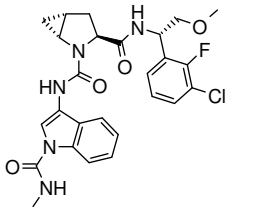
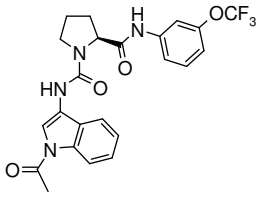
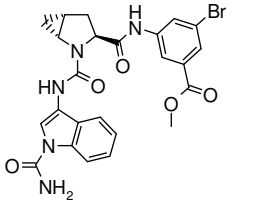
240		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- 5- metilcarbamoil- bencilamida del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(3,6[C3]) 533.0 [M]+; t_R (c): 3.86 min.
241		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Fluoro- 4- fluorometil- pirrolidina- 1,2- dicarboxílico	(8) R_f (EtOAc) = 0.38; 508/510 [M+H]+, 530/532 [M+Na]+, 506/508 [M- H]- , 463.1/465.1 [M- $CONH_2$]- ; t_R (f): 1.92 min.
242		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(3- fluoro- piridin- 2- ilmetil)- amida] del ácido 1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	437.2 [M+H]+, 895.3 [2M+Na]+; t_R (a): 2.36 min.
243		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Fluoro- 4- morfolin- 4- ilmetil- pirrolidina- 1,2- dicarboxílico	(8[B14]) 575 [M+H]+, 502 [M- H]- ; tR (f): 1.51 min.
244		Éster metilo del ácido 3- ({[(2S,4R)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- metil)- 5- cloro- 4- fluoro- benzoico	(3,6) 534.0 [M]+; t_R (c): 3.24 min.

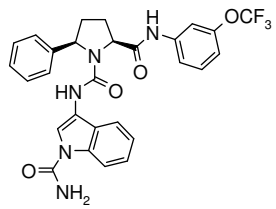
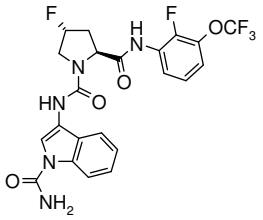
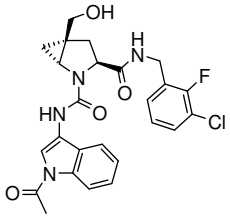
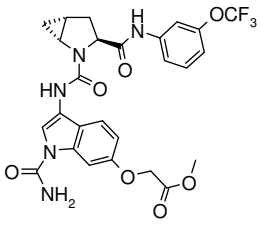
245		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etil]- amida} del ácido (1S,2S,5R)- 3- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(5,8[B9]) polvo blanco. R_f (EtOAc): 0.20; 514.4/516.4 [M+H]+, 558.4/560.3 [M+HCOO]- ; t_R (a): 3.25 min.
246		Ácido {[(2S,4R)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- (3- cloro- fenil)- acetico	(8) (mixture of diastereosisomers) R_f (CH_2Cl_2/MeOH 4:1) = 0.2; 502/504, [M+H]+, 500/502 [M-H]- ; t_R (a): 2.86 and 2.92 min.
247		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(5- cloro- piridin- 3- il)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(4) Sólido blanco.R_f (EtOAc) = 0.46; 439.0 [M+H]+; t_R (c): 4.01 min.
248		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- dimetilamino- etil]- amida} del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(5,6[C4]) 533.4/535.5 [M+H]+, 577.5/579.4 [M+HCOO]; t_R (a): 2.60 min.
249		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- Hidroxi- pirrolidina- 1,2- dicarboxílico	492.1 [M+H]+, 514.2 [M+H]+, 490.1 [M-H]- ; t_R (a): 3.19 min.

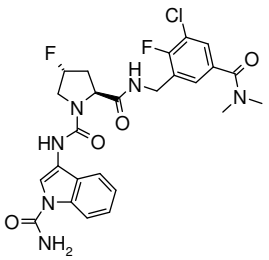
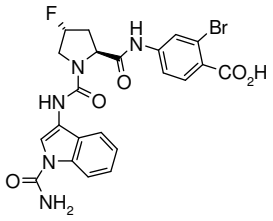
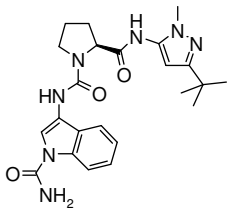
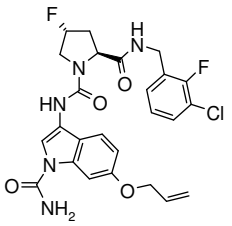
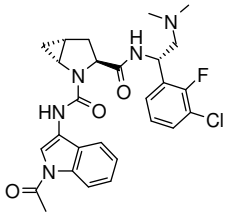
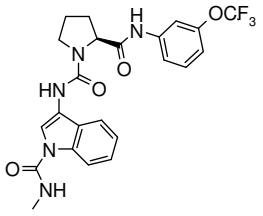
250		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [3- cloro- 2- fluoro- 5- (morfolina- 4- carbonil)- bencilamida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(3,6[C3]) 589.3 [M]+; t_R (c): 3.96 min.
251		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(3- metoxi- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(1)434.0 [M+H]+, 388.9 [M- $CONH_2$]- ; t_R (b) 3.64 min.
252		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 5- dietilamino- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(3,6[C1]) 547.2 [M]+; t_R (c): 3.67 min.
253		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida} del ácido (S)- Tazolidina- 2,3- dicarboxílico	(5) R_f (EtOAc) = 0.2; 506.3/508.2 [M+H]+, 550.2/552.2 [M+HCOO]- ; t_R (a): 3.06 min.
254		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(3- cloro- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(1)438.0/440.0 [M+H]+, 437.8 [M-H]- , 393/395 [M- $CONH_2$]- ; t_R (b) 4.12 min.

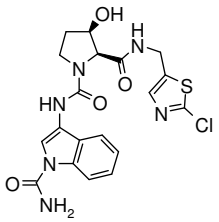
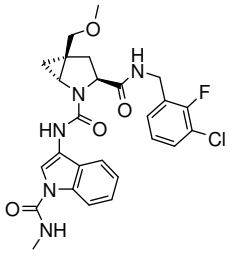
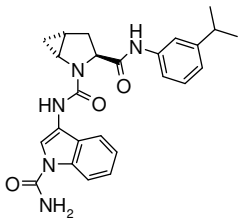
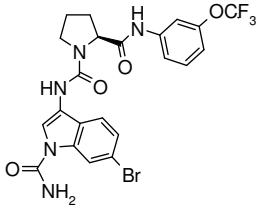
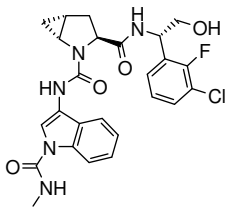
255		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [3- cloro- 2- fluoro- 5- (3- metoxi- azetidine- 1- carbonil)- bencilamida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(3,6[C3]) 589.3 [M]+; t_R (c): 4.06 min.
256		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- Ciano- pirrolidina- 1,2- dicarboxílico	501.1 [M+H]+; t_R(b): 4.22 min.
257		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- bencilamida) del ácido (2S,3S)- 3- Hidroxi- pirrolidina- 1,2- dicarboxílico	(1)Sólido blanco.456 [M+H]+; t_R (b): 2.99 min.
258		3- bencilamida 2- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	418.3 [M+H]+, 416.3 [M- H]- ; t_R (a): 2.94 min.
259		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- cloro- tiofen- 2- ilmetil)- amida] del ácido (2S,3R)- 3- Hidroxi- pirrolidina- 1,2- dicarboxílico	(1) Sólido blanco.462/463 [M+H]+; t_R (b): 2.92 min.
260		1- [(1- acetil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Hidroximetil- pirrolidina- 1,2- dicarboxílico	(8,9[A1])R_f (EtOAc) = 0.15; 487.4/489.4 [M+H], 485.4/486.4 [M- H]- ; t_R (a): 3.11 min.

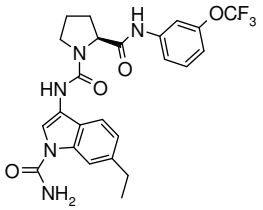
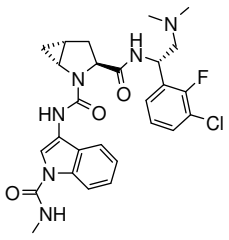
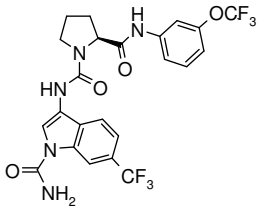
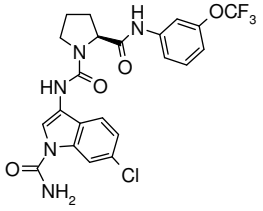
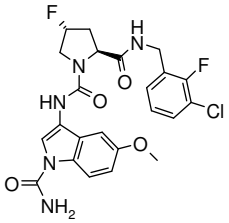
261		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- (2- fluoro- 3- trifluorometil- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(1) Sólido blanco.504 [M+H]+; t_R (b): 4.08 min.
262		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (2,3- difluoro- 6- metoxi- bencilamida) del ácido (S)- Tazolidina- 2,3- dicarboxílico	(2,3) Sólido blanco. R_f(c- hexano/EtOAc 1:3) = 0.19; 490.1 [M+H]+; t_R (c): 4.45 min.
263		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(2- cloro- tiazol- 5- ilmetil)- amida] del ácido (S)- Tazolidina- 2,3- dicarboxílico	(1) Sólido blanco.465 [M+H]+; t_R (b): 3.06 min.
264		3- [(1- carbamoil- 5- fluoro- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- Tazolidina- 2,3- dicarboxílico	(9[A4]) 494 [M+H]+; t_R (b): 4.01 min.
265		3- (3- cloro- 2- fluoro- bencilamida) 2- [(1- metilcarbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5S)- 5- Hidroximetil- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(5,8[B28],9[A2]) Sólido blanco. R_f (EtOAc) = 0.20; 514.4/516.4 [M+H]+, 558.4/560.3 [M+HCOO]- ;t_R (f): 1.80 min.
266		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- 4- Metilene- pirrolidina- 1,2- dicarboxílico	(1) R_f (c- hexano/EtOAc 1:3) = 0.38; 486. [M- H]- , 443 [M- $CONH_2$]- ; t_R (i): 3.52 min.

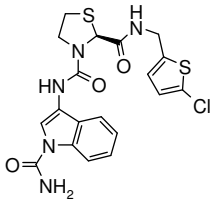
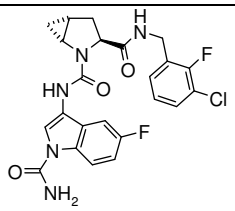
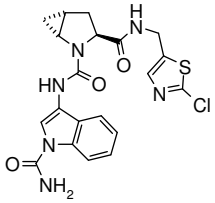
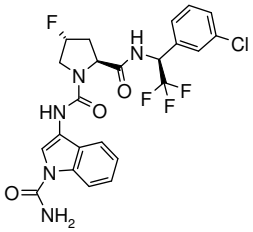
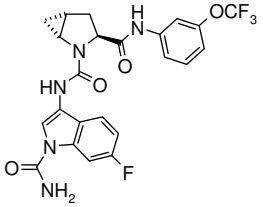
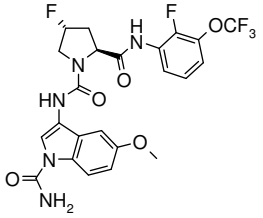
267		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Tazolidina- 2,3- dicarboxílico	494.0 [M+H]+, 492.1 [M- H]- ; t_R (a): 3.52 min.
268		2- [(5- aliloxi- 1- carbamoil- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(9) R_f (EtOAc) = 0.47; 526/528 [M+H]+, 481.1/483.3 [M- $CONH_2$]- ; t_R (f): 2.01 min.
269		1- [(1- carbamoil- 6- metil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido S)- Pirrolidina- 1,2- dicarboxílico	(9[A4])R_f (c-hexano/EtOAc 8:2)= 0.4; 490.1 [M+H]+, 488 [M- H]- ; t_R (a): 3.57 min.
270		3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etil]- amida} 2- [(1- metilcarbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(5,8[B9],9[A2]) Polvo blanco. R_f (EtOAc): 0.30; 528.4/530.4 [M+H]+, 572.4 [M+HCOO]- ; t_R (a): 3.41 min.
271		1- [(1- acetil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico	(9[A1])R_f (c-hexano/EtOAc 1:2) = 0.35; 475.1 [M+H]+, 473.2 [M- H]- ; t_R (a): 3.94 min.
272		Éster metilo del ácido 3- Bromo- 5- {[(1R,3S,5R)- 2- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 2- aza-	(1) Sólido blanco. 538.0 [M+H]+; t_R (b): 4.3 min.

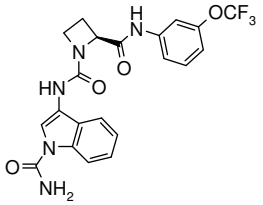
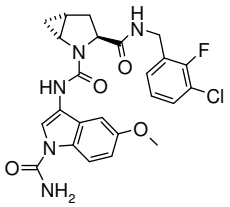
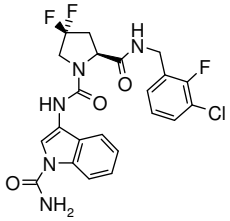
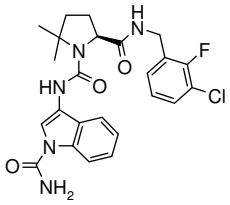
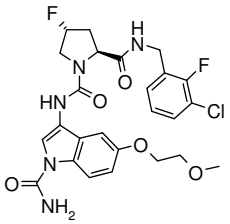
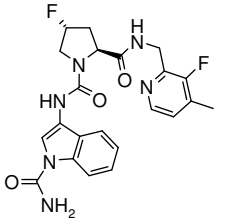
		biciclo[3.1.0]hexano- 3-carbonil]- amino}- benzoico	
273		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida del (2S,5R)- 5- Fenil- pirrolidina- 1,2- dicarboxílico	(1) 552.1 [M+H]+; t_R (c): 5.53 min.
274		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(2- fluoro- 3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(1,6) 512 [M+H]+; t_R (b) 4.15 min.
275		2- [(1- acetil- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5S)- 5- Hidroximetil- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(5,8[B28],9[A1]) Sólido blanco. R_f (EtOAc) = 0.25; 499.3/501.3 [M+H]+, 521.3/523.2 [M+Na]+, 497.3/499.3 [M- H]- , 543.2/545.3 [M+HCOO]- ;t_R (f): 1.90 min.
276		Éster metilo del ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- trifluorometoxi- fenilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 6- iloxi)- acetico	(9)R_f (EtOAc) = 0.6; 576.3 [M+H]+, 574.3 [M- H]- , 620.3 [M+HCOO]- ; t_R (f): 2.12 min.

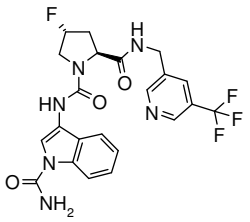
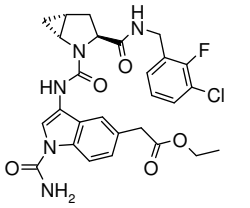
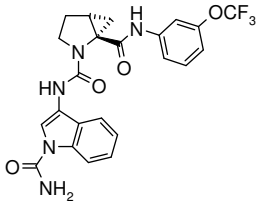
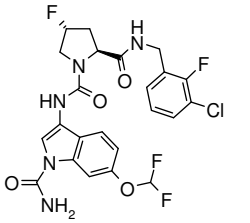
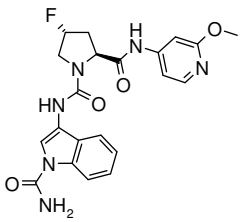
277		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 5- dimetilcarbamoil- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(3,6[C3]) 547.2 [M]+; t_R (c): 3.97 min.
278		Ácido 2- Bromo- 4- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- benzoico	(8) 530/531[M+H]+; t_R (b): 3.0 min.
279		2- [(5- tert- butil- 2- metil- 2H- pirazol- 3- il)- amida] 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico	452.2 [M+H]+, 450.2 [M- H]- ; t_R (a): 2.79 min.
280		1- [(6- aliloxi- 1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(9[A4]) R_f (EtOAc) = 0.55; 532 [M+H]+; t_R (b): 4.08 min.
281		2- [(1- acetil- 1H- indol- 3- il)- amida] 3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- dimetilamino- etil]- amida} del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(5,6[C4],9[A1]) R_f (CH_2Cl_2/MeOH 9:1) = 0.65; 526.3/528.3 [M+H]+, 570.3/572.3 [M+HCOO]; t_R (a): 3.06 min.
282		1- [(1- metilcarbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico	(9[A2])490.1 [M+H]+, 488.2 [M- H]- ; t_R (a): 3.65 min.

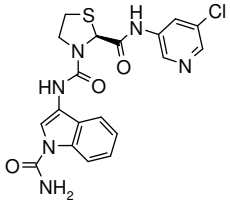
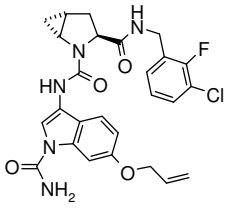
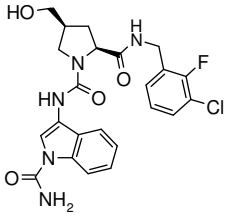
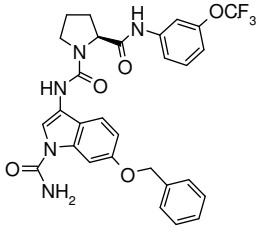
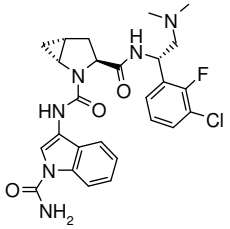
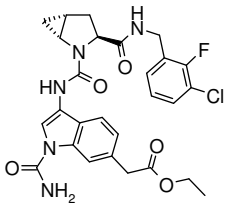
283		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(2- cloro- tiazol- 5- ilmetil)- amida] del ácido (2S,3R)- 3- Hidroxi- pirrolidina- 1,2- dicarboxílico	(1) Sólido blanco.463 [M+H]+; t_R (b): 2.03 min.
284		3- (3- cloro- 2- fluoro- bencilamida) 2- [(1- metilcarbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5S)- 5- metoximetil- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(5,8,9[A2]) Sólido blanco. 528.4 [M+H]+, 526.2 [M+H]- , 572.3 [M+HCOO]- ; t_R (a): 3.34 min.
285		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(3- isopropil- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	R_f (c- hexano/EtOAc 1:2) = 0.29; 446.2 [M+H]+, 891.3 [2M+H]+, 913.3 [2M+Na]+, 401.2 [M-$CONH_2$]- ; t_R (a): 3.54 min.
286		1- [(6- bromo- 1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico	(9[A4])R_f (c- hexano/EtOAc 1:1) = 0.5; 554/556 [M+H]+; t_R (a): 3.74 min.
287		3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida}2- [(1- metilcarbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- Azabiciclo[3.1.0]hexano- 2,3- dicarboxílico	(5, 8[B9],9[A2])R_f (EtOAc) = 0.2; 514.4 [M+H]+ 558.4 [M+HCOO]- ; t_R (a): 3.12 min.

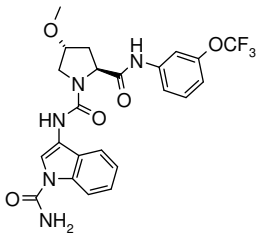
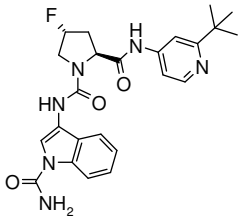
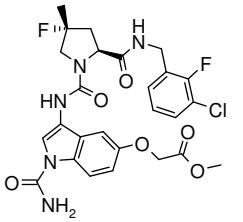
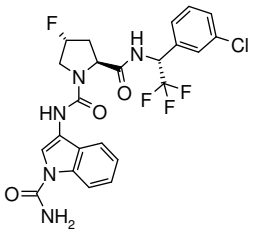
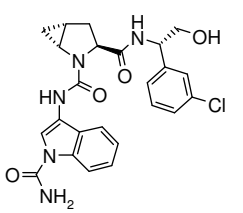
288		1- [(1- carbamoil- 6- etil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico	(9[A3])504.1 [M+H]+, 526.2 [M+Na]+, 502 [M-H]- ; t_R (a): 3.68 min.
289		3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- dimetilamino- etil]- amida} 2- [(1- metilcarbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(5,6[C4],9[A2])Sólido blanco. R_f (EtOAc) = 0.25; 541.4/543.4 [M+H]+, 585.3/587.2 [M+HCOO]; t_R (a): 2.88 min.
290		1- [(1- carbamoil- 6- trifluorometil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico	(9)499 [M- H]- ; t_R (a): 4.15 min.
291		1- [(1- carbamoil- 6- cloro- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico	(9[A4])R_f (c-hexano/EtOAc 1:1)= 0.5; 510.1 [M+H]+, 532 [M+Na]+, 508 [M- H]- ; t_R (a): 3.67 min.
292		1- [(1- carbamoil- 5- metoxi- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(9[A4])R_f (EtOAc) = 0.45; 506.0/508.0 [M+H]+, 504.1/506.1 [M- H]- , 461.0/463.0 [M- $CONH_2$]- ; t_R (f): 1.80 min.

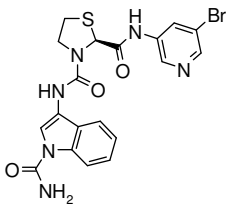
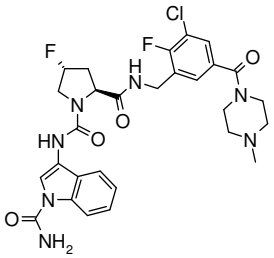
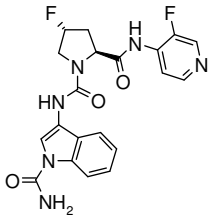
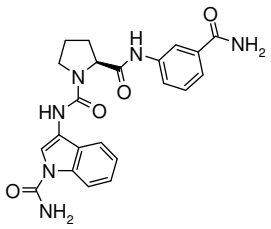
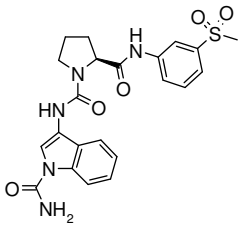
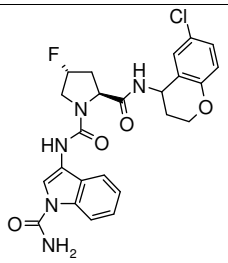
293		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- cloro- tiofen- 2- ilmetil)- amida] del ácido (S)- tazolidina- 2,3- dicarboxílico	464.0 [M+H]+, 462.0 [M- H]- , 419.0 [M- $CONH_2$]- ; t_R (f): 2.02 min.
294		2- [(1- carbamoil- 5- fluoro- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(9[A4]) R_f (EtOAc) = 0.47; 488 [M+H]+; t_R (b): 4.01 min.
295		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(2- cloro- tiazol- 5- ilmetil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(1) Sólido blanco.459 [M+H]+; t_R (b): 3.11 min.
296		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- fenil)- 2,2,2- trifluoro- etil]- amida} del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(4) R_f (c-hexano/EtOAc 25/75)= 0.55; 526.0 [M+H]+; t_R (c): 4.80 min.
297		2- [(1- carbamoil- 6- fluoro- 1H- indol- 3- il)- amida] 3- [(3- trifluorometoxi- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(9[A4]) 506 [M+H]+; t_R (b): 4.62 min.
298		1- [(1- carbamoil- 5- metoxi- 1H- indol- 3- il)- amida] 2- [(2- fluoro- 3- trifluorometoxi- fenil)- amida] del ácido	(6,9[A4]) 542.0 [M+H]+, 564.0 [M+Na]+; t_R (k): 3.47 min

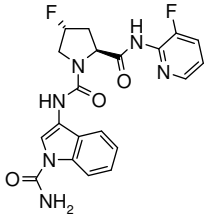
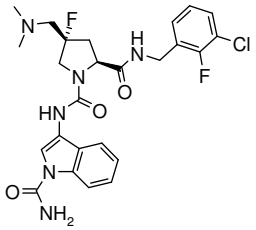
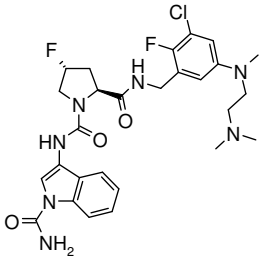
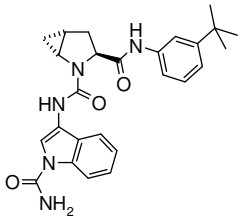
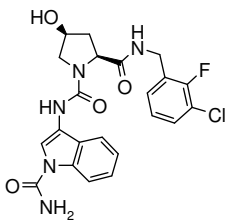
		(2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	
299		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Azetidine- 1,2- dicarboxílico	462.1 [M+H]+, 460.1 [M- H]- ; t_R (a): 3.52 min.
300		2- [(1- carbamoil- 5- metoxi- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(9[A4])R_f (EtOAc) = 0.45; 500/502.1 [M+H]+, 455/457 [M- $CONH_2$]- ; t_R (f): 1.91 min.
301		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- 4,4- Difluoro- pirrolidina- 1,2- dicarboxílico	R_f (EtOAc) = 0.65; 492 [M+H]+, 494 [M- H]- ; t_R (f): 1.96 min.
302		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- 5,5- dimetil- pirrolidina- 1,2- dicarboxílico	(1) Off- Sólido blanco.R_f (EtOAc) = 0.53; 486.2 [M+H]+; t_R (c): 4.87 min.
303		1- {[1- carbamoil- 5- (2- metoxi- etoxi)- 1H- indol- 3- il]- amida} 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(9)R_f (EtOAc) = 0.3; 550.2/552.1 [M+H]+, 572/574.1 [M+Na]+, 548 [M- H]- , 505 [M- $CONH_2$]- ; t_R (f): 1.76 min.
304		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- fluoro- 4- metil- piridin- 2- ilmetil)- amida] del ácido (2S,4R)- 4-	(1) 457.0 [M+H]+; t_R (c): 3.20 min.

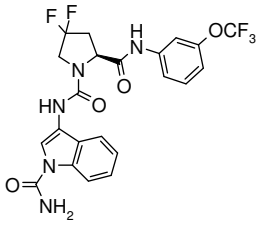
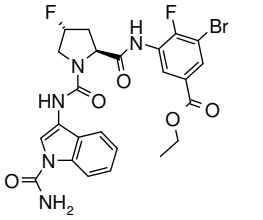
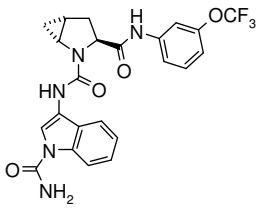
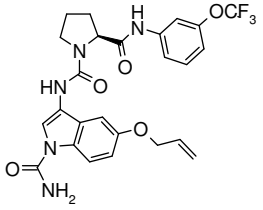
		Fluoro- pirrolidina- 1,2-dicarboxílico	
305		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- trifluorometil- piridin- 3- ilmetil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(1) Sólido blanco.493 [M+H]+; t_R (b): 3.76 min.
306		Éster etilo del ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- il)- acetico	(9)R_f (EtOAc) = 0.45; 556.3/558.4 [M+H]+, 554.3/556.3 [M- H]- , 511.3/513.3 [M- $CONH_2$]- ; t_R (f): 2.02 min.
307		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 1- [(3- trifluorometoxi- fenil)- amida] del ácido (1S,5R)- 2- Aza- biciclo[3.1.0]hexano- 1,2- dicarboxílico	R_f (c- hexano/EtOAc 1:2) = 0.15; 488 [M+H]+, 486.1 [M- H]- ; t_R (a): 3.51 min.
308		1- [(1- carbamoil- 6- difluorometoxi- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(9[A4]) Sólido blanco. 542.0 [M+H]+; 564.0 [M+Na]+; t_R (k): 3.41 min.
309		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(2- metoxi- piridin- 4- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(3,4) Off- Sólido blanco. R_f (c- hexano/EtOAc 1:1) = 0.42; 441.2 [M+H]+; t_R (c): 3.28 min.

310		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- cloro- piridin- 3- il)- amida] del ácido (S)- Tazolidina- 2,3- dicarboxílico	(3,4) Off- Sólido blanco. R_f (EtOAc) = 0.47; 445.0 [M+H]+; t_R (c): 4.03 min.
311		2- [(6- aliloxi- 1- carbamoil- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(9[A4]) R_f (EtOAc) = 0.4; 526 [M+H]+; t_R (b) : 4.33 min.
312		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Hidroximetil- pirrolidina- 1,2- dicarboxílico	(8) 488.2 [M+H]+, 433.0 [M- $CONH_2$]- ; t_R (f): 1.63 min.
313		1- [(6- benciloxi- 1- carbamoil- 1H- indol- 3- il)- amida]2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico	(9[A4])R_f (EtOAc)= 0.44; 582.1 [M+H]+, 580.2 [M- H]- ; t_R (a): 3.91 min.
314		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- dimetilamino- etil]- amida} del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(5,6[C4])Sólido blanco. R_f (EtOAc) = 0.1; 527.3/529.3 [M+H]+, 571.3 [M+HCOO]; t_R (a): 2.84 min.
315		Éster etilo del ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2-	(9)R_f (EtOAc) = 0.4; 556.3/558.4 [M+H]+, 573.4/575.2 [M+H_3O]+, 1111.7/1113.7

		carbonil]- amino}- 1H- indol- 6- il)- acetico	[2M+H]+, 554.3/556.4 [M- H]- , 600.3/602.8 [M+HCOO]- ; t_R (f): 2.02 min.
316		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- Metoxi- pirrolidina- 1,2- dicarboxílico	R_f (c- hexano/EtOAc 1:2) = 0.1; 506.0 [M+H]+, 504.1 [M-H]; t_R (a): 3.36 min.
317		2- [(2- tert- butil- piridin- 4- il)- amida] 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(4) Off- Sólido blanco. R_f(c-hexano/EtOAc 1:1) = 0.42; 467.3 [M+H]+; t_R (c): 3.58 min.
318		Éster etilo del ácido (1- Carbamoil- 3- {[(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil- pirrolidina- 1- carbonil]- amino}- 1H- indol- 5- iloxi)- acetico	(8[B13],9) R_f (EtOAc) = 0.6; 578.4/580.4 [M+H]+, 576.3/578.2 [M- H]- , 533.5/535.5 [M-$CONH_2$]- ; t_R (f): 1.90 min.
319		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(R)- 1- (3- cloro- fenil)- 2,2,2- trifluoro- etil]- amida} del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(4) R_f (c-hexano/EtOAc 1:3)= 0.56; 526.0 [M+H]+; t_R (c): 4.79 min.
320		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- {[(S)- 1- (3- cloro- fenil)- 2- hidroxi- etil]- amida} del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano-	(5) 482.4 [M+H]+; t_R (a): 3.05 min.

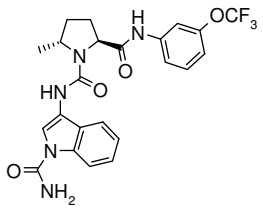
		2,3- dicarboxílico	
321		3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- bromo- piridin- 3- il)- amida] del ácido (S)- Tazolidina- 2,3- dicarboxílico	(3,4) Off- Sólido blanco. R_f(EtOAc) = 0.38; 489.0 [M+H]+; t_R (c): 4.10min.
322		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [3- cloro- 2- fluoro- 5- (4- metil- piperazina- 1- carbonil)- bencilamida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(3,6[C3]) 602.2 [M]+; t_R (c): 3.47 min.
323		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- fluoro- piridin- 4- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(4) Espuma blanca. R_f (EtOAc) = 0.18; 429.0 [M+H]+; t_R (c): 3.14 min.
324		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- carbamoil- fenil)- amida] del (S)- Pirrolidina- 1,2- dicarboxílico	435.1 [M+H]+, 891.3 [2M+Na]+, 433.1 [M-H]- ; t_R (a): 2.39 min.
325		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- metanosulfonil- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico	470.0 [M+H]+, 939.1 [2MH]+, 961.2 [2M+Na]+, 468.1 [M-H]- ; t_R (a): 2.70 min.
326		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(6- cloro- croman- 4- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(3) 500.0 [M]+; t_R (c): 4.39 min.

		(mezcla de 2 diastereoisomeros)	
327		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- fluoro- piridin- 2- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(4) Sólido blanco.R_f (EtOAc) = 0.25; 429.0 [M+H]+; t_R (c): 3.42 min.
328		(2S,4S)- 4- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido Dimetilaminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico	(8[B15]) 532 [M+H]+, 530 [M- H]- ; t_R (f): 1.62 min, 19F NMR (DMSO- d_6): - 120, - 149.
329		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {3- cloro- 5- [(2- dimetilamino- etil)- metil- amino]- 2- fluoro- bencilamida} del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico	(3,6[C1]) 576.2 [M]+; t_R (c): 3.91 min.
330		3- [(3- tert- butil- fenil)- amida] 2- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	(1)460.1 [M+H]+, 415.1 [M- $CONH_2$]- ; t_R (b) 4.68 min.
331		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Hidroxi- pirrolidina- 1,2- dicarboxílico	R_f (EtOAc) = 0.2; 474.1/476.2 [M+H]+, 496.1/498 [M+Na]+, 472/474.1 [M- H]- , 429.1/431 [M- $CONH_2$]- ; t_R (a): 2.88 min.

332		1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- 4,4- Difluoro- pirrolidina- 1,2- dicarboxílico	512.2 [M+H]+, 510.1 [M- H]- ; t_R (a): 3.63 min.
333		Éster etilo del ácido 3- Bromo- 5- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- 4- fluoro- benzoico	(4,6) 578/580 [M+H]+, 576/578 [M- H]- ; t_R (b): 4.3 min.
334		2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(3- trifluorometoxi- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico	R_f (c- hexano/EtOAc 1:2) = 0.40; 488 [M+H]+, 997.2 [2M+Na]+, 486.1 [M- H]- , 443.2 [M- $CONH_2$]- ; t_R (a): 3.55 min.
335		1- [(5- aliloxi- 1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico	(9[A4])R_f (EtOAc)= 0.51; 532.2 [M+H]+, 530 [M- H]- ; t_R (a): 3.64 min.

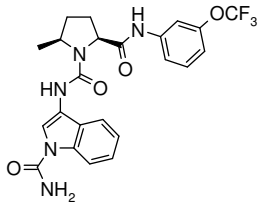
(1) CH_2Cl_2 se utilizó en lugar de DMF en el paso A; (2) de CH_3CN se utilizó en lugar de DMF en el paso A; (3) HATU se utilizó como reactivo de acoplamiento en el paso A; (4) La mezcla de reacción en el paso A se calentó a 70 ° C; (5) HCl (4 M en dioxano) en dioxano se utilizó en lugar de TFA en CH_2Cl_2 en el paso B; (6) La bencilamina sustituida o derivado de anilina usado en el paso A se preparó como se describe en la Parte C [Esquema]; (7) El derivado de prolina sustituido utilizado en el paso A se preparó como se describe en la Parte B [Esquema]; (8) El compuesto del título se preparó de acuerdo con el procedimiento general descrito en el Esquema D5 los pasos B y C a partir del derivado de prolina sustituido preparado como se describe en la Parte B [Esquema]; (9) El reactivo de isocianato usado en el paso C se preparó como se describe en la Parte A.

Ejemplo 336: 1 - [(1- carbamoil- 1H- indol- 3- il)] 2 - [(3- trifluorometoxi- fenil) - amida] del ácido (2S, 5R)- 5- metil- pirrolidina- 1 ,2- dicarboxílico



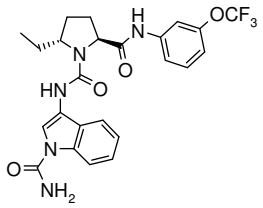
El compuesto del título se preparó de acuerdo con el procedimiento general descrito en el Esquema D5 excepto que CH_2Cl_2 se utilizó en lugar de DMF en el paso A, a partir de una mezcla de éster 1- terc- butilo del ácido (2S, 5R) - y (2S, 5S)- 5- metil- pirrolidina- 1,2- dicarboxílico en una relación de 7:1 (preparado como se describe en el Esquema B1). Los diastereoisómeros se separaron por HPLC quiral (Chiracel OJ, 20 µM, 185 x 48 mm, caudal: 100 ml/min, fase móvil: n- hexano/EtOH 9:1)para proporcionar el compuesto del título: TLC, R_f (c- hexano/EtOAc 1:3) = 0,45; MS (LC/MS): 490,0 [M+H]+, 488,0 [MH] - ; t_R (HPLC condiciones c): 4,99 min.

Ejemplo 337: 1 - [(1- carbamoil- 1H- indol- 3- il)] 2 - [(3- trifluorometoxi- fenil) - amida] del ácido (2S, 5S)- 5- metil- pirrolidina- 1 ,2- dicarboxílico



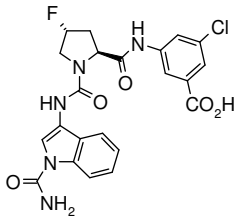
El compuesto del título se preparó de acuerdo con el procedimiento general descrito en el Esquema D5 excepto que CH_2Cl_2 se utilizó en lugar de DMF en el paso A, a partir de un (7:1)- mezcla de éster 1- terc- butilo del ácido (2S, 5R) - y (2S, 5S) - 5- metil- pirrolidina- 1 ,2- dicarboxílico (preparado como se describe en el Esquema B1). El producto diastereoisomérico se separó medainte HPLC quiral (Chiracel OJ, 20 µM, 185 x 48 mm, caudal: 100 ml/min, fase móvil: n- hexano/EtOH 9:1) para proporcionar el compuesto del título. TLC Rf (c- hexano/EtOAc 1:3) = 0,45; MS (LC/MS): 490,0 [M+H]+, 488,0 [MH] - ; t_R (condiciones de HPLC c): 5,21 min.

Ejemplo 338: 1 - [(1- carbamoil- 1H- indol- 3- il)] 2 - [(3- trifluoromtoxi- fenil) - amida] del ácido (2S, 5R)- 5- etil- pirrolidina- 1 ,2- dicarboxílico



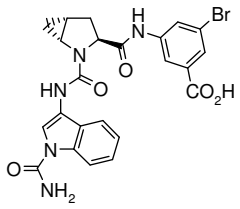
El compuesto del título se preparó de acuerdo con el procedimiento general descrito en el Esquema D5 excepto que CH_2Cl_2 se utilizó en lugar de DMF en el paso A, a partir de una mezcla diastereoisomérica > 9:1 de éster 1- terc- butilo del ácido (2S, 5R) - y (2S, 5S) - 5 - etil- pirrolidina- 1 ,2- diarboxilico (preparado como se describe en la Parte B). La purificación del producto en el paso de reacción final mediante HPLC preparativa quiral (Chiralcel OJ H 5 µM fase estacionaria) proporcionó el compuesto del título en forma de un solo diastereómero. TLC R_f (EtOAc) = 0,60; MS (LC/MS): 504,1 [M+H]+; t_R (Chiralcel OJ H 5 µM, columna de 250 x 4,0 mm, n- hexano/EtOH 8:2, flujo de 1,1 ml /min, 25 °C, detección 200 nm): 4,73 min; t_R (condiciones de HPLC c): 5.21 min.

Ejemplo 339: Ácido 3- cloro- 5- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- benzoico



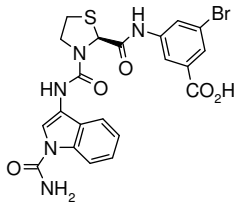
El compuesto del título se preparó de acuerdo con el procedimiento general descrito en el Esquema D5 (pasos B y C) a partir de (2S, 4R) - 2 - (3- carboxi- 5- cloro- fenilcarbamoil)- 4- fluoro- pirrolidina- 1- ácido carboxílico éster de terc- butilo) (preparado mediante el uso de protocolos similares como se describe en el Esquema B7). Sólido blanco. MS (LC/MS): 486 [MH]+; t_R (condiciones de HPLC b): 3.31 min.

Ejemplo 340: Ácido 3- bromo- 5- {[(1R,3S,5R)- 2- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 3- carbonil]- amino}- benzoico



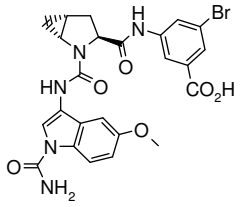
El compuesto del título (Sólido blanco) se preparó de acuerdo con el procedimiento general descrito en el Esquema D5 (pasos B y C) a partir de éster terc- butilo del ácido (1R, 3S, 5R) - 3 - (3- bromo- 5- carboxi- fenilcarbamoil) - 2 - aza- biciclo [3.1.0] hexano- 2- carboxílico) (preparado mediante el uso de protocolos similares como se describe en el Esquema B7, excepto que la mezcla de reacción se calentó a 65 °C en el paso A y se utilizó dioxano en lugar de MeOH en el paso B). Sólido blanco. MS (LC/MS): 524.3/525.3 [M+H]+; t_R (condiciones de HPLC b): 3.6 min.

Ejemplo 341: Ácido 3- bromo- 5- {[(S) - 3 (1- carbamoil- 1H- indol- 3- ilcarbamoil)- tiazolidina- 2- carbonil]- amino}- benzoico



El compuesto del título se preparó de acuerdo con el procedimiento general descrito en el Esquema D5 (pasos B y C) a partir de éster terc- butilo del ácido (S) - 2 - (3- bromo- 5- carboxi- fenilcarbamoil)- tiazolidin- 3- carboxílico) (preparado mediante el uso de protocolos similares como se describe en el Esquema B7). MS (LC/MS): 530.2/532.2/533.1 [MH] - ; t_R (condiciones de HPLC b): 3.55 min.

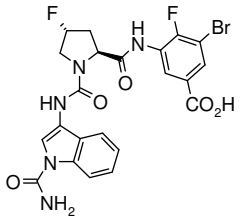
Ejemplo 342: Ácido 3- bromo- 5- {[(1R,3S,5R)- 2- (1- carbamoil- 5- metoxi- 1H- indol- 3- ilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 3- carbonil]- amino}- benzoico



El compuesto del título (Sólido blanco) se preparó de acuerdo con el procedimiento general descrito en el Esquema D5 (pasos B y C) usando éster terc- butilo del ácido (1R, 3S, 5R) - 3 - (3- bromo- 5- carboxi- fenilcarbamoil)- 2- aza - biciclo [3.1.0] hexano- 2- carboxílico) (preparado mediante el uso de protocolos similares como se describe en el Esquema B7, excepto que la mezcla de reacción se calentó a 65 °C en el paso A y se utilizó en lugar de dioxano MeOH en el paso B) y ácido 3- isocianato- 5- metoxi- indol- 1- carboxílico (preparado

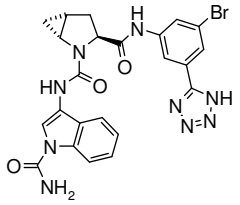
como se describe en el Esquema A1). MS (LC/MS): 556,0 [M+H]+; t_R (condiciones de HPLC c): 4.32 min.

Ejemplo 343: Ácido 3- bromo- 5- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- 4- fluoro- benzoico



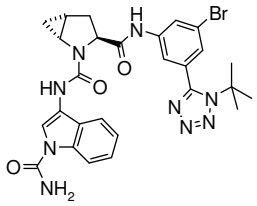
El compuesto del título se preparó de acuerdo con el procedimiento general descrito en el Esquema D5 (pasos B y C) a partir de éster terc- butilo del ácido (2S, 4R) - 2 - (3- bromo- 5- carboxi- 2- fluoro- fenilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico (preparado mediante el uso de protocolos similares como se describe en el Esquema B7 a partir de Éster etílo del ácido 3- amino- 5- bromo- 4- fluoro- benzoico descrito Parte C). MS (LC/MS): 550/552 [M+H]+; t_R (condiciones de HPLC b): 3.3 min.

Ejemplo 344: 3 - {[3- bromo- 5- (1H- tetrazol- 5- il)- fenil]- amida} 2 - [(1- carbamoil- 1H- indol- 3- il)] del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico



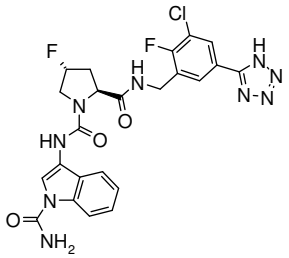
El compuesto del título se preparó de acuerdo con el procedimiento general descrito en el Esquema D5 paso C a partir de una mezcla de (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico [3- bromo- 5 - (1H- tetrazol- 5- il)- fenil]- amida y [3- bromo- 5- (1 - terc- butil- 1H- tetrazol- 5- il)- fenil]- amida del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico (proporción 2:3, preparado como se describe en el Esquema B8). La purificación por HPLC preparativa (Sunfire, C18- ODB, 5 µm, 30x100 mm, flujo: 40 ml/min, eluyente: 5-100% CH_3CN/H_2O/20 min, 100% de CH_3CN/2 min, CH_3CN y H_2O que contiene TFA al 0,1%) proporcionó el compuesto del título 3 - {[3- bromo- 5- (1H- tetrazol- 5- il)- fenil]- amida} del ácido 2 - [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico como un polvo blanco, MS (LC/MS): 550.0 [M+H]+; t_R (condiciones de HPLC c): 4.35 min.

Ejemplo 345: 3 - {[3- bromo- 5- (1- terc- butil- 1H- tetrazol- 5- il)- fenil]- amida} 2 - [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico



El compuesto del título se preparó de acuerdo con el procedimiento general descrito en el Esquema D5 paso C a partir de una mezcla de (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico [3- bromo- 5 - (1H- tetrazol- 5- il)- fenil]- amida y [3- bromo- 5- (1 - terc- butil- 1H- tetrazol- 5- il)- fenil]- amida del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico (proporción 2:3, preparado como se describe en el Esquema B8). La purificación mediante HPLC preparativa (Sunfire, C18- ODB, 5µm, 30x100 mm, flujo: 40 ml/min, eluyente: 5- 100% CH_3CN/H_2O/20 min, 100% de CH3CN / 2 min, CH3CN y H2O que contiene 0,1% de TFA) proporcionó el compuesto del título 3 - {[3- bromo- 5- (1- terc- butil- 1H - tetrazol- 5- il)- fenil]- amida} 2 - [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico como un Sólido blanco. MS (LC/MS): 606.0 [M+H]+; t_R (condiciones de HPLC c): 5.60 min.

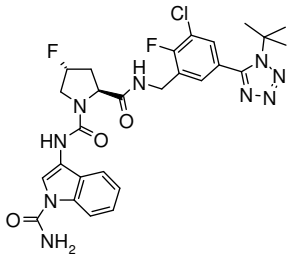
Ejemplo 346: 1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [3- cloro- 2- fluoro- 5- (1H- tetrazol- 5- il)- bencilamida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico



El compuesto del título se preparó de acuerdo con el procedimiento general descrito en el Esquema D5 paso C a partir de una mezcla 2:1 de 3- cloro- 2- fluoro- 5- (2H- tetrazol- 5- il)- bencilamida del ácido (2S,4R)- 4- fluoro- pirrolidina- 2- carboxílico y 5- (1- terc- butil- 1H- tetrazol- 5- il)- 3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 4- fluoro- pirrolidina- 2- carboxílico (preparado como se describe en la Parte B). Los productos crudos se purificaron sin tratamiento acuoso mediante HPLC- RP preparativa (Waters Sunfire, C18- ODB, 5 µm, 30x100

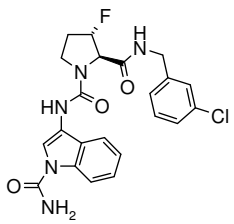
mm, 5- 80% CH_3CN/H_2O/20 min, 100% CH_3CN / 2 min, CH_3CN y H_2O que contiene 0,1 % de TFA, flujo: 40 ml / min) para dar el compuesto del título 2- [3- cloro- 2- fluoro- 5- (1H- tetrazol- 5- il)- bencilamida] de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico: MS (LC / MS): 544,0 [M]+; t_R (condiciones de HPLC c): 3,09 min .

Ejemplo 347: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [5- (1- terc- butil- 1H- tetrazol- 5- il)- 3- cloro- 2- fluoro- bencilamida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico



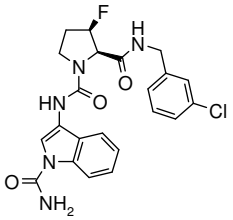
El compuesto del título se preparó según el procedimiento general descrito en el Esquema D5 paso C a partir de una mezcla 2:1 de 3- cloro- 2- fluoro- 5- (2H- tetrazol- 5- il)- bencilamida del ácido (2S,4R)- 4- fluoro- pirrolidina- 2- carboxílico y 5- (1- terc- butil- 1H- tetrazol- 5- il)- 3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 4- fluoro- pirrolidina- 2- carboxílico (preparado como se describe en la Parte B). Los productos crudos se purificaron sin tratamiento acuoso mediante HPLC- RP preparativa (Waters Sunfire, C18- ODB, 5 µm, 30x100 mm, 5- 80% CH_3CN/H_2O/20 min, 100% CH_3CN / 2 min, CH_3CN y H_2O que contiene 0,1 % de TFA, flujo: 40 ml / min) para dar el compuesto del título 1- [(1- carbamoil- 1H- indol- 3- il)- amida] de 2- [5- (1- terc- butil- 1H- tetrazol- 5- il)- 3- cloro- 2- fluoro- bencilamida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico: MS (LC / MS): 600,2 [M]+; t_R (condiciones HPLC c): 3,63 min.

Ejemplo 348: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (2R,3S)- 3- fluoro- pirrolidina- 1,2- dicarboxílico



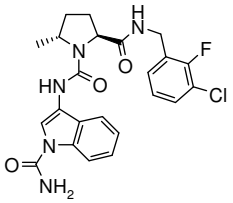
El compuesto del título se preparó según el procedimiento general descrito en el Esquema D5 (pasos B y C) a partir del ester terc- butilo del ácido (2R,3S)- 2- (3- cloro- bencilcarbamoil)- 3- fluoro- pirrolidina- 1- carboxílico (preparada mediante el uso de protocolos similares a los descritos para la preparación del Ester terc- butilo del ácido (2R,3S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- fluoro- pirrolidina- 1- carboxílico en la Parte B). Sólido blanco. MS (LC / MS): 458 [M + H]+; t_R (condiciones de HPLC b): 3,56 min.

Ejemplo 349: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (2R, 3R)- 3- fluoro- pirrolidina- 1,2- dicarboxílico



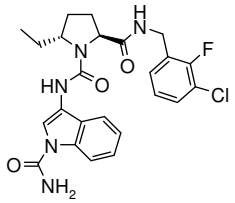
El compuesto del título se preparó según el procedimiento general descrito en el Esquema D5 (pasos B y C) partiendo del Ester terc- butilo del ácido (2R, 3R)- 2- (3- cloro- bencilcarbamoil)- 3- fluoro- pirrolidina- 1- carboxílico (preparada mediante el uso de protocolos similares a los descritos para la preparación del Ester terc- butilo del ácido (2R, 3R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- fluoro- pirrolidina- 1- carboxílico en Parte B). Sólido blanco. MS (LC / MS): 458 [M + H]+; t_R (condiciones de HPLC b): 3,42 min.

Ejemplo 350: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S, 5R)- 5- metil- pirrolidina- 1 ,2- dicarboxílico



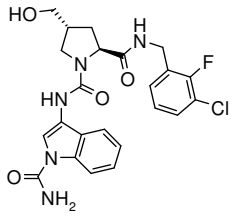
El compuesto del título (proporción de 1:11 cis/trans) se preparó según el procedimiento general descrito en el Esquema D5 excepto que CH_2Cl_2 se utiliza en lugar de DMF en la etapa A, y éster 1- terc- butílico del ácido (2S, 5R)- 5- metil- pirrolidina- 1,2- dicarboxílico de partida (preparado en proporción de 1:11 cis / trans como se describe en el Esquema B1). Sólido blanco. TLC R_f (EtOAc) = 0,35; MS (LC / MS): 472 [M + H]+, 494 [M + Na]+; t_R (condiciones de HPLC c): 4,52 min.

Ejemplo 351: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S, 5R)- 5- etil- pirrolidina- 1 ,2- dicarboxílico



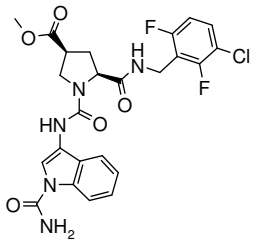
El compuesto del título se preparó según el procedimiento general descrito en el Esquema D5 excepto que CH_2Cl_2se utilizó en lugar de DMF en la etapa A, a partir de una mezcla diastereoisomérica>9:1 de ester 1- terc- butilo del ácido (2S, 5R)- y (2S, 5S)- 5 éster- etil- pirrolidina- 1 ,2- diarboxílico (preparado como se describe en la Parte B). La mezcla del producto diastereoisoméricocrudo se purificó mediante HPLC preparativa quiral (Chiracel OJ, 10 μM, 250 x 4,6 mm, flujo: 1,0 ml / min, fase móvil: heptano / EtOH 8:2; t_R = 5,61 minutos (principal) y 14,3 min (menor) en una proporción pico de 87:13)para dar el compuesto del título como un solo diastereoisómero. TLC, R_f (EtOAc / c- hexano 4:1) = 0,31; MS (LC / MS): 486,1 [M + H]+; t_R (condiciones de HPLC c): 4,76 min.

Ejemplo 352: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- hidroximetil- pirrolidina- 1 ,2- dicarboxílico



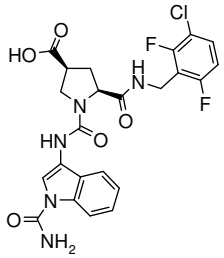
El compuesto del título se preparó según el Esquema D5 (Pasos B y C) a partir de ester terc- butilo del ácido (2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroximetil- pirrolidina- 1- carboxílico preparado usando el mismo protocolo que para la preparación de ester terc- butilo del ácido (2S, 4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroximetil- pirrolidina- 1- carboxílico (preparado como se describe en la Parte B). TLC, R_f (EtOAc) = 0,05; MS (LC / MS): 488.1/490.1 [M + H]+, 510.1/512.1 [M + Na]+, 443.0/445.0 [M- $CONH_2$]- ; t_R (condiciones de HPLC a): 2,87 min.

Ejemplo 353: Éster metílico del ácido (3S,5S)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 5- (3- cloro- 2,6- difluoro- bencilcarbamoil)- pirrolidina- 3- carboxílico



El compuesto del título se preparó según el Esquema D5 (pasos B y C) a partir del éster 3- metílico del éster 1- terc- butílico del ácido (3S, 5S)- 5- (3- cloro- 2,6- difluoro- bencilcarbamoil)- pirrolidina- 1,3- dicarboxílico preparó usando los protocolos descritos para la preparación de éster 3- metílico del éster 1- terc- butílico del ácido (3S,5S)- 5- (3- cloro- 2- fluoro- bencilcarbamoil)- pirrolidina- 1,3- dicarboxílico en la Parte B. R_f, TLC (CH_2Cl_2/MeOH, 95:5) = 0,2; MS (LC- MS): 534.3/536.2 [M+H]+, 532,2 [MH]- ; t_R (condiciones de HPLC de un): 2,96 min.

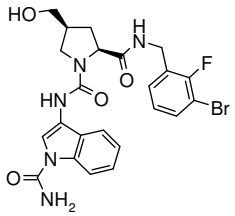
Ejemplo 354: Ácido (3S,5S)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- 5- (3- cloro- 2,6- difluoro- bencilcarbamoil)- pirrolidina- 3- carboxílico



A una solución de ester metilo del ácido (3S,5S)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 5- (3- cloro- 2,6- difluoro- bencilcarbamoil)- pirrolidina- 3- carboxílico **Ejemplo 353** (50 mg, 0,094 mmol) en THF (0,3 ml) / Et_2O (3 ml) / H_2O (0,3 ml) se añadió trimetilsilanolato de potasio (19,5 mg, 0,2 mmol) y la suspensión resultante se agitó a temperatura ambiente durante 1,30 h. La reacción se diluyó con EtOAc (15 ml) y H_2O (3 ml), y la mezcla bifásica se agitó vigorosamente durante 5 min. Las capas se separaron, y la acuosa se extrajo con EtOAc (x2). La capa acuosa se acidificó mediante la adición de HCl 1 N y se extrajo con EtOAc, las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El material en crudose purificó mediante HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 19x50 mm, eluyente: 20% a 100% CH_3CN en H_2O en 25 min, CH_3CN y H_2O que contiene 0,1% de HCOOH, flujo: 20 ml / min) para proporcionar, después de la liofilización de las fracciones purificadas el compuesto del título en forma de un sólido blanco.

MS (LC- MS): 518,4 [M- H]- , 520,1 [M + H]+, 1039,3 [2M + H]+; t_R (condiciones de HPLC f): 1,70 min.

Ejemplo 355: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- bromo- 2- fluoro- bencilamida) del ácido (2S, 4S)- 4- hidroximetil- pirrolidina- 1 ,2- dicarboxílico

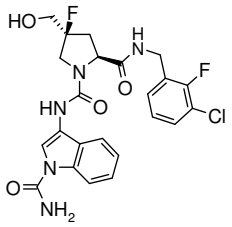


A una solución de ester metilo del ácido (3S,5S)- 5- (3- bromo- 2- fluoro- bencilcarbamoil)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 3- carboxílico (85 mg, 0,14 mmol) en THF (1,5 ml),bajo atmósfera de nitrógeno, se le añadió $LiBH_4$ (2 M en THF, 0,14 ml, 0,29 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 30 min, y después se vertió lentamente en una solución acuosa saturada de $NaHCO_3$ y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudose purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (eluyente: 100% CH_2Cl_2 a CH_2Cl_2 / MeOH 91- 9) para dar el material deseado en forma de sólido de color blanco. R_f, TLC (EtOAc) = 0,2; EM (UPLC- MS): 532.3/534.4 [M+H]+, 576.3/578.3 [M+HCOO]- , 530.4/532.5 [M- H]- ; t_R (condiciones de HPLC f): 1,69 min.

<u>Ester metilo del ácido (3S,5S)- 5- (3- Bromo- 2- fluoro- bencilcarbamoil)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 3- carboxílico</u>

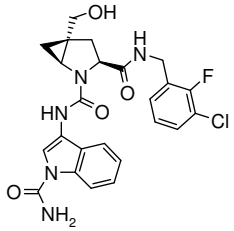
El compuesto del título se preparó según el Esquema D5 (Pasos B y C) a partir del éster 3- metílico del éster 1- terc- butílico del ácido (3S,5S)- 5- (3- bromo- 2- fluoro- bencilcarbamoil)- pirrolidina- 1,3- dicarboxílico preparado utilizando los protocolos como para la preparación de 3- metílico del éster 1- terc- butílico del ácido (3S,5S)- 5- (3- cloro- 2- fluoro- bencilcarbamoil)- pirrolidina- 1,3- dicarboxílico descrito en la Parte B. R_f, TLC (EtOAc) = 0,45, MS (UPLC- MS): 560.5/562.4 [M+H]+, 577.3/579.4 [M+NH4]+, 582.3/584.3 [M+Na]+, 604.4/606.3 [M+HCOO]- , 558.2/560.2 [M- H]- , t_R (condiciones de HPLC f): 1,88 min.

Ejemplo 356: 2- (3- cloro- 2- fluoro- bencilamida) de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- fluoro- 4- hidroximetil- pirrolidina- 1,2- dicarboxílico



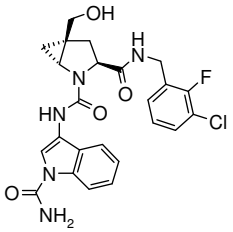
El compuesto del título se preparó según el Esquema D5 (pasos B y C) a partir de ester terc- butiloácido (2S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- hidroximetil- pirrolidina- 1- carboxílico (preparado usando protocolos similares a los descritos en el Esquema B12). TLC, R_f (EtOAc) = 0,15; MS (LC- MS): 506.0/508.0 [M+H]+, 528.1/530.1 [M+Na]+, 504.1/506.1 [M- H], 461.0/463.0 [M- $CONH_2$]- ; t_R (condiciones de HPLC f): 1,71 min.

Ejemplo 357: 3- (3- cloro- 2- fluoro- bencilamida) de 2- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1S, 3S, 5R)- 5- hidroximetil- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico



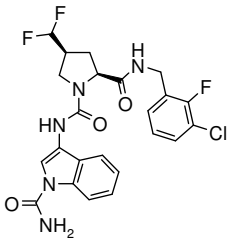
El compuesto del título se preparó según el Esquema D5 (pasos B y C) en la etapa B utilizando HCl 4 N en dioxano en vez de TFA a partir de una mezcla de 3- cloro- 2- fluoro- bencilamida del ácido (1S,3S,5R) y (1R,3S,5S)- 5- hidroximetil- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico. Sal de HCl (preparada como se describe en la Parte B Esquema B28). La mezcla de diastereoisómeros se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (CH_2Cl_2 a CH_2Cl_2/MeOH: 90:10) para dar: 3- (3- cloro- 2- fluoro- bencilamida) de 2- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5S)- 5- hidroximetil- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico y 3- (3- cloro- 2- fluoro- bencilamida) de 2- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1S,3S,5R)- 5- hidroximetil- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico que se purificó de nuevo por HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 19x50 mm, eluyente: 20% a 100% (CH_3CN/MeOH 1:4) / H_2O en 30 min, (CH_3CN/MeOH 1:4) y H_2O que contiene 0,1% de HCOOH, flujo: 20 ml / min): UPLC- MS: 500 [M+H]+, 544.3/546.4 [M+HCOO-]- ; t_R (condiciones de HPLC f): 1,78 min. La estereoquímica absoluta se asignó provisionalmente por RMN y se basó en los resultados de la prueba para los compuestos finales **Ejemplo 357** y **Ejemplo 358**.

Ejemplo 358: 3- (3- cloro- 2- fluoro- bencilamida) de 2- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5S)- 5- hidroximetil- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico



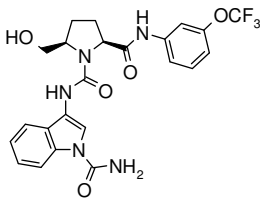
El compuesto del título se preparó según el Esquema D5 (pasos B y C) en la etapa B utilizando HCl 4 N en dioxano en vez de TFA a partir de una mezcla de 3- cloro- 2- fluoro- bencilamida del ácido (1S,3S,5R) y (1R,3S,5S)- 5- hidroximetil- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico. Sal de HCl (preparada como se describe en la Parte B Esquema B28). La mezcla de diastereoisómeros se purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (CH_2Cl_2 a CH_2Cl_2/MeOH: 90:10) para dar: 3- (3- cloro- 2- fluoro- bencilamida) de 2- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5S)- 5- hidroximetil- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico que se purificó de nuevo mediante HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 19x50 mm, eluyente: 20% a 100% (CH_3CN/MeOH 1:4) / H_2O en 30 min, (CH_3CN/MeOH 1:4) y H_2O que contiene 0,1% de HCOOH, flujo: 20 mL/min) para dar un sólido blanco: 500.4/502.4 [M+H]+, 544.4/546.5 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,72 min. La estereoquímica absoluta se asignó provisionalmente mediante RMN y se basó enlos resultados de la prueba para los compuestos finales **Ejemplo 357** y **Ejemplo 358**.

Ejemplo 359: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- difluorometil- pirrolidina- 1 ,2- dicarboxílico



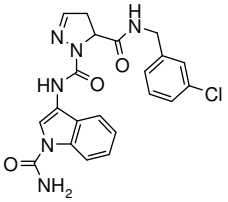
El compuesto del título se preparó según el Esquema D5 a partir de éster 1- terc- butílico del ácido (2S,4S)- 4- difluorometil- pirrolidina- 1,2- dicarboxílico (preparado siguiendo el procedimiento descrito en *J. Org. Chem.***2002**, *67*, 7162). Sólido blanco. MS (LC/MS): 508 [M+H]+; t_R (condiciones de HPLC b) 4,03 min.

Ejemplo 360: 1- [(1- carbamoil- 1H- indol- 3- il)]- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S, 5R)- 5- hidroximetil- pirrolidina- 1,2- dicarboxílico



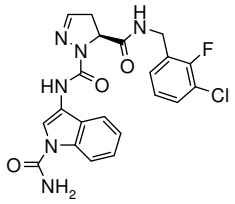
se preparó según el Esquema D5 (paso C), utilizando (3- trifluorometoxi- fenil)- amida del ácido (2S, 5R)- 5- (terc- butil- dimetil- silaniloximetil)- pirrolidina- 2- carboxílico (preparado como se describe en la Parte B). Excepto que después de la finalización de la reacción, la mezcla se vertió en HCl 1 N y se añadió EtOAc. Las capas se separaron y la fase acuosa, se extrajo de nuevo dos veces con EtOAc. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudose purificó mediante HPLC preparativa (Waters SunFire C18- ODB, 5 µm, 19x50 mm, 20% CH_3CN/H_2O 2,5 min, 20-100% CH_3CN/H_2O en 10 min, CH_3CN/H_2O que contiene 0,1% HCOOH, flujo: 20 ml/min) para proporcionar, después de liofilización de las fracciones purificadas por HPLC el compuesto del título. MS (LC- MS): 506 [M+H]+; t_R (condiciones de HPLC b) 4,13 min.

Ejemplo 361: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 5- (3- cloro- bencilamida) del ácido 4,5- dihidro- pirazol- 1,5- dicarboxílico



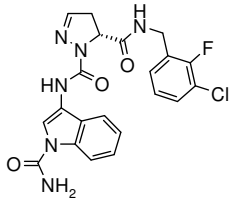
El compuesto del título se preparó según el Esquema D5 (paso C) a partir de 3- cloro-bencilamida del ácido 3,4- dihidro- 2H- pirazol- 3- carboxílico (preparado usando protocolos similares a los descritos en el Esquema B5). MS (LC- MS): 439,0 [M+H]; t_R (condiciones de HPLC b): 3,55 min.

Ejemplo 362: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 5- (3- cloro- 2- fluoro- bencilamida) del ácido ($S^{§}$)- 4,5- dihidro- pirazol- 1,5- dicarboxílico



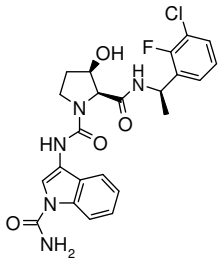
Se obtiene a partir de 5- (3- cloro- 2- fluoro- bencilamida) de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido 4,5- dihidro- pirazol- 1,5- dicarboxílico racémico Eje**mplo 201**mediante separación por HPLC quiral (Chiralpak ADi 5 □m, 1mL/min, disolvente: TBME/CH_2Cl_2/EtOH 50:30:20, t_R = 9,08 min). MS (LC- MS): 457 [M+H]+; t_R (condiciones de HPLC b): 3,73 min. La estereoquímica absoluta se ha asignado provisionalmente en base a los resultados de la prueba para los compuestos finales **Ejemplo 362** y el **Ejemplo 363** en el ensayo biológico.

Ejemplo 363: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 5- (3- cloro- 2- fluoro- bencilamida) del ácido ($R^{§}$)- 4,5- dihidro- pirazol- 1,5- dicarboxílico



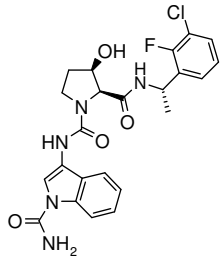
Se obtiene de 5- (3- cloro- 2- fluoro- bencilamida) de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido 4,5- dihidro- pirazol- 1,5- dicarboxílico racémico Eje**mplo 201**mediante separación por HPLC quiral (Chiralpak ADi 5 □m, 1mL/min, disolvente: TBME/CH_2Cl_2/EtOH 50:30:20, t_R = 6,49 min). MS (LC- MS): 457 [M+H]+; t_R (condiciones de HPLC b): 3,73 min. La estereoquímica absoluta se ha asignado provisionalmente en base a los resultados de la prueba para los compuestos finales **Ejemplo 362** y el **Ejemplo 363** en el ensayo biológico.

Ejemplo 364: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {[($R^{§}$)- 1- (3- cloro- 2- fluoro- fenil)- etil]- amida} del ácido (2S, 3R)- 3- hidroxi- pirrolidina- 1 ,2- dicarboxílico



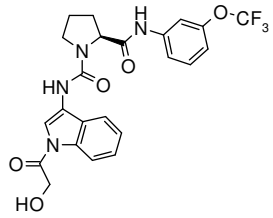
El compuesto del título se preparó según el procedimiento general descrito en el Esquema D5 (CH_2Cl_2 se utilizó en lugar de DMF en la etapa A) a partir de una ca. (1:1)-mezcla de diastereoisómeros 2- {[(R) y (S)- 1- (3- cloro- 2- fluoro- fenil)- etil]- amida} de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,3R)- 3- hidroxi- pirrolidina- 1,2-dicarboxílico y la purificación del compuesto del título mediante separación cromatográfica preparativa en una Chiralpak IA 5 □m fase estacionaria (columna de 250 x 10 µmm) utilizando heptano/TBME/MeOH/TFA 50:35:15:0.05 como eluyente (caudal: 8 ml/min, detección 254 nm, 25 °C). Sólido blanco. MS (LC/MS): 488 [M+H]+; t_R (condiciones de HPLC b): 3,28 min. t_R (condiciones de HPLC quiral: Chiralpak IA 5 □m; columna de 250 x 4,6 mm; heptano/TBME/MeOH/TFA 50:35:15:0.05; flujo: 2,00 ml/min, detección 254 nm, 25 °C): 10,1 min.La estereoquímica absoluta se ha asignado provisionalmente en base a los resultados de la prueba para los compuestos finales **Ejemplo 364** y el **Ejemplo 365** en el ensayo biológico.

Ejemplo 365: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {[(S)- 1- (3- cloro- 2- fluoro-fenil)- etil]- amida} del ácido (2S,3R)- 3- hidroxi- pirrolidina- 1,2- dicarboxílico



El compuesto del título se preparó según el procedimiento general descrito en el Esquema D5 (CH_2Cl_2 se utilizó en lugar de DMF en la etapa A) a partir de una ca. (1:1)-mezcla de diastereoisómeros 2- {[(R) y (S)- 1- (3- cloro- 2- fluoro- fenil)- etil]- amida} de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,3R)- 3- hidroxi- pirrolidina- 1,2-dicarboxílico por separación cromatográfica preparativa en una IA 5 □m fase estacionaria Chiralpak (columna de 250 x 10 µmm) utilizando heptano/TBME/MeOH/TFA 50:35:15:0.05 como eluyente (caudal: 8 ml/min, detección 254 nm, 25 °C). Sólido blanco. MS (LC/MS): 488 [M+H]+; t_R (condiciones de HPLC b): 3,28 min. t_R (condiciones de HPLC quiral: Chiralpak IA 5 □m; columna de 250 x 4,6 mm; heptano/TBME/MeOH/TFA 50:35:15:0.05; flujo: 2,00 ml/min, detección 254 nm, 25 °C): 14,3 min. La estereoquímica absoluta se ha asignado provisionalmente en base a los resultados de la prueba para los compuestos finales **Ejemplo 364** y el **Ejemplo 365** en el ensayo biológico.

Ejemplo 366: 1- {[1- (2- hidroxi- acetil)- 1H- indol- 3- il]- amida}- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico

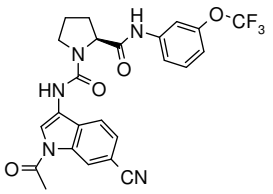


2- [(3- trifluorometoxi- fenil)- amida] de 1- {[1- (2- benciloxi- acetil)- 1H- indol- 3- il]- amida} del ácido (S)- pirrolidina- 1,2- dicarboxílico (55 mg, 0,095 mmol) se disolvió en MeOH (1 ml) y se añadió Pd/C 10% (12 mg) y la solución se desgasificó 3 veces sustituyendo aire por nitrógeno y, finalmente, nitrógeno por hidrógeno. La mezcla de reacción se agitó adicionalmente en atmósfera de hidrógeno durante la noche y se eliminó el catalizador a través de una almohadilla de Celite y se lavó con MeOH. El disolvente se concentró y el residuo en crudose purificó mediante HPLC preparativa (Waters SunFire C18- ODB, 5 µm, 19x50 mm, 20% de CH_3CN/H_2O 2,5 min, 20- 100% CH_3CN/H_2O en 10 min, CH_3CN/H_2O que contiene 0,1% HCOOH, flujo: 20 ml/min) para proporcionar, después de la liofilización de las fracciones puras, el compuesto deseado. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0,49; MS (LC/MS): 491,1 [M+H]+, 513,2 [M+Na]+, 489,1 [M- H]- ; t_R (condiciones de HPLC a): 3,47 min.

1- {[1- (2- benciloxi- acetil)- 1H- indol- 3- il]- amida}- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico

A una solución de sal de TFA de (3- trifluorometoxi- fenil)- amida del ácido (S)- pirrolidina- 2- carboxílico (177 mg, 0,457 mmol) y Et_3N (191 µl, 1,37 mmol) en THF seco (3,5 ml) se añadió una solución de 2- benciloxi- 1- (3- isocianato- indol- 1- il)- etanona (140 mg, 0,457 mmol, preparado como se describe en el Esquema A5) en THF seco (3,5 ml). La solución se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 15 min hasta que se complete. La mezcla se vertió en agua, se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El material en crudose purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano a c- hexano/EtOAc 65:35) para proporcionar el compuesto deseado. TLC, R_f (c- hexano/EtOAc 1:1) = 0,3; MS (LC/MS): 581,2 [M+H]+, 579,1 [M- H]- ; t_R (condiciones de HPLC a): 4,18 min.

Ejemplo 367: 1- [(1- acetil- 6- ciano- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico

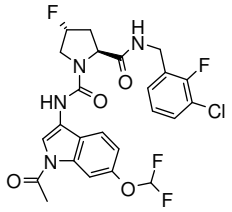


A una solución de 2- [(3- trifluorometoxi- fenil)- amida] de 1- [(6- ciano- 1H- indol- 3- il)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico (60 mg, 0,131 mmol) en THF seco (1 ml) a 0 °C bajo atmósfera de nitrógenose añadióterc- butóxido de potasio (17,7 mg, 0,157 mmol). La suspensión se agitó a 0 °C durante 5 minutos antes de la adición de cloruro de acetilo (0,011 ml, 0,157 mmol) y la solución resultante se agitó a temperatura ambiente bajo nitrógeno durante la noche. La mezcla se vertió en una solución acuosa saturada de $NaHCO_3$ y se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El material en crudo se purificó sucesivamente mediante cromatografía en columna ultrarrápida sobre gel de sílice (CH_2Cl_2 a CH_2Cl_2/MeOH 95:5) y HPLC preparativa (Waters Sunfire C18- ODB, 5 um, 19x50mm, flujo: 20 ml/min, gradiente: 0-2.5 min 20% de CH_3CN, 2.5 a 12.5 min 20 a 100% CH_3CN, 12,5- 15 min 100% CH_3CN, H_2O y CH_3CN que contiene 0,1% de HCOOH) para dar después de la liofilización de las fracciones purificadas el compuesto deseado. MS (LC/MS): 500 [M+H]+, 498,1 [M- H]- ; t_R (condiciones de HPLC a): 3,69 min.

1- [(6- ciano- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico

Se añadió una solución de sal de TFA de (3- trifluorometoxi- fenil)- amida del ácido (S)- pirrolidina- 2- carboxílico (315 mg, 0,81 mmol) en THF (10 µml) a una solución de 3- isocianato- 1H- indol- 6- carbonitrilo (270 mg, preparado como se describe en la Parte A, 70% de pureza según lo medido mediante RMN) en tolueno (4 ml). Se añadió trietilamina (338 □l, 2,43 mmol) y la solución resultante se agitó a temperatura ambiente bajo nitrógeno durante la noche. La mezcla se vertió en HCl 1 N y se extrajo con EtOAc (x3). Las capas orgánicas combinadas se lavaron con una solución acuosa saturada de $NaHCO_3$, se secó sobre Na_2SO_4, se filtró y se concentró. El material en crudose purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano a c- hexano/EtOAc 1:1) para dar el compuesto del título. TLC, R_f (c- hexano/EtOAc 1:1) = 0.5; MS (LC- MS): 554.0 [M+H]+, 556.0 [M- H]- ; t_R (condiciones de HPLC a): 3,74 min.

Ejemplo 368: 1- [- (1- acetil- 6- difluorometoxi- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico

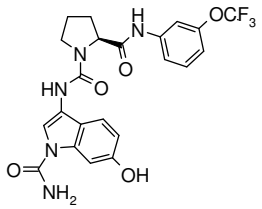


A una solución de 1- [(6- difluorometoxi- 1H- indol- 3- il)- amida] de 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico (105 mg, 0,210 µmmol) en THF seco (5 ml) se añadió Ac_2O (1 ml, 10,5 mmol) y DMAP (26 mg, 0,210 µmmol). La mezcla de reacción se agitó a 60 °C durante 18 h. Los volátiles se evaporaron bajo presión reducida, y el residuo se purificó mediante HPLC preparativa (Macherey- Nagel Nucleosil C18 100- 10, 5 □m, 40x250 mm, flujo: 40 mL/min, eluyente: 5- 100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN y H_2O que contiene 0,1% de TFA) para proporcionar después de la liofilización de las fracciones purificadas el compuesto del título como un sólido blanco. MS (LC/MS): 541 [M+H]+, 563 [M+Na]+; t_R (condiciones de HPLC k): 3,65 min.

2- (3- cloro- 2- fluoro- bencilamida)- 1- [(6- difluorometoxi- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico

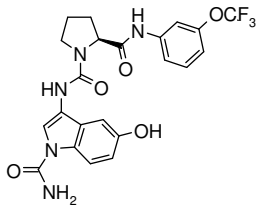
El compuesto del título se preparó según el protocolo general descrito en el Esquema D5. En el paso Cse utilizó 6- difluorometoxi- 3- isocianato- 1H- indol (preparado como se describe en la Parte A) y después de la finalización de la reacción, la mezcla se concentró y se purificó directamente mediante HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 30x100 mm, flujo: 40 ml/min, eluyente: 5- 100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN y H_2O que contiene 0.1% de TFA). Sólido blanco. MS (LC/MS): 499 [M+H]+, 521 [M+Na]+; t_R (condiciones de HPLC k): 3,49 min).

Ejemplo 369: 1- [(1- carbamoil- 6- hidroxi- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico



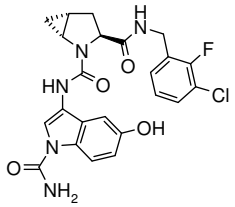
2- [(3- trifluorometoxi- fenil)- amida] de 1- [(6- benciloxi- 1- carbamoil- 1H- indol- 3- il)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico **Ejemplo 313** (75 mg, 0,129 mmol) se disolvió en una mezcla de THF/DMF 1- 1 (3 ml), se añadió Pd/C al 10% (20 mg) a la solución y la solución se desgasificó 3 veces reemplazando aire por nitrógeno y finalmente nitrógeno por hidrógeno. La mezcla de reacción se agitó adicionalmente en atmósfera de hidrógeno durante 3 h y se eliminó el catalizador a través de una almohadilla de Celite y se lavó con THF. Los disolventes se concentraron y el aceite resultante se vertió en agua y se extrajo con EtOAc (x3). Las capas orgánicas combinadas se lavaron dos veces con agua, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudose purificó mediante HPLC preparativa (Waters SunFire C18- ODB, 5 µm, 19x50 mm, 20% a 100% CH_3CN en H_2O en 25 min, CH_3CN/H_2O que contiene 0,1% de HCOOH, flujo: 20 ml/min) para proporcionar, después de liofilizar las fracciones purificadas, el compuesto deseado. TLC, R_f (EtOAc) = 0,39; MS (LC/MS): 492,1 [M+H]+, 490,1 [M- H]- ; t_R (condiciones de HPLC a): 3,22 min.

Ejemplo 370: 1- [(1- carbamoil- 5- hidroxi- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico



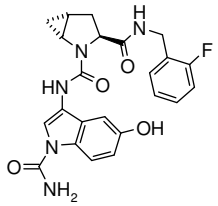
Una mezcla de 2- [(3- trifluorometoxi- fenil)- amida de 1- [(5- aliloxi- 1- carbamoil- 1H- indol- 3- il)]- amida]del ácido (S)- pirrolidina- 1,2- dicarboxílico **Ejemplo 335** (30 mg, 0,056 mmol), acetato de paladio (1,4 mg, 2,82 µmol) y trifenilfosfina (1,5 mg, 5,64 mmol) en ácido fórmico (0,7 ml) se calentó a 90 °C durante 30 min en atmósfera de nitrógeno. La mezcla se vertió en agua y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El material en crudose purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:1 a EtOAc) para dar el compuesto deseado. TLC, R_f (EtOAc) = 0,56; MS (LC/MS): 492 [M+H]+, 514,2 [M+Na]+, 490 [M- H]- , 447,1 [M- $CONH_2$]- ; t_R (condiciones de HPLC a): 3,13 min.

Ejemplo 371: 2- [(1- carbamoil- 5- hidroxi- 1H- indol- 3- il)- amida]- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico



Se disolvieron dímero de cloruro de paladio de alilo (4,9 mg, 0,013 mmol) y 2- di- terc-butilfosfino- 2'- metilbifenilo (16,6 mg, 0,053 mmol) en DMF (0,4 ml) y la mezcla se agitó durante 5 min bajo atmósfera de nitrógeno. Se añadieron en ese orden ácido fórmico (30 µl, 0,772 mmol), trietilamina (107 µl, 0,772 mmol) y 3- (3- cloro- 2- fluoro- bencilamida) de 2- [(5- aliloxi- 1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico Eje**mplo 268** (70 mg, 0,133 mmol) en DMF (1 ml). La mezcla se agitó a 10 °C durante 1 h, a continuación a temperatura ambiente durante 2 días. La mezcla se vertió en agua y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El material en crudose purificó mediante HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 19x50 mm, eluyente: 20% a 100% CH_3CN en H_2O en 15 min, CH_3CN y H_2O que contiene 0,1% de HCOOH, flujo: 20 ml/min) para proporcionar el compuesto deseado después de la liofilización de las fracciones purificadas. TLC, R_f (EtOAc) = 0,4; MS (LC- MS): 486,0 [M+H]+, 441,1 [M- $CONH_2$]- ; t_R (condiciones de HPLC f): 1,65 min.

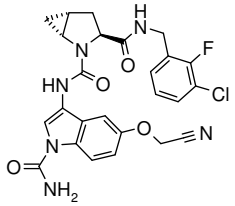
Ejemplo 372: 2- [(1- carbamoil- 5- hidroxi- 1H- indol- 3- il)- amida]- 3- (2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico



Se disolvieron dímero de cloruro de paladio de alilo (17,8 mg, 0,048 mmol) y 2- di- terc- butilfosfino- 2'- metilbifenilo (60,6 mg, 0,194 mmol) en DMF (2 ml) y la mezcla se agitó durante 5 min. Se añadieron en ese orden ácido fórmico (108 µl, 2,81 mmol), trietilamina (391 µl, 2,81 mmol) y 3- (3- cloro- 2- fluoro- bencilamida) de 2- [(5- aliloxi- 1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico **Ejemplo 268** (255 mg, 0,485 mmol) en DMF (3 ml) y la solución resultante se agitó a temperatura ambiente durante una noche en atmósfera de nitrógeno. La mezcla se vertió en agua y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se secaron sobre

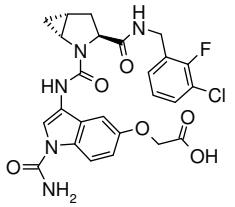
Na_2SO_4, se filtraron y se concentraron. El residuo crudose purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano 100% a 100% de EtOAc a CH_2Cl_2/MeOH 90- 10) para proporcionar una mezcla del compuesto deseado junto con el análogo desclorado. La mezcla se purificó mediante HPLC preparativa (Interchrom, C18- ODB, 10 µm, 28x250 mm, eluyente: 20% a 100% CH_3CN en H_2O en 40 min, CH_3CN y H_2O que contiene 0,1% de HCOOH, flujo: 40 ml/min) para proporcionar, después de la extracción de las fracciones purificadas con EtOAc,3- (3- cloro- 2- fluoro- bencilamida) de 2- [(1- carbamoil- 5- hidroxi- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico y 3- (2- fluoro- bencilamida) de 2- [(1- carbamoil- 5- hidroxi- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico. TLC, R_f (EtOAc) = 0,3; MS (LC- MS): 452,1 [M+H]+, 474,1 [M+Na]+, 407 [M- $CONH_2$]- ; t_R (condiciones de HPLC f): 1,81 min.

Ejemplo 373: 2- [(1- carbamoil- 5- cianometoxi- 1H- indol- 3- il)- amida]- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico



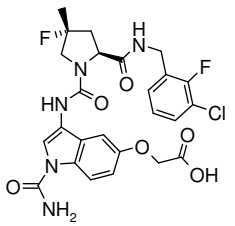
A una solución del **Ejemplo 371** 3- (3- cloro- 2- fluoro- bencilamida) de 2- [(1- carbamoil- 5- hidroxi- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico (50 mg, 0,103 mmol) en acetona (0,5 ml) se añadieron carbonato de cesio (36,9 mg, 0,11 mmoles) y bromo- acetonitrilo (8,13 µl, 0,11 mmoles) y la mezcla de reacción se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 4 h. La acetona se concentró. El residuo se disolvió en agua y se extrajo dos veces con EtOAc. Los extractos orgánicos combinados se secaron sobre Na_2SO_4, se filtraron y se concentraron. El material crudose purificó mediante HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 19x50 mm, eluyente: 20% a 100% (CH_3CN/MeOH 1- 4)/H_2O en 15 min, (CH_3CN/MeOH 1- 4) y H_2O que contiene 0,1% de HCOOH, flujo: 20 ml/min). TLC, R_f (EtOAc) = 0,45; MS (UPLC/MS): 525.4/527.2 [M+H]+, 542.4/544.7 [M+NH4]+, 569.4/571.4 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,89 min.

Ejemplo 374: Ácido (1- carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- iloxi)- acético



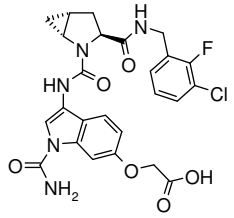
A una solución de ester metilo del ácido (1- carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- iloxi)- acético Ej**emplo 133** (85 mg, 0,145 mmol) en THF (1,2 ml) y H_2O (120 µl) se añadió NaOH 1 N (290 µl, 0,29 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 20 min. El producto crudo se purificó directamente usando cartucho de trimetilaminopropilo (Mega Bond Elut- SAX, 1 g de Varian) pre- lavada con CH_3CN (10 ml) y el compuesto fue liberado con 10 ml de HCl 0,1 N en CH_3CN. La solución resultante se concentró y se purificó mediante HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 19x50 mm, eluyente: 20% a 100% CH_3CN en H_2O en 15 min, CH_3CN y H_2O que contiene 0,1% de HCOOH, flujo: 20 ml/min) para proporcionar el material deseado después de la liofilización de las fracciones purificadas. MS (UPLC- MS): 544.3/546.3 [M+H]+, 566.4/568.3 [M+Na]+, 542.3/544.4 [M- H]- , tr (condiciones de HPLC f): 1,72 min.

Ejemplo 375: Ácido (1- carbamoil- 3- {[(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil- pirrolidina- 1- carbonil]- amino}- 1H- indol- 5- iloxi)- acético



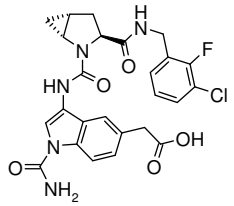
El compuesto del título se preparó según el protocolo descrito para la preparación del **Ejemplo 374** a partir de ester metilo del ácido (1- carbamoil- 3- {[(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metilpirrolidina- 1- carbonil]- amino}- 1H- indol- 5- iloxi)- acético Ej**emplo 318**. MS (UPLC): 564,2 [M+H]+, 562,3 [M- H]- ; t_R (condiciones de HPLC f): 1,72 min.

Ejemplo 376: Ácido (1- carbamoil- 3- {[(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metilpirrolidina- 1- carbonil]- amino}- 1H- indol- 5- iloxi)- acético



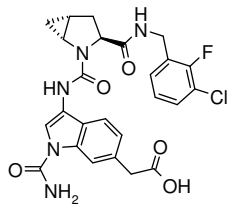
El compuesto del título se preparó según el protocolo descrito para la preparación del **Ejemplo 374** a partir de ester metilo del ácido (1- carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 6- iloxi)- acético **Ejemplo 394**. MS (UPLC): 544.3/546.3 [M+H]+, 542.3/544.3 [M- H]- ; t_R (condiciones de HPLC f): 1,78 min.

Ejemplo 377: Ácido (1- carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- il)- acético



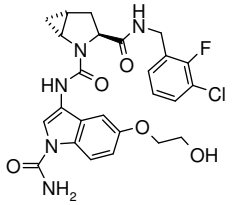
El compuesto del título se preparó según el protocolo descrito para la preparación del **Ejemplo 374** a partir de(1- carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- 3**Ejemplo 306**.TLC, R_f (EtOAc) = 0,2; MS (UPLC): 528.3/530.2 [M+H]+, 526.3/528.6 [M- H]- , 483.3/485.3 [M- $CONH_2$]- ; t_R (condiciones de HPLC f): 1,74 min.

Ejemplo 378: Ácido (1- carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 6- il)- acético



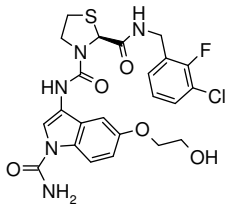
A una solución de ester terc- butilo del ácido (1- carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonilo]- amino}- 1H- indol- 6- il)- acético del **Ejemplo 127** (30 mg, 0,051 mmol) en CH_2Cl_2 (0,5 ml) se añadió TFA (157 µl, 2,05 mmol) y la mezcla se agitó a temperatura ambiente durante 1 h. A continuación, se concentró y el residuo crudo se recogió en Et_2O y se separómediante filtración para proporcionar el material deseado. MS (UPLC): 528.2/530.3 [M+H]+, 1055.6/1057.2 [2M+H]+, 483.1/485.1 [M- $CONH_2$]- , 1053.6/1055.6 [2M- H]- ; t_R (condiciones de HPLC f): 1,75 min.

Ejemplo 379: 3- (3- cloro- 2- fluoro- bencilamida) de 2- {[1- carbamoil- 5- (2- hidroxi- etoxi)- 1H- indol- 3- il]- amida} del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico



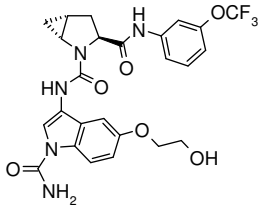
A una solución de ester metilo del ácido (1- carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- iloxi)- acético **Ejemplo 133** (344 mg, 0,573 mmol) en THF (3 ml) en atmósfera de nitrógeno se agregóLiBH$_4$ 2M en THF (573 µl, 1,15 mmol). La solución resultante se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 30 min, después se vertió lentamente en una solución acuosa saturada de $NaHCO_3$ y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudo se recogió en CH_2Cl_2 y se filtró, después se purificó mediante HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 19x50 mm, eluyente: 20% a 100% CH_3CN en H_2O en 15 min, CH_3CN y H_2O que contiene 0,1 % de HCOOH, flujo: 20 ml/min) para proporcionar el material deseado después de la liofilización de las fracciones purificadas. R_f, TLC (EtOAc) = 0,15; MS (LC-MS): 530/532 [M+H]+, 552.1/554.1 [M+Na]+, 528.1/530.1 [M- H]- , 485/487 [M- $CONH_2$]- ; t_R (condiciones de HPLC f): 1,64 min.

Ejemplo 380: 3- {[1- carbamoil- 5- (2- hidroxi- etoxi)- 1H- indol- 3- il]- amida}- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- tiazolidin- 2,3- dicarboxílico



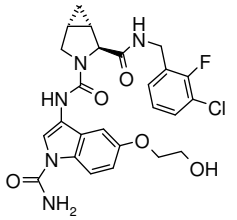
El compuesto del título se preparó según el protocolo descrito para la preparación del **Ejemplo 379** a partir de ester metilo del ácido (1- carbamoil- 3- {[(S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- tiazolidine- 3- carbonil]- amino}- 1H- indol- 5- iloxi)- acético (preparado usando protocolos similares como para el **Ejemplo 133**). TLC, R_f (EtOAc) = 0,45; EM (UPLC): 564.2/566.2 [M+H]+, 581.2/583.2 [M+NH4]+, 562.3/564.3 [M- H]- , 608.4/610.4 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,82 min.

Ejemplo 381: 2- {[1- carbamoil- 5- (2- hidroxi- etoxi)- 1H- indol- 3- il]- amida}- 3- [(3- trifluorometoxi- fenil)- amida] del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico



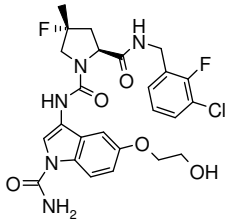
El compuesto del título se preparó según el protocolo descrito para la preparación del **Ejemplo 379** a partir de ester metilo del ácido (1- carbamoil- 3- {[(1R,3S,5R)- 3- (3- trifluorometoxi- fenilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- iloxi)- acético (preparado usando protocolos similares como para el **Ejemplo 133**). MS (UPLC): 548,3 [M+H]+, 546,3 [M- H]- , 592,3 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,80 min.

Ejemplo 382: 3- {[1- carbamoil- 5- (2- hidroxi- etoxi)- 1H- indol- 3- il]- amida}- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (1S*, 2S*, 5R*)- 3- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico



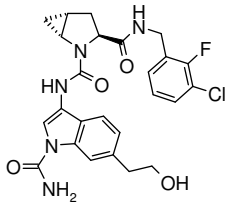
El compuesto del título se preparó según el protocolo descrito para la preparación del **Ejemplo 379** a partir de ester metilo del ácido (1- carbamoil- 3- {[(1S*, 2S*, 5R*)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- aza- biciclo[3.1.0]hexano- 3- carbonil]- amino}- 1H- indol- 5- iloxi)- acético (preparado usando protocolos similares como para el **Ejemplo 133**). MS (UPLC): 530.3/532.2 [M+H]+, 528.2/530.4 [M- H]- , 574.3/576.3 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,58 min.

Ejemplo 383: 1- {[1- carbamoil- 5- (2- hidroxi- etoxi)- 1H- indol- 3- il]- amida}- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- fluoro- 4- metil- pirrolidina- 1,2- dicarboxílico



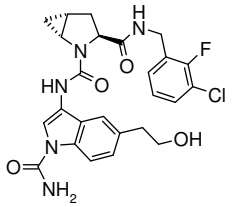
El compuesto del título se preparó según el protocolo descrito para la preparación del **Ejemplo 379** a partir de éster métilico del ácido (1- carbamoil- 3- {[(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil- pirrolidina- 1- carbonil]- amino}- 1H- indol- 5- iloxi)- acético **Ejemplo 318**. TLC, R_f (EtOAc) = 0,30; EM (UPLC): 550.3/552.5 [M+H]+, 505.7/507.1 [M- $CONH_2$]- ; t_R (condiciones de HPLC f): 1,72 min.

Ejemplo 384: 2- {[1- carbamoil- 6- (2- hidroxi- etil)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico



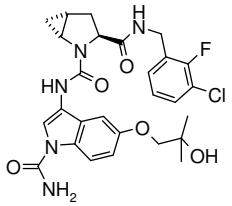
El compuesto del título se preparó según el protocolo descrito para la preparación del **Ejemplo 379** a partir de ester etilo del ácido (1- carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 6- il)- acético **Ejemplo 315**. MS (UPLC): 514.3/516.3 [M+H]+, 512.3/514.3 [M- H]- , 558.3/560.2 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,75 min.

Ejemplo 385: 2- {[1- carbamoil- 5- (2- hidroxi- etil)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico



El compuesto del título se preparó según el protocolo descrito para la preparación del **Ejemplo 379** a partir de ester etilo del ácido (1- carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- il)- acético Eje**mplo 306**. TLC, R_f (EtOAc) = 0,2; EM (UPLC): 514.2/516.3 [M+H]+, 512.3/514.1 [M- H]- , 558.3/560.2 [M+HCOO]- , 469.2/471.4 [M- $CONH_2$]- ; t_R (condiciones de HPLC f): 1,72 min.

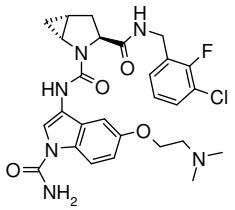
Ejemplo 386: 2- {[1- carbamoil- 5- (2- hidroxi- 2- metil- propoxi)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico



A una solución de ester metilo del ácido (1- carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- iloxi)- acético **Ejemplo 133** (50 mg, 0,083 mmol) en THF seco (0,5 ml) a 0 º C se añadió bromuro de metilmagnesio (3 M en Et_2O, 61 µl, 0,183 mmol). La mezcla se agitó bajo nitrógeno a 0 °C durante 10 min, a continuación se dejó llegar a temperatura ambiente y se agitó adicionalmente durante 24 h. Se añadió agua (2 ml) y el precipitado se filtró. El filtrado se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudose purificó mediante HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 19x50 mm, eluyente: 20% a 100% CH_3CN en H_2O en 15 min, CH_3CN y H_2O que contiene 0,1% de HCOOH, flujo: 20 ml/min)para proporcionar el material deseado después de la liofilización de las fracciones purificadas. TLC, R_f (EtOAc) = 0,25; MS

(LC- MS): 558/560 [M+H]+, 513.1/515.2 [M- $CONH_2$]- ; t_R (condiciones de HPLC f): 1,84 min.

Ejemplo 387: 2- {[1- carbamoil- 5- (2- dimetilamino- etoxi)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico



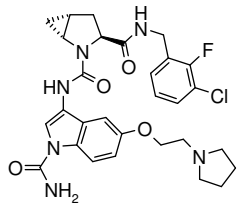
Una solución de éster 2- (1- carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- iloxi)- etílico del ácido metanosulfónico (35 mg, 0,054 mmol) y dimetilamina 5,6 M en EtOH (0,5 ml) se calentó a 70 °C durante 4 h en un tubo sellado. La reacción se vertió en una solución acuosa saturada de $NaHCO_3$ y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudose purificó mediante HPLC preparativa (Nucleosil, C18- HD, 5 µm, 21x50 mm, eluyente: 20% a 100% CH_3CN en H_2O en 15 min, CH_3CN y H_2O que contiene 0,1% de HCOOH, flujo: 20 ml/min) para proporcionar después de la liofilización de las fracciones purificadas el material deseado en forma de una sal de ácido fórmico. MS (UPLC): 557.3/559.3 [M+H]+, 555.6/558.4 [M- H]- , 512.3/514.5 [M- $CONH_2$]- ; t_R (condiciones de HPLC f): 1,47 min.

<u>Éster 2- (1- carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- iloxi)- etilo del ácido metanosulfónico</u>

A una solución de 3- (3- cloro- 2- fluoro- bencilamida) de 2- {[1- carbamoil- 5- (2- hidroxi- etoxi)- 1H- indol- 3- il]- amida} del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico **Ejemplo 379** (50 mg, 0,09 mmol) y Et_3N (62 µl, 0,448 mmol) en CH_2Cl_2 (1 ml) a 0 °C bajo atmósfera de nitrógeno, se añadió cloruro de metanosulfonilo (35 µl, 0,448 mmol). La solución resultante se agitó a temperatura ambiente durante la noche. Se añadieron Et_3N (31 µl, 0,224 mmol) y cloruro de metanosulfonilo (17 µl, 0,224 mmol) y la mezcla se agitó adicionalmente a temperatura ambiente durante 1,5 h para completar la reacción. La reacción se vertió en una solución acuosa saturada de $NaHCO_3$, se extrajo dos veces con

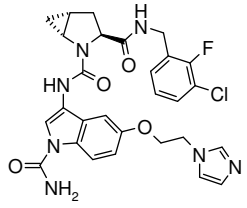
CH_2Cl_2, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo crudose purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1- 1a 100% EtOAc) para proporcionar el material deseado. TLC, R_f (EtOAc) = 0,25; EM (UPLC): 608.5/610.2 [M+H]+, 563,4 [M- $CONH_2$]- , 606.4/608.0 [M- H]- ; t_R (condiciones de HPLC f): 1,88 min.

Ejemplo 388: 3- (3- cloro- 2- fluoro- bencilamida) de 2- {[1- carbamoil- 5- (2- pirrolidin- 1- il- etoxi)- 1H- indol- 3- il]- amida} del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico



El compuesto del título se preparó como una sal de ácido fórmico a partir de éster 2- (1- carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- iloxi)- etilo del ácido metanosulfónico y pirrolidina de acuerdo con el procedimiento descrito para la preparación del **Ejemplo 387**: 3- (3- cloro- 2- fluoro- bencilamida) de 2- {[1- carbamoil- 5- (2- dimetilamino- etoxi)- 1H- indol- 3- il]- amida} del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico. TLC, R_f (CH_2Cl_2/MeOH 8- 2) = 0.3; MS (UPLC/MS): 583.5/585.5 [M+H]+, 627.5/629.3 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,51 min.

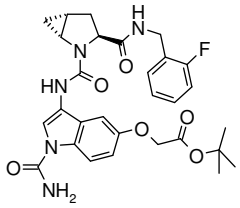
Ejemplo 389: 2- {[1- carbamoil- 5- (2- imidazol- 1- il- etoxi)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico



El compuesto del título se preparó a partir de éster 2- (1- carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- iloxi)- etílico del ácido metanosulfónicoe imidazol de acuerdo con el procedimiento descrito para la preparación del **Ejemplo 387**: 3- (3- cloro- 2- fluoro- bencilamida) de 2- {[1-

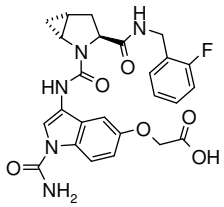
carbamoil- 5- (2- dimetilamino- etoxi)- 1H- indol- 3- il]- amida}del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico. TLC, R_f (CH_2Cl_2/MeOH 8- 2) = 0,60; MS (UPLC/MS): 580.5/582.5 [M+H]+, 578.5/580.7 [M- H]- , 624.5/626.5 [M+HCOO]- ; t_R (f) Condiciones de HPLC: 1,49 min.

Ejemplo 390: Ester terc- butilo del ácido (1- carbamoil- 3- {[(1R,3S,5R)- 3- (2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- iloxi)- acético



Se añadió A3- (2- fluoro- bencilamida) de 2- [(1- carbamoil- 5- hidroxi- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico **Ejemplo 372** (38 mg, 0,084 mmol) en acetona (0,45 ml), carbonato de cesio (30,2 mg, 0,093 mmoles) y bromoacetato de terc- butilo (14 µl, 0,093 mmol), y la suspensión resultante se agitó a temperatura ambiente bajo nitrógeno durante la noche. La acetona se concentró y al residuo se le añadió agua y la mezcla se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudose purificó mediante HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 19x50 mm, eluyente: 20% a 100% CH_3CN en H_2O en 15 min, CH_3CN y H_2O que contiene 0,1% de HCOOH, flujo: 20 ml/min)para proporcionar el material deseado después de la liofilización de las fracciones purificadas. MS (LC- MS): 588,3 [M+Na]+, 510,1 [MH- tBu]+, 521,2 [M- $CONH_2$]- ; t_R (condiciones de HPLC f): 2,04 min.

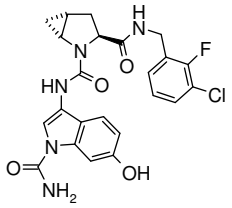
Ejemplo 391: Ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- iloxi)- acético



A éster terc- butilo del ácido (1- carbamoil- 3- {[(1R,3S,5R)- 3- (2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- iloxi)-

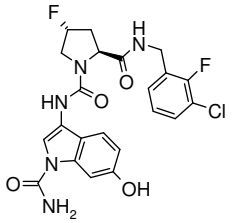
acético **Ejemplo 390** (18 mg, 0,032 mmol) en CH_2Cl_2 (0,5 ml) se añadió TFA (97 µl, 1,27 mmol) y la mezcla se agitó a temperatura ambiente durante la noche. A continuación, se concentró, se recogió en CH_2Cl_2 y se filtrópara proporcionar el material deseado, que se secó adicionalmente a alto vacío. MS (LC- MS): 510,1 [M+H]+, 532,2 [M+Na]+, 508,1 [M- H]- , 465,1 [M- $CONH_2$]- ; t_R (condiciones de HPLC f): 1,52 min.

Ejemplo 392: 2- [(1- carbamoil- 6- hidroxi- 1H- indol- 3- il)- amida]- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico



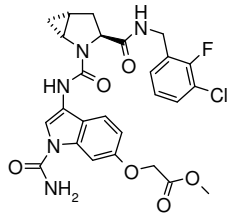
El compuesto del título se preparó a partir de 2- [(6- aliloxi- 1- carbamoil- 1H- indol- 3- il)- amida]- 3- (3- cloro- 2- fluoro- bencilamida) de del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico de acuerdo con el procedimiento descrito para la preparación de 3- (3- cloro- 2- fluoro- bencilamida) de 2- [(1- carbamoil- 5- hidroxi- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico Eje**mplo 371**. MS (LC- MS): 486,0 [M+H]+; t_R (condiciones de HPLC b): 3,39 min.

Ejemplo 393: 1- [(1- carbamoil- 6- hidroxi- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico



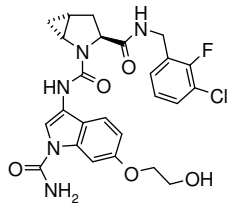
El compuesto del título se preparó a partir de 2- (3- cloro- 2- fluoro- bencilamida) de 1- [(6- aliloxi- 1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico de acuerdo con el procedimiento descrito para la preparación de 3- (3- cloro- 2- fluoro- bencilamida) de 2- [(1- carbamoil- 5- hidroxi- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico Eje**mplo 371**. MS (LC- MS): 492 [M+H]+; t_R (condiciones de HPLC b): 3,12 min.

Ejemplo 394: Ester metilo del ácido (1- carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 6- iloxi)- acético



2- [(1- carbamoil- 6- hidroxi- 1H- indol- 3- il)- amida]- A3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico Eje**mplo 392** (70 mg, 0,144 mmol) en acetona (720 µl) se añadieron Cs_2CO_3 (56,3 mg, 0,173 mmol) y bromoacetato de metilo (16,4 µl, 0,173 mmol) y la mezcla de reacción se agitó a 23 °C durante la noche. Se añadieron 0.5 eq de bromoacetato de metilo y 0,5 equivalentes de Cs_2CO_3 y la mezcla de reacción se agitó a 23 °C durante 4 horas para completar la reacción. La mezcla bruta se vertió en agua y se extrajo con EtOAc (x2). Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se evaporaron hasta sequedad. El material en crudose purificó mediante HPLC preparativa (Waters SunFire C18ODB, 5 µm, 30x100, eluyente: 20% CH_3CN/80% de H_2O a 100% CH_3CN en 20 min, CH_3CN y H_2O que contiene 0.1% de TFA, flujo de 40 ml/min) para proporcionar el material deseado después de la liofilización de las fracciones purificadas. MS (LC- MS): 558 [M+H]+; t_R (condiciones de HPLC b): 3,84 min.

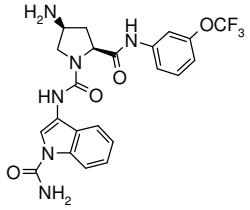
Ejemplo 395: 2- {[1- carbamoil- 6- (2- hidroxi- etoxi)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico



El compuesto del título se preparó a partir de ester metilo del ácido (1- carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 6- iloxi)- acético **Ejemplo 394** de acuerdo con el procedimiento descrito para la preparación de3- (3- cloro- 2- fluoro- bencilamida)de 2- {[1- carbamoil- 5- (2- hidroxi- etoxi)- 1H- indol- 3- il]- amida} del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano-

2,3- dicarboxílico Ejemplo **379**. TLC, R_f (EtOAc) = 0,12; EM (UPLC): 530.3/532.3 [M+H]+, 528.2/530.5 [M- H]- , 574.2/576.4 [M+HCOO]- ; t_R (f) Condiciones de HPLC: 1,71 min.

Ejemplo 396: 2- [(3- trifluorometoxi- fenil)- amida] de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico

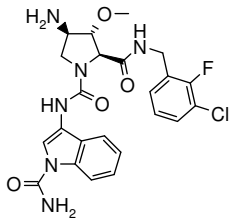


Se disolvió 2- [(3- trifluorometoxi- fenil)- amida] de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- N- fmoc- amino- pirrolidina- 1,2- dicarboxílico (380 mg, 0,533 mmol) se disolvió en una solución de piperidina al 20% en DMF (2 ml). La mezcla se agitó a temperatura ambiente durante 1 h y se purificó directamente mediante HPLC preparativa (C18- ODB Interchrom, 10 µm, 28x250 mm, 5% de CH_3CN en H_2O 2,5 min, a continuación, 5% a 100% CH_3CN en H_2O en 32,5 min, CH_3CN y H_2O que contiene 0,1% HCOOH; flujo: 40 ml/min). Para las fracciones purificadas de HPLC se añadió NaOH 1 N y el compuesto se extrajo con EtOAc (x3). Los extractos orgánicos combinados se secaron sobre Na_2SO_4, se filtraron y se concentraron y este material se purificó de nuevo mediante HPLC preparativa (agua SunFire C18- ODB, 5 µm, 19x50 mm, eluyente: 5% a 60% de CH_3CN en H_2O en 18 min, CH_3CN y H_2O que contiene 0,1% HCOOH; flujo: 20 ml/min) para proporcionar, después de liofilización de las fracciones purificadas, el compuesto deseado en forma de una sal de formiato. MS (LC- MS): 491,2 [M+H]+, 489,1 [M- H]- .

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- N- fmoc- amino- pirrolidina- 1,2- dicarboxílico

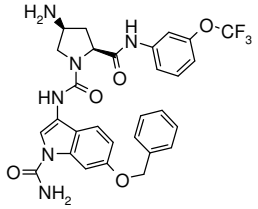
El compuesto del título se preparó como se describe en el Esquema D5 a partir de (4S)- 4- N- fmoc- amino- 1- Boc- L- prolina. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0,45; t_R (condiciones de HPLC a): 4,20 min.

Ejemplo 397: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S, 3S,4R)- 4- amino- 3- metoxi- pirrolidina- 1,2- dicarboxílico



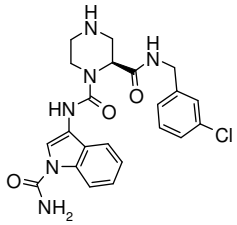
El compuesto del título se preparó según el Esquema D5 (pasos B y C) a partir de ester terc- butilo del ácido (2S,3S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- (9H- fluoren- 9- ilmetoxicarbonilamino)- 3- metoxi- pirrolidina- 1- carboxílico (que se describe en el Esquema B21) seguido por la desprotección de Fmoc utilizando el mismo protocolo que el descrito para el **Ejemplo 396**. MS (UPLC- MS): 547 [M+H]+; t_R (f) Condiciones de HPLC: 1,50 min; 19F RMN (100 MHz, DMSO- d_6) δ (ppm):- 120.

Ejemplo 398: 1- [(6- benciloxi- 1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico



El compuesto del título se preparó como se describe en el Esquema D5 utilizando (4S)- 4- N- Fmoc- amino- 1- Boc- L- prolina en la etapa A y amida del ácido 6- benciloxi- 3- isocianato- indol- 1- carboxílico (preparado como se describe en la Parte A4) en la etapa C, seguido por la desprotección de Fmoc como se describe en el Esquema D2 etapa B. MS (LC/MS): 597,1 [M+H]+, 595,2 [M- H]; t_R (condiciones de HPLC a): 3,16 min.

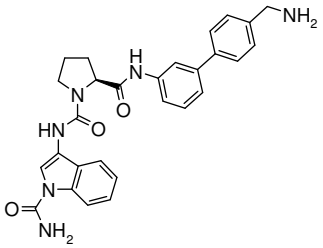
Ejemplo 399: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (S)- piperazina- 1,2- dicarboxílico



El compuesto del título como una sal de formiato se preparó como se describe en el Esquema D5 usando ácido (S)- 1- N- Boc- 4- N- Fmoc- piperazina- 2- carboxílico y 1 equivalente de 3- clorobencilamina en la etapa A seguido por la desprotección de Fmoc como

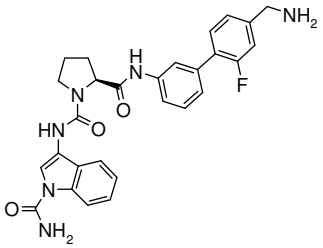
se describe en el Esquema D2 etapa B. MS (LC/MS): 455.2/457.2 [M+H]+, 410/412 [M-$CONH_2$]- ; t_R (condiciones de HPLC a): 2,58 min.

Ejemplo 400: 2- [(4'- aminometil- bifenil- 3- il)- amida]- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico



A una solución de 2- [(4'- ciano- bifenil- 3- il)- amida] 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico **Ejemplo 152**(25 mg, 0,051 mmol) en EtOH (1 ml) que contenía 5% de NH_3, se añadió una gota de Ni Raney disuelta en EtOH (0.5 ml). La mezcla resultante se agitó a temperatura ambiente en una atmósfera de hidrógeno durante 26 h, después se filtró a través de Celite y se concentró. El residuo crudose purificó mediante HPLC preparativa (Waters SunFire C18ODB, 5 µm, flujo de 20 ml/min, eluyente: 5%CH_3CN/95%H_2O a 100% CH_3CN en 15 min, CH_3CN y H_2Oque contiene 1% de HCOOH) para proporcionar después de la liofilización de las fracciones purificadas el compuesto deseado en forma de una sal de formiato. MS (LC/MS): 497 [M+H]+; t_R (Waters Symmetry C18, 3.5um, 2.1x50mm, 5- 95% CH_3CN/H_2O/3.5 min, 95% de CH_3CN/2 min, CH_3CN y H_2O que contiene 0,1 % de TFA, flujo: 0,6 ml/min) 3,04 min.

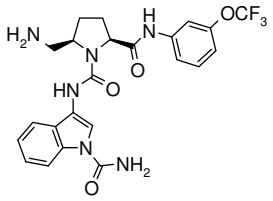
Ejemplo 401: 2- [(4'- aminometil- 2'- fluoro- bifenil- 3- il)- amida]- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico



A una solución de 2- [(4'- ciano- 2'- fluoro- bifenil- 3- il)- amida] de1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico (140 mg, 0,274 mmol) (preparado de acuerdo con el procedimiento general descrito en el Esquema D5, usando en la etapa A 3'- amino- 2- fluoro- bifenil- 4- carbonitrilo (preparado como se describe en la Parte C)

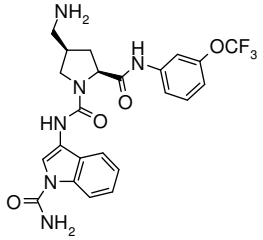
en EtOH (15 ml) que contiene 4% de NH_3 se añadió Ra- níquel (70 mg) y la mezcla se agitó bajo atmósfera de H_2durante 18 h. La mezcla de reacción se filtró a través de Celite y se concentró. El residuo en crudose purificó mediante HPLC preparativa (Waters Sunfire (ODB C18, 5µm, 19x50, flujo = 20mL/min, 20% de CH_3CN/80% de agua a 100% CH_3CN) para proporcionar el compuesto deseado MS (LC/MS): 515 [M+H]+; t_R (Waters Symmetry C18, 3.5um, 2.1x50mm, 5- 95% CH_3CN/H_2O/3.5 min, 95% de CH_3CN/2 min, CH_3CN y H_2O que contiene 0.1% de TFA, flujo: 0,6 ml/min) 3,1 min .

Ejemplo 402: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,5R)- 5- aminometil- pirrolidina- 1,2- dicarboxílico



Una mezcla de 2- [(3- trifluorometoxi- fenil)- amida] de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S, 5R)- 5- azidometil- pirrolidina- 1,2- dicarboxílico Eje**mplo 179**(50 mg, 0,094 mmol) y trifenilfosfina (29,7 mg, 0,113 mmol) en THF (1 ml) se agitó a temperatura ambiente durante la noche. Después de la terminación de la reacción MeOH (1 ml) y agua (1 ml) se añadió y la solución se agitó durante 1 h, luego se concentró la mezcla de reacción cruda y se purificó mediante HPLC preparativa (Waters SunFire C18- ODB 5 □m, 19x50, 5- 100% CH_3CN/H_2O en 17 min, 100% CH_3CN durante 3 min, CH_3CN y H_2O que contiene 0.1% de TFA, flujo: 20 ml/min) para proporcionar el compuesto del título. MS: 505 [M+H]+; t_R (condiciones HPLCb) condiciones:3.24 min.

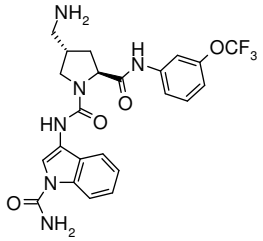
Ejemplo 403: 1- [(1- carbamoil- 1H- indol- 3- il)- amida] - 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- aminometil- pirrolidina- 1,2- dicarboxílico



Se disolvió2- [(3- trifluorometoxi- fenil)- amida] de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- ciano- pirrolidina- 1,2- dicarboxílico Eje**mplo 125** (20 mg, 0,04 mmol) en MeOH (0.2 ml). Se añadieron amoniaco (25% en agua, 0,02 ml) y níquel Raney

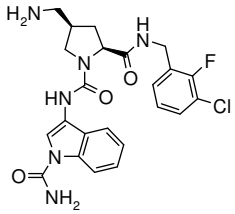
(7,11 mg). Se retiró aire del matraz y se reemplazó con nitrógeno tres veces. Por último, el matraz se desgasificó de nuevo y la mezcla se colocó bajo una atmósfera de hidrógeno, y se agitó a temperatura ambiente durante la noche. El catalizador se eliminó a través de una almohadilla de Celite y se lavó con MeOH. El filtrado se concentró, y el residuo se purificó mediante HPLC preparativa (Waters SunFire C18- ODB, 5 µm, 19x50 mm, eluyente: 5- 100% CH_3CN/H_2O en 17 min, CH_3CN y H_2O que contiene 0.1% de TFA, flujo: 20 ml/min) para proporcionar el compuesto del título como una sal de TFA. MS (LC- MS): 505 [M+H]+; t_R (condiciones de HPLC b): 3,1 min.

Ejemplo 404: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- aminometil- pirrolidina- 1,2- dicarboxílico



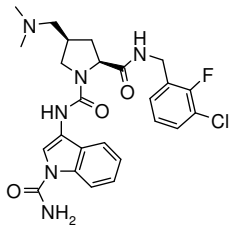
El compuesto del título se obtuvo a partir de 2- [(3- trifluorometoxi- fenil)- amida] de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- ciano- pirrolidina- 1,2- dicarboxílico **Ejemplo 256** usando el protocolo descrito para la preparación del **Ejemplo 403**. MS (LC/MS): 505 [M+H]+; t_R (condiciones de HPLC b): 3,1 min.

Ejemplo 405: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- aminometil- pirrolidina- 1,2- dicarboxílico



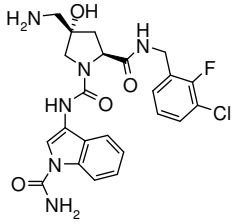
El compuesto del título se preparó de manera análoga como se describe para el compuesto del título **Ejemplo 403** usando 2- (3- cloro- 2- fluoro- bencilamida) de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- ciano- pirrolidina- 1,2- dicarboxílico preparado de acuerdo con el esquema D5. MS (LC/MS): 487 [M+H]+, 442 [M- CONH2]- ; t_R (condiciones de HPLC f): 1,46 min.

Ejemplo 406: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- dimetilaminometil- pirrolidina- 1,2- dicarboxílico



A una solución del **Ejemplo 405** (132 mg, 0,271 mmol) en MeOH (0,9 ml) se añadió formaldehído al 20% en MeOH (373 µl, 2,71 mmol), cianoborohidruro de sodio (56 mg, 0,895 mmoles) y ácido acético (31,5 µl, 0,542 mmol). La mezcla de reacción se agitó durante 16 h a temperatura ambiente y después se concentró. El material crudose purificó mediante HPLC preparativa (Waters SunFire C18- ODB, 5 µm, 19x50 mm, eluyente: 10- 100% CH_3CN/H_2O en 30 min, CH_3CN y H_2O que contiene 0.1% de TFA, flujo: 20 ml/min) para proporcionar el material deseado. TLC, R_f (EtOAc) = 0,02; MS (LC/MS): 515 [M+H]+, 470 [M- CONH2]- ; t_R (condiciones de HPLC f): 1,47 min.

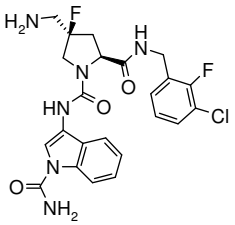
Ejemplo 407: 2- (3- cloro- 2- fluoro- bencilamida) de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- aminometil- 4- hidroxi- pirrolidina- 1,2- dicarboxílico



A una solución de 2- (3- cloro- 2- fluoro- bencilamida) de 1- [- amida del ácido (1- carbamoil- 1H- indol- 3- il)] del ácido (2S,4R)- 4- azidometil- 4- hidroxi- pirrolidina- 1,2- dicarboxílico (300 mg, 0,567 mmol) preparado de acuerdo con el Esquema D5 a partir del ester terc- butilo del ácido (2S,4R)- 4- azidometil- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- hidroxi- pirrolidina- 1- carboxílico (descrito en la parte B) en EtOAc (10 ml) se le añadió Pd/C (10 mg). Se retiró aire del matraz y se reemplazó con nitrógeno tres veces. Finalmente el matraz se desgasificó de nuevo y la mezcla se colocó bajo una atmósfera de hidrógeno, y se agitó a temperatura ambiente durante la noche. El catalizador se eliminó a través de una almohadilla de Celite y se lavó con EtOAc. El filtrado se concentró, y el residuo se purificó mediante HPLC preparativa (Waters SunFire C18- ODB, 5 µm, 19x50 mm, eluyente: 5- 100% CH_3CN/H_2O en 17 min, CH_3CN y H_2O que contiene 0.1% de TFA, flujo: 20 ml/min) para proporcionar el

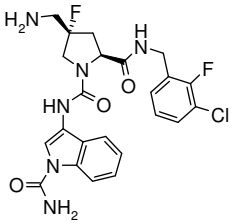
compuesto del título como una sal de TFA. MS (LC- MS): 503 [M+H]+; t_R (c) Condiciones de HPLC: 3,57 min; 19F RMN (100 MHz, DMSO- d_6) δ (ppm):- 122.

Ejemplo 408: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico



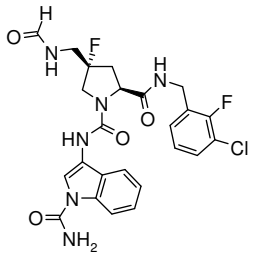
El compuesto del título se preparó de manera análoga a como se describe para el **Ejemplo 407** usando 2- (3- cloro- 2- fluoro- bencilamida) de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- azidometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico preparado de acuerdo con el esquema D5 a partir de ester terc- butilo del ácido (2S,4S)- 4- azidometil- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico (descrito en la parte B). MS (LC- MS): 505/507 [M+H]+; t_R (f) Condiciones de HPLC: 1,46 min; 19F RMN (100 MHz, DMSO- d_6) δ (ppm):- 121,- 150.

Ejemplo 409: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico



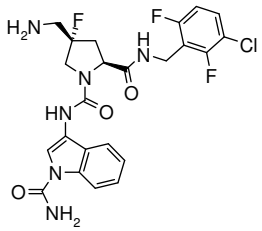
El compuesto del título se preparó de manera análoga a la descrita para el**Ejemplo 407** usando 2- (3- cloro- 2- fluoro- bencilamida) de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- azidometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico preparado de acuerdo con el esquema D5 a partir de ésterterc- butílicodel ácido (2S,4R)- 4- azidometil- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico (descrito en el Esquema B15). MS (LC- MS): 505/507 [M+H]+; t_R (f) Condiciones de HPLC: 1,47 min; 19F RMN (100 MHz, DMSO- d_6) δ (ppm):- 121,- 150.

Ejemplo 410: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- fluoro- 4- formilaminometil- pirrolidina- 1,2- dicarboxílico



El compuesto del título se obtuvo a partir del **Ejemplo 409**2- (3- cloro- 2- fluoro- bencilamida) de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico como formilación producida durante la concentración de las fracciones HPLC purificadas del E**jemplo 409**a partir de la HPLC preparativa que contiene 1% de HCOOH. MS (LC- MS): 531 [M- H]- , 533 [M+H]+; t_R(condiciones de HPLC f): 0,56 min; 19F RMN (100 MHz, DMSO- d_6) δ (ppm):- 121,- 150.

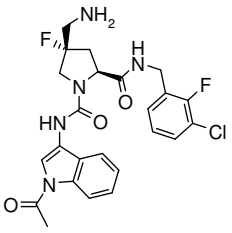
Ejemplo 411: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2,6- difluoro- bencilamida) del ácido (2S,4S)- 4- aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico



A una solución de 2- (3- cloro- 2,6- difluoro- bencilamida) de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- azidometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico (100 mg, 0,182 mmol) (preparado de acuerdo con el esquema D5 usando ester terc- butilo del ácido (2S,4R)- 4- azidometil- 2- (3- cloro- 2,6- difluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico preparado de forma análoga a la descrita en el Esquema B15) en THF (5 ml) y agua (6,56 µl) en atmósfera de N_2a temperatura ambiente se añadió 1M PMe3 en THF (0,219 ml, 0,219 mmol). La mezcla de reacción se agitó durante 16 h, después se inactivó con agua y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudose purificó mediante HPLC preparativa (Waters SunFire C18- ODB, 5 µm, 19x50 mm, 5% de CH_3CN/H_2O 2,5 min, 5- 100% CH_3CN/H_2O en 10 min, CH_3CN/H_2O que contiene 0,1% de HCOOH, flujo: 20 ml/min) para proporcionar después de la liofilización de las fracciones purificadas el compuesto del

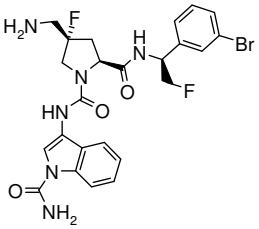
título (sal de ácido fórmico). MS (UPLC- MS): 523/525 [M+H]+, 521/523 [M- H]- , tr (condiciones de HPLC f): 1,42 min; 19F RMN (100 MHz, DMSO- d_6) δ (ppm):- 115 (2F),- 150.

Ejemplo 412: 1- [(1- acetil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico



El compuesto del título se preparó de manera análoga a la descrita para el Ejemplo **411** usando 2- (3- cloro- 2- fluoro- bencilamida) de 1- [(1- acetil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- azidometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico preparado de acuerdo con el esquema D5 a partir de ester terc- butilo del ácido (2S,4R)- 4- azidometil- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico (descrito en el Esquema B15) y 1- (3- isocianato- indol- 1- il)- etanona (descrito en el Esquema A1). MS (UPLC- MS): 504/506 [M+H]+, 502/504 [M- H]- ; t_R (condiciones de HPLC f): 1,62 min; 19F RMN (100 MHz, DMSO- d_6) δ (ppm):- 121,- 153.

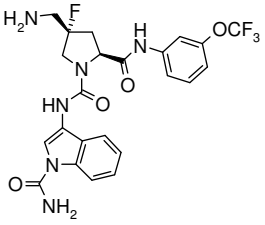
Ejemplo 413: 2- {[(S)- 1- (3- bromo- fenil)- 2- fluoro- etil]- amida}- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] de del ácido (2S,4S)- 4- aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico



El compuesto del título se preparó de manera análoga a la descrita para el Ejemplo **411** a partir de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] de 2- {[(S)- 1- (3- bromo- fenil)- 2- fluoro- etil]- amida}del ácido (2S,4R)- 4- azidometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico (82 mg, 0,115 mmol) (preparado de acuerdo con el esquema D5 etapa C utilizando ester terc- butilo del ácido (2S,4R)- 4- azidometil- 2- [(S)- 1- (3- bromo- fenil)- 2- fluoro- etilcarbamoil]- 4- fluoro- pirrolidina- 1- carboxílicopreparado como se describe en el Esquema B16). La

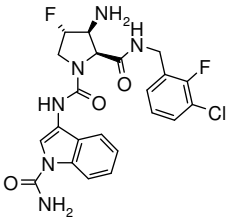
purificación en HPLC preparativa (Waters SunFire C18- ODB, 5 µm, 19x50 mm, 5% de CH_3CN/H_2O 2,5 min, 5- 100% CH_3CN/H_2O en 10 min, CH_3CN/H_2O que contiene 0,1% de HCOOH, flujo: 20 ml/min) para proporcionar después de la liofilización de las fracciones purificadas el compuesto del título (sal de ácido fórmico). MS (UPLC- MS): 561/563 [M+H]+, 561/563 [M- H]- ; t_R (condiciones de HPLC f): 1,42 min.

Ejemplo 414: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico



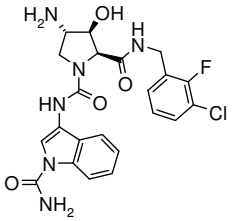
El compuesto del título se preparó de manera análoga a la descrita para el Ejemplo **411** a partir de 2- [(3- trifluorometoxi- fenil)- amida] de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- azidometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico (43 mg, 0,078 mmol) (preparado de acuerdo con el esquema D5 Paso C, usando ester terc- butilo del ácido (2S,4R)- 4- azidometil- 4- fluoro- 2- (3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 1- carboxílico preparado como se describe Esquema B16 usando 2- trifluorometoxi- fenilamina en la etapa G en lugar de 3(S)- 1- (3- bromo- fenil)- 2- fluoro- etilamina). La purificación por HPLC preparativa (Waters SunFire C18- ODB, 5 µm, 19x50 mm, 5% de CH_3CN/H_2O 2,5 min, 5- 100% CH_3CN/H_2O en 10 min, CH_3CN/H_2O que contiene 0,1% de HCOOH, flujo: 20 ml/min) proporcionó después de la liofilización de las fracciones purificadas el compuesto del título (sal de ácido fórmico). MS (UPLC- MS): 523 [M+H]+, 521 [M- H]- , t_R(condiciones de HPLC f): 1,59 min; 19F RMN (100 MHz, DMSO- d_6) δ (ppm):- 57 (3F),- 150.

Ejemplo 415: 1- [(1- acetil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3S,4S)- 3- amino- 4- fluoro- pirrolidina- 1,2- dicarboxílico



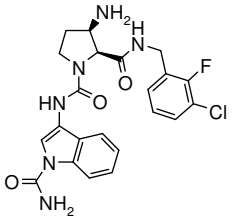
El compuesto del título se preparó según el Esquema D5 a partir de ester terc- butilo del ácido (2S,3S,4S)- 3- azido- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico (descrito en el esquema B19) seguido de la reducción de la azida como se describe para la preparación del **Ejemplo 411**. TLC, R_f (CH_2Cl_2/MeOH 95/5) = 0,2; MS (LC- MS): 491 [M+H]+, 489 [M- H]- ; t_R (condiciones de HPLC f): 1,55 min.

Ejemplo 416: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R, 4S)- 4- amino- 3- hidroxi- pirrolidina- 1,2- dicarboxílico



El compuesto del título se preparó según el Esquema D5 a partir de (2S,3S,4S)- 4- azido- 2- éster (3- cloro- 2- fluoro- bencilcarbamoil)- 3- hidroxi- pirrolidina- 1- carboxilato de terc- butilo (descrito en el esquema B19) seguido de la reducción de la azida como se describe para la preparación del **Ejemplo 411**. TLC, R_f (CH2Cl_2/MeOH 95/5) = 0,2; MS (LC- MS): 489 [M+H]+, 487 [M- H]- ; t_R (condiciones de HPLC f): 1,34 min.

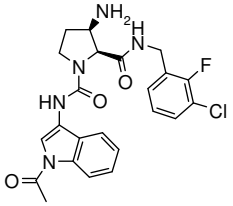
Ejemplo 417: 2- (3- cloro- 2- fluoro- bencilamida) de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,3R)- 3- amino- pirrolidina- 1,2- dicarboxílico



Una solución de 2- (3- cloro- 2- fluoro- bencilamida) de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,3R)- 3- azido- pirrolidina- 1,2- dicarboxílico (preparado de acuerdo con el esquema D5 etapa C utilizando trifluoroacetato de 3- cloro- 2- fluoro- bencilamida del ácido (2S,3R)- 3- azido- pirrolidina- 2- carboxílico (preparado como se describe en la Parte B) (70 mg, 0,140 mmol) en MeOH (10 ml) se hidrogenó a temperatura ambiente (1 atm) sobre Pd/C 10% (14 mg, 20% w/w) durante 4 h. La mezcla de reacción se filtró a través de un filtro de 0,45 µm y se concentró bajo presión reducida. El producto crudose purificó mediante HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 30x100 mm; flujo: 40 ml/min; eluyente: 5- 60% de CH_3CN/H_2O durante 20 min, CH_3CN al 60% para 2 min, CH_3CN y H_2O que contiene 0,1%

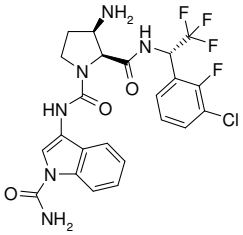
de TFA) para proporcionar el compuesto del título como un sólido blanco MS (LC/MS): 473 [M+H]+; t_R (condiciones de HPLC b): 2.75 min.

Ejemplo 418: 2- (3- cloro- 2- fluoro- bencilamida) de 1- [(1- acetil- 1H- indol- 3- il)- amida] del ácido (2S,3R)- 3- amino- pirrolidina- 1,2- dicarboxílico



Preparado como se describe para el **Ejemplo 417** a partir de 2- (3- cloro- 2- fluoro- bencilamida) de 1- [(1- acetil- 1H- indol- 3- il)- amida] del ácido (2S,3R)- 3- azido- pirrolidina- 1,2- dicarboxílico preparado de acuerdo con el Esquema D5 mediante el uso de trifluoroacetato de 3- cloro- 2- fluoro- bencilamida de ácido (2S,3R)- 3- azido- pirrolidina- 2- carboxílico (preparado como se describe en la Parte B) y 1- (3- isocianato- indol- 1- il)- etanona (preparada como se describe en el Esquema A1). Sólido blanco. MS (LC/MS): 473 [M+H]+; t_R (condiciones de HPLC b): 2,91 min.

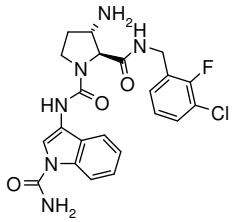
Ejemplo 419: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2,2,2- trifluoro- etil]- amida} del ácido (2S,3R)- 3- amino- pirrolidina- 1,2- dicarboxílico



El compuesto del título se preparó como se describe para el **Ejemplo 417** a partir de 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2,2,2- trifluor- etil]- amida} del ácido (2S,3R)- 3- azido- pirrolidina- 1,2- dicarboxílico (preparado de acuerdo con el Esquema D5 (paso C) a partir de [(S)- 1- (3- cloro- 2- fluoro- fenil)- 2,2,2- trifluoro- etil]- amida del ácido (2S,3R)- 3- azido- pirrolidina- 2- carboxílico (preparado de una manera similar a la descrita en la parte B de trifluoroacetato de 3- cloro- 2- fluoro- bencilamida del ácido (2S,3R)- 3- azido- pirrolidina- 2- carboxílico partiendo de (S)- 1- (3- cloro- 2-

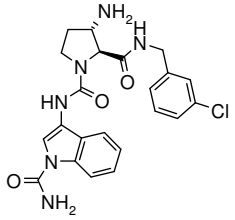
fluorofenil)- 2,2,2- trifluoroetanamina. Sólido blanco. MS (LC/MS): 541,0 [M+H]+; t_R (condiciones de HPLC c): 4,07 min.

Ejemplo 420: 1- [(1- carbamoil- 1H- indol- 3- il)- amida- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3S)- 3- amino- pirrolidina- 1,2- dicarboxílico



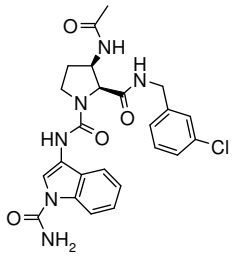
Preparado como se describe para el **Ejemplo 417** a partir de 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3S)- 3- azido- pirrolidina- 1,2- dicarboxílico (preparado de acuerdo con el esquema D5 etapa C mediante el uso de 3- cloro- 2- fluoro- bencilamida del ácido (2S,3S)- 3- azido- pirrolidina- 2- carboxílico (preparado como se describe en la Parte B). Sólido blanco MS. (LC/MS): 473 [M+H]+; t_R (condiciones de HPLC b): 2,91 min.

Ejemplo 421: 1- [(1- carbamoil- 1H- indol- 3- il)]- 2- (3- cloro- bencilamida) del ácido (2S,3S)- 3- amino- pirrolidina- 1,2- dicarboxílico



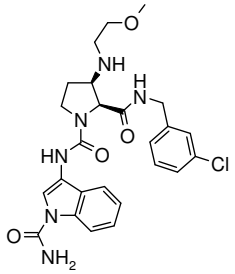
Preparado como se describe para el **Ejemplo 417** a partir de 2- (3- cloro- bencilamida)1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,3S)- 3- azido- pirrolidina- 1,2- dicarboxílico (preparado de acuerdo con el esquema D5 etapa C mediante el uso de 3- cloro- bencilamida del ácido (2S,3S)- 3- azido- pirrolidina- 2- carboxílico (preparado usando protocolos similares a los descritos en la Parte B para3- cloro- 2- fluoro- bencilamida del ácido (2S,3S)- 3- azido- pirrolidina- 2- carboxílico. Sólido de color blanco. MS (LC/MS): 455 [M+H]+; t_R (condiciones de HPLC b): 2.79 min.

Ejemplo 422: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R)- 3- acetilamino- pirrolidina- 1,2- dicarboxílico



A una solución enfriada con hielo de 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R)- 3- amino- pirrolidina- 1,2- dicarboxílico Eje**mplo 417**(27,0 mg, 0,057 mmol) en CH_2Cl_2 seco (5 ml) y THF seco (2,5 ml) se añadieron trietilamina (0,024 ml, 0,171 mmol) y anhídrido acético (0,108 ml, 1,14 mmol) bajo una atmósfera de argón. La mezcla de reacción se agitó a temperatura ambiente durante 16 h. Los volátiles se eliminaron a presión reducida, y el residuo se purificó mediante HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 19x50 mm, eluyente: 5- 100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN y H_2O que contiene 0.1% de TFA, flujo: 20 ml/min) para proporcionar después de la liofilización, el compuesto del título como un sólido blanco. MS (LC/MS): 515,0 [M+H]+;t_R (condiciones de HPLC k): 2,96 min.

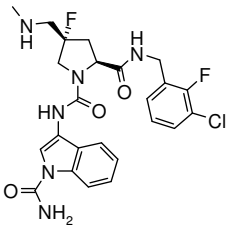
Ejemplo 423: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R)- 3- (2- metoxi- etilamino)- pirrolidina- 1,2- dicarboxílico



A una solución de 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R)- 3- amino- pirrolidina- 1,2- dicarboxílico Eje**mplo 417** (36 mg, 0,076 mmol) en DMF seca (1,5 ml) se añadieron trietilamina (0,032 ml, 0,228 mmol) y 1- bromo- 2- metoxietano (0,014 ml, 0,144 mmol) bajo una atmósfera de argón, seguido de agitación a temperatura ambiente durante 60 h. UPLC- MS mostró la formación de producto y la presencia de material de partida sin reaccionar 2- (3- cloro- 2- fluoro- bencilamida)1- [(1- carbamoil- 1H- indol- 3- il)] del ácido (2S,3R)- 3- amino- pirrolidina- 1,2- dicarboxílico. Un exceso de 1- bromo- 2- metoxietano (10 eq) y trietilamina (10 eq) se añadieron a la mezcla de reacción, y se continuó la agitación a temperatura ambiente durante 18 h, y después a 50 º C

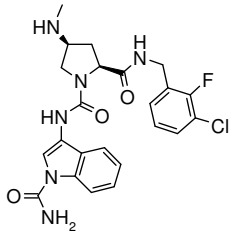
durante 24 h. El material crudo se purificó directamente mediante HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 19x50 mm, eluyente: 5- 100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN y H_2O que contiene 0,1% de TFA, flujo: 20 ml/min) para proporcionar, después de la liofilización, el compuesto del título como un sólido. MS (LC/MS): 531 [M+H]+; t_R (condiciones de HPLC k): 2,97 min.

Ejemplo 424: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- fluoro- 4- metilaminometil- pirrolidina- 1,2- dicarboxílico



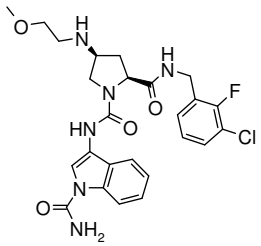
Ester 2,2,2- tricloro- etilo del ácido [(3R,5S)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 5- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- fluoro- pirrolidin- 3- ilmetil]- metil-carbámico (preparado de acuerdo con el esquema D5 Pasos B y C utilizando éster 2- bencilo del ácido (2S,4S)- 4- fluoro- 4- {[metil- (2,2,2- tricloro- etoxicarbonil)- amino]- metil}- pirrolidina- 1,2- dicarboxílico - ester 1- terc- butilo (preparado como se describe en el Esquema B17) (56 mg, 0,08 mmol) se disolvió en MeOH (5 ml) en atmósfera de N_2a temperatura ambiente. El polvo de cinc se añadió (0,24 mg, 3,7 mmol), el pH se ajustó a pH 5 ~ 6 mediante la adición de un poco de ácido acético. La mezcla de reacción se agitó durante 1 h, después se filtró y se concentró. El residuo crudose purificó mediante HPLC preparativa (Waters SunFire C18- ODB, 5 µm, 19x50 mm, 5% de CH_3CN/H_2O 2,5 min, 5- 100% CH_3CN/H_2O en 10 min, CH_3CN/H_2O que contiene 0,1% de HCOOH, flujo: 20 ml/min) para proporcionar, después de liofilización de las fracciones purificadas el compuesto del título. MS (UPLC- MS): 519 [M+H]+; t_R(condiciones de HPLC f): 1,32 min; 19F RMN (100 MHz, DMSO- d_6) δ (ppm):- 120,- 150.

Ejemplo 425: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- metilamino- pirrolidina- 1,2- dicarboxílico



El compuesto del título se preparó según el Esquema D5 pasos B y C de ester terc-butilo del ácido (2S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- [metil- (2,2,2- tricloro-etoxicarbonil)- amino]- pirrolidina- 1- carboxílico (37 mg, 0,05 mmol) (preparado como se describe en el Esquema B6) seguido por la desprotección del grupo protector Troc como se describe para el **Ejemplo 424**. La purificación por HPLC preparativa (Waters SunFire C18-ODB, 5 µm, 19x50 mm, 5% de CH_3CN/H_2O 2,5 min, 5- 100% CH_3CN/H_2O en 10 min, CH_3CN/H_2O que contiene 0,1% de HCOOH, flujo: 20 ml/min) dio después de la liofilización de las fracciones purificadas el compuesto del título (sal de ácido fórmico). MS (UPLC/MS): 489 [M+H]+; t_R(condiciones de HPLC f): 1,48 min; 19F RMN (100 MHz, DMSO- d_6) δ (ppm):- 120.

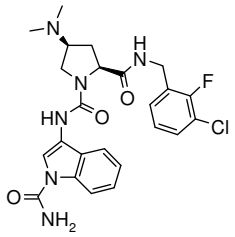
Ejemplo 426: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S[§])- 4- (2- metoxi- etilamino)- pirrolidina- 1,2- dicarboxílico



A una solución de 2- metoxietilamina (219 µl, 2,54 mmol) en MeOH (265 µl) se añadió HCl 1,25 N en MeOH (339 µl, 0,424 mmol) seguido de 2- (3- cloro- 2- fluoro- bencilamida) de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (S)- 4- oxo- pirrolidina- 1,2- dicarboxílico (100 mg, 0,212 mmol) (preparado como se describe en el esquema D5 a partir de (S)- 4- oxo-pirrolidina- 1,2- dicarboxílico éster 1- terc- butilo) y NaBH3CN (16 mg, 0,254 mmol) y la mezcla de reacción se agitó a 23 °C durante 1 semana. 2- metoxietilamina (219 µl, 2,54 mmol) y $NaBH_3CN$ (16 mg, 0,254 mmol) y se añadieron de nuevo y la mezcla de reacción se agitó a 23 °C durante 2 días. La mezcla cruda se diluyó en EtOAc y se lavó con una solución de $NaHCO_3$ acuoso saturado. Las capas se separaron y la fase acuosa se volvió a extraer con EtOAc. Las capas orgánicas combinadas se secaron, se filtraron y se concentraron a sequedad. El residuo crudose purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice

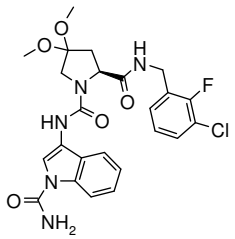
(CH_2Cl_2/MeOH gradiente de 100:0 a 9:1) seguido de HPLC preparativa (Waters SunFire C18ODB, 5 µm, 30x100, eluyente: 5% CH_3CN/95% de H_2O a 100 % de CH_3CN en 20 min, CH_3CN y H_2O que contiene 0.1% de TFA, flujo de 40 ml/min) para proporcionar, después de la liofilización de las fracciones purificadas, el material deseado.MS: 531,1 [M+H]+; t_R (condiciones de HPLC b): 3,1 min. La estereoquímica absoluta se ha asignado provisionalmente en base a los resultados de la prueba para el compuesto final **Ejemplo 426** en el ensayo biológico.

Ejemplo 427: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- dimetilamino- pirrolidina- 1,2- dicarboxílico



A una solución de 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico Eje**mplo 26** (20 mg, 0,042 mmol) en MeOH (140 µl) se añadió formaldehído (58,3 µl, 0,423 mmol), $NaBH_3CN$ (8,77 mg, 0,140 mmol) y AcOH (4,84 µl, 0,085 mmoles), y la mezcla de reacción se agitó a 23 °C bajo nitrógeno durante 16 h. Después de la terminación, la mezcla de reacción crudase purificó mediante HPLC preparativa (Waters SunFire C18ODB, 5 µm, 19x50, eluyente: 5% CH_3CN/95% de H_2O a 100% CH_3CN en 17 min, CH_3CN y H_2O que contiene 0.1% de TFA, flujo 20 ml/min) para proporcionar, después de liofilización de las fracciones purificadas el material deseado. MS (LC/MS): 501,1 [M+H]+; t_R (condiciones de HPLC b): 2,75 min.

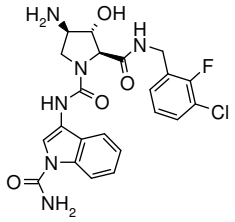
Ejemplo 428: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- 4,4- dimetoxi- pirrolidina- 1,2- dicarboxílico



A una solución de hidrocloruro de metilamina (14,3 mg, 0,212 mmol) en MeOH (300 µl) se añadió HCl 1,25 N en MeOH (400 µl, 0,50 mmoles), 1- [(1- carbamoil- 1H- indol- 3- il)-

amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- 4- oxo- pirrolidina- 1,2- dicarboxílico (100 mg, 0,212 mmol) (preparado como se describe en el esquema D5 a partir de éster 1- terc- butílicodel ácido (S)- 4- oxo- pirrolidina- 1,2- dicarboxílico) y $NaBH_3CN$ (8 mg, 0,127 mmol) y la mezcla de reacción se agitó a 23 °C durante 16 h. La mezcla de reacción cruda se diluyó con EtOAc y se lavó con solución acuosa saturada de $NaHCO_3$. La capa orgánica se secó, se filtró y se concentró a sequedad, se purificó finalmente mediante HPLC preparativa (Waters SunFire C18ODB, 5 µm, 19x50, eluyente: 20% CH_3CN/80% de H_2O a 100% CH_3CN en 12,5 min, CH_3CN y H_2O que contiene 0,1% HCOOH, flujo de 20 ml/min) para proporcionar, después de liofilización de las fracciones purificadas, el material deseado. MS: 518 [M+H]+; t_R (condiciones de HPLC b): 3,79 min.

Ejemplo 429: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3S,4R)- 4- amino- 3- hidroxi- pirrolidina- 1,2- dicarboxílico

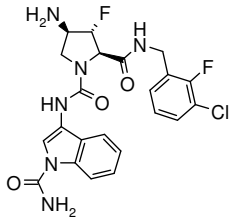


El compuesto del título se preparó como se describe para el **Ejemplo 411** utilizando 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R,4R)- 4- azido- 3- hidroxi- pirrolidina- 1,2- dicarboxílico. TLC, R_f (EtOAc) = 0,02; MS (LC- MS): 489 [M+H]+, 487 [M- H]- ; t_R (condiciones HPLC g): 1,96 min.

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R,4R)- 4- azido- 3- hidroxi- pirrolidina- 1,2- dicarboxílico

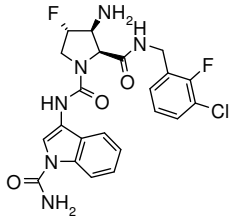
El compuesto del título se preparó según el Esquema D5 (pasos B y C) a partir de una mezcla de ester terc- butilo del ácido (2S,3R,4R)- 4- azido- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- hidroxi- pirrolidina- 1- carboxílico y 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3S,4S)- 3- azido- 4- hidroxi- pirrolidina- 1,2- dicarboxílico en proporción 6:4(descrito en el esquema B19). Los regioisómeros se separaron mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano 100% a EtOAc al 100%) para proporcionar el compuesto del título. TLC, R_f (EtOAc) = 0,23; MS (LC- MS): 515/517 [M+H]+, 513 [M- H]- ; t_R (condiciones de HPLC f): 1,81 min.

Ejemplo 430: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2R,3S,4R)- 4- amino- 3- fluoro- pirrolidina- 1,2- dicarboxílico



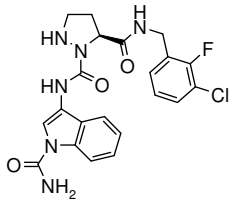
El compuesto del título se preparó según el Esquema D5 (pasos B y C) a partir de ester terc- butilo del ácido (2R, 3R,4R)- 4- azido- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- fluoro- pirrolidina- 1- carboxílico (descrito en el esquema B19) seguido por la reducción de la azida como se describe para la preparación del **Ejemplo 411**. TLC, R_f (EtOAc) = 0,12; MS (LC- MS): 491 [M+H]+, 489 [M- H]- ; t_R (condiciones de HPLC f): 1,45 min.

Ejemplo 431: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluorobencilamida) del ácido (2S,3S,4S)- 3- amino- 4- fluoro- pirrolidina- 1,2- dicarboxílico



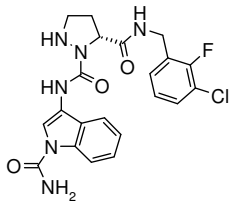
El compuesto del título se preparó según el Esquema D5 (pasos B y C) a partir de ester terc- butilo del ácido (2S,3S,4S)- 3- azido- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico (descrito en el esquema B19) seguido por la reducción de la azida como se describe para la preparación del **Ejemplo 411**. (Estereoquímica absoluta asignada provisionalmente mediante RMN).TLC, R_f (CH_2Cl_2/MeOH 95/5) = 0,2; MS (LC- MS): 491 [M+H]+, 489 [M- H]- ; t_R (condiciones de HPLC f): 1,46 min.

Ejemplo 432: Amida del ácido3- {2- [(S)- 5- (3- cloro- 2- fluoro- bencilcarbamoil)- pirazolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico



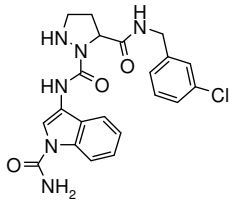
A una soluciónde ester terc- butilo del ácido (S)- 2- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- pirazolidina- 1- carboxílico (20 mg, 0,036 mmol) en CH_2Cl_2 (200 µl), TFA (27,6 µl, 0,358 mmol), y la mezcla de reacción se agitó a 23 °C durante 20 h. Los disolventes se concentraron y el residuo crudose purificó mediante HPLC preparativa (Waters SunFire C18ODB, 5 µm, 19x50, eluyente: 20% CH_3CN/80% de H_2O a 100% CH_3CN en 12,5 min, CH_3CN y H_2O que contiene ambos 0,1% de HCOOH, flujo de 20 ml/min) para proporcionar el material deseado después de la liofilización de las fracciones purificadas. MS (LC- MS): 459 [M+H]+; t_R (condiciones de HPLC b): 3,72 min. ester terc- butilo del ácido (S)- 2- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- pirazolidina- 1- carboxílicose preparó tal como se describe en el Esquema D5 etapa C utilizando ester terc- butilo del ácido (S)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 1- carboxílico- pirazolidina (preparado como se describe en el Esquema B5).

Ejemplo 433: Amida del ácido 3- {2- [(R)- 5- (3- cloro- 2- fluoro- bencilcarbamoil)- pirazolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico



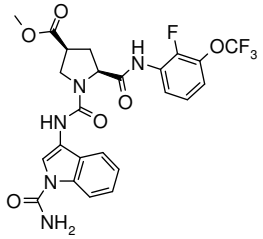
El compuesto del título se preparó a partir de ester terc- butilo del ácido (R)- 2- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- pirazolidina- 1- carboxílico de acuerdo con el procedimiento descrito para la preparación del **Ejemplo 432** usando 10 equivalentes de TFA para la desprotección Boc. MS: 459 [M+H]+; t_R (condiciones de HPLC b): 3,73 min. Ester terc- butilo del ácido (R)- 2- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- pirazolidina- 1- carboxílico se preparó tal como se describe en el Esquema D5 etapa C utilizando ester terc- butilo del ácido (R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- pirazolidin- 1- carboxílico (preparado como se describe en el Esquema B5).

Ejemplo 434: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 5- (3- cloro- bencilamida) del ácido pirazolidin- 1,5- dicarboxílico



El compuesto del título se preparó a partir de ester terc- butilo del ácido 2- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 3- (3- cloro- bencilcarbamoil)- pirazolidin- 1- carboxílico de acuerdo con el procedimiento descrito para la preparación del **Ejemplo 432**. MS (LC/MS) 441,1 [M+H]+; t_R (condiciones de HPLC b): 3,67 min. Ester terc- butilo del ácido 2- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 3- (3- cloro- bencilcarbamoil)- pirazolidin- 1- carboxílico se preparó tal como se describe en el Esquema D5 etapa C utilizando ester terc- butilo del ácido 3- (3- cloro- bencilcarbamoil)- pirazolidin- 1- carboxílico (preparado usando protocolos similares a los descritos en el Esquema B5).

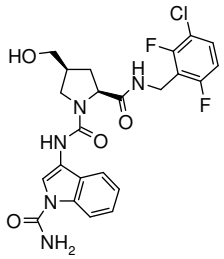
Ejemplo 435: Ester metilo del ácido (3S,5S)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- 5- (2- fluoro- 3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 3- carboxílico



Se añadió clorotrimetilsilano (537 µl, 4,24 mmol) gota a gota paraa secar MeOH (700 µl) a 0 º C, seguido de una solución de 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(2- fluoro- 3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- ciano- pirrolidina- 1,2- dicarboxílico del **Ejemplo 188** (110 mg, 0,212 mmol) en CH_2Cl_2 seco (600 µl). La mezcla de reacción se agitó a temperatura ambiente bajoN_2 durante la noche. A continuación, se enfrió a 0 °C se añadieron, agua y CH_2Cl_2. Las capas se separaron y la fase acuosa se extrajo de nuevo con CH_2Cl_2. Los extractos orgánicos combinados se neutralizaron con una solución acuosa saturada de $NaHCO_3$ y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo crudose purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:1 a 1:3 c- hexano/EtOAc a EtOAc) para proporcionar el compuesto deseado.

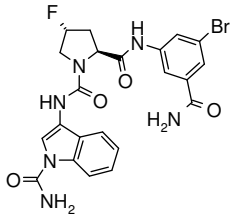
R_f, TLC (EtOAc) = 0,6; MS (LC- MS): 552,1 [M+H]+, 574,2 [M+Na]+, 550,2 [M- H]- ; t_R (condiciones de HPLC f): 1,98 min.

Ejemplo 436: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2, 6- difluoro- bencilamida) del ácido (2S,4S)- 4- hidroximetil- pirrolidina- 1,2- dicarboxílico



A una solución de ester metilo del ácido (3S,5S)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 5- (3- cloro- 2,6- difluoro- bencilcarbamoil)- pirrolidina- 3- carboxílico Eje**mplo 353**(88 mg, 0,165 mmol) en THF (2 ml) se agregó borohidruro de litio 2 M en THF (0,18 ml, 0,36 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 2 h bajo atmósfera de N_2. Después de la terminación, la mezcla se inactivó con salmuera y se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudose purificó mediante HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 19x50 mm, eluyente: 20% a 100% CH_3CN en H_2O en 15 min, CH_3CN y H_2O que contiene 0,1% de HCOOH, flujo: 20 ml/min)para proporcionar el material deseadodespués de la liofilización de las fracciones purificadas. R_f, TLC (CH_2Cl_2/MeOH 90:10) = 0,65; MS (LC-MS): 506,2 [M+H]+, 1011,4 [2M+H]+, 504,2 [M- H]- ; t_R (condiciones de HPLC f): 1,62 min.

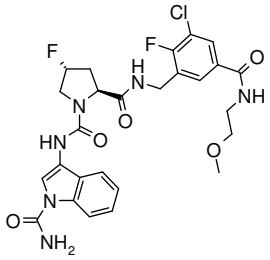
Ejemplo 437: 2- [(3- bromo- 5- carbamoil- fenil)- amida]- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico



A una solución de ácido 3- bromo- 5- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- benzóico Eje**mplo 159** (100 mg, 0,188 mmol), cloruro de amonio (12 mg, 0,225 mmol) y HBTU (107 mg, 0,282 mmol) en DMF (3 ml) se añadió DIPEA (64 µl, 0,374 mmol) y la solución resultante se agitó a temperatura ambiente en atmósfera de nitrógeno durante 7 h. La mezcla de reacción se vertió en agua y se

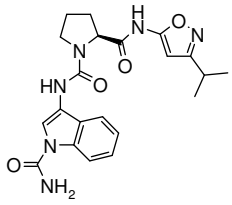
extrajo dos veces con EtOAc. Las capas orgánicas combinadas se lavaron con agua (x2), se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudose purificó mediante HPLC preparativa (C18- ODB, 5 µm, 19x50 mm, aguas, eluyente: CH_3CN/H_2O+0,1% HCOOH de flujo: 20 ml/min, método estándar de 20%) para proporcionar el material deseado después de la liofilización de las fracciones purificadas. TLC, R_f (EtOAc) = 0,3; MS (LC- MS): 531/533 [M+H]+, 553/555 [M+Na]+, 529/531 [M- H]- ; t_R (condiciones de HPLC a): 2,79 min.

Ejemplo 438: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [3- cloro- 2- fluoro- 5- (2- metoxi- etilcarbamoil)- bencilamida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico



A una mezcla de ácido 3- ({[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- metil)- 5- cloro- 4- fluoro- benzóico Eje**mplo 144** (30 mg, 0,06 mmol), 2- metoxietilamina (5 mg, 0,07 mmol) y HATU (33 mg, 0,09 mmol) en DMF (1 ml) se añadió DIPEA (0,04 ml, 0,23 mmol) y la solución resultante se agitó a temperatura ambiente en atmósfera de nitrógeno. El producto crudo se purificó sin tratamiento acuoso mediante HPLC- RP preparativa (Waters Sunfire, C18- ODB, 5 µm, 30x100 mm, 5- 100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN y H_2O que contiene 0,1 % de TFA, flujo: 40 ml/min) para proporcionar el compuesto del título. MS (LC- MS): 577,0 [M]+; t_R (condiciones de HPLC c): 3,95 min.

Ejemplo 439: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- isopropil- isoxazol- 5- il)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico



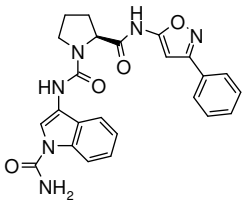
El compuesto del título se obtuvo como se describe en los pasos B y C Esquema D5 usando ester terc- butilo del ácido (S)- 2- (3- isopropil- isoxazol- 5- ilcarbamoil)- pirrolidina- 1-

carboxílico. MS (LC- MS): 425,2 [M+H]+, 447,1 [M+Na]+, 871,3 [2M+Na]+, 423,1 [M- H]- ; t_R (condiciones de HPLC a): 3,06 min.

Ester terc- butilo del ácido (S)- 2- (3- isopropil- isoxazol- 5- ilcarbamoil)- pirrolidina- 1- carboxílico

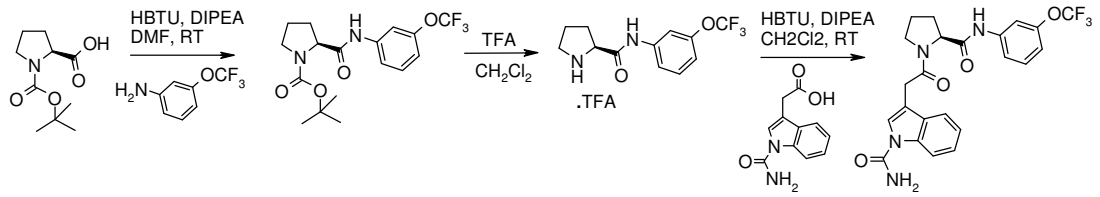
A una mezcla de Boc- L- prolina (150 mg, 0,697 mmol), 3- isopropilisoxazol- 5- amina (88 mg, 0,697 mmol) y HBTU (264 mg, 0,697 mmol) en DMF (7 ml) se añadió 2- terc- butilimino- 2- dietilamino- 1,3- dimetilperhidro- 1,3,2- diazafosforina (BEMP) (201 µl, 0,697 mmol) y la mezcla de reacción se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 48 h. La mezcla se vertió en HCl 1N y se extrajo tres veces con EtOAc. Las capas orgánicas combinadas se lavaron con una solución acuosa saturada de $NaHCO_3$, con agua, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo crudose purificó mediante cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano a c- hexano/EtOAc 7- 3) para proporcionar el compuesto del título. TLC, R_f (c- hexano/EtOAc 1:1) = 0,6; MS (LC- MS): 324,1 [M+H]+, 346,1 [M+Na]+, 669,2 [2M+Na]+, 322,1 [M- H]- ; t_R(condiciones de HPLC a): 3,42 min.

Ejemplo 440: 1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- fenil- isoxazol- 5- il)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico



El compuesto del título se preparó en 3 etapas como se describe para la preparación del **Ejemplo 439**. MS (LC/MS): 459,1 [M+H]+, 481,1 [M+Na]+, 918,3 [2M+H]+, 940,2 [2M+Na]+, 457,1 [M- H]- ; t_R (condiciones de HPLC a): 3,29 min.

Esquema D6: Protocolo general descrito para la preparación del Ejemplo 441: amida del ácido 3- {2- [(S)- 2- (3- trifluorometoxi- fenilcarbamoil)- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico,



A. Ester terc- butilo del ácido (S)- 2- (3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 1- carboxílico.

El compuesto del título se preparó de acuerdo con los procedimientos generales descritos en el Esquema D5 Paso A. TLC, R_f (c- hexano/EtOAc 1:1) = 0,57; MS (LC/MS): 397,1 [M+Na]+, 275,2 [MH- Boc]+, 373,3 [M- H]- ; t_R (condiciones de HPLC a) 3,81 min.

También se puede utilizar diclorometano en lugar de DMF.

B. (3- trifluorometoxi- fenil)- amida del ácido (S)- pirrolidina- 2- carboxílico

El compuesto del título en forma de una sal de TFA se preparó de acuerdo con los procedimientos generales descritos en el Esquema D5 Paso B. MS (LC/MS): 275,2 [M+H]+, 273,3 [M- H]- ; t_R (condiciones de HPLC a) 2,47 min.

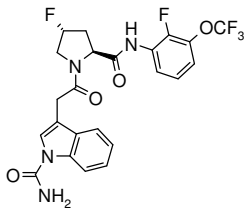
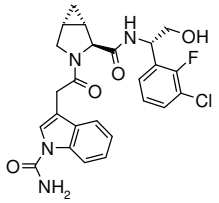
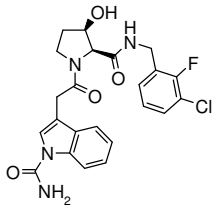
C. Ejemplo 441: Amida del ácido 3- {2- [(S)- 2- (3- trifluorometoxi- fenilcarbamoil)- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico

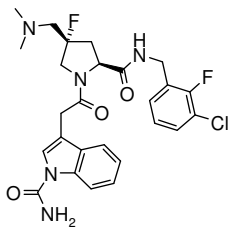
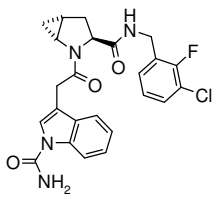
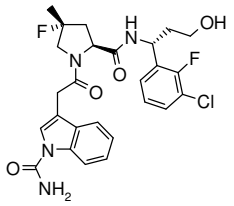
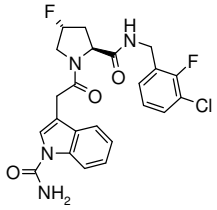
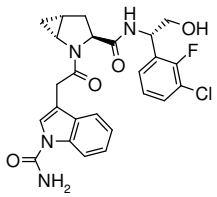
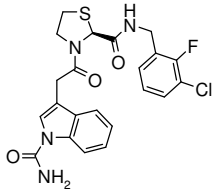
Se disolvió sal de TFA de (3- trifluorometoxi- fenil)- amida del ácido (S)- pirrolidina- 2- carboxílico (59,3 mg, 0,153 mmol, preparado como se describe en el Esquema D5 pasos A y B), ácido (1- carbamoil- 1H- indol- 3- il)- acético (40 mg, 0,183 mmol, preparado como se describe en el Esquema A8) y HBTU (86,9 mg, 0,229 mmoles) en CH_2Cl_2 (4 ml) bajo atmósfera de nitrógeno, se añadió DIPEA (52,3 µl, 0,306 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 5 h. Después de la terminación de la reacción acuosa se añadió HCl 1 N y EtOAc, las capas se separaron y la fase acuosa se extrajó de nuevo dos veces con EtOAc. Los extractos orgánicos combinados se lavaron con una solución acuosa saturada de $NaHCO_3$, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo crudose purificó mediante HPLC preparativa (Waters SunFire C18- ODB, 5 µm, 19x50 mm, 20% de CH_3CN/H_2O 2,5 min, 20- 100% CH_3CN/H_2O en 10 min, CH_3CN/H_2O que contiene 0,1% de HCOOH, flujo: 20 ml/min) para proporcionar el compuesto deseadodespués de la extracción de las fracciones puras. MS (LC/MS): 475 [M+H]+, 497 [M+Na]+; t_R (condiciones de HPLC a) 3,47 min.

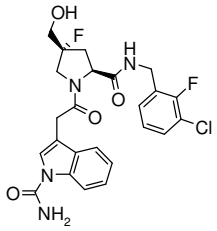
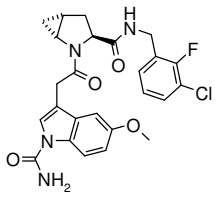
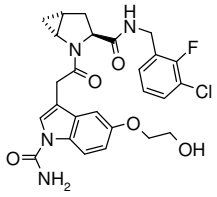
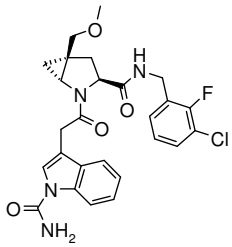
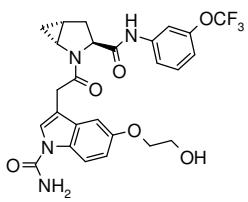
También se puede utilizar DMF en lugar de Diclorometano.

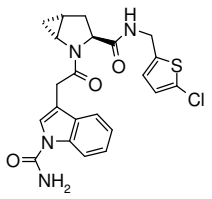
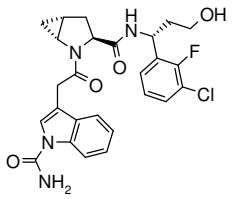
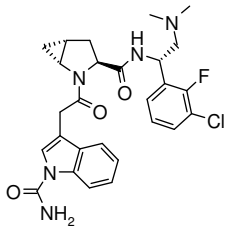
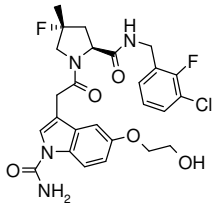
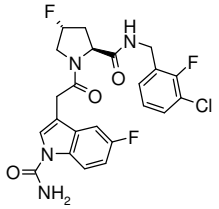
Los ejemplos siguientes se prepararon de acuerdo a los procedimientos generales descritos en el Esquema D6 para la preparación del **Ejemplo 441,** *a partir de precursores de síntesis disponibles en el mercado, si no se indica lo contrario (ver notas al final del cuadro 5):*

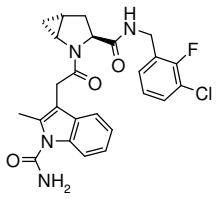
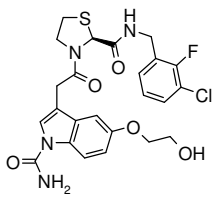
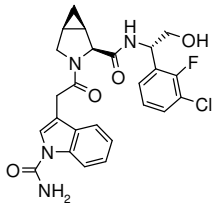
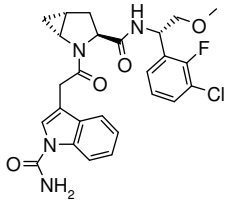
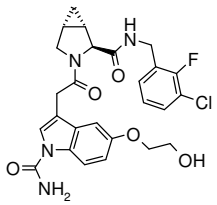
Tabla 5:

Ejemplo	Estructura	Nombre	Caracterización (Notas al final de la tabla), TLC, R_f (eluyente); MS (LC/MS); t_R (condiciones HPLC); 19F RMN (100 MHz, disolvente) δ (ppm)
442		Amida del ácido 3- {2- [(2S,4R)- 4- fluoro- 2- (2- fluoro- 3- trifluorometoxi- fenilcarbamoil)- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico	(2,3) 511 [M+H]+, 533 [M+Na]+; t_R (b): 3,88 min.
443		Amida del ácido3- (2- {(1S,2S,5R)- 2- [(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etilcarbamoil]- 3- azabiciclo[3.1.0]hex- 3- il}- 2- oxo- etil)- indol- 1- carboxílico	(5 [B9]) R_f (EtOAc) = 0,15;499.3/501.3 [M+H]+, 543.3/545.3 [M+HCOO]- ; t_R (a): 3,0 min.
444		Amida del ácido 3- {2- [(2S,3R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 3- hidroxi- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico	(2) 473 [M+H]+; t_R (b): 3,20 min.

445		Amida del ácido 3- {2- [(2S,4S)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- dimetilaminometil- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico	(5 [B15], 6) 532/534 [M+H]+; t_R (f): 1,53 min; 19F RMN (DMSO- d_6): - 120,- 149.
446		Amida del ácido 3- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- indol- 1- carboxílico	Sólido blanco. R_f (EtOAc/n- hexano 3:01) = 0,11; 469 [M+H]+; t_R (b): 3,94 min.
447		Amida del ácido 3- (2- {(2S,4R)- 2- [(R)- 1- (3- Cloro- 2- fluoro- fenil)- 3- hidroxi- propilcarbamoil]- 4- fluoro- 4- metil- pirrolidin- 1- il}- 2- oxo- etil)- indol- 1- carboxílico	(5 [B9]) Sólido blanco, R_f (CH_2Cl_2/MeOH 9:1) = 0,6; 519.3/521.3 [M+H]+, 563.3/565.3 [M+HCOO]- ; t_R (a): 3,1 min.
448		Amida del ácido 3- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico	475/477 [M+H]+; t_R (b): 3,76 min.
449		Amida del ácido 3- (2- {(1R,3S,5R)- 3- [(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil- carbamoil]- 2- aza- biciclo[3.1 0,0]hex- 2- il}- 2- oxo- etil)- indol- 1- carboxílico	(5 [B9]) 499,1 [M+H]+, 520.7/521.4 [M+Na]+, 543.2/545.2 [M+HCOO]- ; t_R (f): 1,79 min.
450		Amida del ácido 3- {2- [(S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- tiazolidin- 3- il]- 2- oxo- etil}- indol- 1-	475/477 [M+H]+; t_R (b): 3,95 min.

		carboxílico	
451		Amida del ácido 3- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- hidroximetil- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico	(5 [B12]). R_f (EtOAc) = 0,1; 505.1/507.2 [M+H]+, 527.0/529.2 [M+Na]+, 503/505 [M-H]- , 549.1/551 [M+HCOO]- ; t_R (a): 2,96 min.
452		Amida del ácido 3- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 5- metoxi- indol- 1- carboxílico	(1 [A4], 6) R_f (EtOAc) = 0,3; 499.1/501.1 [M+H]+, 543.1/545 [M+HCOO]- , 454/456 [M- CONH2]- ; t_R (a): 2,25 min.
453		Amida del ácido 3- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 5- (2- hidroxi- etoxi)- indol- 1- carboxílico	(1 [A9]) 529.2/531.1 [M+H]+, 551/553.2 [M+Na]+, 573.1/575 [M+HCOO]- , 484.1/486.1 [M-CONH2]- ; t_R (a): 1,64 min.
454		Amida del ácido 3- {2- [(1R,3S,5S)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 5- metoximetil- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- indol- 1- carboxílico	(4,5) Sólido blanco. R_f (EtOAc) = 0,25; 513.3/515.3 [M+H]+, 557.4/559.4 [M+HCOO]- ; t_R (a): 3,23 min.
455		Amida del ácido 5- (2- Hidroxi- etoxi)- 3- {2- oxo- 2- [(1R,3S,5R)- 3- (3- trifluorometoxi- fenilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- etil}-	(1 [A9]) 547,2 [M+H]+, 564,3 [M+NH4]+, 545,2 [M- H]- , 591,2 [M+HCOO]- ; t_R (f): 1,85 min.

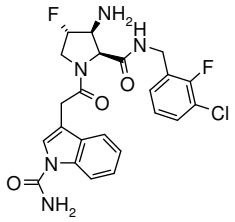
		indol- 1- carboxílico	
456		Amida del ácido 3- (2- {(1R,3S,5R)- 3- [(5- Cloro- tiofen- 2- ilmetil)- carbamoil]- 2- aza- biciclo[3.1.0]hex- 2- il}- 2- oxo- etil)- indol- 1- carboxílico	Rf (CH_2Cl_2/MeOH 9:1) = 0,43; 457 [M+H]+; t_R (b): 3,84 min.
457		Amida del ácido 3- (2- {(1R,3S,5R)- 3- [(R)- 1- (3- Cloro- 2- fluoro- fenil)- 3- hidroxi- propilcarbamoil]- 2- azabiciclo[3.1.0]hex- 2- il}- 2- oxo- etil)- indol- 1- carboxílico	(5 [B9]) R_f (EtOAc) = 0,2; 513,3 [M+H]+, 557.3/559.2 [M+HCOO]-; t_R (f): 1,86 min.
458		Amida del ácido 3- (2- {(1R,3S,5R)- 3- [(S)- 1- (3- Cloro- 2- fluoro- fenil)- 2- dimetilamino- etilcarbamoil]- 2- aza- biciclo[3.1.0]hex- 2- il}- 2- oxo- etil)- indol- 1- carboxílico	(3 [C4], 4) Sólido blanco.R_f (CH_2Cl_2/MeOH 9:1) = 0,45; 526.4/528.4 [M+H]+, 570.4/572.2 [M+HCOO]; t_R (a): 2,80 min.
459		Amida del ácido 3- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil- pirrolidin- 1- il]- 2- oxo- etil}- 5- (2- hidroxi- etoxi)- indol- 1- carboxílico	(1 [A9], 5 [B13]) R_f (EtOAc) = 0,2; 549.3/551.2 [M+H]+, 593.2/595.3 [M+HCOO]-; t_R (f): 1,70 min.
460		Amida del ácido 3- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 5- fluoro- indol- 1- carboxílico	(1 [A4]) 493 [M+H]+; t_R (b): 3,9 min.

461		Amida del ácido 3- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 2- metil- indol- 1- carboxílico	(1) 484 [M+H]+; t_R (b): 3,93 min
462		Amida del ácido 3- {2- [(S)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- tiazolidin- 3- il]- 2- oxo- etil}- 5- (2- hidroxi- etoxi)- indol- 1- carboxílico	(1 [A9]) R_f (EtOAc): 0,15; 535.2/537.3 [M+H]+, 579.3/581.1 [M+HCOO]- ; t_R (f): 1,70 min.
463		Amida del ácido 3- (2- {(1R,2S,5S)- 2- [(S)- 1- (3- Cloro- 2- fluoro- fenil)- 2- hidroxi- etilcarbamoil]- 3- azabiciclo[3.1.0]hex- 3- il}- 2- oxo- etil)- indol- 1- carboxílico	(5 [B9]) R_f (CH_2Cl_2/MeOH 9:1) = 0,6;499.3/501.3 [M+H]+, 543.3/545.3 [M+HCOO]- ; t_R (a): 3,02 min.
464		Amida del ácido 3- (2- {(1R,3S,5R)- 3- [(S)- 1- (3- Cloro- 2- fluoro- fenil)- 2- metoxi- etilcarbamoil]- 2- aza- biciclo[3.1.0]hex- 2- il}- 2- oxo- etil)- indol- 1- carboxílico	(5 [B9]) Sólido blanco. R_f (EtOAc) = 0,35; 513.0/515.0 [M+H]+, 557/559 [M+HCOO]- ; t_R (a): 3,33 min.
465		Amida del ácido 3- {2- [(1S*,2S*,5R*)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 3- aza- biciclo[3.1.0]hex- 3- il]- 2- oxo- etil}- 5- (2- hidroxi- etoxi)- indol- 1- carboxílico	(1 [A9]) R_f (EtOAc) = 0,1, 529.3/531.3 [M+H]+, 573.2/575.4 [M+HCOO]- ; t_R (f): 1,61 min.

(1) El derivado del ácido (1- carbamoil- 1H- indol- 3- il]- acético utilizado en la etapa C se preparó como se describe en la parte A; (2) se utilizó CH_2Cl_2 en lugar de DMF en la etapa A; (3) La bencilamina sustituida o derivada de anilina usada en la etapa A se preparó como se describe en la Parte C [Esquema]; (4) HCl (4 M/dioxano) en dioxano se utilizó en lugar de TFA

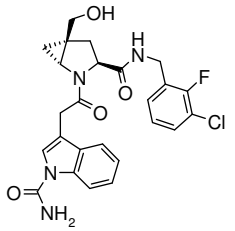
en CH_2Cl_2 en la etapa B; (5) El compuesto del título fue preparado de acuerdo con el procedimiento general descrito en el Esquema D6pasos B y C a partir del derivado de prolina sustituido preparado como se describe en la Parte B [Esquema]; (6) se utilizó DMF como disolvente en el paso C.

Ejemplo 466:Amida del ácido3- {2- [(2S,3S,4S)- 3- Amino- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico



El compuesto del título se preparó según el Esquema D6 a partir del ester terc- butilo del ácido (2S,3S,4S)- 3- azido- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico (descrito en el esquema B19) seguido de la reducción de la azida como se describe para la preparación del **Ejemplo 411**2- (3- cloro- 2,6- difluoro- bencilamida) de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico. TLC, R_f (CH_2Cl_2/MeOH 95/5) = 0.3; MS (LC- MS): 490 [M+H]+, 488 [M-H]- ; t_R (condiciones de HPLC f): 1,42 min.

Ejemplo 467: Amida del ácido 3- {2- [(1R,3S,5S)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 5- hidroximetil- 2- aza- biciclo[3.1.0] hex- 2- ilo]- 2- oxo- etil}- indol- 1- carboxílico



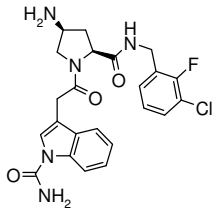
Una solución de éster (1R,3S,5S)- 2- [2- (1- carbamoil- 1H- indol- 3- il)- acetil]- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 5- ilmetil del ácido (1- carbamoil- 1H- indol- 3- il)- acético (65 mg, 0,084 mmol) y NaOH 1 N (0,5 ml, 0,5 mmol) en THF (0,4 ml)/agua (40 µl) se agitó a temperatura ambiente durante 1 h. Se añadieron agua y CH_2Cl_2, las capas se separaron y la fase acuosa se volvió a extraer con CH_2Cl_2 (x3). Los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron. El material crudose purificó mediante HPLC preparativa (Waters Sunfire C18- ODB, 5 µm, 30x100 mm, eluyente:

5% a 100% CH_3CN en H_2O en 25 min, CH_3CN y H_2O que contiene 0.1% de TFA, flujo: 40 ml/min). EtOAc y $NaHCO_3$ acuoso saturado se han añadido a las fracciones purificadas combinadas, las capas se separaron y la fase acuosa se volvió a extraer con EtOAc (x3). Los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron para proporcionar el material deseado.
TLC, R_f (CH_2Cl_2/MeOH 4- 1) = 0,35; MS (UPLC/MS): 499.4/501.4 [M+H]+, 521.3/523.3 [M+Na]+, 543.3/545.2; t_R (condiciones de HPLC f): 1,75 min.

Éster (1R,3S,5S)- 2- [2- (1- carbamoil- 1H- indol- 3- il)- acetil]- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 5- ilmetilo del ácido (1- carbamoil- 1H- indol- 3- il)- acético

El compuesto del título N, O bis- acilado se preparó según el Esquema D6 a partir de ester terc- butilo (1R,3S,5S)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 5- hidroximetil- 2- aza- biciclo[3.1.0]hexano- 2- carboxílico (preparado como se describe en la Parte B Esquema B28) usando HCl 4 N en dioxano en vez de TFA en la Etapa B.(46,2 mg, 0,14 mmol) utilizando ácido (1- carbamoil- 1H- indol- 3- il)- acético (60,2 mg, 0,28 mmol), HBTU (105 mg, 0,28 mmoles) y DIPEA (94 µl, 0,55 mmol) en CH_2Cl_2 (1 ml). TLC, R_f (EtOAc) = 0,25; MS (UPLC/MS): 699.4/701.3 [M+H]+, 721.3/723.3 [M+Na]+, 743.4/745.5 [M+HCOO]- ; t_R (condiciones de HPLC f): 2,05 min.

Ejemplo 468: Amida del ácido 3- {2- [(2S,4S)- 4- Amino- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico

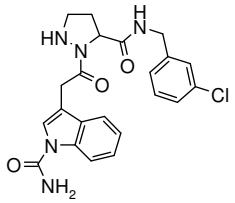


Una solución de amida del ácido 3- {2- [(2S,4S)- 4- azido- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico (80 mg, 0,161 mmol) en MeOH (8 ml) se hidrogenó sobre Pd/C al 10% (8 mg, 10% w/w) a temperatura ambiente (1 atm). La mezcla de reacción se filtró a través de un filtro de 0,45 µm y se concentró bajo presión reducida para proporcionar el compuesto del título como una espuma incolora. MS (LC/MS): 472 [M+H]+; t_R (condiciones de HPLC b) 2,94 min.

Amida del ácido 3- {2- [(2S,4S)- 4- Azido- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico

El compuesto del título se preparó como se describe en el Esquema D6 usando éster 1- terc- butílico del ácido (2S,4S)- 4- azido- pirrolidina- 1,2- dicarboxílico. TLC, R_f (EtOAc) = 0,4; MS (UPLC/MS): 583.5/585.4 [M+H]+, 600.5/602.7 [M+NH4]+, 605.5/607.4 [M+Na]+, 627.4/629.4 [M+HCOO]- ; t_R (condiciones de HPLC f) 2,20 min.

Ejemplo 469: Amida del ácido 3- {2- [5- (3- cloro- bencilcarbamoil)- pirazolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico

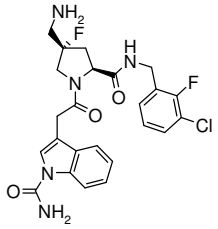


Una solución de ester terc- butilo del ácido 2- [2- (1- carbamoil- 1H- indol- 3- il)- acetil]- 3- (3- cloro- bencilcarbamoil)- pirazolidin- 1- carboxílico (15 mg, 0,03 mmol) en HCl 4 N en dioxano (69,4 µl, 0,278 mmol) se agitó a 23 °C durante 1 h. El material crudo se purificó directamente mediante HPLC preparativa (waters SunFire C18 ODB 5 um, 19x50, 5- 100% CH_3CN/H_2O/15min, 100% CH_3CN/2.5min, CH_3CN y que contiene 0,1% de TFA, flujo de H_2O: 20 ml/min)para proporcionar el material deseadodespués de la liofilización de las fracciones purificadas. MS (LC- MS): 440 [M+H]+; t_R (condiciones de HPLC b): 3,49 min.

Ester terc- butilo del ácido 2- [2- (1- carbamoil- 1H- indol- 3- il)- acetil]- 3- (3- cloro- bencilcarbamoil)- pirazolidin- 1- carboxílico

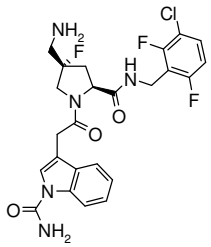
El compuesto del título se preparó como se describe en el Esquema D6 usando ester terc- butilo del ácido 3- (3- cloro- bencilcarbamoil)- pirazolidin- 1- carboxílico (preparado usando un procedimiento similar al descrito en el Esquema B5 para la preparación de ester terc- butilo del ácido 3- (3- cloro- 2- fluoro- bencilcarbamoil)- pirazolidin- 1- carboxílico.

Ejemplo 470: Amida del ácido3- {2- [(2S,4S)- 4- aminometil- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico



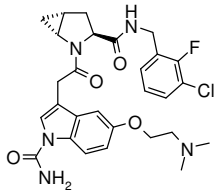
El compuesto del título se preparó según el Esquema D6 a partir de ester terc- butilo del ácido (2S,4R)- 4- azidometil- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico (preparado como se describe esquema B15) utilizando DMF como disolvente, seguido por la reducción de la azida como se describe para la preparación del **Ejemplo 411**. MS (LC- MS): 504/506 [M+H]+; t_R(condiciones de HPLC f): 1,42 min; 19F RMN (100 MHz, DMSO- d_6) δ (ppm):- 120,- 152.

Ejemplo 471: Amida del ácido3- {2- [(2S,4S)- 4- Aminometil- 2- (3- cloro- 2,6- difluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico



El compuesto del título se preparó según el Esquema D6 a partir de ester terc- butilo (2S,4R)- 4- azidometil- 2- (3- cloro- 2,6- difluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico del ácido (preparado usando protocolos similares a los descritos para ester terc- butilo del ácido (2S,4R)- 4- azidometil- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílicoesquema B15) utilizando DMF como disolvente seguido por la reducción de la azida como se describe para la preparación del **Ejemplo 411**. MS (UPLC- MS): 522/524 [M+H]+; t_R(condiciones de HPLC f): 1,47 min; 19F RMN (100 MHz, DMSO- d_6) δ (ppm):- 117 (2F),- 150.

Ejemplo 472: Amida del ácido 3- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0] hex- 2- il]- 2- oxo- etil}- 5- (2- dimetilamino- etoxi)- indol- 1- carboxílico

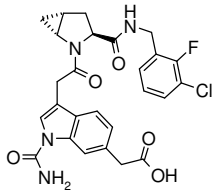


Éster 2- (1- carbamoil- 3- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 5- iloxi)- etilo del ácido metanosulfónico en una solución de dimetilamina 5,6 M en EtOH (1 ml) se selló en un vial de microondas y se calentó a 70 °C durante 2 h (Emrys Optimizer; química personal). La mezcla de reacción se inactivó mediante la adición de $NaHCO_3$ acuoso saturado, se extrajo con EtOAc, se secó (Na_2SO_4) y se evaporó a vacío. Entonces el residuo crudose purificó mediantecaptura de liberación (SCX Tosic Acid- 1g de Silicycle; eluyente MeOH (10 ml) a amoniaco 2 M en MeOH (10 ml)) para proporcionar el material deseado que se precipitó en Et_2O. MS (UPLC/MS): 556.5/558.5 [M+H]+, 600.4/602.5 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,46 min.

Éster 2- (1- carbamoil- 3- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 5- iloxi)- etílico del ácido metanesulfónico

A una solución del **Ejemplo 453**:Amida del ácido3- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 5- (2- hidroxi- etoxi)- indol- 1- carboxílico (45 mg, 0,08 mmol) y Et_3N (56 µl, 0,41 mmol) en CH_2Cl_2 (1 ml) a 0 º C se añadió cloruro de metanosulfonilo (31 µl, 0,41 mmol) y la suspensión blanca se agitó a temperatura ambiente bajo nitrógeno durante la noche . Se añadieron Et_3N (56 µl, 0,41 mmol) y cloruro de metanosulfonilo (31 µl, 0,41 mmol) y la mezcla se agitó adicionalmente durante 1,5 h para completar la reacción. La mezcla de reacción se inactivó mediante la adición de $NaHCO_3$ acuoso saturado, se extrajo con CH_2Cl_2, se secó (Na_2SO_4) y se evaporó a vacío. El residuo crudose purificó mediante cromatografía en columna sobre gel de sílice (eluyente: EtOAc a EtOAc/acetona 1- 1). TLC, R_f (EtOAc) = 0,2; MS (UPLC/MS): 607.4/609.3 [M+H]+, 629.2/631.2 [M+Na]+, 562.2/564.1 [M- CONH2]- , 651.3/653.3 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,88 min.

Ejemplo 473: Ácido (1- carbamoil- 3- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 6- il)- acético

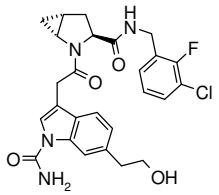


Una solución de ester terc- butilo del ácido (1- carbamoil- 3- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 6- il)- acético (265 mg, 0,46 mmol) y TFA (1,05 ml, 23,5 mmol) en CH_2Cl_2 (4,8 ml) se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se concentró, recogió en EtOAc, se añadió c- hexano hasta que se formó un precipitado y se filtró. La purificación adicional en el cartucho trimetilaminopropilo (Mega Bond Elut- SAX, 1 g de 6 ml, de Varian) (eluyente: 10 ml de CH_3CNluego HCl 0,1 N en CH_3CN10 ml) proporcionó un sólido que se precipitó en Et_2O. MS (UPLC): 527.4/529.5 [M+H]+, 544.4/546.3 [M+NH_4]+, 571.3/573.4 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,74 min.

Ester terc- butilo del ácido (1- carbamoil- 3- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 6- il)- acético

El compuesto del título se preparó según el protocolo descrito en el Esquema D6 usando ácido (6- terc- butoxicarbonilmetil- 1- carbamoil- 1H- indol- 3- il)- acético (preparado como se describe en la Parte A) y ester terc- butilo del ácido (2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil- pirrolidina- 1- carboxílico (preparado como se describe en el Esquema B13). TLC, R_f (EtOAc) = 0,2; EM (UPLC): 549.3/551.2 [M+H]+, 593.2/595.3 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,70 min.

Ejemplo 474: Amida del ácido 3- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0] hex- 2- il]- 2- oxo- etil}- 6- (2- hidroxi- etil)- indol- 1- carboxílico



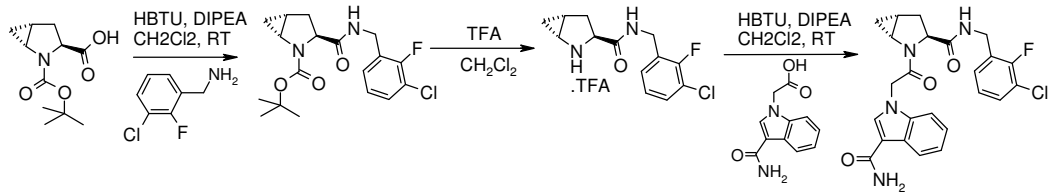
A una solución de ester metilo del ácido 3- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 6- (2- hidroxi- etil)- indol- 1- carboxílico (35 mg, 0,047 mmol) en THF (0,25 ml) se le añadió $LiBH_4$ (2 M en THF, 47 µl, 0,094 mmol) bajo atmósfera de nitrógeno. Y la mezcla de reacción se agitó a temperatura ambiente durante 2 h. $LiBH_4$ (2 M en THF, 47 µl, 0,094 mmol) se añadió de nuevo y la mezcla

se agitó adicionalmente a temperatura ambiente durante 2 h, después se vertió en $NaHCO_3$ acuoso, se extrajo dos veces con EtOAc, se secó (Na_2SO_4) y el disolvente se eliminó a vacío . El material crudose purificó mediante HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 19x50 mm, eluyente: 20% a 100% (CH_3CN/MeOH 1- 4)/H_2O en 15 min, (1- 4 CH_3CN/MeOH) y H_2O que contiene 0,1% de HCOOH, flujo: 20 ml/min) para proporcionar, después de liofilización de la fracción purificada del material deseado como un polvo blanco. TLC, R_f (EtOAc) = 0,25; MS (UPLC/MS): 513.4/515.5 [M+H]+, 530.5/532.7 [M+NH4]+, 557.4/559.4 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,74 min.

Ester metilo del ácido (1- carbamoil- 3- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 6- il)- acético

A una suspensión del **Ejemplo 473**: se añadió ácido (1- carbamoil- 3- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 6- il)- acético (98 mg, 0,18 mmol) en CH_2Cl_2 (1 ml) (40 mg, 0,195 mmol), DMAP (2,2 mg, 0,018 mmol) y MeOH (7,17 µl, 0,177 mmol) y la mezcla se agitó a temperatura ambiente en atmósfera de nitrógeno durante 1,5 h. La mezcla se vertió en agua y se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El material crudo se recogió en MeOH y se filtró. El filtrado se concentró y se purificó mediante HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 19x50 mm, eluyente: 20% a 100% (CH_3CN/MeOH 1- 4)/H_2O en 22,5 min, (CH_3CN/MeOH 1- 4) y H_2O que contiene 0,1% de HCOOH, flujo: 20 ml/min). TLC, R_f (EtOAc) = 0,35; MS (UPLC/MS): 541.4/543.4 [M+H]+, 558.5/560.5 [M+NH4]+, 563.4/565.0 [M+Na]+, 585.3/587.3 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,92 min.

Esquema D7: preparación del Ejemplo 475: Amida del ácido 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico



A.ester terc- butilo del ácido (1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carboxílico

A una mezcla de ester 2- terc- butilo del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico (4 g, 17,6 mmol), 3- cloro- 2- fluorobencilamina (3,09 g, 19,36 mmol) y HBTU (10,01 g, 26,4 mmol) en CH_2Cl_2 (88 ml) se añadió DIPEA (6,03 ml, 35,2 mmol) y la solución de color amarillo resultante se agitó a temperatura ambiente bajo atmósfera de nitrógeno. La mezcla de reacción se vertió en HCl 1 N y se extrajo dos veces con CH_2Cl_2. Las capas orgánicas combinadas se neutralizaron con solución sat. de $NaHCO_3$, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo crudose purificó mediante cromatografía ultrarápida (c- hexano a c- hexano/EtOAc 1- 9) para proporcionar el material deseado como un sólido blanco. TLC, R_f (EtOAc) = 0,75; MS (LC/MS): 391.1/393.1 [M+Na]+, 269.0/271.0 [MH- Boc]+, 413.0/415.1 [M+HCOO]- ; t_R (condiciones de HPLC f) 2,1 min.

DMF también se puede utilizar en lugar de diclorometano.

B. 3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico

A una solución de ester terc- butilo del ácido (1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carboxílico (6,35 g, 17,22 mmol) en CH_2Cl_2 (60 ml) se le añadió TFA (13,18 ml, 172 mmol) y la solución se agitó a temperatura ambiente durante 3 h. La mezcla de reacción cruda se concentró a vacío, se añadió Et_2O y el precipitado blanco se separó mediante filtración para proporcionar el compuesto deseado en forma de una sal de TFA. MS (LC/MS): 287,0 [M+H]+, 285,1 [M- H]- ; t_R (condiciones de HPLC f) 1,27 min.

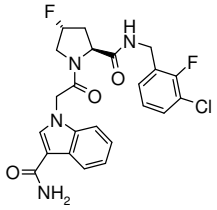
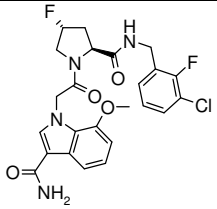
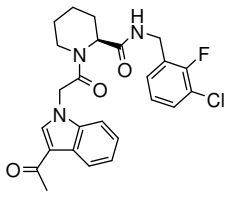
C. Ejemplo 475: Amida del ácido 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico

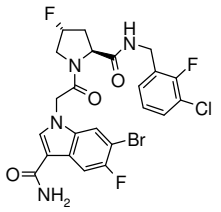
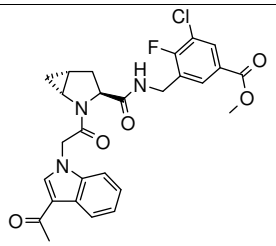
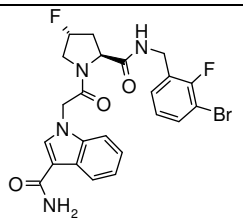
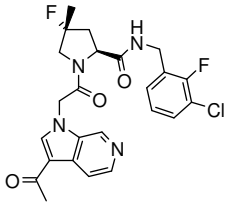
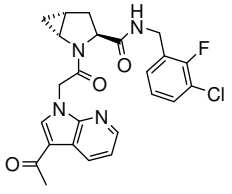
La mezcla de trifluoroacetato de 3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico (70,2 mg, 0,183 mmol), ácido (3- carbamoil- indol- 1- il)- acético [1016689- 54- 5] (40,0 mg, 0,183 mmol), HBTU (104 mg, 0,275 mmoles) y DIPEA (0,128 ml, 0,733 mmol) en CH_2Cl_2 (8 ml) se agitó a temperatura ambiente durante 60 h. La mezcla de reacción se diluyó con CH_2Cl_2, y la solución se lavó dos veces con HCl 0,1 N. El precipitado formado en la capa acuosa se separó mediante filtración, se lavó con CH_2Cl_2 y se secó al vacío para proporcionar el producto del título como un sólido blanco. MS (LC/MS): 469 [M+H]+, 491 [M+Na]+; t_R (condiciones de HPLC b): 3,56 min.

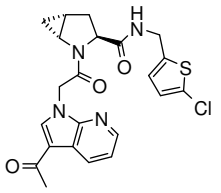
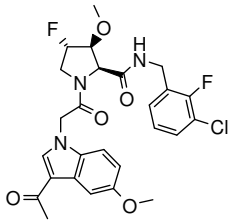
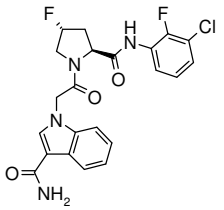
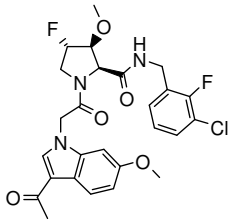
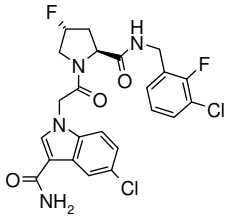
Alternativamente, para los compuestos finales que contienen un residuo básico, las fracciones de HPLC puras se neutralizaron con una solución acuosa saturada de $Na2CO_3$, se extrajo con EtOAc, se secó (Na_2SO_4), se filtró y se concentró para proporcionar el material deseado en forma de una base libre.

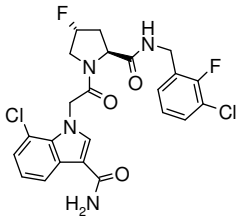
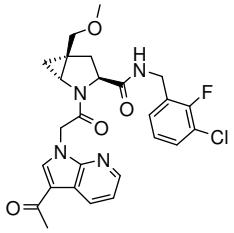
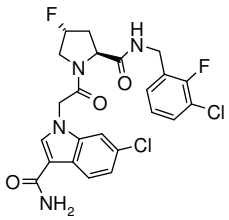
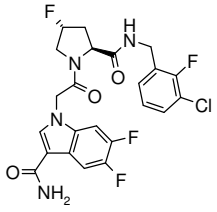
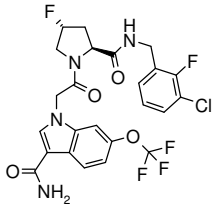
Los ejemplos siguientes se prepararon de acuerdo con el procedimiento general descrito en el Esquema D7 para la preparación de los precursores de síntesis disponibles en el mercado **Ejemplo 475** *si no se menciona lo contrario (ver notas al final del cuadro 6):*

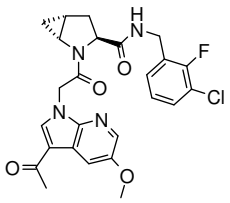
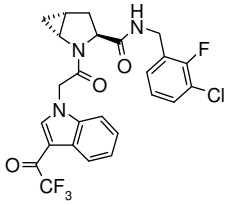
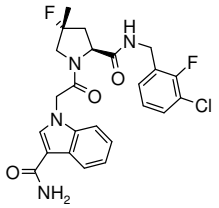
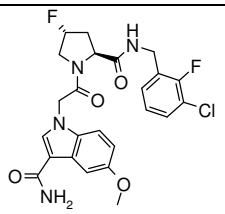
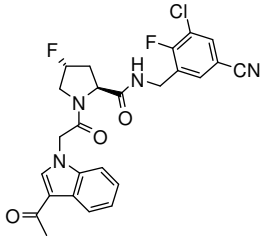
Tabla 6:

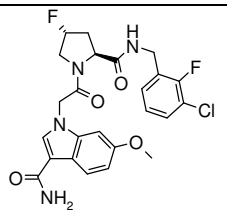
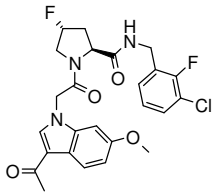
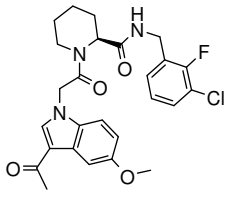
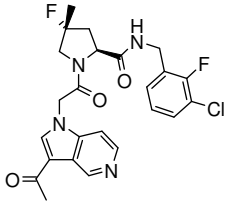
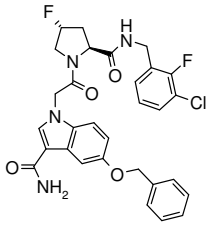
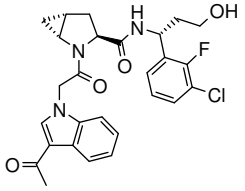
Ejemplo	Estructura	Nombre	Caracterización (Notas al final de la tabla), TLC, R_f (eluyente); MS (LC/MS); t_R (condiciones de HPLC)
476		Amida del ácido 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico	Sólido blanco. 475 [M+H]+; t_R (b): 4,19 min.
477		Amida del ácido1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 7- metoxi- 1H- indol- 3- carboxílico	(4 [A11], 5) Sólido. 505 [M+H]+, 527 [M+Na]+; t_R (c): 4,27 min
478		3- cloro- 2- fluoro- bencilamida de (S)- 1- [2- (3- acetil- indol- 1- il)- acetil]- piperidina- 2- carboxílico	Sólido blanco. 470 [M+H]+, 492 [M+Na]+; t_R (c): 5,01 min.

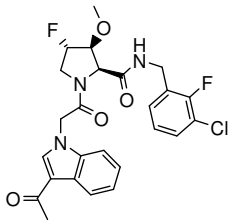
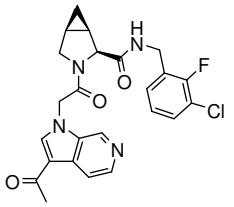
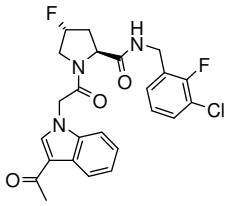
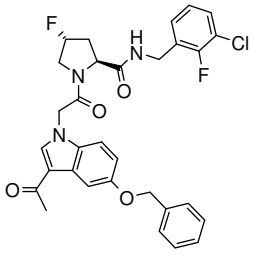
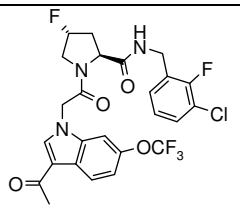
479		Amida del ácido6- Bromo- 1- {2- [(2S,4R)- 2- (3- chloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 5- fluoro- 1H- indol- 3- carboxílico	(4,5) Solid. 573,0 [M+H]+; t_R (k): 3,35 min.
480		Ester metilo del ácido3- [({(1R,3S,5R)- 2- [2- (3- acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carbonil}- amino)- metil]- 5- cloro- 4- fluoro- benzóico	(1) Sólido blanco. R_f (EtOAc al 100) = 0,35; 526,0 [M+H]+, 548,0 [M+Na]+; t_R (c): 4,90 min.
481		Amida del ácido1- {2- [(2S,4R)- 2- (3- bromo- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico	(1,5) R_f (CH_2Cl_2/MeOH 95:5) = 0,24; 521,0 [M+H]+; t_R (k): 3,10 min.
482		3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- acetil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico	(3 [B13], 4 [A15]) R_f (CH_2Cl_2/MeOH 9:1) = 0,40; 489.2/491.2 [M+H]+, 533.3/535.2 [M+HCOO]- ; t_R (f): 1,49 min .
483		3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico	(4 [A13]) R_f (EtOAc) = 0,10; 469.3/471.3 [M+H]+, 937.5/939.5 [2M+H]+, 513.3/515.3 [M+HCOO]- , 981.4/983.5 [2M+HCOO]- ; tr (f): 1,90 min.

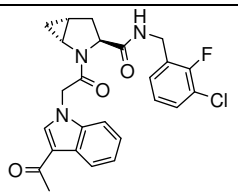
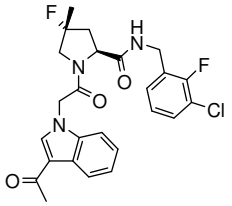
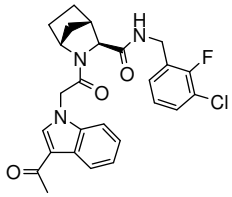
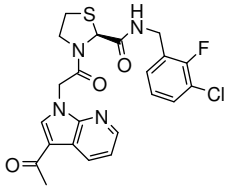
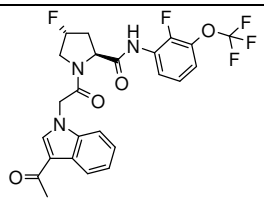
484		(5- cloro- tiofen- 2- ilmetil)- amida ácido (1R,3S,5R)- 2- [2- (3- acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico	(4 [A13]) R_f (CH_2Cl_2/MeOH 4:1) = 0,45; 457.3/459.2 [M+H]+, 479.2/481, 1 [M+Na]+, 501.3/503.2 [M+HCOO]- ; tr (f): 1,86 min.
485		3- cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- acetil- 5- metoxi- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico	(3 [B24], 4) 578 [M+HCOO]- , 534 [M+H]+; t_R (f): 1,99 min.
486		Amida del ácido1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- fenilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico	461 [M+H]+; t_R (b): 4,25 min.
487		3- cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- 6- metoxi- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico	(3 [B24], 4 [A13]) y (3- acetil- 6- metoxi- indol- 1- il)- acético (preparado como se describe en la Parte A). 578 [M+HCOO]- , 534 [M+H]+; t_R (f): 2,03 min.
488		Amida del ácido 5- cloro- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico	(4 [A11]) Sólido blanco. 509/510 [M+H]+, 532/533 [M+Na]+; t_R (b): 4,50 min.

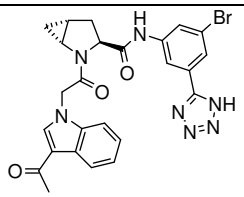
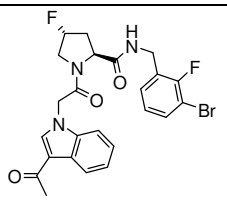
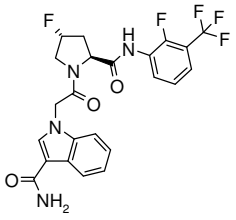
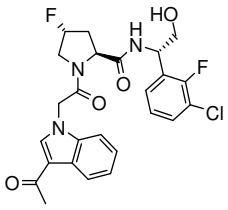
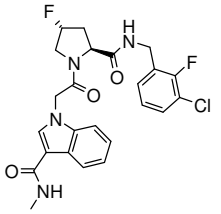
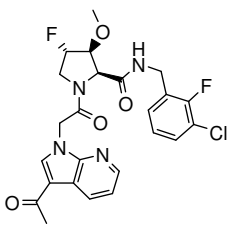
489		Amida del ácido7- cloro- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico	(4 [A11]) Sólido blanco. 509/510 [M+H]+, 532/533 [M+Na]+; t_R (b): 4,42 min.
490		3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5S)- 2- [2- (3- acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 5- metoximetil- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico	(2,3,4 [A13]) Sólido blanco. R_f (EtOAc) = 0,25; 513.3/515.3 [M+H]+, 557.4/559.4 [M+HCOO]- ; t_R (a): 3,23 min.
491		Amida del ácido6- cloro- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico	(4) Sólido blanco. 509/510 [M+H]+; 532/533 [M+Na]+; t_R (b): 4,52 min.
492		Amida del ácido1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 5,6- difluoro- 1H- indol- 3- carboxílico	(4,5) Solid. 511 [M+H]+; t_R (k): 3,28 min.
493		Amida del ácido1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 6- trifluorometoxi- 1H- indol- 3- carboxílico	(4,5) Solid. 560,0 [M+H]+; t_R (k): 3,45 min.

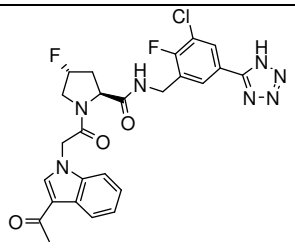
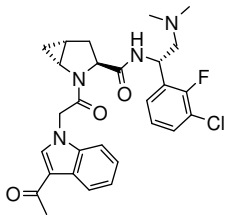
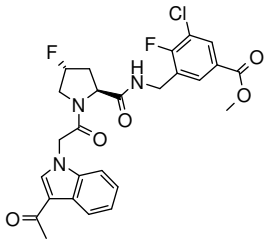
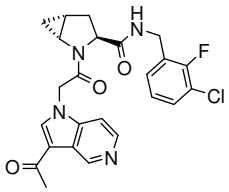
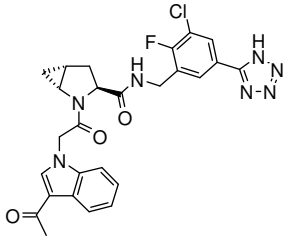
494		3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- acetil- 5- metoxi- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico	(4 [A15]) R_f (CH_2Cl_2/MeOH 9:1) = 0,50; 499.3/501.3 [M+H]+, 543.3/545.3 [M+HCOO]- ; tr (f): 2,08 min.
495		3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- {2- [3- (2,2,2- Trifluoro- acetil)- indol- 1- il]- acetil}- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico	(4 [A13], 5) Sólido blanco. 522,0 [M+H]+; t_R (c): 5,53 min.
496		Amida del ácido1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico	(3 [B13], 5) Sólido blanco. 489 [M+H]+; t_R (c): 4,35 min.
497		Amida del ácido1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 5- metoxi- 1H- indol- 3- carboxílico	(4 [A12], 5) Sólido blanco. 505 [M+H]+; t_R (c): 4,17 min.
498		3- cloro- 5- ciano- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico	(1) Sólido blanco. 499,0 [M+H]+, 497,0 [M- H]- ; t_R (c): 4,55 min.

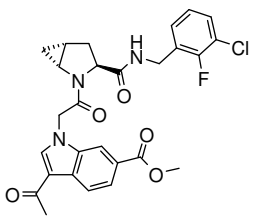
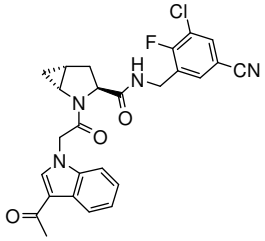
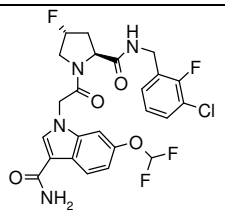
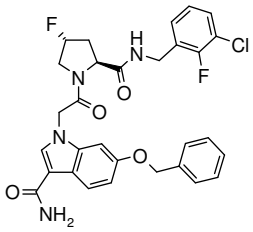
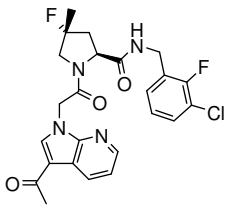
499		Amida del ácido1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 6- metoxi- 1H- indol- 3- carboxílico	(4 [A10], 5) Sólido blanco. 505 [M+H]+; t_R (c): 4,19 min.
500		3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- acetil- 6- metoxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico	(4 [A13], 5) Sólido. 504 [M+H]+, 526 [M+Na]+; t_R (k): 3,43 min.
501		3- cloro- 2- fluoro- bencilamida del ácido (S)- 1- [2- (3- acetil- 5- metoxi- indol- 1- il)- acetil]- piperidina- 2- carboxílico	(4) Sólido blanco. 500 [M+H]+; t_R (c): 4,96 min.
502		3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- acetil- pirrolo[3,2- c]piridin- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico	(3 [B13], 4 [A15]) R_f (CH_2Cl_2/MeOH 9:1) = 0,40; 489.3/491.3 [M+H]+, 533.3/535.3 [M+HCOO]- ; t_R (f): 1,50 min .
503		Amida del ácido 5- Benciloxi- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico	(4 [A11]) Sólido blanco. R_f (EtOAc/MeOH 95:5) = 0,27; 581/582 [M+H]+; t_R (b): 4,90 min.
504		[(R)- 1- (3- cloro- 2- fluoro- fenil)- 3- hidroxi- propil]- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)-	(3 [B9])Rf (EtOAc) = 0,15; 512,3 [M+H]+, 556.3/558.4 [M+HCOO]- ; t_R (a):

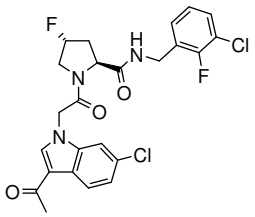
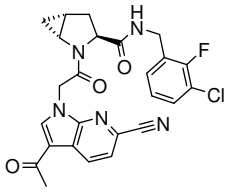
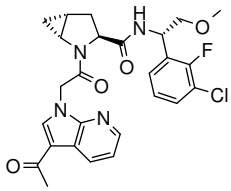
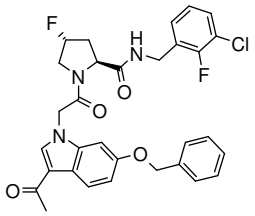
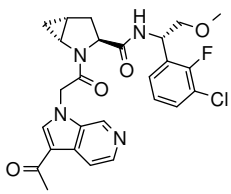
		acetil]- 2- aza-biciclo[3.1.0]hexano- 3- carboxílico	3,22 min.
505		3- cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico	(3 [B24]) 504 [M+H]+; t_R (f): 2,01 min.
506		3- cloro- 2- fluoro- bencilamida del ácido (1R,2S,5S)- 3- [2- (3- acetil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 3- aza-biciclo[3.1.0]hexano- 2- carboxílico	(4 [A15]) R_f (CH_2Cl_2/MeOH 9:1) = 0,30; 469.3/471.3 [M+H]+, 513.2/515.2 [M+HCOO]- ; tr (f): 1,48 min.
507		3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico	Sólido blanco. 474 [M+H]+; t_R (b): 3,90 min.
508		3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 5- benciloxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico	(4 [A13], 5) Sólido blanco. 580/582 [M+H]+; t_R (k): 3,81 min.
509		3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 6- trifluorometoxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina-	(4,5) Sólido blanco.R_f (CH_2Cl_2/MeOH 95:5) = 0,31; 558,0 [M+H]+; t_R (c): 5,26 min.

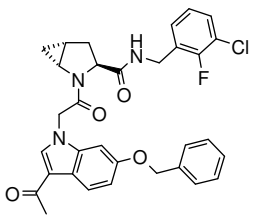
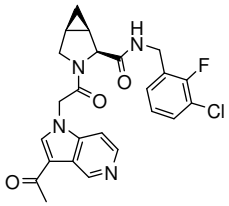
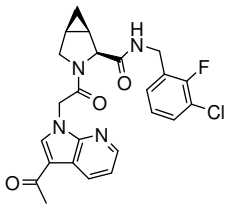
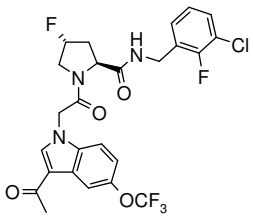
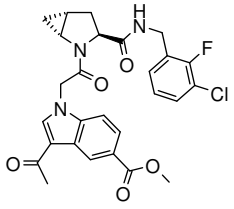
		2- carboxílico	
510		3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico	(5) Sólido blanco. 468,0 [M+H]+; t_R (c): 4,77 min.
511		3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico	(3 [B13], 5) Sólido blanco.R_f (CH_2Cl_2/MeOH 95:5) = 0,31; 488,0 [M+H]+; t_R (c): 4,82 min.
512		3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,4S)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[2.2.1]heptano- 3- carboxílico	482 [M+H]+, 480 [M-H]- ; t_R (f): 0,98 min.
513		3- cloro- 2- fluoro- bencilamida del ácido (S)- 3- [2- (3- acetil- pirrolo [2,3- b] piridin- 1- il)- acetil]- tiazolidina- 2- carboxílico	(4 [A13]) R_f (EtOAc) = 0,80; 475.3/477.2 [M+H]+, 949.4/951.3 [2M+H]+, 519.2/521.2 [M+HCOO]- ; tr (f): 1,91 min.
514		(2- fluoro- 3- trifluorometoxi- fenil)- amida del ácido (2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico	(1,5) Sólido blanco. 510 [M+H]+, 532 [M+Na]+; t_R (k): 3,62 min
515		[3- bromo- 5- (2H- tetrazol- 5- il)- fenil]- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil-	(1,2) Sólido blanco. 548,0 [M+H]+; t_R (c): 4,51 min.

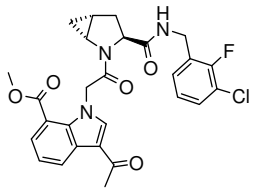
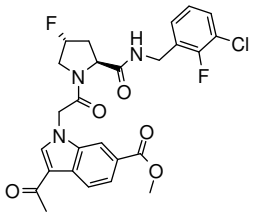
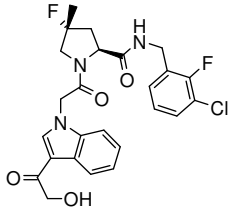
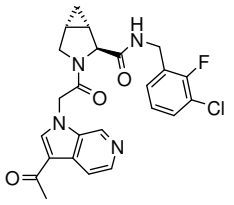
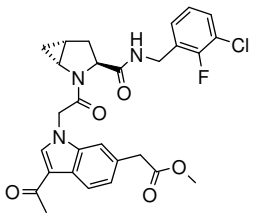
		indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico	
516		3- bromo- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico	(1,5) Sólido blanco. R_f (CH_2Cl_2/MeOH 95:5) = 0,41; 518,0 [M+H]+; t_R (k): 3,45 min
517		Amida del ácido1- {2- [(2S,4R)- 4- Fluoro- 2- (2- fluoro- 3- trifluorometil- fenilcarbamoil)- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico	(5,6) Sólido blanco. 495 [M+H]+, 989 [2M +1]+; t_R (c): 4,46 min.
518		[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido (2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico	(5) Sólido blanco.R_f (CH_2Cl_2/MeOH 95:5) = 0,32; 504,0 [M+H]+; t_R (c): 4,21 min.
519		metilamida del ácido 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico	(4) 489 [M+H]+; t_R (b): 3,57 min.
520		3- cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico	(3 [B24], 4 [A13]) 549 [M+HCOO]- , 505 [M+H]+; t_R (f): 1,90 min.

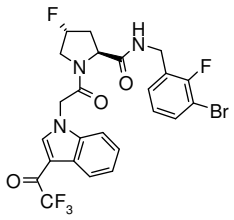
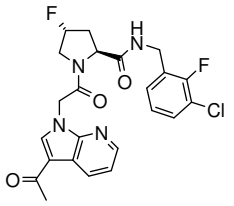
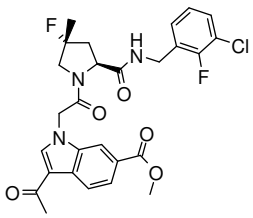
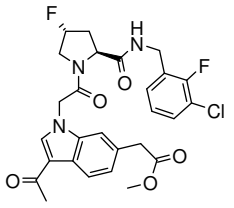
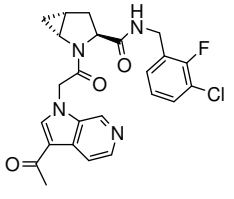
521		3- cloro- 2- fluoro- 5- (1H- tetrazol- 5- il)- bencilamida del ácido (2S,4R)- 1- [2- (3- acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico	(1,2) Sólido blanco. 542,3 [M+H]+, 540,3 [M- H]- ; t_R (c): 4,27 min
522		[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- dimetilamino- etil]- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico	(1 [C4], 2) R_f (EtOAc) = 0,1; 527/527 [M+H]+; t_R (f): 1,66 min.
523		Ester metilo del ácido 3- [({(2S,4R)- 1- [2- (3- acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carbonil}- amino)- metil]- 5- cloro- 4- fluoro- benzóico	(1,5) Sólido blanco. 530,0 [M- H]- ; t_R (c): 4,73 min.
524		3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- acetil- pirrolo[3,2- c]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico	(4 [A15]) R_f (CH_2Cl_2/MeOH 4:1) = 0,35, 469.3/471.3 [M+H]+, 513.3/515.3 [M+HCOO]- ; tr (f): 1,46 min.
525		3- cloro- 2- fluoro- 5- (1H- tetrazol- 5- il)- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico	(1,2) Sólido blanco. 536,3 [M+H]+, 534,3 [M- H]- ; t_R (c): 4,41 min.

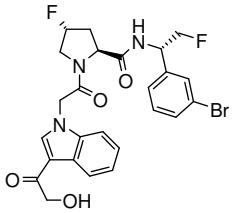
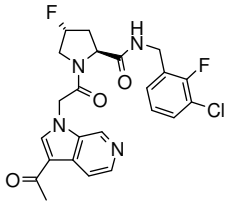
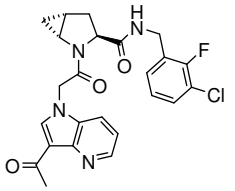
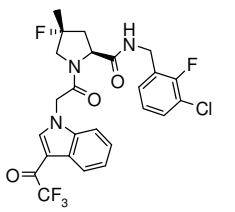
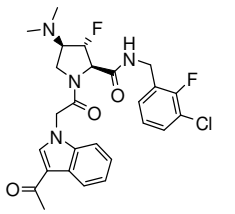
526		Ester metilo del ácido 3- Acetil- 1- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 6- carboxílico	(4 [A13], 5) Sólido. 526 [M+H]+, 1021 [2M+H]+; t_R (k): 3,52 min.
527		3- cloro- 5- ciano- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico	(1) Sólido blanco. 493,0 [M+H]+; t_R (c): 4,68 min
528		Amida del ácido1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 6- difluorometoxi- 1H- indol- 3- carboxílico	(4,5) Solid. 541/543 [M+H]+; t_R (k): 3,33 min.
529		Amida del ácido 6- Benciloxi- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico	(4 [A11]) Sólido blanco. 581/582 [M+H]+, 603/604 [M+Na]+; t_R (b): 4,94 min.
530		3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico	(3 [B13], 4 [A13]) R_f (EtOAc) = 0,35; 489.3/491.2 [M+H]+, 533.3/535.2 [M+HCOO]- ; t_R (f): 1,93 min.

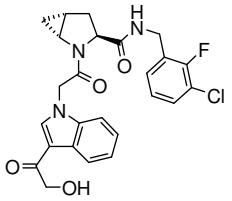
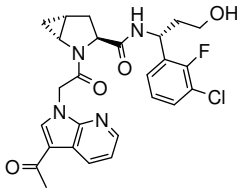
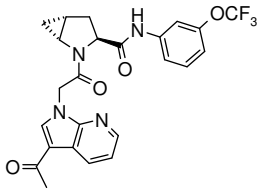
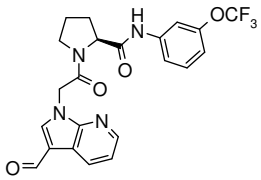
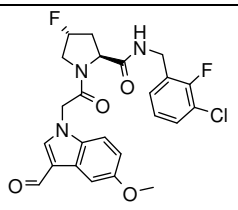
531		3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 6- cloro- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico	(4 [A13], 5) Sólido. 508/510 [M+H]+, 530 [M+Na]+; t_R (k): 3,63 min.
532		3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- acetil- 6- ciano- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico	(4 [A15]) R_f (EtOAc) = 0,25; 494.3/496.3 [M+H]+, 538.2/540.2 [M+HCOO]- ; tr (f): 2,03 min.
533		[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etil]- amida del ácido (1R,3S,5R)- 2- [2- (3- acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico	(2,3 [B9], 4 [A13]) Sólido blanco.R_f (EtOAc) = 0,50; 513.2/515.2 [M+H]+, 511,2 [M- H]- , 557.2/559.2 [M+HCOO]- ; t_R (a): 3,26 min.
534		3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 6- benciloxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico	(4 [A13], 5) Sólido. 580/581 [M+H]+; t_R (k): 3,83 min.
535		[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etil]- amida del ácido (1R,3S,5R)- 2- [2- (3- acetil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 2-	(2,3 [B9], 4 [A15]) R_f (CH_2Cl_2/MeOH 9:1) = 0,45; 513.3/515.3 [M+H]+, 557.2/559.2 [M+HCOO]- ; t_R (f):

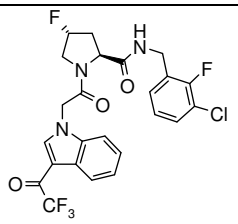
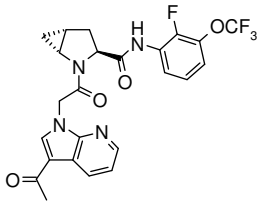
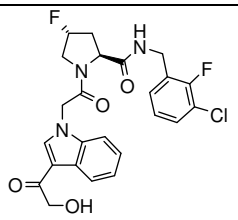
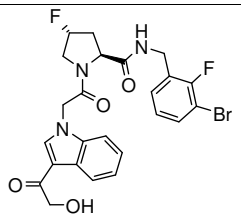
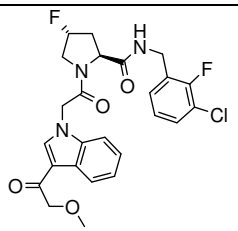
		aza- biciclo[3.1.0]hexano- 3- carboxílico	1.50.
536		3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- 6- benciloxi- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico	(4 [A13], 5) Sólido. 574 [M+H]+; t_R (k): 3,89 min.
537		3- cloro- 2- fluoro- bencilamida del ácido (1R,2S,5S)- 3- [2- (3- acetil- pirrolo[3,2- c]piridin- 1- il)- acetil]- 3- aza- biciclo[3.1.0]hexano- 2- carboxílico	(4 [A15]) R_f (CH_2Cl_2/MeOH 9:1) = 0,40, 469.3/471.3 [M+H]+, 513.3/515.3 [M+HCOO]- ; tr (f): 1,47 min.
538		3- cloro- 2- fluoro- bencilamida del ácido (1R,2S,5S)- 3- [2- (3- acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 3- aza- biciclo[3.1.0]hexano- 2- carboxílico	(4 [A13]) R_f (CH_2Cl_2/MeOH 4:1) = 0,35; 469.3/471.3 [M+H]+, 513.3/515.2 M+HCOO]- ; t_R (a): 3,15 min.
539		3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 5- trifluorometoxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico	(4 [A13], 5) Sólido blanco. 558,0 [M+H]+; t_R (c): 5,25 min.
540		ester metilo del ácido 3- acetil- 1- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza-	(4 [A13], 5) Sólido. 526/528 [M+H]+, 548/550 [M+Na]+; t_R (k): 3,54 min.

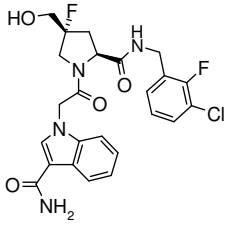
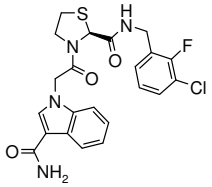
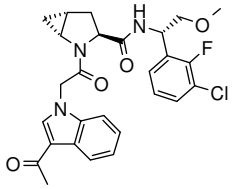
		biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 5- carboxílico	
541		Ester metilo del ácido 3- acetil- 1- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluorobencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 7- carboxílico	(4 [A13], 5) Sólido. MS (LC/MS): 526 [M+H]+, 1051 [2M+H]+; t_R (k): 3,68 min.
542		Ester metilo del ácido3- acetil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- carboxílico	(4 [A13], 5) Sólido. 532 [M+H]+, 554 [M+Na]+; t_R (k): 3,44 min.
543		3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 4- fluoro- 1- {2- [3- (2- hidroxi- acetil)- indol- 1- il]- acetil}- 4- metil- pirrolidina- 2- carboxílico	(3 [B13], 4 [A13], 5) Sólido blanco. 504,0 [M+H]+; t_R (c): 4,56 min.
544		3- cloro- 2- fluoro- bencilamida del ácido (1S,2S,5R)- 3- [2- (3- acetil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 3- aza- biciclo[3.1.0]hexano- 2- carboxílico	(4 [A15]) R_f (CH_2Cl_2/MeOH 9:1) = 0,45; 469.2/471.2 [M+H]+, 513.2/515.3 [M+HCOO]- ; tr (f): 1,49 min.
545		ester metilo del ácido (3- acetil- 1- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza-	(4,5) Solid. 540 [M+H]+, 562 [M+Na]+; t_R (k): 3,51 min.

		biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 6- il)- acético	
546		3- bromo- 2- fluoro- bencilamida del ácido (2S,4R)- 4- fluoro- 1- {2- [3- (2,2,2- trifluoro- acetil)- indol- 1- il]- acetil}- pirrolidina- 2- carboxílico	(1,4 [A13], 5) Sólido blanco.R_f (CH_2Cl_2/acetona 9:1) = 0,41; 573,0 [M+H]+; t_R (k): 3,87 min
547		3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico	(4 [A13]) R_f (CH_2Cl_2/MeOH 4:1) = 0,80; 475.3/477.3 [M+H]+, 519.2/521.2 [M+HCOO]- ; tr (f): 1,84 min.
548		Ester metilo del ácido3- acetil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- carboxílico	(3 [B13], 4 [A13], 5) Sólido. 546 [M+H]+, 568 [M+Na]+; t_R (k): 3,58 min.
549		Ester metilo del ácido (3- acetil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- il)- acético	(4,5) Solid. 546 [M+H]+, 568 [M+Na]+; t_R (k): 3,46 min.
550		3- cloro- 2- fluorobencilamida del ácido (1R,3S,5R)- 2- [2- (3- acetil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3-	(4 [A15]) Sólido blanco. 469.3/471.3 [M+H]+, 513.2/515.2 [M+HCOO]- ; tr (f): 1,48 min.

		carboxílico	
551		[(S)- 1- (2S,4R)- 4- fluoro- 1- (3- bromo- fenil)- 2- fluoro- etil]- amida del ácido (2S,4R)- 4- fluoro- 1- {2- [3- (2- hidroxi- acetil)- indol- 1- il]- acetil}- pirrolidina- 2- carboxílico	(1,4 [A13], 5) Sólido blanco. 548,0 [M+H]+; t_R (c): 4,47 min.
552		3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- acetil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico	(4 [A15]) R_f (CH_2Cl_2/MeOH 9:1) = 0,40; 475.4/477.3 [M+H]+, 519.3/521.4 [M+HCOO]- ; tr (f): 1,45 min.
553		3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- acetil- pirrolo[3,2- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico	(4 [A13]) R_f (CH_2Cl_2/MeOH 4:1) = 0,35, 469.2/471.3 [M+H]+, 513.3/515.3 [M+HCOO]- ; tr (f): 1,45 min.
554		3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 4- Fluoro- 4- metil- 1- {2- [3- (2,2,2- trifluoro- acetil)- indol- 1- il]- acetil}- pirrolidina- 2- carboxílico	(3 [B13], 4 [A13], 5) Sólido blanco.R_f (CH_2Cl_2/MeOH 95:5) = 0,56; 542,0 [M+H]+; t_R (c): 5,54 min.
555		3- cloro- 2- fluoro- bencilamida del ácido (2R,3S,4R)- 1- [2- (3- acetil- indol- 1- il)- acetil]- 4- dimetilamino- 3- fluoro- pirrolidina- 2- carboxílico	(3 [B20]) R_f (C- hexano/EtOAc 1/1) = 0,17; 517 [M+H]+, 561 [M- H]- , tr (f): 1,63 min.

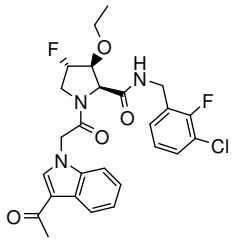
556		3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- {2- [3- (2- hidroxi- acetil)- indol- 1- il]- acetil}- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico	(4 [A13], 5) Sólido blanco. 484,0 [M+H]+; t_R (c): 4,50 min.
557		[(R)- 1- (3- cloro- 2- fluoro- fenil)- 3- hidroxi- propil]- amida del ácido (1R,3S,5R)- 2- [2- (3- acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico	(3 [B9], 4 [A13]) R_f (CH_2Cl_2/MeOH 9:1) = 0,7; 513.3/515.3 [M+H]+, 557,2 [M+HCOO]- ; t_R (a): 3,02 min.
558		(3- trifluorometoxi- fenil)- amida del ácido (1R,3S,5R)- 2- [2- (3- acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico	(4 [A13]) R_f (EtOAc) = 0,30; 487,3 [M+H]+, 973,5 [2M+H]+, 485,3 [M-H]- , 531,3 [M+HCOO]- , 1017,5 [2M+HCOO]- ; tr (f): 2,08 min.
559		(3- trifluorometoxi- fenil)- amida del ácido (S)- 1- [2- (3- formil- indol- 1- il)- acetil]- pirrolidina- 2- carboxílico	Rf (c- hexano/EtOAc 01:02) = 0,04; 460,1 [M+H]+, 482 [M+Na]+, 941,2 [2M+Na]+, 458,2 [M-H]- ; t_R (a): 3,58 min.
560		3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 4- fluoro- 1- [2- (3- formil- 5- metoxi- indol- 1- il)- acetil]- pirrolidina- 2-	MS (LC/MS): 490,0 [M+H]+; t_R (l): 1,77 min.

		carboxílico	
561		3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 4- fluoro- 1- {2- [3- (2,2,2- trifluoro- acetil)- indol- 1- il]- acetil}- pirrolidina- 2- carboxílico	(4 [A13], 5) Sólido blanco.Rf (c-hexano/EtOAc 1:1) = 0,18; 528,0 [M+H]+; t_R (c): 5,44 min.
562		(2- fluoro- 3- trifluorometoxi- fenil)- amida del ácido (1R,3S,5R)- 2- [2- (3- acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico	(1,4 [A13]) R_f (EtOAc) = 0,45; 505,4 [M+H]+, 1009,6 [2M+H]+, 503,3 [M-H]- , 549,3 [M+HCOO]- , 1007,7 [2M+HCOO]- ; tr (f): 2,08 min.
563		3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 4- fluoro- 1- {2- [3- (2- hidroxi- acetil)- indol- 1- il]- acetil}- pirrolidina- 2- carboxílico	(4 [A13], 5) Sólido blanco. 490,1 [M+H]+, 485,5 [M-H]- ; t_R (c): 4,39 min.
564		3- bromo- 2- fluoro- bencilamida del ácido (2S,4R)- 4- fluoro- 1- {2- [3- (2- hidroxi- acetil)- indol- 1- il]- acetil}- pirrolidina- 2- carboxílico	(1,4 [A13], 5) Sólido. R_f (CH_2Cl_2/MeOH 9:1) = 0,50; 534,0 [M+H]+; t_R (k): 3,25 min.
565		3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 4- fluoro- 1- {2- - [3- (2- metoxi- acetil)- indol- 1- il]- acetil}- pirrolidina- 2- carboxílico	(4 [A13], 5) Sólido blanco. 504,0 [M+H]+; t_R (c): 4,63 min.

566		Amida del ácido 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- hidroximetil- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico	(3 [B12]) 503 [M- H], 505 [M+H]+; t_R (f): 1,66 min.
567		Amida del ácido 1- {2- [(S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- tiazolidin- 3- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico	Sólido blanco. 475 [M+H]+; t_R (c): 4,32 min.
568		[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etil]- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico	(2,3 [B9]). Sólido blanco.R_f (EtOAc) = 0,35; 511,9 [M+H]+, 510,1 [M- H]- , 556,2 [M+HCOO]- ; t_R (a): 3,43 min.

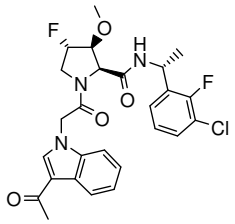
(1) La bencilamina sustituida o derivado de anilina usado en el paso A se preparó como se describe en la Parte C; (2) HCl (4 M en dioxano) en lugar de TFA en la etapa B; (3) el compuesto del título se preparó según el procedimiento general descrito en el Esquema D6 pasos B y C a partir del derivado de prolina sustituido preparado como se describe en la Parte B [Esquema]; (4) El compuesto se preparó como se describe en el Esquema D7 usando el derivado de ácido (3- carbamoil- indol- 1- il)- acético o el derivado de ácido (3- acetil- indol- 1- il)- acético (preparado como se describe en la Parte A); (5) se utilizó DMF en lugar de CH_2Cl_2 en la etapa C; (6) HATU se utilizó como el acoplamiento reactivo en el paso C.

Ejemplo 569:3- cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- acetil- indol- 1- il)- acetil]- 4- fluoro- 3- etoxi- pirrolidina- 2- carboxílico



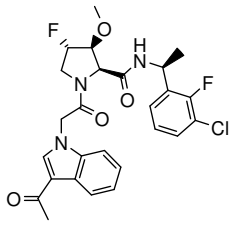
El compuesto del título se preparó según el Esquema D7 a partir de 3- cloro- 2- fluoro-bencilamida del ácido (2S,3S,4S)- 4- fluoro- 3- etoxi- pirrolidina- 2- carboxílico (preparado como se describe en el Esquema B24usando yoduro de etilo en lugar de yoduro de metilo en la Etapa B). MS (UPLC- MS): 518 [M+H]+, 562 [M+HCOO]- ; t_R (condiciones de HPLC F): 2,11 min.

Ejemplo 570:[(R)- 1- (3- cloro- 2- fluoro- fenil)- etil]- amida del ácido (2S,3S,4S)- 1- [2- (3- acetil- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico



El compuesto del título se preparó según el Esquema D7 a partir de (R)- 1- (3- cloro- 2- fluoro- fenil)- etil]- amida del ácido (2S,3S,4S)- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico preparada como se describe en el Esquema B24 usando (R)- 1- (3- cloro- 2- fluorofenil) etanamina en el paso D. MS (UPLC- MS): 562 [M+HCOO]- , 518 [M+H]+; t_R (condiciones de HPLC f): 2,11 min.

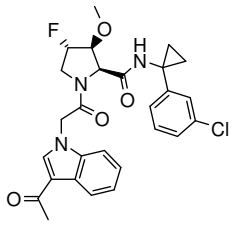
Ejemplo 571:[(S)- 1- (3- cloro- 2- fluoro- fenil)- etil]- amida del ácido (2S,3S,4S)- 1- [2- (3- acetil- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico



El compuesto del título se preparó según el Esquema D7 a partir de (S)- 1- (3- cloro- 2- fluoro- fenil)- etil]- amida del ácido (2S,3S,4S)- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico preparada como se describe en el Esquema B24 usando (S)- 1- (3- cloro- 2-

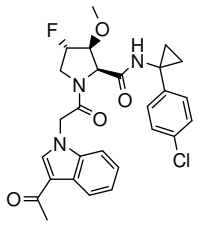
fluorofenil)etanamina en el paso D. MS (UPLC- MS): 562 [M+HCOO]- , 518 [M+H]+; t_R (condiciones de HPLC f): 2,09 min.

Ejemplo 572:[1- (3- cloro- fenil)- ciclopropil]- amida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico



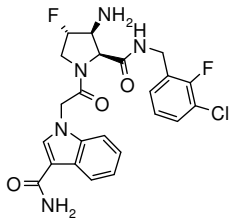
El compuesto del título se preparó según el Esquema D7 a partir de ester terc- butilo del ácido (2S,3S,4S)- 2- [1- (3- cloro- fenil)- ciclopropilcarbamoil]- 4- fluoro- 3- metoxi- pirrolidina- 1- carboxílico (preparado usando los mismos protocolos que se describen en el Esquema B24 utilizando 1- (3- cloro- fenil)- ciclopropilamina en la Etapa D). La preparación de 1- (3- cloro- fenil)- ciclopropilamina se describe en la Parte C. MS (UPLC- MS): 556 [M+HCOO]- , 512 [M+H]+; t_R (condiciones de HPLC f): 2,05 min.

Ejemplo 573: [1- (4- cloro- fenil)- ciclopropil]- amida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico



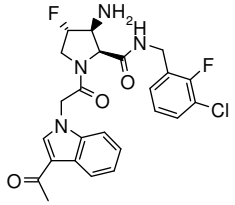
El compuesto del título se preparó según el Esquema D7 a partir de ester terc- butilo del ácido (2S,3S,4S)- 2- [1- (3- cloro- fenil)- ciclopropilcarbamoil]- 4- fluoro- 3- metoxi- pirrolidina- 1- carboxílico (preparado usando los mismos protocolos que se describen en el Esquema B24 utilizando 1- (4- cloro- fenil)- ciclopropilamina en la Etapa D). La preparación de 1- (4- cloro- fenil)- ciclopropilamina se describe en la Parte C. MS (UPLC- MS): 556 [M+HCOO]- , 512 [M+H]+; t_R (condiciones de HPLC f): 2,05 min.

Ejemplo 574:Amida del ácido1- {2- [(2S,3S,4S)- 3- amino- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico



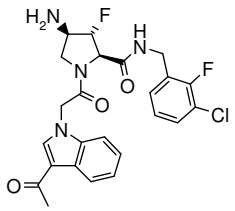
El compuesto del título se preparó según el Esquema D7 a partir de ester terc- butilo del ácido (2S,3S,4S)- 3- azido- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico (descrito en el esquema B19) seguido de la reducción de la azida como se describe para la preparación del **Ejemplo 411**2- (3- cloro- 2,6- difluoro- bencilamida)de 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico. TLC, R_f (CH_2Cl_2/MeOH 95/5) = 0,2; MS (LC- MS): 490 [M+H]+, 488 [M- H]- ; t_R (condiciones de HPLC F): 1,46 min.

Ejemplo 575:3- cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- acetil- indol- 1- il)- acetil]- 3- amino- 4- fluoro- pirrolidina- 2- carboxílico



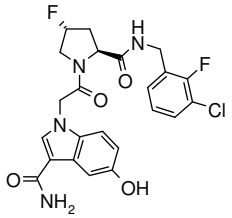
El compuesto del título se preparó según el Esquema D7a partir de una mezcla de ester terc- butilo del ácido (2R,3S,4R) y (2S,3S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- (9H- fluoren- 9- ilmetoxicarbonilamino)- 3- fluoro- pirrolidina- 1- carboxílico en una relación de 2:1 (preparado como se describe en Esquema B22) seguido de la desprotección Fmoc utilizando el protocolo descrito para la preparación del **Ejemplo 396**.Los regioisómeros se separaron por HPLC preparativa para proporcionar el compuesto del título: MS (UPLC- MS): 489 [M+H]+, 533 [M- H]- ; t_R (condiciones de HPLC F): 1,62 min.

Ejemplo 576:3- cloro- 2- fluoro- bencilamida del ácido (2R,3S,4R)- 1- [2- (3- acetil- indol- 1- il)- acetil]- 4- amino- 3- fluoro- pirrolidina- 2- carboxílico



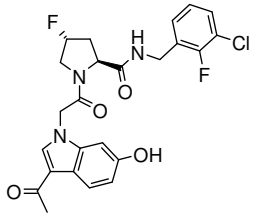
El compuesto del título se preparó según el Esquema D7a partir de una mezcla de ester terc- butilo del ácido (2R,3S,4R) y (2S,3S,4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- (9H- fluoren- 9- ilmethoxicarbonilamino)- 3- fluoro- pirrolidina- 1- carboxílicoen una relación de 2:1 (preparado como se describe en el Esquema B22) seguido de la desprotección Fmoc utilizando los protocolos descritos para la preparación del **Ejemplo 396**. TLC, R_f (CH_2Cl_2/MeOH 95/5) = 0,26; MS (UPLC- MS): 489 [M+H]+, 533 [M+HCOO]- ; t_R (condiciones de HPLC f): 1,63 min.

Ejemplo 577: Amida del ácido1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 5- hidroxi- 1H- indol- 3- carboxílico



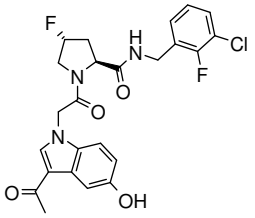
A una suspensión de amida del ácido5- benziloxi- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico Eje**mplo 503**(148 mg, 0,255 mmol) en TFA (2,5 ml), se enfrió a 0 °C, se añadió tioanisol (0,301 ml, 2,55 mmoles), y la mezcla de reacción se agitó a temperatura ambiente durante 3 h. Los volátiles se evaporaron bajo presión reducida, y el residuo se suspendió en una solución de $NaHCO_3$ acuosa saturada, seguido de secado por congelación al vacío. El residuo se suspendió en una pequeña cantidad de metanol y el sólido se separó por filtración. El filtrado se purificó mediante HPLC preparativa (Sunfire, C18- ODB, 5 µm, 30x100 mm, flujo: 40 ml/min, 20-100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN y H_2O que contiene 0,1 % de TFA). El compuesto del título se obtuvo como un sólido de color blanco. MS (LC/MS): 491 [M+H]+; 983 [2M+H]+; t_R (HPLC, condiciones B): 3,75 min.

Ejemplo 578: Amida del ácido1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 6- hidroxi- 1H- indol- 3- carboxílico



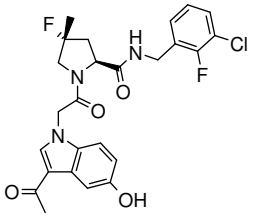
El compuesto del título se preparó de una manera similar a la descrita anteriormente para el **Ejemplo 577** a partir de amida del ácido (6- benciloxi- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico Ejemplo **529**(220 mg, 0,379 mmol). Sólido blanco. MS (LC/MS): 491 [M+H]+; t_R (condiciones de HPLC b): 3,76 min.

Ejemplo 579: 3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- acetil- 5- hidroxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico



El compuesto del título se preparó de una manera similar a la descrita para el **Ejemplo 577** a partir de 3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- acetil- 5- benciloxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico **Ejemplo 508**(167 mg, 0,288 mmol). Sólido blanco. MS (LC/MS): 490 [M+H]+; t_R (condiciones de HPLC k): 3,03 min.

Ejemplo 580: 3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 5- hidroxi- indol- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico

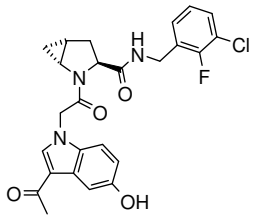


El compuesto del título se preparó de una manera similar a la descrita anteriormente para el **Ejemplo 577** a partir de 3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- acetil- 5- benciloxi- indol- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico (57,0 mg, 0,096 mmol), TFA (3 ml), y tioanisol (0,114 ml, 0,960 mmol). Sólido. MS (LC/MS): 504 [M+H]+; t_R (HPLC, condiciones k): 3,22 min.

3- Cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- acetil- 5- benciloxi- indol- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico

Se preparó como se describe en el Esquema D7 a partir de ácido (3- acetil- 5- benciloxi- indol- 1- il)- acético (preparado como se describe en la parte A) utilizando DMF en lugar de CH_2Cl_2 en el Paso C. Sólido blanco. MS (LC/MS): 594 [M+H]+; t_R (condiciones de HPLC k): 3,89 min.

Ejemplo 581: 3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- 5- hidroxi- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico

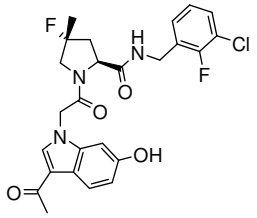


El compuesto del título se preparó de una manera similar a la descrita anteriormente para el **Ejemplo 577** a partir de 3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- acetil- 5- benciloxi- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico (79,0 mg, 0,138 mmol), TFA (3 ml) y tioanisol (0,163 ml, 1,38 mmol). Sólido. MS (LC/MS): 484 [M+H]+; t_R (HPLC, condiciones k): 3,18 min.

3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- acetil- 5- benciloxi- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico

se preparó como se describe en el Esquema D7 a partir del ácido (3- acetil- 5- benciloxi- indol- 1- il)- acético (preparado como se describe en la parte A) utilizando DMF en lugar de CH_2Cl_2 en el Paso C. Sólido blanco. MS (LC/MS): 574 [M+H]+; t_R (condiciones de HPLC k): 3,88 min.

Ejemplo 582: **3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 6- hidroxi- indol- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico**



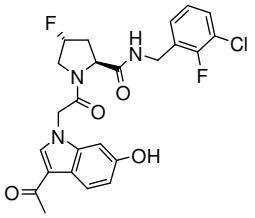
El compuesto del título se preparó de una manera similar a la descrita anteriormente para el **Ejemplo 577** a partir de 3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3-

acetil- 6- benciloxi- indol- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico (96,0 mg, 0,137 mmol), TFA (2 ml) y tioanisol (0,162 ml, 1,374 mmol). Sólido. MS (LC/MS): 504 [M+H]+; t_R (HPLC, condiciones k): 3,26 min.

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- acetil- 6- benciloxi- indol- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico

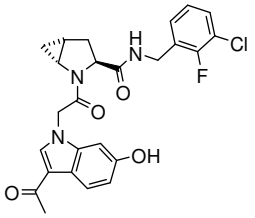
se preparó como se describe en el Esquema D7 a partir de ácido (3- acetil- 6- benciloxi- indol- 1- il)- acético (preparado como se describe en la parte A) utilizando DMF en lugar de CH_2Cl_2 en el Paso C. Sólido. MS (LC/MS): 594 [M+H]+; t_R (condiciones de HPLC k): 3,94 min.

Ejemplo 583:3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- acetil- 6- hidroxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico



El compuesto del título se preparó de una manera similar a la descrita para el **Ejemplo 577** a partir de 3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- acetil- 6- benciloxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico Eje**mplo 534**(100 mg, 0,172 mmol). Sólido blanco. MS (LC/MS): 490 [M+H]+, 512 [M+Na]+; t_R (condiciones de HPLC k): 3,15 min.

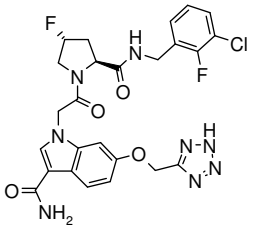
Ejemplo 584: 3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- acetil- 6- hidroxi- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico



El compuesto del título se preparó de una manera similar a la descrita para el **Ejemplo 577** a partir de 3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- acetil- 6-

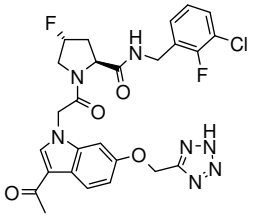
benciloxi- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico **Ejemplo 536**(360 mg, 0,527 mmol). Sólido. MS (LC/MS): 484 [M+H]+; t_R (condiciones de HPLC k): 3,21 min.

Ejemplo 585:Amida del ácido1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 6- (1H- tetrazol- 5- ilmetoxi)- 1H- indol- 3- carboxílico



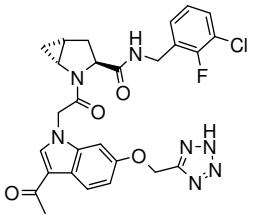
Una solución de amida del ácido1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 6- hidroxi- 1H- indol- 3- carboxílico Eje**mplo 578**(148 mg, 0,283 mmol) en DMSO (3 ml) se trató con Cs_2CO_3 (0,28 g, 0,85 mmol). La mezcla se agitó a temperatura ambiente durante 5 min, seguido de la adición de 5- (clorometil)- 1H- tetrazol (35 mg, 0,098 mmoles) y agitación a temperatura ambiente durante 36 h. La mezcla de reacción se neutralizó mediante adición de HCl 1N. Después se añadió agua a la mezcla para formar un precipitado. El material sólido se separó por filtración, se lavó con agua, y se secó a vacío para proporcionar el compuesto del título como un sólido. MS (LC/MS): 573 [M+H]+; t_R (condiciones de HPLC k): 2,92 min.

Ejemplo 586: 3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- {2- [3- acetil- 6- (1H- tetrazol- 5- ilmetoxi)- indol- 1- il]- acetil}- 4- fluoro- irrolidine- 2- carboxílico



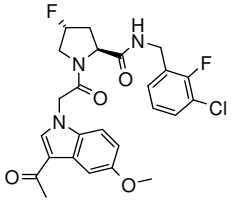
El compuesto del título se preparó de una manera similar a la descrita anteriormente para el **Ejemplo 585**a partir de 3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- acetil- 6- hidroxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico **Ejemplo 583**(60,0 mg, 0,122 mmol), carbonato de cesio (120 mg, 0,367 mmol) y 5- (clorometil)- 1H- tetrazol (44,0 mg, 0,366 mmol) en DMSO (2,5 ml). Sólido.MS (LC/MS): 572 [M+H]+; t_R (condiciones de HPLC k): 3,23 min.

Ejemplo 587: 3- Cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- {2- [3- acetil- 6- (1H- tetrazol- 5- ilmetoxi)- indol- 1- il]- acetil}- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico



Una solución de 3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- acetil- 6- hidroxi- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico Eje**mplo 584**(80,0 mg, 0,165 mmol) en DMSO (2 ml) se trató con carbonato de cesio (162 mg, 0,496 mmol). Después de agitar a temperatura ambiente durante 5 min, 5- (clorometil)- 1H- tetrazol (21,0 mg, 0,174 mmol) se añadió y la agitación se continuó a temperatura ambiente durante 36 h. La mezcla se neutralizó mediante la adición de HCl 1 N, se diluyó con agua, se extrajo con EtOAc (2x). Las capas orgánicas combinadas se lavaron con agua (2x) y salmuera. La suspensión resultante se filtró sobre separador de fases y se concentró. El sólido filtrado se trituró con metanol, se decantó y se secó al vacío para proporcionar el compuesto del título. El filtrado se purificó mediante HPLC preparativa (Macherey- Nagel Nucleosil 100- 10 C18, 5 µm, 40x250 mm, flujo: 40 mL/min, eluyente: 20- 100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN y H_2O que contiene 0,1% de TFA)para proporcionar, después de la liofilización de las fracciones purificadas,un segundo lote del compuesto del título como un sólido blanco. MS (LC/MS): 566 [M+H]+; t_R (condiciones de HPLC k): 3,22 min.

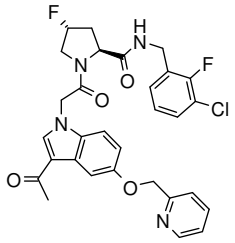
Ejemplo 588: 3- Cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- acetil- 5- metoxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico



Una solución de 3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- acetil- 5- hidroxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico Eje**mplo 579**(28,0 mg, 0,057 mmol) en DMSO (2 ml) se trató con hidróxido de potasio (15,0 mg, 0,257 mmol). La mezcla se agitó a temperatura ambiente durante 5 min, seguido de la adición de yodometano (0,006 ml, 0,089 mmoles) y agitación a temperatura ambiente durante 60 h. La mezcla de reacción se

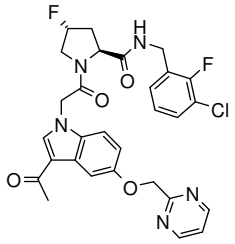
particionó entre agua y CH_2Cl_2 y la capa acuosa se extrajo con CH_2Cl_2 (2x). Los extractos orgánicos combinados se lavaron con salmuera (3x), se secaron (separador de fases) y se concentraron a presión reducida. El producto crudose purificó mediante HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 19x50 mm, flujo: 20 ml/min, eluyente: 5- 100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN y H_2O que contiene 0,1% de TFA)para proporcionar,después de la liofilización de las fracciones purificadas, el compuesto del título como un sólido. MS (LC/MS): 504 [M+H]+, 526 [M+Na]+; t_R (condiciones de HPLC k): 3,38 min.

Ejemplo 589: 3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- {2- [3- acetil- 5- (piridin- 2- ilmetoxi)- indol- 1- il]- acetil}- 4- fluoro- pirrolidina- 2- carboxílico



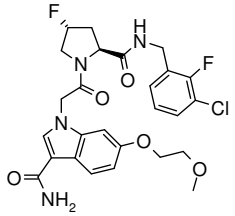
Una solución de 3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- acetil- 5- hidroxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico Eje**mplo 579**(60,0 mg, 0,122 mmol) en DMSO (2,5 ml) se trató con carbonato de cesio (160 mg, 0,490 mmol). Después de agitar a temperatura ambiente durante 5 min, 2- (bromometil)piridina (31,0 mg, 0,122 mmol) se añadió a la mezcla de reacción y se continuó la agitación a temperatura ambiente durante 16 h. Después se añadió agua a la mezcla para formar un precipitado sólido que se separó por filtración, se lavó con agua y se secó al vacío. La purificación por HPLC preparativa (Waters Sunfire, C18- ODB, 5 µm, 30x100 mm, flujo: 40 ml/min, eluyente: 20- 100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN y H_2O que contiene 0,1 % de TFA)proporcionó, después de la liofilización de las fracciones purificadas, el compuesto del título en forma de un sólido blanco. MS (LC/MS): 580/581 [M+H]+; t_R (condiciones de HPLC k): 3,00 min.

Ejemplo 590: 3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- {2- [3- acetil- 5- (pirimidin- 2- ilmetoxi)- indol- 1- il]- acetil}- 4- fluoro- pirrolidina- 2- carboxílico



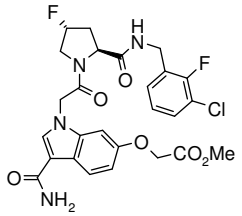
El compuesto del título se preparó de acuerdo al procedimiento descrito para la preparación del **Ejemplo 589**3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- {2- [3- acetil- 5- (piridin- 2- ilmetoxi)- indol- 1- il]- acetil}- 4- fluoro- pirrolidina- 2- carboxílico a partir de 3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- acetil- 5- hidroxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico **Ejemplo 579**(23,0 mg, 0,047 mmol), carbonato de cesio (61 mg, 0,188 mmol) y 2- (clorometil)pirimidina (0,012 mg, 0,070 mmol) en DMSO (2 ml). Sólido blanco.MS (LC/MS): 582/583 [M+H]+; t_R (condiciones de HPLC k): 3,19 min.

Ejemplo 591:Amida del ácido1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 6- (2- metoxi- etoxi)- 1H- indol- 3- carboxílico



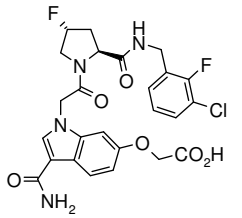
Una solución de amida del ácido1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 6- hidroxi- 1H- indol- 3- carboxílico Eje**mplo 578**(50 mg, 0,102 mmol) en DMSO (1 ml) se trató con KOH (26,0 mg, 0,458 mmol). La mezcla se agitó a temperatura ambiente durante 5 min, seguido de la adición de éter (2- bromoetil)- metílico (0,015 ml, 0,158 mmoles) y agitación a temperatura ambiente durante 2 h. La mezcla se repartió entre agua y CH_2Cl_2 y la fase acuosa se extrajo dos veces con CH_2Cl_2. Los extractos orgánicos combinados se lavaron con salmuera (3x), se secaron (separador de fases) y se concentraron a presión reducida. La purificación mediante HPLC preparativa (SunFire C18- ODB, 5 µm, 30x100 mm, eluyente: 20- 100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN y H_2O que contiene 0.1% de TFA, flujo: 40 mL/min) proporcionó después de la liofilización de las fracciones purificadas el compuesto del título en forma de un sólido blanco. MS: 549 [M+H]+; t_R (condiciones de HPLC c): 4,17 min.

Ejemplo 592: Ester metilo del ácido (3- carbamoil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- iloxi)- acético



Una solución de amida del ácido1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 6- hidroxi- 1H- indol- 3- carboxílico Ej**emplo 578**(140 mg, 0,285 mmol) en DMSO (3 ml) se trató con Cs_2CO_3 (0,28 g, 0,85 mmol). La mezcla se agitó a temperatura ambiente durante 5 min, seguido de la adición de 2- bromoacetato de metilo (0,039 ml, 0,428 mmoles) y agitación a temperatura ambiente durante 4 h. La mezcla se particionó entre agua y CH_2Cl_2 y la fase orgánica se lavó dos veces con salmuera (los lavados acuosos combinados se filtraron y el sólido así obtenido se secó al vacío para proporcionar una alícuota del compuesto del título), se secó (separador de fases) y se concentró bajo presión reducida. La purificación mediante HPLC preparativa (SunFire C18- ODB, 5 µm, 30x100 mm, eluyente: 20- 100% CH_3CN/H_2O/20 min, 100% CH_3CN/2 min, CH_3CN y H_2O que contiene 0.1% de TFA, flujo: 40 mL/min) proporcionó después de la liofilización de las fracciones purificadas el compuesto del título en forma de un sólido blanco. MS: 563 [M+H]+; t_R (condiciones de HPLC c): 4,17 min.

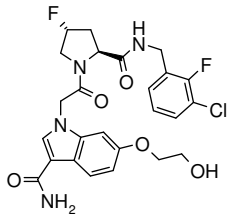
Ejemplo 593: ácido (3- Carbamoil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- iloxi)- acético



A una solución de éster metílico del ácido (3- carbamoil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pyirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- iloxi)- acético **Ejemplo 592**(18 mg, 0,032 mmol) en una mezcla de THF (2 ml) y agua (0,2 ml) se agregó NaOH 1 N (0,064 ml), seguido de agitación a temperatura ambiente durante 4 h. La mezcla de reacción se particionó entre CH_2Cl_2 y agua. La fase acuosa se ajustó a pH = 2 por adición de HCl 1N, seguido de la extracción con CH_2Cl_2 (3x). Los extractos orgánicos combinados se secaron (separador de fases) y se concentraron bajo presión reducida para

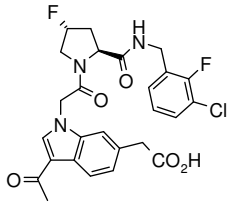
proporcionar el compuesto de título como un sólido blanco. MS: 549 [M + H] +; t_R (condiciones HPLC C): 3,74 min.

Ejemplo 594: Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 6- (2- hidroxi- etoxi)- 1H- indol- 3- carboxílico



A una solución de éster metílico del ácido (3- carbamoil- 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- iloxi)- acético **Ejemplo 592**(30,0 mg, 0,049 mmol) en THF (1 ml) se añadió LiBH4 (2M en THF, 0,049 ml, 0,098 mmol) y se continuó la agitación a temperatura ambiente durante 2 h. La mezcla de reacción se particionó entre CH_2Cl_2 y agua, y la capa acuosa se extrajo con CH_2Cl_2 (3x). Los extractos orgánicos combinados se secaron (separador de fase) y se concentraron bajo presión reducida. La purificación por HPLC preparativa (SunFire C18- ODB, 5 m, 19x50 mm, eluyente: 5- 100% CH_3CN/H_2O/20 min, CH_3CN al 100%/ 2 min, CH_3CN y H_2O que contiene TFA al 0.1%, flujo: 20 mL / min) proporcionó después de la liofilización de las fracciones purificadas del compuesto deseado como un sólido blanco. MS: 535 [M + H] +; t_R (condiciones de HPLC C): 3,72 min.

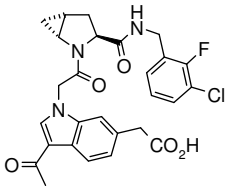
Ejemplo 595: ácido (3- acetil- 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- il)- acético



A una solución de éster metílico del ácido 3- acetil- 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- il)- acético **Ejemplo 549**(200 mg, 0,366 mmol) en THF (5 ml) y agua (0,5 ml) se le añadió 1N NaOH (1,46 ml, 1,46 mmol) y la reacción se agitó a temperatura ambiente durante 60 h. La mezcla se particionó entre éter dietílico y agua. Las capas se separaron y la fase acuosa se ajustó a pH = 2 mediante la adición de una solución de HCl 1 N para formar un precipitado. El sólido se separó

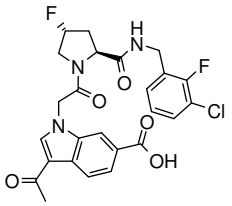
por filtración, se lavó con agua y éter dietílico y se secó al vacío para proporcionar el compuesto del título como un sólido. MS (LC / MS): 532 [M + H] +; tR (condiciones de HPLC k): 3,19 min.

Ejemplo 596: ácido (3- acetil- 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 6- il)- acético



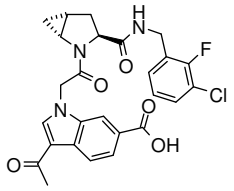
El compuesto del título se preparó de una manera similar a la descrita para el **Ejemplo 595** a partir de éster metílico del ácido (3- acetil- 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 6- il)- acético **Ejemplo 545** (200 mg, 0,370 mmol). Sólido. MS (LC / MS): 526 [M + H] +; tR (condiciones de HPLC k): 3,24 min.

Ejemplo 597: ácido 3- Acetil- 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- carboxílico

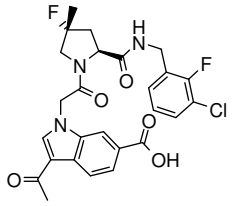


El compuesto del título se preparó de una manera similar a la descrita para el **Ejemplo 595** a partir de éster metílico del ácido 3- acetil- 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- carboxílico **Ejemplo 542** (200 mg, 0,370 mmol). Sólido. MS (LC / MS): 518 [M + H] +; tR (condiciones HPLC k): 3,14 min.

Ejemplo 598: ácido 3- acetil- 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 6- carboxílico

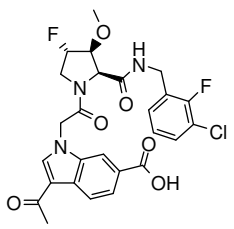


Ejemplo 599: ácido 3- Acetil- 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- carboxílico



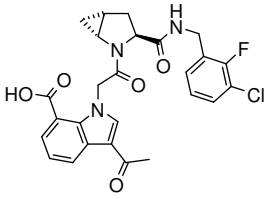
El compuesto del título se preparó de una manera similar a la descrita para el **Ejemplo 595** a partir de éster metílico del ácido 3- acetil- 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- carboxílico **Ejemplo 548** (70 mg, 0,128 mmol). Sólido. MS (LC / MS): 532 [M + H] +; t_R (condiciones HPLC C): 4,34 min.

Ejemplo 600: 1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S, 3S, 4S)- 4- fluoro- 3- metoxi- pirrolidina- 1 ,2- dicarboxílico



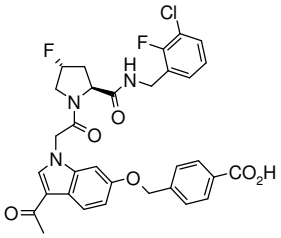
El compuesto del título se preparó de una manera similar a la descrita para el **Ejemplo 595** a partir de 3- cloro- 2- fluoro- bencilamida del ácido (2S, 3S, 4S)- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico (preparado como se describe en el Esquema D7 a partir de éster metílico del ácido 3- acetil- 1- carboximetil- 1H- indol- 6- carboxílico (descrito en la Parte C) y 3- cloro- 2- fluoro- bencilamida del ácido (2S, 3S, 4S)- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico (Esquema describe B24) MS (UPLC- MS): 548 [M + H] +, 592 [M + HCOO]- ; tR (condiciones HPLC f):. 1.84 min.

Ejemplo 601: ácido 3- Acetil- 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 7- carboxílico



A una solución de éster metílico del ácido 3- acetil- 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 7- carboxílico **Ejemplo 541** (110 mg, 0,209 mmol) en THF (3 ml) y agua (0,3 ml) se le añadió LiOH 2 N (1,05 ml, 2,09 mmol). La agitación de la mezcla de reacción se continuó a temperatura ambiente durante 18 h. Se añadió una solución de HCl 1 N para ajustar a pH = 2- 3 y la suspensión acuosa resultante se filtró. El sólido se lavó con agua y después se secó al vacío. El residuo se purificó por HPLC preparativa (Waters Sunfire, C18- ODB, 5 micras, 30x100 mm, flujo: 40 ml / min, eluyente: 20- 100% CH3CN/H2O/20 min, 100% CH3CN / 2 min, CH3CN y H2O que contiene TFA al 0,1%) para dar después de la liofilización de las fracciones purificadas el compuesto del título en forma de un sólido blanco. MS (LC / MS): 512 [M + H] +; tR (condiciones HPLC k): 3,34 min.

Ejemplo 602: ácido 4- (3- Acetil- 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- iloximetil)- benzoico

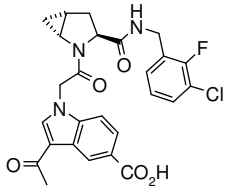


El compuesto del título se preparó de una manera similar a la descrita para el **Ejemplo 595** a partir de éster metílico del ácido 4- (3- acetil- 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- iloximetil)- benzoico (37,0 mg, 0,058 mmol) y NaOH 1 N (0,928 ml, 0,928 mmol) en THF (5 ml) y agua (0,5 ml). Sólido. MS (LC / MS): 624/626 [M + H] +; tR (condiciones HPLC k): 3,48 min.

<u>Éster metílico del ácido 4- (3- Acetil- 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- iloximetil)- benzoico</u>

Una solución de 3- cloro- 2- fluoro- bencilamida del ácido (2S, 4R)- 1- [2- (3- acetil- 6- hidroxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico **Ejemplo 583** (60,0 mg, 0,122 mmol) en DMSO (2,5 ml) se trató con carbonato de cesio (160 mg, 0,490 mmol). Después de agitar a temperatura ambiente durante 5 min, se añadió 4- (bromometil)benzoato de metilo (28,0 mg, 0,122 mmol) y la reacción se agitó a temperatura ambiente durante 1 h. La mezcla se neutralizó con HCl 1 N y se diluyó con agua para formar un precipitado. El sólido se separó por filtración, se lavó con agua y se secó al vacío. El producto bruto se purificó por HPLC preparativa (Waters Sunfire, C18- ODB, 5 micras, 30x100 mm, flujo: 40 ml / min, eluyente: 20- 100% CH_3CN/H_2O/20 min, 100% CH_3CN / 2 min, CH_3CN y H_2O que contiene TFA al 0,1%) para proporcionar después de la liofilización, el compuesto del título como un sólido blanco. MS (LC / MS): 639 [M + H] +; tR (condiciones HPLC k): 3,82 min.

Ejemplo 603: ácido 3- acetil- 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 5- carboxílico

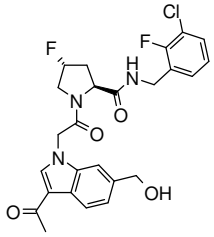


A una solución de éster metílico del ácido 3- acetil- 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 5- carboxílico (141 mg, 0,268 mmol) en THF (3 ml) y agua (0,3 ml) se añadió LiOH 2 N (1,07 ml, 2,14 mmol). La agitación de la mezcla de reacción se continuó a 50 ° C durante 60 h. Después de enfriar a temperatura ambiente, se añadió una solución de HCl 1 N para ajustar a pH = 2- 3, y la suspensión acuosa resultante se extrajo con CH_2Cl_2 (3x). Los extractos orgánicos combinados se secaron (separador de fase) y se concentraron a presión reducida. El residuo se purificó por HPLC preparativa (Waters Sunfire, C18- ODB, 5 micras, 30x100 mm, flujo: 40 ml / min, eluyente: 20- 100% CH_3CN/H_2O/20 min, 100% CH_3CN / 2 min, CH_3CN y H_2O que contiene TFA al 0,1%) para proporcionar después de la liofilización de las fracciones purificadas el compuesto del título en forma de un sólido blanco. MS (LC / MS): 512 [M + H] +; tR (condiciones HPLC C): 4,33 min.

Éster metílico del ácido 3- Acetil- 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 5- carboxílico

El compuesto del título se preparó como se describe en el Esquema D7 a partir de éster metílico del ácido 3- acetil- 1- carboximetil- 1H- indol- 5- carboxílico (preparado como se describe en la Parte A) y mediante el uso de DMF en lugar de CH_2Cl_2. Sólido. MS (LC / MS): 526 [M + H] +, 548 [M + Na] +; tR (condiciones HPLC k): 3,54 min.

Ejemplo 604: 3- cloro- 2- fluoro- bencilamida del ácido (2S, 4R)- 1- [2- (3- Acetil- 6- hidroximetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico

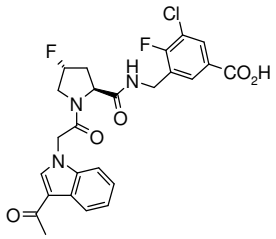


A una solución de 3- Cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- acetil- 6- triisopropilsilaniloximetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico (50,0 mg, 0,057 mmol) en THF (5 ml), se enfrió a 0 ° en C, se añadió TBAF (1 M en THF, 0,057 ml, 0,057 mmol), y se continuó la agitación durante 3 h. La reacción se inactivó con $NaHCO_3$ acuoso saturado seguido de la adición de EtOAc. Las capas se separaron y la fase acuosa se extrajo con EtOAc. Los extractos orgánicos combinados se lavaron con agua (1x) y salmuera, se secaron (separador de fases) y se concentraron al vacío. La purificación por HPLC preparativa (Waters Sunfire, C18- ODB, 5 micras, 30x100 mm, flujo: 40 ml / min, eluyente: 20% CH_3CN/H_2O/20 min, 100% CH_3CN / 2 min, CH_3CN y H_2O que contiene TFA al 0,1%) proporcionó después de la liofilización de las fracciones purificadas el compuesto del título en forma de un sólido blanco. MS (LC / MS): 504 [M + H] +; tR (condiciones HPLC k): 3,10 min.

3- Cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 6- triisopropilsilaniloximetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico

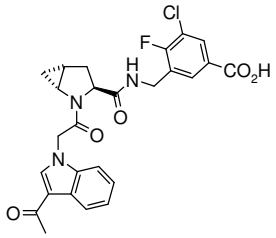
El compuesto del título se preparó como se describe en el Esquema D7 a partir del ácido (3- acetil- 5- triisopropilsilaniloximetil- indol- 1- il)- acético (preparado como se describe en el Esquema A14) y mediante el uso de DMF en lugar de CH_2Cl2. Cera amarilla. MS (LC / MS): 683 [M + Na] +; tR (condiciones HPLC k): 4,72 min.

Ejemplo 605: ácido 3- [({(2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carbonil}- amino)- metil]- 5- Cloro- 4- fluoro- benzoico



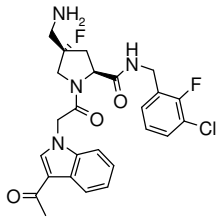
A éster metílico del ácido 3- [({(2S,4R)- 1- [2- (3- acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carbonil}- amino)- metil]- 5- Cloro- 4- fluoro- benzoico **Ejemplo 523** (35,0 mg, 0,066 mmol) en THF- MeOH- H_2O (relación de 02:1:1; 1 ml) se añadió LiOH · H_2O (2,76 mg, 0,066 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 4 h. Los volátiles se evaporaron y el residuo se recogió en agua, ácidoificación a pH = 1 por adición de una solución 6M HCl formó un precipitado que se filtró y se secó a 50 ° C al vacío durante 1 h para proporcionar el compuesto del título como un sólido. MS: 518,0 [M + H] +; tR (condiciones HPLC C): 4,26 min.

Ejemplo 606: ácido 3- [({(1R,3S,5R)- 2- [2- (3- acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carbonil}- amino)- metil]- 5- Cloro- 4- fluoro- benzoico



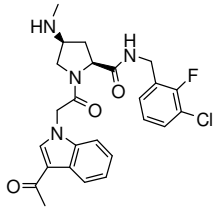
El compuesto del título se preparó de acuerdo al procedimiento descrito para la preparación de ácido 3- [({(2S,4R)- 1- [2- (3- acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carbonil}- amino)- metil]- 5- Cloro- 4- fluoro- benzoico **Ejemplo 605** a partir de éster metílico del ácido 3- [({(1R,3S,5R)- 2- [2- (3- acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carbonil}- amino)- metil]- 5- Cloro- 4- fluoro- benzoico Ejemplo 480. MS: 512,0 [M + H] +; tR (condiciones HPLC C): 4,41 min.

Ejemplo 607: 3- cloro- 2- fluoro- bencilamida del ácido (2S, 4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- aminometil- 4- fluoro- pirrolidina- 2- carboxílico



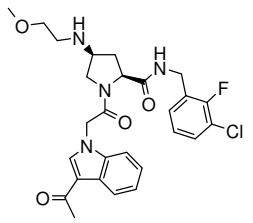
El compuesto del título se preparó de acuerdo con el Esquema D7 a partir de éster terc-butílico del ácido (2S, 4R)- 4- azidometil- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro-pirrolidina- 1- carboxílico (descrito en el esquema B15) usando DMF como disolvente en la etapa C, seguido de la reducción de la azida como se describe para la preparación del **Ejemplo 411** 1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- (3- cloro- 2 ,6- difluoro- bencilamida) del ácido (2S, 4S)- 4- aminometil- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico. MS (UPLC- MS): 503 [M + H] +; tR (f) Condiciones HPLC: 1,60 min; 19F RMN (100 MHz, DMSO- d6) δ (ppm):- 117,- 150.

Ejemplo 608: 3- cloro- 2- fluoro- bencilamida del ácido (2S, 4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- metilamino- pirrolidina- 2- carboxílico



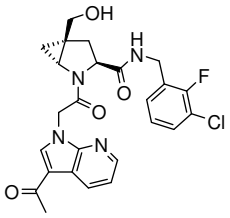
El compuesto del título se preparó de acuerdo con el Esquema D7 éster terc- butílico del ácido (2S,4S)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- [metil- (2,2,2- tricloro-etoxicarbonil)- amino]- pirrolidina- 1- carboxílico (preparado como se describe en el Esquema B6) seguido por la desprotección del grupo protector Troc como se describe para el Ejemplo 424. La purificación por HPLC preparativa (Waters SunFire C18- ODB, 5 micras, 19x50 mm, 5% CH_3CN/H_2O 2,5 min, 5- 100% CH_3CN/H_2O en 10 min, CH_3CN/H_2O que contiene 0,1% HCOOH flujo: 20 ml / min) proporcionó después de la liofilización de las fracciones purificadas el compuesto del título (sal de ácido fórmico). MS (UPLC- MS): 487 [M + H] +; t_R (f) Condiciones HPLC: 1,60 min; 19F RMN (100 MHz, DMSO- d_6) δ (ppm):- 120.

Ejemplo 609: 3- cloro- 2- fluoro- bencilamida del ácido (2S, 4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- ácido (2- metoxi- etilamino)- pirrolidina- 2- carboxílico



El compuesto del título se preparó de acuerdo con el Esquema D7 a partir de éster terc-butílico del ácido (2S,4S)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- [(2- metoxi- etil)- (2,2,2- tricloro- etoxicarbonil)- amino]- pirrolidina- 1- carboxílico (preparado como se describe en el Esquema B6 usando 1- bromo- 2- metoxietano en lugar de yoduro de metilo en la etapa B), seguido por la desprotección del grupo protector Troc como se describe para el Ejemplo 424. La purificación en HPLC preparativa (Waters SunFire C18- ODB, 5 micras, 19x50 mm, 5% CH_3CN/H_2O 2,5 min, 5- 100% CH_3CN/H_2O en 10 min, CH_3CN/H_2O que contiene 0,1% HCOOH flujo: 20 ml / min) proporcionó después de la liofilización de las fracciones purificadas el compuesto del título (sal de ácido fórmico). MS (UPLC / MS): 531 [M + H] +; tR (f) Condiciones HPLC: 1,66 min; 19F RMN (100 MHz, DMSO- d6) δ (ppm):- 120.

Ejemplo 610: 3- cloro- 2- fluoro- bencilamida del ácido (1R, 3S, 5S)- 2- [2- (3- acetil- pirrolo [2,3- b] piridin- 1- il)- acetil]- 5- hidroxi metil- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico



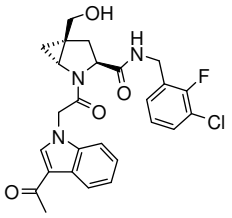
Una solución de éster (1R,3S,5S)- 2- [2- (3- acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]- hex- 5- il- metilo del ácido (3- acetil- pirrolo[2,3- b]piridin- 1- il)- acético (90 mg, 0,115 mmol) y NaOH 1 N (0,58 ml, 0,58 mmol) en THF (0,55 ml) / agua (55 µl) se agitó a temperatura ambiente durante 1 h. Se añadieron agua y CH_2Cl_2, las capas se separaron y la fase acuosa volvió a extraer con CH_2Cl_2 (x3). Los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron. El material en bruto se purificó por HPLC preparativa (Waters Sunfire C18- ODB, 5 micras, 30x100 mm, eluyente: 5% a 100% CH_3CN en H_2O en 25 min, CH_3CN y H_2O que contiene 0.1% TFA, flujo: 40 ml / min). EtOAc y $NaHCO_3$ acuoso saturado se han añadido a las fracciones purificadas combinadas, las capas se separaron y la fase acuosa se volvió a extraer

con EtOAc (x3). Los extractos orgánicos combinados se secaron (Na2SO4), se filtraron y se concentraron para proporcionar el material deseado. TLC, R_f (CH_2Cl_2 / MeOH 9- 1) = 0,45; EM (UPLC / MS): 499.3/501.3 [M + H] +, 521.1/523.2 [M + Na] +; t_R (condiciones HPLC f): 1,73 min .

Éster (1R,3S,5S)- 2- [2- (3- acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0] hex- 5- il- metilo del ácido (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acético

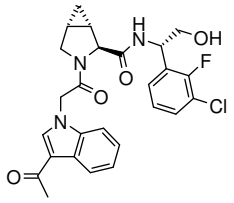
El compuesto de título N, O- bis- acilado se preparó de acuerdo con el Esquema D7 Pasos B y C a partir de éster terc- butílico del ácido (1R,3S,5S)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 5- hidroximetil- 2- aza- biciclo[3.1.0]hexano- 2- carboxílico (preparado como se describe en la Parte B Esquema B28) usando HCl 4 N en dioxano en vez de TFA en la Etapa B y 2 equivalentes del ácido (3- acetil- pirrolo [2,3- b] piridin- 1- il)- acético (descrito en la parte A) en la Etapa C. La purificación por cromatografía en columna ultrarrápida sobre gel de sílice (CH_2Cl_2 a CH_2Cl_2/MeOH 94- 6). TLC, Rf (CH_2Cl_2 / MeOH 9- 1) = 0,48; EM (UPLC / MS): 699.4/701.3 [M + H] +, 743.4/745.4 [M + HCOO]- ; tR (condiciones HPLC f): 2,05 min .

Ejemplo 611: 3- Cloro- 2- fluoro- bencilamida del ácido (1R,3S,5S)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 5- hidroximetil- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico



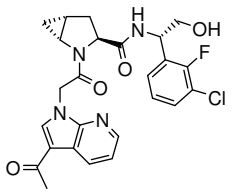
El compuesto del título se preparó en 2 etapas de acuerdo con el procedimiento descrito para la preparación del **Ejemplo 610** 3- Cloro- 2- fluoro- bencilamida del ácido (1R,3S,5S)- 2- [2- (3- acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 5- hidroximetil- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico utilizando ácido (3- acetil- indol- 1- il)- acético en lugar de ácido (3- acetil- pirrolo [2,3- b] piridin- 1- il)- acético. Polvo blanco. TLC, Rf (EtOAc) = 0,05; MS (LC / MS): 498/500 [M + H] +, 520/522 [M + Na] +; tR (condiciones HPLC f): 1,84 min.

Ejemplo 612: [(S)- 1- (3- cloro- 2- fluoro- fenil)- 2hidroxi- etil]- amida del ácido (1S, 2S, 5R)- 3- [2- (3- Acetil- indol- 1- il)- acetil]- 3- aza- biciclo [3.1.0] hexano- 2- carboxílico



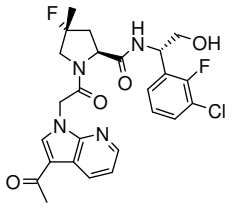
El compuesto del título se preparó en 2 etapas de acuerdo con el procedimiento descrito para la preparación del Ejemplo 610 3- Cloro- 2- fluoro- bencilamida del ácido (1R,3S,5S)- 2- [2- (3- acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 5- hidroximetil- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico a partir de éster tert- butílico del ácido (1S,2S,5R)- 2- [(S)- 1- (3- Cloro- 2- fluoro- fenil)- 2- hidroxi- etilcarbamoil]- 3- aza- biciclo[3.1.0]hexano- 3- carboxílico (preparado usando protocolos similares a los descritos en el Esquema B9) y ácido (3- acetil- indol- 1- il)- acético. Polvo blanco. TLC, R_f (EtOAc) = 0,10; EM (UPLC / MS): 498.3/500.4 [M + H] +, 542.4/544.3 [M + HCOO]- ; t_R (condiciones HPLC A): 3,10 min.

Ejemplo 613: [(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido (1R, 3S, 5R)- 2- [2- (3- acetil- pirrolo [2,3- b] piridin- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico



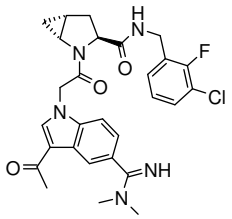
El compuesto del título se preparó en 2 etapas de acuerdo con el procedimiento descrito para la preparación del **Ejemplo 610** 3- Cloro- 2- fluoro- bencilamida del ácido (1R,3S,5S)- 2- [2- (3- acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 5- hidroximetil- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico a partir de éster tert- butílico del ácido (1R,3S,5R)- 3- [(S)- 1- (3- Cloro- 2- fluoro- fenil)- 2- hidroxi- etilcarbamoil]- 2- aza- biciclo[3.1.0]hexano- 2- carboxílico (preparado como se describe en el Esquema B9).Polvo blanco. TLC, Rf (CH_2/Cl_2/EtOAc 09:01) = 0,70; EM (UPLC / MS): 499.3/501.3 [M + H] +, 543.2/545.3 [M + HCOO]- ; t_R (condiciones HPLC a): 3,02 min.

Ejemplo 614: [(S)- 1- (3- Cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido (2S,4R)- 1- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico



El compuesto del título se preparó en 2 etapas de acuerdo con el procedimiento descrito para la preparación del **Ejemplo 610** 3- Cloro- 2- fluoro- bencilamida del ácido (1R,3S,5S)- 2- [2- (3- acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 5- hidroximetil- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico a partir de éster tert- butílico del ácido (2S,4R)- 2- [(S)- 1- (3- Cloro- 2- fluoro- fenil)- 2- hidroxi- etilcarbamoil]- 4- fluoro- 4- metil- pirrolidina- 1- carboxílico (preparado usando protocolos similares a los descritos en el Esquema B9). Polvo blanco. TLC, Rf (CH_2/Cl_2/EtOAc 09:01) = 0,60; EM (UPLC / MS): 519.3/521.3 [M + H] +, 563.3/565.3 [M + HCOO]- ; tR (condiciones HPLC a): 2,96 min.

Ejemplo 615: 3- Cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- {2- [3- Acetil- 5- (N,N- dimetil- carbamimidoil)- indol- 1- il]- acetil}- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico



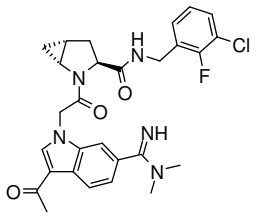
HCl (gas) se burbujeó lentamente durante 3 h en una suspensión de 3- cloro- 2- fluoro- bencilamida del ácido (1R, 3S, 5R)- 2- [2- (3- acetil- 5- ciano- indol- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico (50 mg, 0,1 mmol) en MeOH (3 ml) se enfrió a 0 ° C. La mezcla de reacción se dejó alcanzar la temperatura ambiente y se agitó adicionalmente durante 1 h. Después de la terminación se burbujeó argón para eliminar el exceso de HCl y la mezcla de reacción se concentró. Éster metílico del ácido 3- acetil- 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 5- carboximidico crudo (MS (UPLC / MS): 525.3/527.3 [M + H] +) se diluyó en MeOH (2 ml), dimetilamina (2 M en MeOH, 0,26 ml, 0,524 mmol) se añadió y la mezcla se calentó a reflujo durante la noche. La mezcla de reacción se concentró y el material bruto se purificó por HPLC preparativa (Waters Sunfire C18- ODB, 5 micras, 30x100 mm, 5- 95% de CH_3CN / H_2O, CH_3CN y H_2O que contiene TFA al 0,1% de flujo: 40 ml / min) para proporcionar después de liofilización de las fracciones purificadas el material deseado como una sal de TFA. TLC, Rf

(CH_2Cl_2/MeOH 9:1): 0,65; EM (UPLC / MS): 539.3/541.3 [M + H] +, 583.3/585.4 [M + HCOO]- ; tR (condiciones HPLC A): 3,05 min .

3- cloro- 2- fluoro- bencilamida del ácido (1R, 3S, 5R)- 2- [2- (3- Acetil- 5- ciano- indol- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico

El compuesto del título se preparó de acuerdo con el Esquema D7 a partir del ácido (3- acetil- 5- ciano- indol- 1- il)- acético (preparado como se describe en la Parte C). TLC, Rf (CH_2Cl_2 / MeOH 9- 1) = 0,40; EM (UPLC / MS): 493.3/495.3 [M + H] +, 537.3/539.3 [M + HCOO]- ; tR (condiciones HPLC A): 3,42 min .

Ejemplo 616: 3- Cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- {2- [3- Acetil- 6- (N,N- dimetil- carbamimidoil)- indol- 1- il]- acetil}- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico

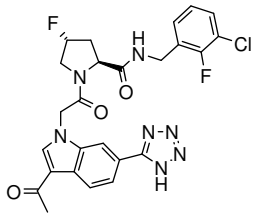


El compuesto del título se preparó de una manera similar a la descrita anteriormente para el **Ejemplo 615** a partir del ácido (3- acetil- 6- ciano- indol- 1- il)- acético (preparado como se describe en la Parte C). TLC, Rf (CH_2Cl_2/MeOH 9:1): 0,65; EM (UPLC / MS): 539.3/541.3 [M + H] + 583.3/585.3 [M + HCOO]- ; t_R (condiciones HPLC A): 3,13 min.

3- cloro- 2- fluoro- bencilamida del ácido (2S, 4R)- 1- [2- (3- acetil- 6- ciano- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico

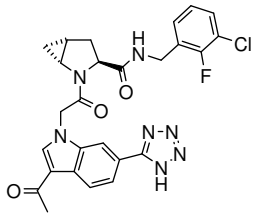
El compuesto del título se preparó de acuerdo con el Esquema D7 a partir del ácido (3- acetil- 6- ciano- indol- 1- il)- acético (preparado como se describe en la Parte C). Polvo. TLC, Rf (CH_2Cl_2 / MeOH 9- 1) = 0,40; EM (UPLC / MS): 493.3/495.3 [M + H] +, 537.3/539.3 [M + HCOO]- ; tR (condiciones HPLC A): 3,46 min .

Ejemplo 617: 3- cloro- 2- fluoro- bencilamida del ácido (2S, 4R)- 1- {2- [3- Acetil- 6- (1H- tetrazol- 5- il)- indol- 1- il]- acetil}- 4- fluoro- pirrolidina- 2- carboxílico



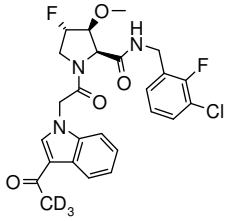
A una suspensión de 3- cloro- 2- fluoro- bencilamida del ácido (2S, 4R)- 1- [2- (3- acetil- 6- ciano- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico (preparada como se describe en **Ejemplo 616** (45,0 mg, 0,09 mmol) en agua (2 ml) e isopropanol (1 ml) a temperatura ambiente se añadieron azida de sodio (24,0 mg, 0,360 mmol) y bromuro de zinc (40,0 mg, 0,180 mmol). La mezcla se calentó a 130 ° C durante 10 h en un aparato de microondas (Química Personnal, Biotage). Después de enfriar a temperatura ambiente, se añadió una solución de HCl 6 N a la mezcla, seguido de extracción con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron (separador de fase) y se concentraron al vacío. La purificación del residuo por HPLC preparativa (Waters Sunfire, C18-ODB, 5 micras, 30x100 mm, eluyente: 20- 100% CH_3CN/H_2O/20 min, 100% CH_3CN / 2 min, CH_3CN y H_2O que contiene 0.1% TFA, flujo : 40 ml / min) proporcionó después de la liofilización, el compuesto del título como sólido. MS (LC / MS): 542,0 [M + H] +; tR (condiciones HPLC k): 3,15 min.

Ejemplo 618: 3- Cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- {2- [3- Acetil- 6- (1H- tetrazol- 5- il)- indol- 1- il]- acetil}- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico



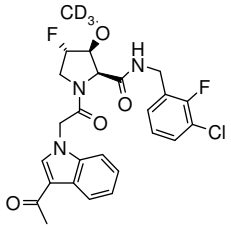
El compuesto del título se preparó de una manera similar a la descrita anteriormente para el **Ejemplo 617** a partir de 3- cloro- 2- fluoro- bencilamida del ácido (1R, 3S, 5R)- 2- [2- (3- acetil- 6- ciano- indol- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico (preparado como se describe en **Ejemplo 616** (100,0 mg, 0,203 mmol), azida de sodio (66,0 mg, 1,014 mmol) y bromuro de zinc (228,0 mg, 1,014 mmol) en agua (2 ml) e isopropanol (1 ml). Sólido blanco. MS (LC / MS): 536,0 [M + H] +; tR (condiciones HPLC k): 3,21 min.

Ejemplo 619: 3- cloro- 2- fluoro- bencilamida del ácido (2S, 3S, 4S)- 1- [2- (3- Acetil- d3- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico



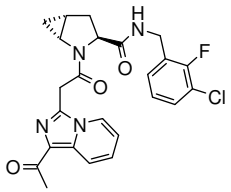
El compuesto del título se preparó de acuerdo con el Esquema D7 a partir de 3- cloro- 2- fluoro- bencilamida del ácido (2S, 3S, 4S)- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico (preparado como se describe en el Esquema B24) y ácido (3- acetil- d3- indol- 1- il)- acético (preparado de una manera similar como se describe en el Esquema A13 usando acetil- d3- cloruro en el paso A) utilizando DMF como disolvente en el paso C. MS (UPLC- MS): 507/509 [M + H] +, 551/553 [M + HCOO]- ; tR (condiciones HPLC f): 2,01 min.

Ejemplo 620: 3- cloro- 2- fluoro- bencilamida del ácido (2S, 3S, 4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- d3- pirrolidina- 2- carboxílico



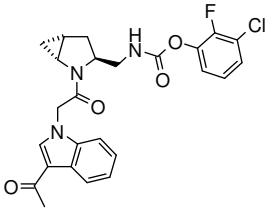
El compuesto del título se preparó de acuerdo con el Esquema D7 a partir de 3- cloro- 2- fluoro- bencilamida del ácido (2S, 3S, 4S)- 4- fluoro- 3- metoxi- d3- pirrolidina- 2- carboxílico (preparado como se describe en el Esquema B24 utilizando metil- d3- yoduro en lugar de yoduro de metilo en la Etapa B). MS (UPLC- MS): 507/509 [M + H] +, 551/553 [M + HCOO]- ; tR (condiciones HPLC f): 2,01 min.

Ejemplo 621: 3- cloro- 2- fluoro- bencilamida del ácido (1R, 3S, 5R)- 2- [2- (1- Acetil- imidazo [1,5- a] piridin- 3- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico



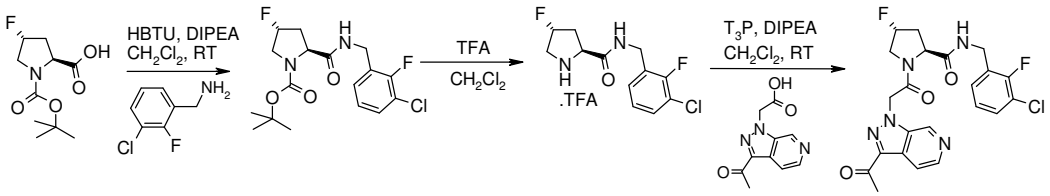
El compuesto del título se preparó de acuerdo con el Esquema D7 utilizando en la Etapa C ácido (1- acetil- imidazo [1,5- a] piridin- 3- il)- acético (preparado como se describe en el Esquema A19) y DMF como disolvente. MS (UPLC- MS): 469.3/471.4 [M + H] +, 513.4/515.5 [M + HCOO]- ; tR (a) Condiciones HPLC: 3,08 min.

Ejemplo 622: éster 3- cloro- 2- fluoro- fenil del ácido {(1R, 3S, 5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hex- 3- ilmetil}- carbámico



A una solución de 3- cloro- 2- fluoro- fenil éster del ácido [(1R, 3S, 5R)- 1- (2- aza- biciclo [3.1.0] hex- 3- il) metil]- carbamato, trifluoroacetato (preparado como se describe en el **Ejemplo 115**) (60,0 mg, 0,211 mmol) en THF (3 mL) se añadió HBTU (120 mg, 0,316 mmol), DIPEA (0,147 ml, 0,843 mmol) y ácido (3- acetil- indol- 1- il)- acético (50 mg, 0,232 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 60 h. Los volátiles se eliminaron a presión reducida y el residuo se purificó por HPLC preparativa (Waters Sunfire, C18- ODB, 5 micras, 30x100 mm, eluyente: 20- 100% CH_3CN/H_2O/20 min, 100% CH_3CN / 2 min, CH_3CN y H_2O que contiene TFA al 0,1%, flujo: 40 ml / min) para proporcionar, después de liofilización de las fracciones purificadas por HPLC el compuesto del título. MS (LC / MS): 484,0 [M + H] +; tR (condiciones HPLC k): 3,69 min.

<u>Esquema D8: preparación del Ejemplo 623: formiato de 3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- pirazolo[3,4- c]piridin- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico</u>



A. Éster terc- butílico del ácido (2S, 4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxílico

A una solución de éster 1- terc- butílico del ácido (2S, 4R)- 4- fluoro- pirrolidina- 1 ,2- dicarboxílico (3,97 g, 17,02 mmol) en CH_2Cl_2 (34 ml) se añadieron sucesivamente 3- cloro- 2- fluoro- bencilamina (2,35 ml, 18,72 mmol), HBTU (9,68 g, 25,5 mmol) y DIPEA (8,92 ml, 51,1 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 h. Se añadió agua y se separaron las fases. La capa orgánica se lavó sucesivamente con HCl 0,1 N (2x), sat. aq. $NaHCO_3$ (2x) y salmuera, después se secó (separador de fase) y se concentró al vacío. El aceite residual se purificó por medio de cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano / EtOAc 9- 1 a 1- 1). MS (LC / MS): 397 [M + Na] +, 319 [MH- tBu] +; 275 [MH- Boc] +; tR (condiciones HPLC k): 3,52 min.

DMF también se puede utilizar en lugar de diclorometano.

B. Trifluoroacetato 3- cloro- 2- fluoro- bencilamida del ácido (2S, 4R)- 4- fluoro- pirrolidina- 2- carboxílico

A una solución de éster terc- butílico del ácido (2S, 4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidina- 1- carboxilato (7,94 g, 21,18 mmol) en CH_2Cl_2 (70.5mL) se le añadió TFA (16,32 ml, 212 mmol) y la solución se agitó a temperatura ambiente durante 16 h. La mezcla de reacción bruta se concentró al vacío y el material que esta obtiene se usó sin purificación adicional en la siguiente etapa. MS (LC / MS): 274,9 [M + H] +; tR (condiciones HPLC B): 2,13 min.

C. Ejemplo 623: formiato 3- cloro- 2- fluoro- bencilamida del ácido (2S, 4R)- 1- ácido- [(3- Acetil- pirazolo [3,4- c] piridin- 1- il)- 2 acetil]- 4- fluoro- pirrolidina- 2- carboxílico

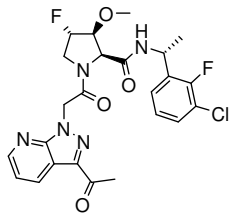
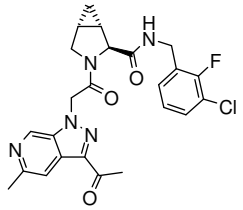
A una solución de trifluoroacetato de 3- cloro- 2- fluoro- bencilamida del ácido (2S, 4R)- 4- fluoro- pirrolidina- 2- carboxílico (50 mg, 0,13 mmol), anhídrido propilfosfónico (50% en EtOAc, 0,057 ml, 0,19 mmol) y trifluoroacetato del ácido (3- acetil- pirazolo [3,4- c] piridin- 1- il)- acético (preparado como se describe en el Esquema A20, 42,9 mg, 0,13 mmol) en CH_2Cl_2 (5 ml) se añadió DIPEA (0,067 ml, 0,386 mmol) bajo atmósfera de nitrógeno. La mezcla de reacción se agitó duante 2 horas a temperatura ambiente y se inactivó mediante la adición de una solución acuosa saturada de $NaHCO_3$. Las capas se separaron, la capa acuosa se extrajo con CH_2Cl_2 (x2), los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo bruto se purificó por HPLC preparativa (Waters Sunfire (ODB C18, 5µm, 19x50, flujo = 20mL/min, 5% de CH3CN en agua durante 2,5 min, 5 a 100% CH3CN en agua en 10 min a 100% CH_3CN para 2,5 min, tanto CH_3CN como agua que contiene HCOOH

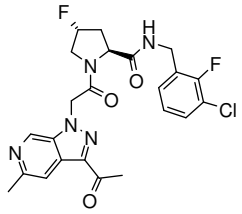
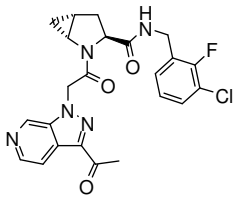
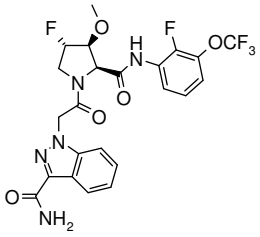
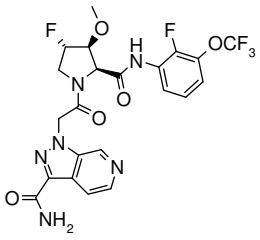
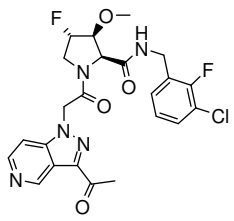
al 0,1%) y las fracciones de HPLC puras se concentraron y se liofilizaron MS (LC / MS):. 476/478 [M + H] +, tR (condiciones HPLC f): 1,51 min.

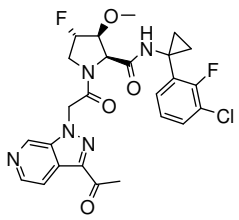
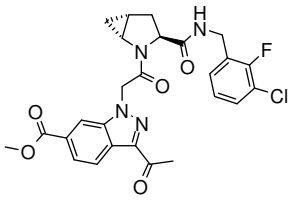
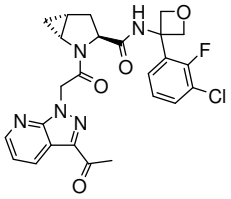
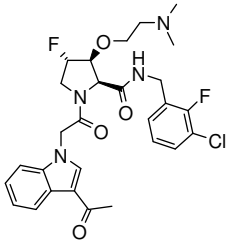
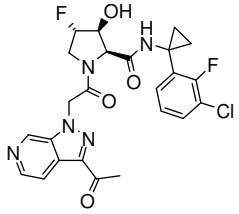
Alternativamente, las fracciones de HPLC puras se neutralizaron con una solución acuosa saturada de Na_2CO_3, se extrajo con EtOAc, se secó (Na_2SO_4), se filtró y se concentró para proporcionar el material deseado en forma de una base libre.

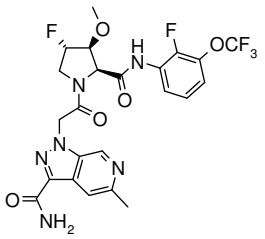
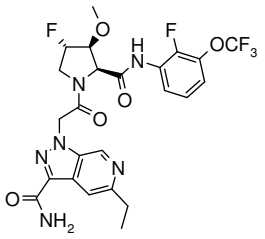
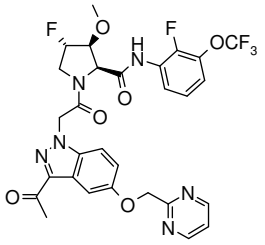
Los ejemplos siguientes se prepararon de acuerdo a los procedimientos generales descritos en el Esquema D8 para la preparación del **Ejemplo 623** *a partir de precursores de síntesis comercialmente disponibles si no se menciona lo contrario (ver notas al final del cuadro 7):*

Tabla 7:

Ejemplo	Estructura	Nombre	Caracterización (Notas al final de la tabla), TLC, Rf (eluyente); MS (LC / MS); tR (condiciones HPLC)
624		[(R)- 1- (3- Cloro- 2- fluoro- fenil)- etil]- amida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- pirazolo[3,4- b]piridin- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico	(1,2) 520 [M + H] +, 564 [M + HCOO]- ; tR (f): 2,04 min.
625		3- cloro- 2- fluoro- bencilamida del ácido (1S, 2S, 5R)- 3- [2- (3- Acetil- 5- metil- pirazolo [3,4- c] piridin- 1- il)- acetil]- 3- aza- biciclo [3.1.0] hexano- 2- carboxílico	(2) 484 [M + H] +, 528 [M + HCOO]- ; tR (f): 1,59 min.

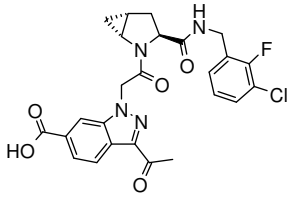
626		3- Cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 5- metil- pirazolo[3,4- c]piridin- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico	(2) 490 [M + H] +, 534 [M + HCOO]- ; tR (f): 1,54 min.
627		3- cloro- 2- fluoro- bencilamida del ácido (1R, 3S, 5R)- 2- [2- (3- Acetil- pirazolo [3,4- c] piridin- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico	(2) 470/472 [M + H] +; tR (f): 1,58 min.
628		amida del ácido 1- {2- [(2S,3S,4S)- 4- Fluoro- 2- (2- fluoro- 3- trifluorometoxi- fenilcarbamoil)- 3- metoxi- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indazol- 3- carboxílico	(1,2) 542,3 [M + H] +, 559,3 [M + NH4] +, 440,3 [MH]- , tr (f): 1,97 min
629		amida trifluoroacetato del ácido 1- {2- [(2S,3S,4S)- 4- Fluoro- 2- (2- fluoro- 3- trifluorometoxi- fenilcarbamoil)- 3- metoxi- pirrolidin- 1- il]- 2- oxo- etil}- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(1,2) 543,2 [M + H] +, 541,2 [MH]- , tr (f): 1,52 min
630		3- Cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- pirazolo[4,3- c]piridin- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico	(1,2) 506.2/508.2 [M + H] +, 504,2 [MH]- , 550.2/552.2 [M + HCOO]- ; tR (f): 1,49 min.

631		[1- (3- Cloro- 2- fluoro- fenil)- ciclopropil]- amida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- pirazolo[3,4- c]piridin- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico	(1,2) 532.4/534.5 [M + H] +, 576.6/578.5 [M + HCOO]- ; tR (f): 1,64 min.
632		Éster metílico del ácido 3- Acetil- 1- {2- [(1R, 3S, 5R)- 3- (3- cloro- 2- fluoro- bencil carbamoil)- 2- aza- biciclo [3.1.0] hex- 2- il]- 2- oxo- etil}- 1H- indazol- 6- carboxílico	(2) 544.1/546.1 [M + NH4] +, 571.2/573.2 [M + HCOO]- ; tR (m): 1,08 min.
633		[3- (3- cloro- 2- fluoro- fenil)- oxetan- 3- il]- amida del ácido (1R, 3S, 5R)- 2- [2- (3- Acetil- pirazolo [3,4- b] piridin- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico	(1,2) 512.1/514.1 [M + H] +, 534.1/536.1 [M + Na] +; tR (f): 1,89 min.
634		Formiato de 3- Cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 3- (2- dimetilamino- etoxi)- 4- fluoro- pirrolidina- 2- carboxílico	(1) 561.4/563.4 [M + H] +, 605.5/607.5 [M + HCOO]- ; tR (f): 1,62 min.
635		Formiat de [1- (3- Cloro- 2- fluoro- fenil)- ciclopropil]- amida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- pirazolo[3,4- c]piridin- 1- il)- acetil]- 4-	(1,2) 518.4/520.4 [M + H] +, 562,5 [M + HCOO]- ; tR (f): 1,51 min.

		fluoro- 3- hidroxi- pirrolidina- 2- carboxílico	
636		Triflato de amida del ácido 1- {2- [(2S,3S,4S)- 4- Fluoro- 2- (2- fluoro- 3- trifluorometoxi- fenilcarbamoil)- 3- metoxi- pirrolidin- 1- il]- 2- oxo- etil}- 5- metil- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(1,2) 557,2 [M + H] +, 555,2 [MH]- , tr (f): 1,50 min
637		Triflato de amida del ácido 5- etil- 1- {2- [(2S, 3S, 4S)- 4- fluoro- 2- (2- fluoro- 3- trifluoro metoxi- fenil carbamoil)- 3- metoxi- pirrolidin- 1- il]- 2- oxo- etil}- 1H- pirazolo [3,4- c] piridina- 3- carboxílico	(1,2) 571,3 [M + H] +, 569,3 [MH]- , tr (f): 1,55 min
638		(2- fluoro- 3- trifluorometoxi- fenil)- amida del ácido (2S,3S,4S)- 1- {2- [3- Acetil- 5- (pirimidin- 2- ilmetoxi)- indazol- 1- il]- acetil}- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico	(1,2) 649,3 [M + H] +, 647,3 [MH]- , tr (f): 1,99 min

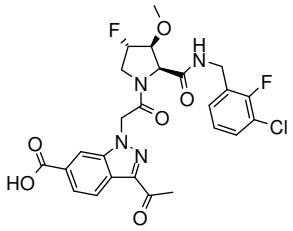
(1) El compuesto del título se preparó de acuerdo con el procedimiento general descrito en el Esquema D8 los pasos B y C a partir del derivado de prolina sustituido preparado como se describe en la Parte B; (2) El reactivo de ácido utilizado en la etapa C se preparó como se describe en la Parte A.

Ejemplo 639: ácido 3- Acetil- 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indazol- 6- carboxílico



Una solución del **Ejemplo 632** (65 mg, 0,123 mmol) en MeOH (5 ml) e hidróxido sódico (d = 1 g / ml, 0,247 ml, 0,617 mmol) se agitó durante 16 h a temperatura ambiente. La reacción se inactivó mediante la adición de HCl (1 N, hasta pH = 1) y se concentró a presión reducida. El residuo acuoso se extrajo con CH_2Cl_2 (x3) y se concentró. El material en bruto se purificó por HPLC preparativa (Waters Sunfire C18- ODB, 5 micras, 30x100 mm, eluyente: 5% a 100% CH_3CN en H_2O en 25 min, CH_3CN y H_2O que contiene 0.1% de TFA, flujo: 40 mL / min) . MS (LC / MS): 530.2/532.2 $[M + H]^+$; 511.1/513.1 [MH]- , 557.2/559.2 [M + HCOO]- ; tR (UPLC condiciones m): 0,91 min.

Ejemplo 640: ácido 3- Acetil- 1- {2- [(2S,3S,4S)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 3- metoxi- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indazol- 6- carboxílico

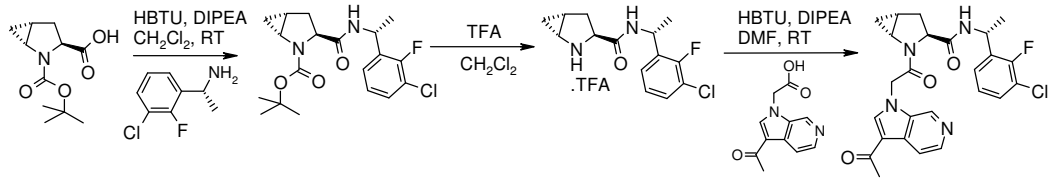


Éster bencílico del ácido 3- Acetil- 1- {2- [(2S, 3S, 4S)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 3- metoxi- pirrolidina din- 1- il]- 2- oxo- etil}- 1H- indazol- 6- carboxílico (47 mg, 0,063 mmol) se disolvió en MeOH (5 ml), se añadió Pd / C (10%, 5 mg) y la solución se desgasificó 3 veces sustituyendo el aire por nitrógeno y finalmente nitrógeno por hidrógeno. La mezcla de reacción se agitó adicionalmente bajo atmósfera de hidrógeno durante 1 h. El catalizador se eliminó a través de una almohadilla de Celite y se lavó con MeOH. El disolvente se concentró bajo presión reducida y el residuo bruto se purificó por HPLC preparativa (Waters Sunfire C18- ODB, 5 micras, 30x100 mm, eluyente: 5% a 100% CH_3CN en H_2O en 25 min, CH_3CN y H_2O que contiene TFA al 0,1% , flujo: 40 ml / min).MS (LC / MS): 549,5 [M + H] +; 547,5 [MH]- ; tR (condiciones HPLC f): 1,93 min.

Éster bencílico del ácido 3- Acetil- 1- {2- [(2S,3S,4S)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 3- metoxi- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indazol- 6- carboxílico

se preparó usando protocolos similares a los descritos en el Esquema D8 Paso C para la preparación del Ejemplo 623 a partir de éster bencílico del ácido 3- acetil- 1- carboximetil- 1H- indazol- 6- carboxílico (preparado como se describe en la Parte A) y trifluoroacetato 3- cloro- 2- fluoro- bencilamida del ácido (2S, 3S, 4S)- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico (preparado como se describe en el Esquema B24).Sólido blanco. MS (UPLC / MS): 683.6/685.7 [M + HCOO]- ; tR (condiciones HPLC f): 2,43 min.

Esquema D9: preparación del Ejemplo 641: [(R)- 1- (3- Cloro- 2- fluoro- fenil)- etil]- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico



A. Éster terc - butílico del ácido (1R, 3S, 5R)- 3- [(R)- 1- (3- cloro- 2- fluoro- fenil)- etilcarbamoil]- 2- aza- biciclo [3.1.0] - hexano- 2- carboxílico

A una solución de (R)- 1- (3- cloro- 2- fluoro- fenil)- etilamina (1,85 g, 8,80 mmol) en CH_2Cl_2 (44 ml) se añadieron sucesivamente éster 2- terc- butilo del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico (2 g, 8,80 mmol), DIPEA (4,61 ml, 26,4 mmol) y HBTU (4,01 g, 10,56 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 h. Se añadió agua y se separaron las fases. La capa orgánica se lavó sucesivamente con HCl 1 N (2x), sat. aq. $NaHCO_3$ (2x) y salmuera, después se secaron (separador de fases) y se concentraron al vacío. El aceite residual se purificó por medio de cromatografía en columna ultrarrápida sobre gel de sílice (C- hexano / EtOAc 9- 1 a 9- 4). MS (LC / MS): 405 [M + Na] +, 283 [MH- Boc] +; tR (condiciones HPLC C): 4,93 min.

DMF también se puede utilizar en lugar de diclorometano.

B. Trifluoroacetato [(R)- 1- (3- cloro- 2- fluoro- fenil)- etil]- amida del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico

A una solución de éster terc- butílico del ácido (1R,3S,5R)- 3- [(R)- 1- (3- Cloro- 2- fluoro- fenil)- etilcarbamoil]- 2- aza- biciclo[3.1.0]hexano- 2- carboxílico (3,2 g, 8,36 mmol) en CH_2Cl_2 (30 ml) se añadió TFA (15 ml, 195 mmol) y la solución se agitó a temperatura ambiente durante 1 h. La mezcla de reacción bruta se concentró al vacío, el residuo se suspendió en MeOH y se concentró de nuevo al vacío. El producto bruto se usó sin purificación adicional en la siguiente etapa. MS (LC / MS): 283,0 [M + H] +; tR (condiciones HPLC C): 3,41 min.

C. Ejemplo 641: [(R)- 1- (3- Cloro- 2- fluoro- fenil)- etil]- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico

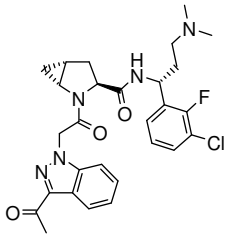
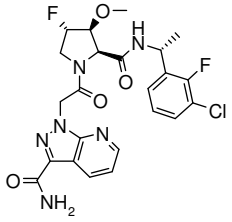
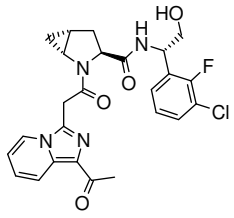
A una solución de trifluoroacetato de ácido (3- acetil- pirrolo [2,3- c] piridin- 1- il)- acético (preparado como se escribe en el Esquema [A15], 52 mg, 0,157 mmol) en DMF (1,5 ml) se añadieron sucesivamente trifluoroacetato de [(R)- 1- (3- cloro- 2- fluoro- fenil)- etil]- amida del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico (62,3 mg, 1,57 mmol), HBTU (89 mg, 0,235 mmoles) y DIPEA (107 □L, 0,626 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 h y se vertió en agua. Las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (x2). Los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron al vacío. El aceite residual se purificó por HPLC preparativa (Waters Sunfire C18- ODB, 5 micras, 30x100 mm, eluyente: 5% a 100% CH_3CN en H_2O en 25 min, CH_3CN y H_2O que contiene 0.1% TFA, flujo: 40 ml / min). Las fracciones puras se combinaron, neutralizaron por filtración a través de un cartucho de VariPure HCO_3- MP Varian y se liofilizó para proporcionar el material deseado como un polvo blanco. TLC, Rf (CH_2Cl_2/MeOH 9:1) = 0,42; MS (LC / MS): 483.4/485.3 [M + H] +, 527.4/529.4 [M + HCOO]- ; tR (condiciones HPLC A): 2,74 min .

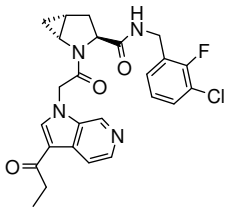
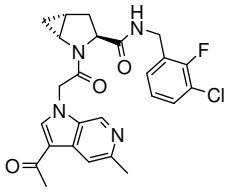
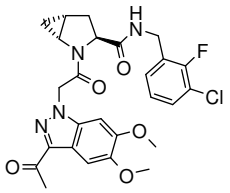
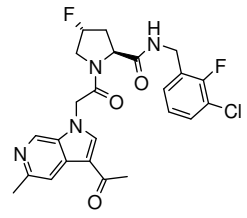
Alternativamente, las fracciones de HPLC puras se neutralizaron con una solución acuosa saturada de Na_2CO_3, se extrajo con EtOAc (x2), se secó (Na2SO4), se filtró y se concentró para proporcionar el material deseado.

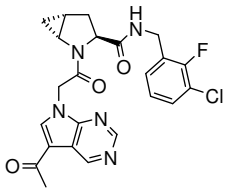
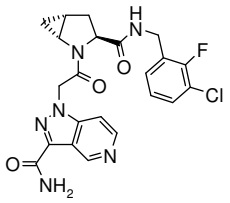
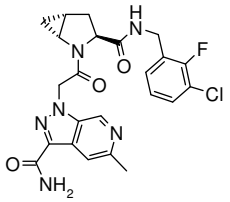
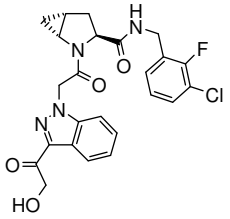
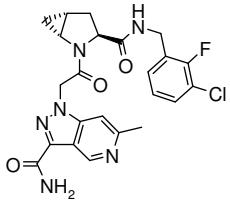
Alternativamente, el residuo bruto se purificó por HPLC preparativa (Waters Sunfire (ODB C18, 5µm, 19x50, flujo = 20mL/min, 5% CH_3CN en H_2O durante 2,5 minutos, 5 a 100% CH_3CN en H_2O en 10 min a 100% CH_3CN para 2,5 min, CH_3CN y H_2O tanto que contiene 0,1% de HCOOH) y las fracciones de HPLC puras se concentraron y se liofilizaron para proporcionar el compuesto deseado en forma de una sal de formiato.

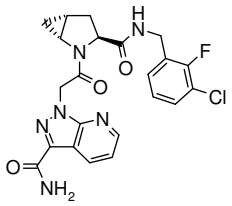
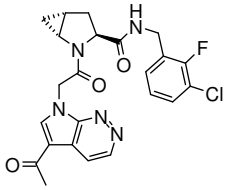
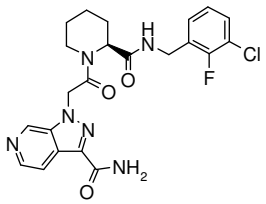
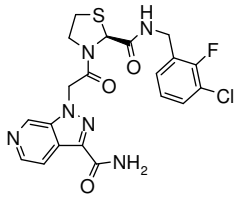
Los ejemplos siguientes se prepararon de acuerdo a los procedimientos generales descritos en el Esquema D9 para la preparación del **Ejemplo 641** *a partir de precursores de síntesis comercialmente disponibles si no se menciona lo contrario (ver notas al final del cuadro 8):*

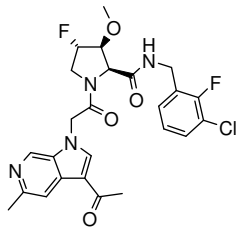
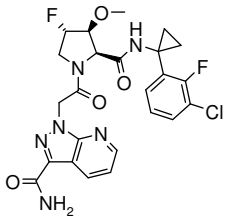
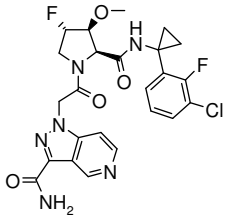
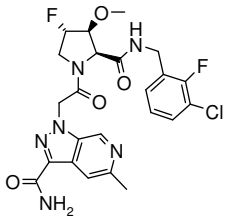
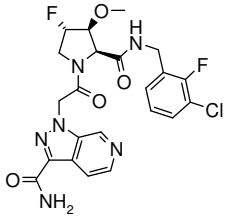
Tabla 8:

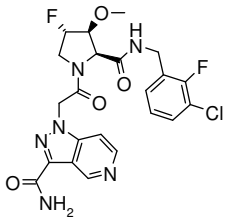
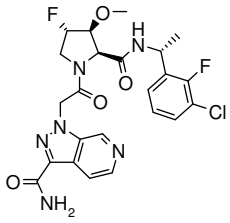
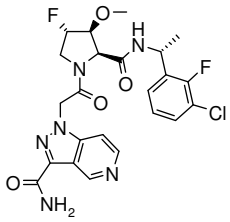
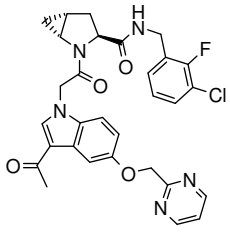
Ejemplo	Estructura	Nombre	Caracterización (Notas al final de la tabla), TLC, Rf (eluyente); MS (LC / MS); tR (condiciones HPLC)
642		[(R)- 1- (3- cloro- 2- fluoro- fenil)- 3- dimetilamino- propil]- amida del ácid (1R, 3S, 5R)- 2- [2- (3- Acetil- indazol- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico	(1,2,4) Sólido blanco. Rf (CH2Cl2/MeOH 9:1) = 0,55; 540.5/542.5 [M + H] +, 584.5/586.5 [M + HCOO]- ; tR (a): 2,93 min.
643		amida del ácido 1- (2- {(2S,3S,4S)- 2- [(R)- 1- (3- Cloro- 2- fluoro- fenil)- etilcarbamoil]- 4- fluoro- 3- metoxi- pirrolidin- 1- il}- 2- oxo- etil)- 1H- pirazolo[3,4- b]piridina- 3- carboxílico	(3,4) 521 [M + H] +, 543 [M + Na] +; tR (k): 3,10 min.
644		[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido (1R, 3S, 5R)- 2- [2- (1- Acetil- imidazo [1,5- a] piridin- 3- il)- acetil]- 2- aza-	(2,3,4) Rf (CH2Cl2/MeOH 9:1) = 0,75; 499.1/501.1 [M + H] +, 543.2/544.3 [M +

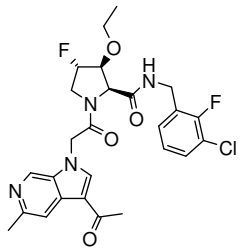
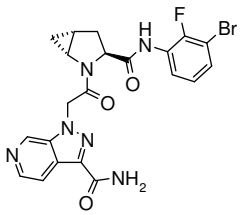
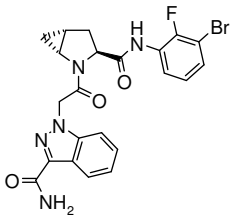
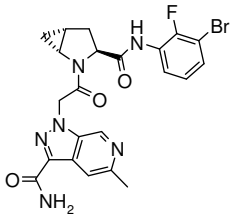
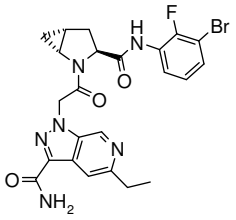
		biciclo [3.1.0] hexano- 3- carboxílico	HCOO]- ; tR (a): 2,74 min.
645		3- cloro- 2- fluoro- bencilamida del ácido (1R, 3S, 5R)- 2- [2- (3- propionil- pirrolo [2,3- c] piridin- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico	(4) Sólido blanco. 483.4/485.4 [M + H] +, 527.3/529.4 [M + HCOO]- ;tr (f): 1,56 min.
646		3- cloro- 2- fluoro- bencilamida del ácido (1R, 3S, 5R)- 2- [2- (3- Acetil- 5- metil- pirrolo [2,3- c] piridin- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico	(4) Sólido blanco. Rf (CH2Cl2/MeOH 9:1) = 0,4; 483.4/485.4 [M + H] +, 527.5/529.4 [M + HCOO]- ; tR (f): 1,52 min.
647		3- cloro- 2- fluoro- bencilamida del ácido (1R, 3S, 5R)- 2- [2- (3- Acetil- 5 ,6- dimetoxi- indazol- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico	(4) 529 [M + H] +; tR (k): 3,46 min.
648		3- cloro- 2- fluoro- bencilamida del ácido (2S, 4R)- 1- [2- (3- Acetil- 5- metil- pirrolo [2,3- c] piridin- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico	(4,5) Sólido blanco. 587,1 [M- H]- ; tR (c): 3,71 min.

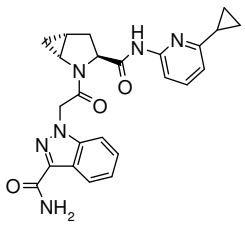
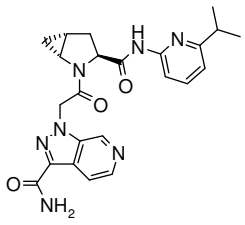
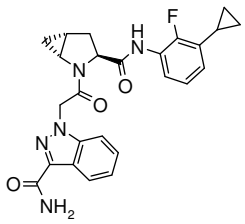
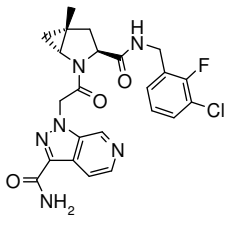
649		3- cloro- 2- fluoro- bencilamida del ácido (1R, 3S, 5R)- 2- [2- (5- Acetil- pirrolo [2,3- d] pirimidin- 7- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico	(4) Sólido blanco. Rf (CH2Cl2/MeOH 9:1) = 0,4; 470.4/472.4 [M + H] +, 514.4/516.5 [M + HCOO]- ; tR (f): 1,54 min.
650		amida del ácido 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- pirazolo[4,3- c]piridina- 3- carboxílico	(4) 471 [M + H] +; tR (k): 2,69 min.
651		amida del ácido 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 5- metil- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(4) 485 [M + H] +; tR (k): 2,71 min.
652		3- cloro- 2- fluoro- bencilamida del ácido (1R, 3S, 5R)- 2- {2- [3- (2- hidroxi- acetil)- indazol- 1- il]- acetil}- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico	(4) 485 [M + H] +, 507 [M + Na] +; tR (k): 3,24 min.
653		amida del ácido 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 6- metil- 1H- pirazolo[4,3- c]piridina- 3-	(4) 485 [M + H] +; tR (k): 2,73 min.

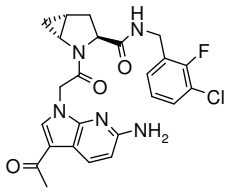
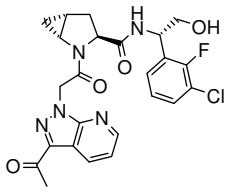
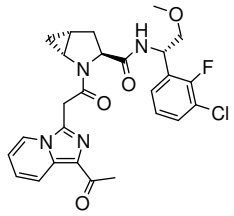
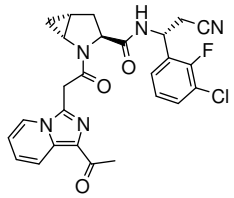
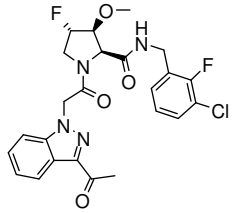
		carboxílico	
654		amida del ácido 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- pirazolo[3,4- b]piridina- 3- carboxílico	(4) 471 [M + H] +; tR (k): 2,99 min.
655		3- cloro- 2- fluoro- bencilamida del ácido (1R, 3S, 5R)- 2- [2- (5- Acetil- pirrolo [2,3- c] piridazin- 7- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico	(4) Rf (CH2Cl2/MeOH 9:1) = 0,4; 470.1/472.2 [M + H] +, 514.2/516.2 [M + HCOO]- ; tR (f): 1,51 min.
656		amida del ácido 1- {2- [(S)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- piperidin- 1- il]- 2- oxo- etil}- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(4) Sólido blanco. 473,0 [M + H] +, 495,0 [M + Na] +; tR (c): 3,63 min.
657		amida del ácido 1- {2- [(S)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- tiazolidin- 3- il]- 2- oxo- etil}- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(4) Sólido blanco. 477,0 [M + H] +, 498,9 [M + Na] +; tR (c): 3,50 min.

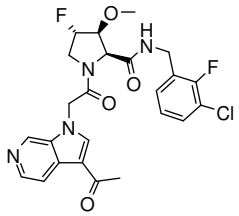
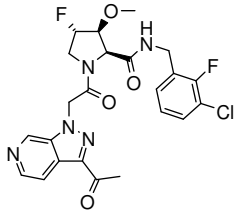
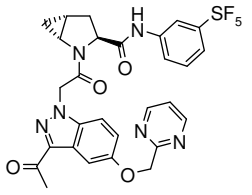
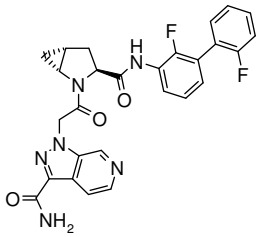
658		formiato 3- Cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- 5- metil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico	(3,4) 519/521 [M + H] +; tr (f): 1,51 min.
659		amida del ácido 1- (2- {(2S, 3S, 4S)- 2- [1- (3- cloro- 2- fluoro- fenil)- ciclopropil carbamoil]- 4- fluoro- 3- metoxi- pirrolidin- 1- il}- 2- oxo- etil)- 1H- pirazolo [3,4- b] piridina- 3- carboxílico	(3,4) 533 [M + H] +; tR (k): 3,16 min.
660		amida del ácido 1- (2- {(2S, 3S, 4S)- 2- [1- (3- cloro- 2- fluoro- fenil)- ciclopropil carbamoil]- 4- fluoro- 3- metoxi- pirrolidin- 1- il}- 2- oxo- etil)- 1H- pirazolo [4,3- c] piridina- 3- carboxílico	(3,4) 533 [M + H] +; tR (k): 2,84 min.
661		amida del ácido 1- {2- [(2S,3S,4S)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 3- metoxi- pirrolidin- 1- il]- 2- oxo- etil}- 5- metil- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(3,4) 521 [M + H] +; tR (k): 2,73 min.
662		amida del ácido 1- {2- [(2S,3S,4S)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 3- metoxi- pirrolidin- 1- il]- 2- oxo- etil}- 1H-	(3,4) 507 [M + H] +; tR (k): 2,71 min.

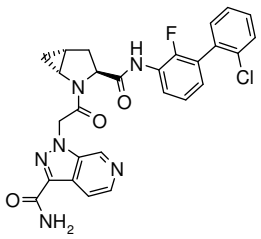
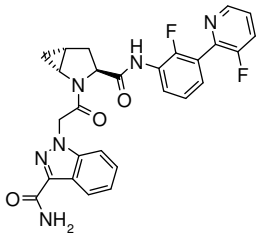
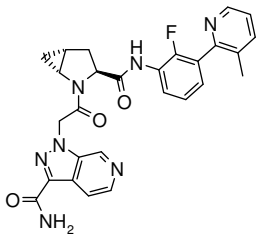
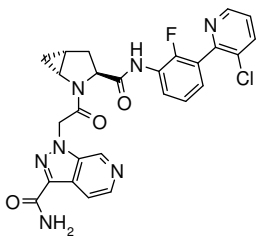
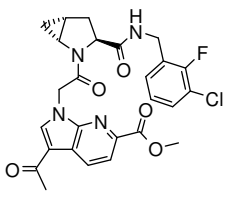
		pirazolo[3,4- c]piridina- 3- carboxílico	
663		amida del ácido 1- {2- [(2S,3S,4S)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 3- metoxi- pirrolidin- 1- il]- 2- oxo- etil}- 1H- pirazolo[4,3- c]piridina- 3- carboxílico	(3,4) 507 [M + H] +; tR (k): 2,71 min.
664		amida del ácido 1- (2- {(2S,3S,4S)- 2- [(R)- 1- (3- cloro- 2- fluoro- fenil)- etilcarbamoil]- 4- fluoro- 3- metoxi- pirrolidin- 1- il}- 2- oxo- etil)- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(3,4) 521 [M + H] +; tR (k): 2,78 min.
665		amida del ácido 1- (2- {(2S,3S,4S)- 2- [(R)- 1- (3- Cloro- 2- fluoro- fenil)- etilcarbamoil]- 4- fluoro- 3- metoxi- pirrolidin- 1- il}- 2- oxo- etil)- 1H- pirazolo[4,3- c]piridina- 3- carboxílico	(3,4) 521 [M + H] +; tR (k): 2,79 min.
666		(1R, 3S, 5R)- 2- {2- [3- cloro- 2- fluoro- bencilamida del ácido 3- Acetil- 5- (pirimidin- 2- ilmetoxi)- indol- 1- il]- acetil}- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico	(4) 576/578 [M + H] +; tR (k): 3,48 min.

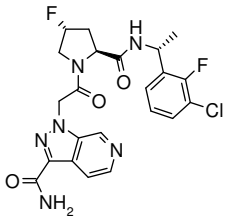
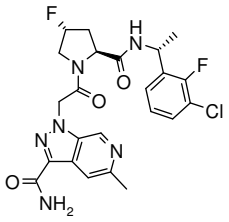
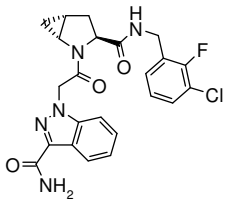
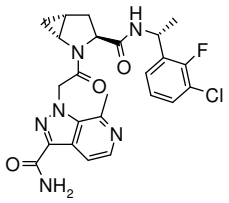
667		formiato 3- Cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- 5- metil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 3- etoxi- 4- fluoro- pirrolidina- 2- carboxílico	(3,4) 533/535 [M + H] +; tR (f): 1,61 min.
668		amida del ácido 1- {2- [(1R,3S,5R)- 3- (3- Bromo- 2- fluoro- fenilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(4) Rf (EtOAc) = 0,1; 501.1/503.0 [M + H] +, 499.0/501.2 [MH]- , 545.1/548.3 [M + HCOO]- ; tR (a): 2,42 min.
669		amida del ácido 1- {2- [(1R,3S,5R)- 3- (3- Bromo- 2- fluoro- fenilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indazol- 3- carboxílico	(4) Rf (EtOAc) = 0,6; 517.1/519.1 [M + NH4] +, 498.2/500.1 [MH]- ; tR (a): 3,18 min.
670		amida del ácido 1- {2- [(1R,3S,5R)- 3- (3- Bromo- 2- fluoro- fenilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 5- metil- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(4) Rf (EtOAc) = 0,1; 515.2/517.1 [M + H] +, 513.2/515.1 [MH]- , 561,2 [M + HCOO]- ; tR (a): 2,48 min.
671		amida del ácido 1- {2- [(1R,3S,5R)- 3- (3- Bromo- 2- fluoro- fenilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 5- etil- 1H- pirazolo[3,4- c]piridina- 3-	(4) Rf (EtOAc) = 0,15; 529.1/531.1 [M + H] +, 527.2/529.1 [MH]- , 573.2/575.3 [M + HCOO]- ; tR (a): 2,55 min.

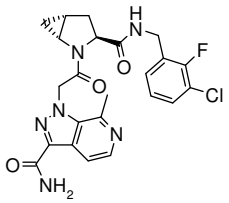
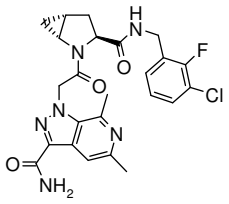
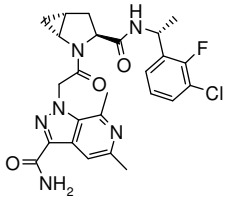
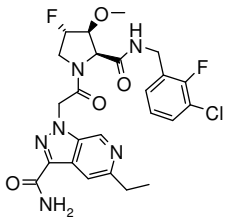
		carboxílico	
672		amida de ácido 1- {2- [(1R, 3S, 5R)- 3- (6- ciclopropil- piridin- 2- ilcarbamoil)- 2- aza- biciclo [3.1.0] hex- 2- il]- 2- oxo- etil}- 1H- indazol- 3- carboxílico	(4,5) Rf (EtOAc) = 0,4; 445.3/446.3 [M + H] +, 489.4/491.4 [M + HCOO]- ; tR (a): 2,53 min.
673		amida del ácido 1- {2- [(1R, 3S, 5R)- 3- (6- isopropil- piridin- 2- ilcarbamoil)- 2- aza- biciclo [3.1.0] hex- 2- il]- 2- oxo- etilo }- 1H- pirazolo [3,4- c] piridina- 3- carboxílico	(4,5) Rf (EtOAc) = 0,1; 448,3 [M + H] +, 446,0 [MH]- , 492,3 [M + HCOO]- ; tR (a): 1,31 min.
674		amida del ácido 1- {2- [(1R,3S,5R)- 3- (3- Ciclopropil- 2- fluoro- fenilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indazol- 3- carboxílico	(1,4) Rf (c-hexano/EtOAc 02:01) = 0,6; 361,2 [M + H] +, 738,4 [2M + Na] +; tR (f): 2,29 min.
675		amida del ácido 1- {2- [(1R, 3S, 5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 5- metil- 2- aza- biciclo [3.1.0] hex- 2- il]- 2- oxo- etil}- 1H- pirazolo [3,4- c] piridina- 3- carboxílico	(2,3,4) Rf (CH2Cl2/MeOH 9:1) = 0,4; 485.3/487.3 [M + H] +, 507.2/509.2 [M + Na] +, 529.3/531.3 [M + HCOO]- ; tR (f): 1,47 min.

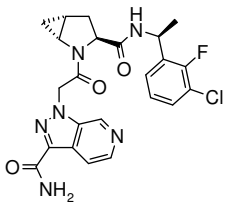
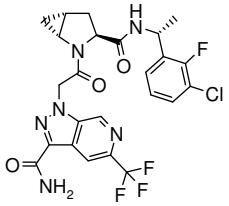
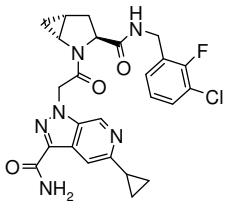
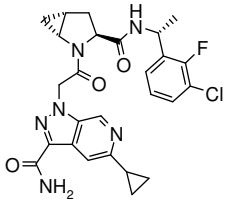
676		3- cloro- 2- fluoro- bencilamida del ácido (1R, 3S, 5R)- 2- [2- (3- Acetil- 6- amino- pirrolo [2,3- b] piridin- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico	(4) Rf (CH2Cl2/MeOH 9:1) = 0,5; 503.1/505.1 [M + H] +, 547.1/549.1 [M + HCOO]- ; tR (f): 2,11 min.
677		[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida de ácido (1R, 3S, 5R)- 2- [2- (3- Acetil- pirazolo [3,4- b] piridin- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico	(2,3,4) Rf (CH2Cl2/MeOH 9:1) = 0,55; 500.1/502.1 [M + H] +, 1000.3/1001.3 [2M + H] +, 544.1/546.1; tR (f): 1,81 min.
678		[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etil]- amida del ácido (1R, 3S, 5R)- 2- [2- (1- Acetil- imidazo [1,5- a] piridin- 3- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico	(2,3,4) Rf (CH2Cl2/MeOH 9:1) = 0,7; 513.2/515.2 [M + H] +, 557.2/558.3 [M + HCOO]- ; tR (a): 3,15 min.
679		[(R)- 1- (3- Cloro- 2- fluoro- fenil)- 2- cyano- etil]- amida del ácido (1R,3S,5R)- 2- [2- (1- Acetil- imidazo[1,5- a]piridin- 3- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico	(4) Rf (EtOAc) = 0,2; 508,3 [M + H] +, 506,2 [M- H]- ; tR (a): 3,05 min.
680		3- cloro- 2- fluoro- bencilamida del ácido (2S, 3S, 4S)- 1- [2- (3- Acetil- indazol- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2-	(3) 505.2/507.2 [M + H] +, 549.3/551.4 [M + HCOO]- ; tR (f): 2,09 min.

		carboxílico	
681		3- Cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico	(3,4) 505.2/507.2 [M + H] +, 549.2/551.2 [M + HCOO]- ; tR (f): 1,49 min.
682		3- Cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- pirazolo[3,4- c]piridin- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico	(3,4) 506.4/508.4 [M + H] +, 550.5/552.6 [M + HCOO]- ; tR (f): 1,59 min.
683		(pentafluoruro de 3- azufre- fenil)- amida del ácido (1R,3S,5R)- 2- {2- [3- Acetil- 5- (pirimidin- 2- ilmetoxi)- indazol- 1- il]- acetil}- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico	(4,7) 451,0 [M + Na] +, 328,9 [M- tBu] +, 427,1 [MH]- ; tR (c): 5,29 min.
684		amida del ácido 1- {2- [(1R,3S,5R)- 3- (2,2'- Difluoro- bifenil- 3- ilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(1,4,7) 517 [M + H] +; tR (k): 3,01 min.

685		amida del ácido 1- {2- [(1R,3S,5R)- 3- (2'- Cloro- 2- fluoro- bifenil- 3- ilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(1,4,7) 533 [M + H] +; tR (k): 3,05 min.
686		amida del ácido 1- (2- {(1R,3S,5R)- 3- [2- Fluoro- 3- (3- fluoro- piridin- 2- il)- fenilcarbamoil]- 2- aza- biciclo[3.1.0]hex- 2- il}- 2- oxo- etil)- 1H- indazol- 3- carboxílico	(1,4,7) 517 [M + H] +; tR (k): 3,10 min.
687		amida del ácido 1- (2- {(1R,3S,5R)- 3- [2- Fluoro- 3- (3- metil- piridin- 2- il)- fenilcarbamoil]- 2- aza- biciclo[3.1.0]hex- 2- il}- 2- oxo- etil)- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(1,4,7) 514 [M + H] +; tR (k): 2,32 min.
688		amida del ácido 1- (2- {(1R,3S,5R)- 3- [3- (3- Cloro- piridin- 2- il)- 2- fluoro- fenilcarbamoil]- 2- aza- biciclo[3.1.0]hex- 2- il}- 2- oxo- etil)- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(1,4,7) 534 [M + H] +; tR (k): 2,72 min.
689		Éster metílico del ácido 3- Acetil- 1- {2- [(1R, 3S, 5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo [3.1.0]	(4) 527 [M + H] +, 549 [M + Na] +; tR (k): 3,43 min.

		hex- 2- il]- 2- oxo- etil}- 1H- pirrolo [2,3- b] piridina- 6- carboxílico	
690		amida del ácido Cloro- 2- fluoro- fenil)- etilcarbamoil]- 4- fluoro- pirrolidin- 1- il}- 2- oxo- etil)- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(4) 489/491 [M + H] +, 513 [M + Na] +; tR (c): 3,43 min.
691		Amida del ácido 1- (2- {(2S,4R)- 2- [(R)- 1- (3- Cloro- 2- fluoro- fenil)- etilcarbamoil]- 4- fluoro- pirrolidin- 1- il}- 2- oxo- etil)- 5- metil- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(4) 505 [M + H] +; tR (k): 2,74 min.
692		amida del ácido 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indazol- 3- carboxílico	(4) 470 [M + H] +, 492 [M + Na] +; tR (c): 4,17 min.
693		amida del ácido 1- (2- {(1R,3S,5R)- 3- [(R)- 1- (3- Cloro- 2- fluoro- fenil)- etilcarbamoil]- 2- aza- biciclo[3.1.0]hex- 2- il}- 2- oxo- etil)- 7- metil- 1H- pirazolo[3,4- c]piridina- 3-	(4) 499 [M + H] +; tR (c): 3,51 min.

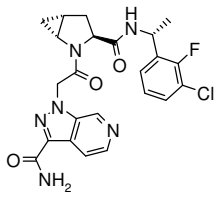
		carboxílico	
694		amida del ácido 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 7- metil- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(4) 485 [M + H] +; tR (c): 3,39 min.
695		amida del ácido 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 5,7- dimetil- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(4) 499 [M + H] +; tR (c): 3,46 min.
696		amida del ácido 1- (2- {(1R,3S,5R)- 3- [(R)- 1- (3- Cloro- 2- fluoro- fenil)- etilcarbamoil]- 2- aza- biciclo[3.1.0]hex- 2- il}- 2- oxo- etil)- 5,7- dimetil- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(4) 513 [M + H] +, 511 [M- H]- ; tR (c): 3,58 min.
697		amida del ácido 1- {2- [(2S,3S,4S)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 3- metoxi- pirrolidin- 1- il]- 2- oxo- etil}- 5- etil-	(3,4) 535 [M + H] +; tR (k): 2,82 min.

		1H- pirazolo[3,4- c]piridina- 3 - carboxílico	
698		Amida del ácido 1- (2- {(1R, 3S, 5R)- 3- [(S)- 1- (3- cloro- 2- fluoro- fenil)- etilcarbamoil]- 2- aza- biciclo [3.1.0] hex- 2- il}- 2- oxo- etil)- 1H- pirazolo [3,4- c] piridina- 3- carboxílico	(4) 485 [M + H] +; tR (c): 3,59 min.
699		amida del ácido 1- (2- {(1R,3S,5R)- 3- [(R)- 1- (3- Cloro- 2- fluoro- fenil)- etilcarbamoil]- 2- aza- biciclo[3.1.0]hex- 2- il}- 2- oxo- etil)- 5- trifluorometil- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(4) 553 [M + H] +; tR (c): 4,48 min.
700		amida del ácido 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 5- ciclopropil- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(4) 511 [M + H] +; tR (c): 3,62 min.
701		amida del ácido 1- (2- {(1R,3S,5R)- 3- [(R)- 1- (3- Cloro- 2- fluoro- fenil)- etilcarbamoil]- 2- aza-	(4) 525 [M + H] +; tR (c): 3,75 min.

		biciclo[3.1.0]hex- 2- il}- 2- oxo- etil)- 5- ciclopropil- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	

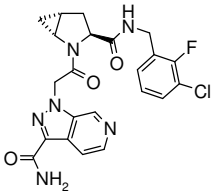
(1) El reactivo de amina en la etapa A se preparó como se describe en la Parte C; (2) HCl (4 M en dioxano) en lugar de TFA en la etapa B; (3) El compuesto del título se preparó de acuerdo con el procedimiento general descrito en el Esquema D9 los pasos B y C a partir del derivado de prolina sustituido preparado como se describe en la Parte B; (4) El reactivo ácido utilizado en la etapa C se preparó como se describe en la parte A; (5) CH_2Cl_2 se utiliza en lugar de DMF en la etapa C ; (6) T_3P se utilizó en lugar de HBTU en la etapa C y la reacción se lleva a cabo en CH_2Cl_2; (7) En la etapa A, DMF se utilizó en lugar de CH_2Cl_2 y la reacción se realizó a 50- 70 ° C.

Ejemplo 702: amida de ácido 1- (2- {(1R,3S,5R)- 3- [(R)- 1- (3- Cloro- 2- fluoro- fenil)- etilcarbamoil]- 2- aza- biciclo[3.1.0]hex- 2- il}- 2- oxo- etil)- 1H- pirazolo[3,4- c]piridina- 3- carboxílico|



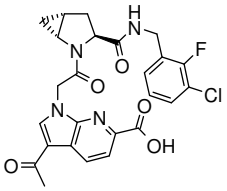
A una solución de sal de trifluoroacetato del ácido (3- carbamoil- pirazolo [3,4- c] piridin- 1- il)- acético (2,65 g, 7,94 mmoles, preparado como se describe en el Esquema A26) en DMF (30 ml) se añadieron sucesivamente ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico, trifluoroacetato sal [(R)- 1- (3- cloro- 2- fluoro- fenil)- etil]- amida (3,00 g, 7,56 mmol), HBTU (3,44 g, 9,07 mmoles) y DIPEA (5,28 ml, 30,2 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 h y luego se concentró al vacío. El aceite residual se particionó entre CH_2Cl_2 y una solución sat. aq. solución de $NaHCO_3$. Un sólido se precipitó apartir de la emulsión resultante y se separó por filtración, se lavó con agua y se secó al vacío. El sólido se suspendió en una mezcla de agua (150 ml) y MeOH (3 ml), se agitó durante 1 h a temperatura ambiente, se filtró, se lavó con agua y finalmente se secó al vacío para proporcionar el material del título como un polvo blanco. MS (LC / MS): 485 [M + H] +; tR (condiciones HPLC C): 3,54 min.

Ejemplo 703: 1- (2- ((1R, 3S, 5R)- 3- ((3- cloro- 2- fluorobencil) carbamoil)- 2- azabiciclo [3.1.0] hexano- 2- il)- 2- oxoetil)- 1H- pirazolo [3,4- c] piridina- 3- carboxamida



A una solución de sal de trifluoroacetato del ácido (3- carbamoil- pirazolo [3,4- c] piridin- 1- il)- acético (2,12 g, 6,35 mmoles, preparado como se describe en el Esquema A26) en DMF (32 ml) se agrearon sucesivamente sal trifluoroacetato (1R, 3S, 5R)- N- (3- cloro- 2- fluorobencil)- 2- azabiciclo [3.1.0] hexano- 3- carboxamida (2,70 g, 6,35 mmol), HBTU (3,37 g, 8,89 mmol) y DIPEA (4,44 ml, 25,4 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 h, y luego se concentró al vacío. El aceite residual se repartió entre CH_2Cl_2 y una solución de $NaHCO_3$ sat. aq. Un sólido se precipito a partir de la emulsión resultante y se separó por filtración, se lavó con agua y se secó al vacío. El sólido se suspendió en una mezcla de agua (150 ml) y MeOH (3 mL), se agitó durante 1 h a temperatura ambiente, se filtró, se lavó con agua y finalmente se secó al vacío para proporcionar el material del título como un polvo blanco. MS (LC / MS): 471 [M + H] +; tR (condiciones HPLC C): 3,41 min.

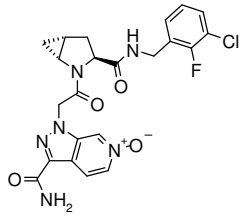
Ejemplo 704: Ácido 3- Acetil- 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- pirrolo[2,3- b]piridina- 6- carboxílico



A una solución de éster metílico del ácido 3- acetil- 1- {2- [(1R, 3S, 5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo [3.1.0] hex- 2- il]- 2- oxo- etil}- 1H- pirrolo [2,3- b] piridina- 6- carboxílico (Ejemplo 689, 70 mg, 0,133 mmol) en THF (3 ml) y agua (0,3 ml) se añadió una solución de LiOH 2 N acuoso (0,664 ml, 1,33 mmol). La mezcla de reacción se agitó a 25 ° C durante 16 h, después se añadió una solución acuosa de HCl 1 N para ácidoificar la mezcla de reacción a pH = 2 a 3. La suspensión acuosa resultante se filtró, el sólido se lavó con agua y después se secó al vacío. El sólido bruto se purificó por HPLC preparativa (Waters Sunfire C18- DAB, 5 micras, 30x100mm, flujo: 40 ml / min, eluyente: 20% a 100% CH_3CN en H_2O en 20 min, 100% CH_3CN 2 min, CH_3CN y H_2O que contiene TFA al 0,1%). Las

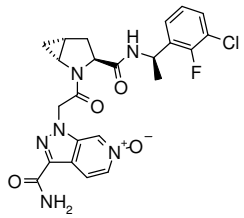
fracciones puras se combinaron, CH_3CN se evaporó bajo presión reducida y la solución acuosa resultante se liofilizó para proporcionar el compuesto del título como un sólido blanco. MS: 513 [M + H] +, 535 [M + Na] +; tR (condiciones HPLC k): 3,14 min.

Ejemplo 705: 6- óxido de 3- Carbamoil- 1- (2- ((1R,3S,5R)- 3- (3- Cloro- 2- fluorobencilcarbamoil)- 2- azabiciclo[3.1.0]hexan- 2- il)- 2- oxoetil)- 1H- pirazolo[3,4- c]piridina



A una solución de 1- (2- ((1R,3S,5R)- 3- (3- Cloro- 2- fluorobencilcarbamoil)- 2- azabiciclo[3.1.0]hexan- 2- il)- 2- oxoetil)- 1H- pirazolo[3,4- c]piridina- 3- carboxamida (**Ejemplo 703**, 100 mg, 0,21 mmol) en ácido acético (4 ml) se le añadió ácido 3- clorobenzoperoxoico (58 mg, 0,34 mmol) a 55 ° C. La mezcla de reacción se agitó a 55 ° C durante 18 h y después se enfrió a temperatura ambiente. Los volátiles se evaporaron y el residuo se purificó por HPLC preparativa (Waters Sunfire, C18- ODB, 5 micras, 30x100 mm, flujo: 40 ml / min, eluyente: 5- 100% CH_3CN/H_2O/20 min, 100% CH3CN / 2 min, CH_3CN y H_2O que contiene TFA al 0,1%) para proporcionar el compuesto del título como un sólido blanco. MS: 487 [M + H] +; tR (condiciones HPLC C): 3,44 min.

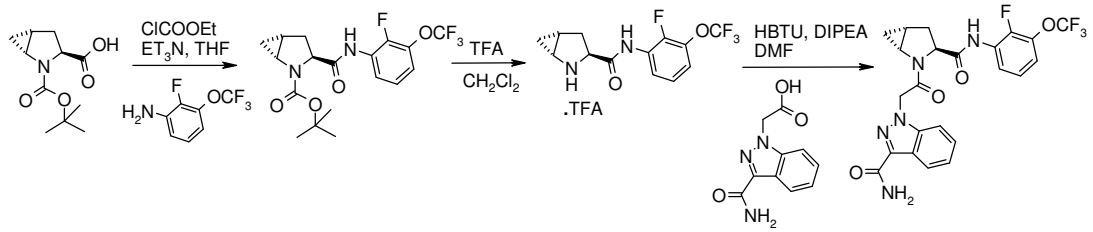
Ejemplo 706: 6- óxido de 3- Carbamoil- 1- (2- ((1R,3S,5R)- 3- ((R)- 1- (3- Cloro- 2- fluorofenil)etilcarbamoil)- 2- azabiciclo[3.1.0]hexan- 2- il)- 2- oxoetil)- 1H- pirazolo[3,4- c]piridina



A una solución de 1- (2- ((1R,3S,5R)- 3- ((R)- 1- (3- Cloro- 2- fluorofenil)etilcarbamoil)- 2- azabiciclo[3.1.0]hexan- 2- il)- 2- oxoetil)- 1H- pirazolo[3,4- c]piridina- 3- carboxamida (Ejemplo 702, 150 mg, 0,31 mmol) en ácido acético (4 ml) se le añadió ácido 3- clorobenzoperoxoico (85 mg, 0,50 mmol) a 55 ° C. La mezcla de reacción se agitó a 55 ° C durante 18 h y después se enfrió a temperatura ambiente. Los volátiles se

evaporaron y el residuo se purificó por HPLC preparativa (Waters Sunfire, C18- ODB, 5 micras, 30x100 mm, flujo: 40 ml / min, eluyente: 5- 100% CH_3CN/H_2O/20 min, 100% CH_3CN / 2 min, CH_3CN y H_2O que contiene TFA al 0,1%) para proporcionar el compuesto del título como un sólido blanco. MS: 501 [M + H] +; tR (condiciones HPLC C): 3,64 min.

Esquema D10: protocolo general descrito para la preparación del Ejemplo 707: amida de ácido 1- {2- [(1R, 3S, 5R)- 3- (2- fluoro- 3- trifluorometoxi- fenilcarbamoil)- 2- aza- biciclo [3.1.0] hex- 2- il]- 2- oxo- etil}- 1H- indazol- 3- carboxílico



A. Éster terc- butilo del ácido (1R, 3S, 5R)- 3- (2- fluoro- 3- trifluorometoxi- fenilcarbamoil)- 2- aza- biciclo [3.1.0] hexano- 2- carboxílico

A una solución de éster 2- terc- butilo del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico (1,83 g, 8,07 mmol) en THF seco (45 ml) a- 20 ° C bajo atmósfera de nitrógeno se añadió trietilamina (3,32 ml, 23,8 mmol) seguido de cloroformiato de etilo (0,775 ml, 8,07 mmol) gota a gota. La mezcla de reacción se agitó a- 20 ° C durante 90 min y una solución de 2- fluoro- 3- (trifluorometoxi) anilina (preparada como se describe en la Parte C, 1,5 g, 7,69 mmol) en THF seco (5 ml) se añadió. La mezcla de reacción se agitó adicionalmente a- 20 ° C durante 1 h, se calentó hasta temperatura ambiente y se agitó a 65 ° C durante 16 h hasta la finalización de la reacción. La mezcla de reacción se diluyó con EtOAc, se lavó con una solución saturada acuosa de $NaHCO_3$ (x3) y salmuera, se secó (separador de fases) y se concentró a presión reducida. El residuo en bruto se purificó por medio de cromatografía en columna ultrarrápida sobre gel de sílice (EtOAc / c- hexano 1:1) para proporcionar el material deseado como un aceite incoloro. MS: 427 [M + Na] +, 304,9 [MH- Boc] +; tR (condiciones HPLC C): 5,23 min.

B. Trifluoroacetato de (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico (2- fluoro- 3- trifluoro metoxi- fenil)- amida

A una solución de éster terc- butilo de ácido ((1R, 3S, 5R)- 3- (2- fluoro- 3- trifluorometoxi- fenilcarbamoil)- 2- aza- biciclo [3.1.0] hexano- 2- carboxílico (2,56 g , 6,33 mmol) en CH_2Cl_2 (20 ml) se añadió TFA (10 ml, 130 mmol) y la solución se agitó a

temperatura ambiente durante 16 h. CH_2Cl_2 se concentró, el residuo se suspendió en MeOH, se concentró de nuevo y se secó a alto vacío para proporcionar el material deseado que se usó sin purificación adicional en la siguiente etapa MS: 305 [M + H] +; tR (HPLC condiciones c): 3.55 min.

C. 707 Ejemplo: amida del ácido 1- {2- [(1R,3S,5R)- 3- (2- Fluoro- 3- trifluorometoxi- fenilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indazol- 3- carboxílico

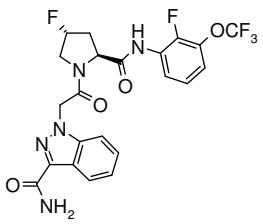
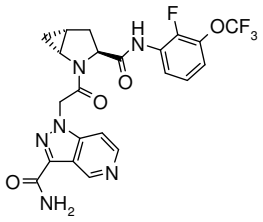
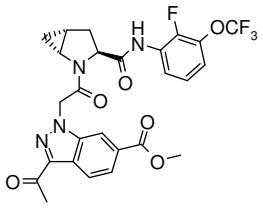
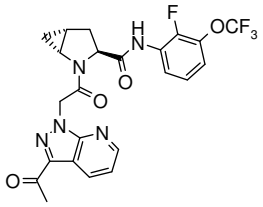
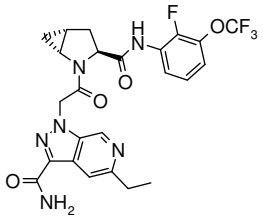
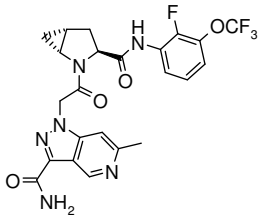
A una solución de ácido (3- carbamoil- indazol- 1- il)- acético (73,4 mg, 0,335 mmol, preparado como se describe en el Esquema A25) en DMF (2 ml) se añadieron sucesivamente trifluoroacetato de (2- fluoro- 3- trifluorometoxi- fenil)- amida del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico (140 mg, 0,335 mmol), DIPEA (0,234 ml, 1,34 mmol) y HBTU (152 mg , 0,402 mmol). La mezcla de reacción se agitó a 25 ° C durante 2 h, se concentró y el residuo se purificó por HPLC preparativa (Waters Sunfire C18- DAB, 5 micras, 30x100mm, flujo: 40 ml / min, eluyente: 5% a 100% CH_3CN en H2O en 20 min, 100% CH_3CN 2 min, CH_3CN y H_2O que contiene TFA al 0,1%). Las fracciones puras se combinaron, CH_3CN se evaporó bajo presión reducida y la solución acuosa resultante se liofilizó. Polvo blanco: MS: 506 [M + H] +; tR (condiciones HPLC k): 3,40 min.

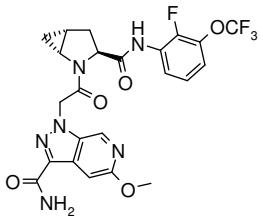
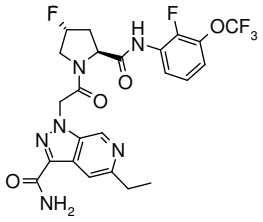
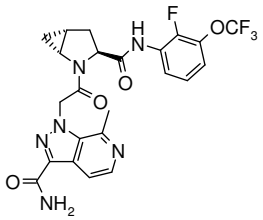
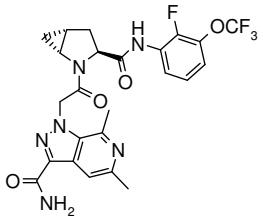
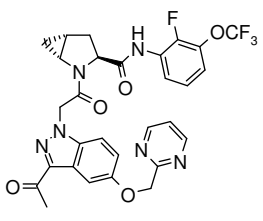
Alternativamente, para los compuestos finales que contienen un residuo básico: las fracciones de HPLC puras se combinaron, CH_3CN se evaporó a presión reducida, la solución acuosa resultante se ajustó a pH 8- 9 por adición de una solución acuosa saturada de $NaHCO_3$, se extrajo con CH_2Cl_2 (x3), los extractos orgánicos combinados se secaron (separador de fases) y se concentraron al vacío.

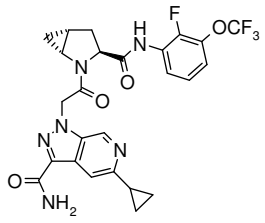
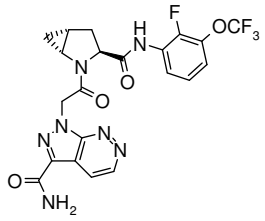
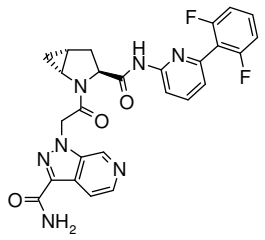
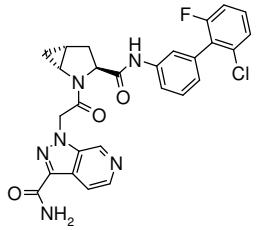
Los ejemplos siguientes se prepararon de acuerdo a los procedimientos generales descritos en el Esquema D10 para el **Ejemplo 707** *utilizando precursores de síntesis comercialmente disponibles si no se indica lo contrario (ver nota al final de la tabla 9):*

Tabla 9:

Ejemplo	Estructura	Nombre	Caracterización (Notas al final de la tabla), TLC, Rf (eluyente); MS (LC / MS); tR (condiciones HPLC)

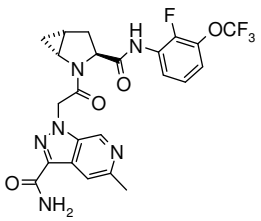
708		1- (2- ((2S,4R)- 4- fluoro- 2- (2- fluoro- 3- (trifluorometoxi)fenilcarbamoil)pirrolidin- 1- il)- 2- oxoetil)- 1H- indazol- 3- carboxamida	(1) 512 [M + H] +; tR (k): 3,31 min.
709		1- (2- ((1R,3S,5R)- 3- (2- fluoro- 3- (trifluorometoxi)fenilcarbamoil)- 2- azabiciclo[3.1.0]hexan- 2- il)- 2- oxoetil)- 1H- pirazolo[4,3- c]piridina- 3- carboxamida	(1) 507 [M + H] +; tR (k): 2,90 min.
710		3- acetil- 1- (2- ((1R, 3S, 5R)- 3- (2- fluoro- 3- (trifluorometoxi) fenilcarbamoil)- 2- azabiciclo [3.1.0] hexano- 2- il)- 2- oxoetil)- 1H- indazol- 6- carboxilato de metilo	(1) 563 [M + H] +, 585 [M + Na] +; tR (k): 3,89 min.
711		(2- fluoro- 3- trifluorometoxi- fenil)- amida del ácido (1R, 3S, 5R)- 2- [2- (3- Acetil- pirazolo [3,4- b] piridin- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico	(1) 506 [M + H] +; tR (k): 3,67 min.
712		amida del ácido 5- Etil- 1- {2- [(1R,3S,5R)- 3- (2- fluoro- 3- trifluorometoxi- fenilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(1) 535 [M + H] +; tR (k): 2,97 min.
713		amida del ácido 1- {2- [(1R,3S,5R)- 3- (2- Fluoro- 3- trifluorometoxi- fenilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 6- metil- 1H- pirazolo[4,3-	(1) 521 [M + H] +; tR (k): 2,92 min.

		c]piridina- 3- carboxílico	
714		amida del ácido 1- {2- [(1R,3S,5R)- 3- (2- Fluoro- 3- trifluorometoxi- fenilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 5- metoxi- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(1) 537 [M + H] +; tR (k): 3,24 min.
715		amida del ácido 5- etil- 1- {2- [(2S, 4R)- 4- fluoro- 2- (2- fluoro- 3- trifluorometoxi- fenil carbamoil)- pirrolidin- 1- il]- 2- oxo- etil}- 1H- pirazolo [3,4- c]piridina- 3- carboxílico	(1) 541 [M + H] +; tR (k): 2,95 min.
716		amida del ácido 1- {2- [(1R,3S,5R)- 3- (2- Fluoro- 3- trifluorometoxi- fenilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 7- metil- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(1) 521 [M + H] +; tR (k): 2,90 min.
717		amida del ácido 1- {2- [(1R,3S,5R)- 3- (2- Fluoro- 3- trifluorometoxi- fenilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 5,7- dimetil- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(1) 535 [M + H] +; tR (c): 3,84 min.
718		amida del ácido (1R,3S,5R)- 2- {2- [3- Acetil- 5- (pirimidin- 2- ilmetoxi)- indazol- 1- il]- acetil}- 2- aza- biciclo[3.1.0]hexano- 3- (2- fluoro- 3- trifluorometoxi- fenil)- carboxílico	(1) 613 [M + H] +, 635 [M + Na] +; tR (c): 4,81 min.

719		5- ciclopropil- 1- (2- ((1R, 3S, 5R)- 3- ((2- fluoro- 3- (trifluorometoxi) fenil) carbamoil)- 2- azabiciclo [3.1.0] hexano- 2- il)- 2- oxoetil)- 1H- pirazolo [3,4- c] piridina- 3- carboxamida	(1) 547 [M + H] +; tR (c): 3,97 min.
720		1- (2- ((1R,3S,5R)- 3- ((2- Fluoro- 3- (trifluorometoxi)fenil)carbamoil)- 2- azabiciclo[3.1.0]hexan- 2- il)- 2- oxoetil)- 1H- pirazolo[3,4- c] piridazina- 3- carboxamida	(1) 508,0 [M + H] +, 529,9 [M + Na] +; tR (c): 4,08 min.
721		1- (2- {(1R,3S,5R)- 3- [6- (2,6- Difluoro- fenil)- piridin- 2- ilcarbamoil]- 2- aza- biciclo[3.1.0]hex- 2- il}- 2- oxo- etil)- 1H- pirazolo[3,4- c]piridina- 3- carboxamida	(1,2) 518 [M + H] +; tR (k): 2,90 min.
722		1- (2- ((1R,3S,5R)- 3- (2'- Cloro- 6'- fluorobifenil- 3- ilcarbamoil)- 2- azabiciclo[3.1.0]hexan- 2- il)- 2- oxoetil)- 1H- pirazolo[3,4- c]piridina- 3- carboxamida	(1,2) 533 [M + H] +; tR (c): 4,12 min.

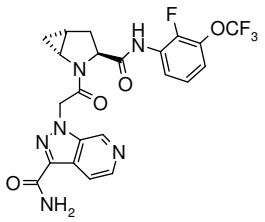
(1) El derivado de ácido utilizado es el paso C se preparó como se describe en la parte A; (2) El derivado de amina utilizada en el paso A se preparó como se describe en la Parte C.

Ejemplo 723: amida de ácido 1- {2- [(1R,3S,5R)- 3- (2- Fluoro- 3- trifluorometoxi- fenilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 5- metil- 1H- pirazolo[3,4- c]piridina- 3- carboxílico



A una solución de sal de trifluoroacetato del ácido (3- carbamoil- 5- metil- pirazolo [3,4- c] piridin- 1- il)- acético (3,87 g, 11,1 mmol, preparado como se describe en el Esquema A27) en DMF (45 ml) se añadieron sucesivamente sal de trifluoroacetato (2- fluoro- 3- trifluoro metoxi- fenil)- amida del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico (5,00 g, 11,1 mmol), DIPEA (7,77 ml, 44,5 mmol) y HBTU (5,06 g, 13,3 mmol). La mezcla de reacción se agitó a 25 ° C durante 2 h y después se concentró al vacío. El residuo se purificó por HPLC preparativa (Waters Sunfire C18- DAB, 5 micras, 30x100mm, flujo: 50 ml / min, eluyente: 5% a 100% CH_3CN en H_2O en 20 min, 100% CH_3CN 2 min, CH_3CN y H_2O que contiene TFA al 0,1%). Las fracciones puras se combinaron y los volátiles se evaporaron bajo presión reducida. La solución acuosa resultante se ajustó de pH 8 a 9 por adición de una solución acuosa saturada de NaHCO3, y después se extrajo con CH_2Cl_2 (x3). Los extractos orgánicos combinados se secaron (separador de fases) y se concentraron al vacío para proporcionar el compuesto del título como un sólido blanco. MS: 521 [M + H] +; tR (condiciones HPLC C): 3,81 min.

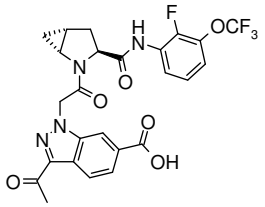
Ejemplo 724: 1- (2- ((1R,3S,5R)- 3- ((2- Fluoro- 3- (trifluorometoxi)fenil)carbamoil)- 2- azabiciclo[3.1.0]hexan- 2- il)- 2- oxoetil)- 1H- pirazolo[3,4- c]piridina- 3- carboxamida



A una solución de sal de trifluoroacetato de ácido (3- carbamoil- pirazolo [3,4- c] piridin- 1- il)- acético (1,60 g, 4,78 mmol, preparado como se describe en el Esquema A26) en DMF (40 ml) se agregaron sucesivamente sal de trifluoroacetato (2- fluoro- 3- trifluoro metoxi- fenil)- amida del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico (2,50 g, 4,78 mmol), DIPEA (3,34 ml, 19,1 mmol) y HBTU (2,17 g, 5,74 mmol). La mezcla de reacción se agitó a 25 ° C durante 2 h y luego se concentró. El residuo se purificó por HPLC preparativa (Waters Sunfire C18- DAB, 5 micras, 30x100mm, flujo: 50 ml / min, eluyente: 5% a 100% CH_3CN en H_2O en 20 min, 100% CH_3CN 2 min, CH_3CN y H_2O que contiene TFA al 0,1%). Las fracciones puras se combinaron y los volátiles se eliminaron a presión reducida. La solución acuosa resultante se ajustó a pH de 8 a 9 por adición de una solución acuosa saturada de $NaHCO_3$ y luego se extrajo con CH_2Cl_2 (x3). Los extractos orgánicos combinados se secaron (separador de fases) y se concentraron al vacío. El sólido residual se suspendió en Et_2O

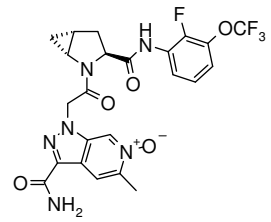
y se agitó a temperatura ambiente durante 16 h. El sólido se filtró y se secó bajo vacío para proporcionar el compuesto del título como un sólido blanco. MS: 507 [M + H] +; tR (condiciones HPLC C): 3,77 min.

Ejemplo 725: Ácido 3- Acetil- 1- {2- [(1R,3S,5R)- 3- (2- fluoro- 3- trifluorometoxi)fenil-carbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indazol- 6- carboxílico



A una solución de 3- acetil- 1- (2- ((1R,3S,5R)- 3- (2- fluoro- 3- trifluorometoxi)fenil-carbamoil)- 2- azabiciclo[3.1.0]hexan- 2- il)- 2- oxo- etil)- 1H- indazol- 6- carboxílato de metilo (**Ejemplo 710**, 25 mg, 0,044 mmol) en THF (2 ml) y agua (0,2 ml) se añadió una solución de LiOH acuoso 2 N (0,089 ml, 0,178 mmol). La mezcla de reacción se agitó a 25 ° C durante 4 h, después se añadió una solución acuosa de HCl 1 N para ácidoificar la mezcla de reacción de pH = 2 a 3. La solución acuosa resultante se extrajo con CH_2Cl_2 (x3), los extractos orgánicos combinados se secaron (separador de fases) y se concentraron luego a presión reducida. El residuo se purificó por HPLC preparativa (Waters Sunfire C18- DAB, 5 micras, 30x100mm, flujo: 40 ml / min, eluyente: 5% a 100% CH_3CN en H_2O en 20 min, 100% CH_3CN 2 min, CH_3CN y H_2O que contiene TFA al 0,1%). Las fracciones puras se combinaron, los volátiles se eliminaron a presión reducida y la solución acuosa resultante se liofilizó para proporcionar el compuesto del título como un sólido blanco. MS: 549 [M + H] +; tR (condiciones HPLC C): 4,76 min.

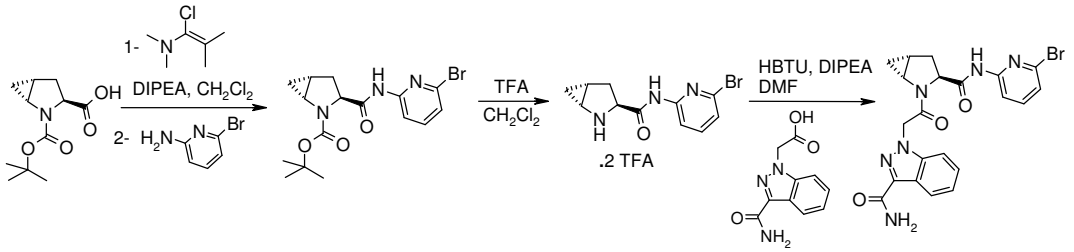
Ejemplo 726: 6- óxido del 3- Carbamoil- 1- (2- ((1R,3S,5R)- 3- ((2- fluoro- 3 hidroxifenil)carbamoil)- 2- azabiciclo[3.1.0]hexan- 2- il)- 2- oxoetil)- 5- metil- 1H- pirazolo[3,4c]piridina



A una solución de amida del ácido 1- {2- [(1R,3S,5R)- 3- (2- fluoro- 3- trifluorometoxi-fenilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 5- metil- 1H- pirazolo[3,4-

c]piridina- 3- carboxílico (Ejemplo 723, 50 mg, 0,096 mmol) en ácido acético (3 ml) se añadió ácido 3- clorobenzoperoxoico (38 mg, 0,154 mmol) a 55 ° C. La mezcla de reacción se agitó a 55 ° C durante 18 h y después se enfrió a temperatura ambiente. Los volátiles se evaporaron, el residuo se disolvió en EtOAc y se lavó con una solución de $NaHCO_3$ sat. aq. (x3) y salmuera, se secó (separador de fases) y se concentró bajo presión reducida para proporcionar el compuesto del título como un sólido blanco. MS: 537 [M + H] +; tR (condiciones HPLC k): 3,00 min.

Esquema D11: protocolo general descrito para la preparación del Ejemplo 727: amida del ácido 727:1- {2- [(1R,3S,5R)- 3- (6- Bromo- piridin- 2- ilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indazol- 3- carboxílico



A. Éster terc- butilo del ácido (1R, 3S, 5R)- 3- (6- bromo- piridin- 2- ilcarbamoil)- 2- aza- biciclo [3.1.0] hexano- 2- carboxílico

A una solución de éster 2- terc- butilo del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico (500 mg, 2,2 mmol) en CH_2Cl_2 seco (2 ml) se añadió 1- cloro- N, N ,2- trimetilpropenilamina (349 l, 2,64 mmol) a 0 ° C bajo atmósfera de nitrógeno. La formación del intermedio de cloruro de acil o se monitoreó por TLC después del temple de una alícuota con MeOH. Después de la terminación (1- 1,5 h), se añadió 2- amino- 6- bromopiridina (457 mg, 2,64 mmol) a 0 ° C, seguido de DIPEA (1,13 ml, 6,60 mmol) y la mezcla de reacción se agitó 2 h más a temperatura ambiente. La mezcla de reacción se vertió en agua y se extrajo dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron. CH_2Cl_2 se añadieron al residuo crudo y el precipitado se filtró para proporcionar el material deseado como un sólido blanco. TLC, Rf (EtOAc) = 0,85; MS: 382.1/384.1 [M + H] +, 380.2/382.3 [MH]- , 426.7/428.3 [M + HCOO]- ; tR (condiciones HPLC h): 2,19 min.

B. Sal de (6- bromo- piridin- 2- il)- amida del ácido (1R, 3S, 5R)- 2- aza- biciclo (trifluoroacetato) di [3.1.0] hexano- 3- carboxílico

A una solución de éster terc- butilo del ácido (1R, 3S, 5R)- 3- (6- bromo- piridin- 2- ilcarbamoil)- 2- aza- biciclo [3.1.0] hexano- 2- carboxilato (561 mg, 1,47 mmol) en CH_2Cl_2 (11 ml) se añadió TFA (1,13 ml, 14,7 mmol) y la solución se agitó a temperatura ambiente durante

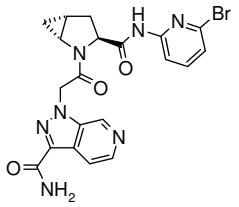
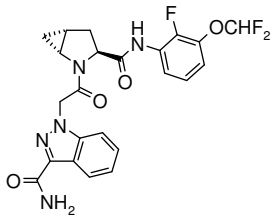
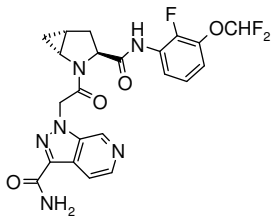
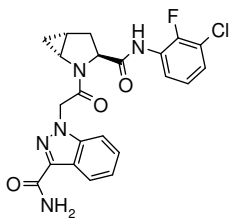
la noche. CH_2Cl_2 se concentró y el residuo bruto se secó a alto vacío para proporcionar el material deseado que se usó sin purificación adicional en la siguiente etapa. MS: 282.1/284.1 [M + H] +, 304.0/306.1 [M + Na] +, 563.1/565.2 [2M + H] +; tR (condiciones HPLC f): 0,96 min.

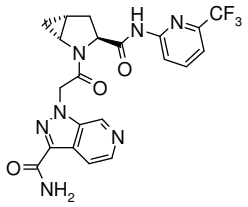
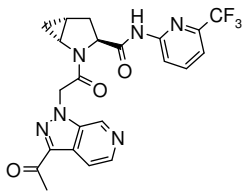
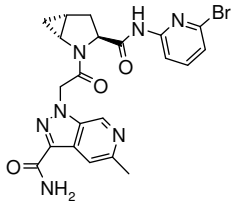
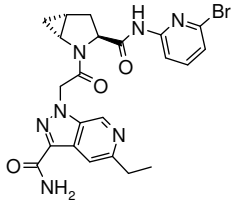
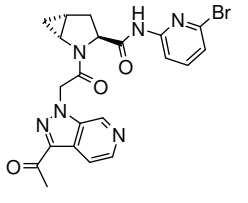
C. Ejemplo 727: amida de ácido 1- {2- [(1R, 3S, 5R)- 3- (6- bromo- piridin- 2- ilcarbamoil)- 2- aza- biciclo [3.1.0] hex- 2- il]- 2- oxo- etil}- 1H- indazol- 3- carboxílico

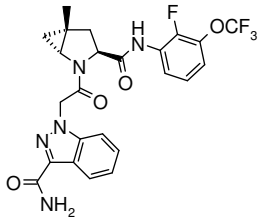
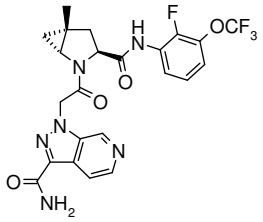
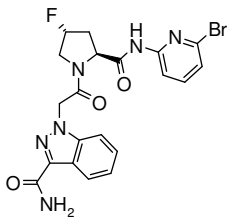
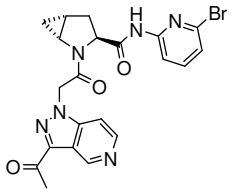
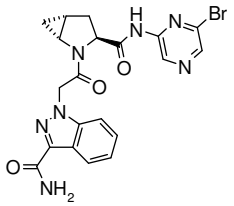
Ácido (3- carbamoil- indazol- 1- il)- acético (130 mg, 0,59 mmol, preparado como se describe en el Esquema A25), (6- bromo- piridin- 2- il)- amida del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico (2 sal de TFA, 303 mg, 0,59 mmol) y HBTU (337 mg, 0,89 mmol) se disolvieron en DMF (3 ml). Se añadió DIPEA (406 µl, 2,37 mmol) y la mezcla de reacción se agitó a 25 ° C durante 1 h. La mezcla de reacción bruta se purificó por HPLC preparativa (Waters Sunfire C18- DAB, 5 micras, 30x100mm, flujo: 40 ml / min, eluyente: 20% a 100% CH_3CN en H_2O en 25 min, CH_3CN y H_2O que contiene TFA al 0,1%). Las fracciones puras se combinaron, se neutralizó con una solución acuosa saturada de $NaHCO_3$ y se extrajo con CH_2Cl_2 para proporcionar el compuesto deseado. TLC, Rf (CH2Cl2/MeOH 9:1) = 0,55; MS: 483.1/485.1 [M + H] +, 965.4/967.4 [2M + H] +, 982.4/984.3 [2M + NH4] +, 481.1/483.2 [MH]- , 527.2/529.1 [M + HCOO]- ; tR (condiciones HPLC a): 2,79 min. Alternativamente, para los compuestos finales que contienen un residuo básico: las fracciones de HPLC puras se combinaron, CH_3CN se evaporó a presión reducida, la solución acuosa resultante se ajustó a pH 8- 9 por adición de una solución acuosa saturada de $NaHCO_3$, se extrajo con CH_2Cl_2(x3), los extractos orgánicos combinados se secaron (Na_2SO_4) y se concentraron al vacío.

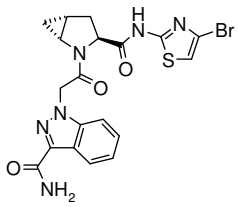
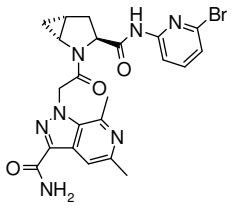
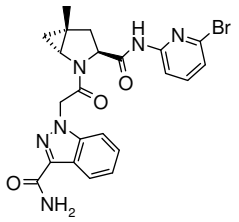
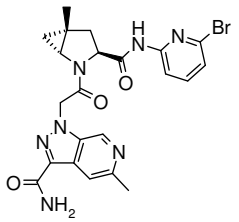
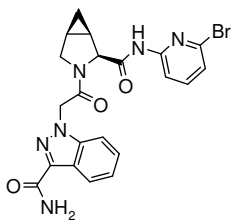
Los ejemplos siguientes se prepararon de acuerdo a los procedimientos generales descritos en el Esquema D11 para el **Ejemplo 727** *utilizando precursores de síntesis comercialmente disponibles si no se indica lo contrario (ver notas al final de la tabla 10):*

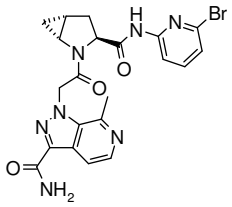
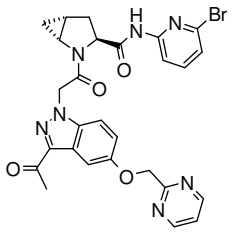
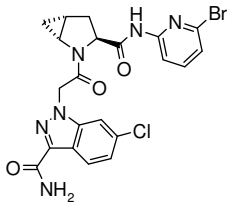
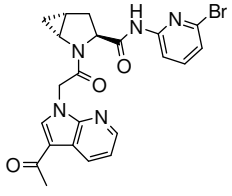
Tabla 10:

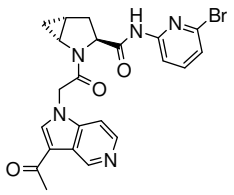
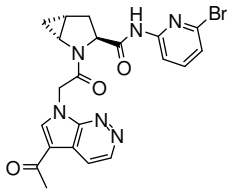
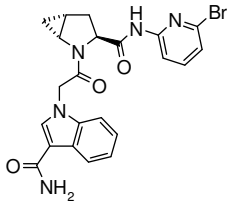
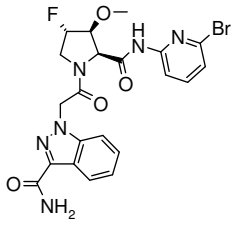
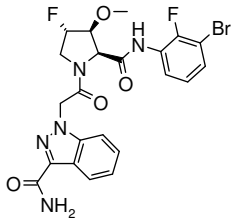
Ejemplo	Estructura	Nombre	Caracterización (Notas al final de la tabla), TLC, Rf (eluyente); MS (LC / MS); tR (condiciones HPLC)
728		amida del ácido 1- {2- [(1R,3S,5R)- 3- (6- bromo- piridin- 2- ilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- pirazolo[3,4- c] piridina- 3- carboxílico	(1) 484.1/486.1 [M + H] +, 482.0/484.1 [MH]- , 528.2/530.1 [M + HCOO]- ; tR (a): 2,22 min.
729		amida de ácido 1- {2- [(1R, 3S, 5R)- 3- (3- fenilcarbamoil difluorometoxi- 2- fluoro)- 2- aza- biciclo [3.1.0] hex- 2- il]- 2- oxo- etil} - 1H- indazol- 3- carboxílico	(1,2,3) 488,2 [M + H] +, 505,2 [M + NH4] +, 486,2 [MH]- , tr (f): 1,90 min
730		amida del ácido 1- {2- [(1R, 3S, 5R)- 3- (3- difluorometoxi- 2- fluoro- fenilcarbamoil)- 2- aza- biciclo [3.1.0] hex- 2- il]- 2- oxo- etil}- 1H- pirazolo [3,4- c] piridina- 3- carboxílico	(1,2,3) 489,2 [M + H] +, 487,2 [MH]- , 533,2 [M + HCOO]- ; tR (f): 1,41 min
731		amida del ácido 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- fenilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indazol- 3- carboxílico	(1) Rf (CH2Cl2/MeOH 9:1) = 0,55; 473.2/475.2 [M + NH4] +, 478.2/480.2 [M + Na] +, 454.3/456.2 [MH]- , 500.2/502.2 [M +

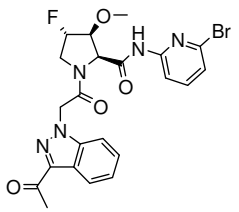
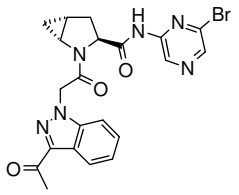
			HCOO]- ; tR (a): 1,86 min.
732		amida del ácido 1- {2- oxo- 2- [(1R, 3S, 5R)- 3- (6- trifluorometil- piridin- 2- ilcarbamoil)- 2- aza- biciclo [3.1.0] hex- 2- il]- acetato }- 1 H- pirazolo [3,4- c] piridina- 3- carboxílico	(1) Rf (EtOAc) = 0,1; 474,2 [M + H] +, 472,2 [MH]- , 518,3 [M + HCOO]- ; tR (a): 2,09 min.
733		ácido carboxílico (1R, 3S, 5R)- 2- [2- (3- Acetil- pirazolo [3,4- c] piridin- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- (6- trifluorometil- piridin- 2- il)- amida	(1) Rf (EtOAc) = 0,25; 473,2 [M + H] +, 471,2 [MH]- , 517,2 [M + HCOO]- ; tR (a): 2,30 min.
734		amida del ácido 1- {2- [(1R,3S,5R)- 3- (6- Bromo- piridin- 2- ilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 5- metil- 1H- pirazolo [3,4- c]piridina- 3- carboxílico	(1) Rf (EtOAc) = 0,1; 498.1/500.1 [M + H] +, 496.2/498.1 [MH]- , 542.3/544.1 [M + HCOO]- ; tR (a): 2,27 min.
735		amida del ácido 1- {2- [(1R,3S,5R)- 3- (6- Bromo- piridin- 2- ilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 5- etil- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(1) Rf (EtOAc) = 0,26; 12.2/514.2 [M + H] +, 510.2/512.2 [MH]- , 556.2/558.2 [M + HCOO]- ; tR (a): 2,35 min.
736		(6- bromo- piridin- 2- il)- amida del ácido (1R, 3S, 5R)- 2- [2- (3- Acetil- pirazolo [3,4- c] piridin- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico	(1) Rf (CH2Cl2/MeOH 9:1) = 0,5; 483.1/485.1 [M + H] +, 481.1/483.1 [MH]- , tr (f): 1,38 min.

737		amida del ácido 1- {2- [(1R,3S,5R)- 3- (2- Fluoro- 3- trifluorometoxi- fenilcarbamoil)- 5- metil- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indazol- 3- carboxílico	(1,4) 419,2 [M + H] +, 436,2 [M + NH4] +, 417,2 [MH]- , 463,2 [M + HCOO]- ; tR (f): 2,46 min.
738		amida del ácido 1- {2- [(1R, 3S, 5R)- 3- (2- fluoro- 3- trifluorometoxi- fenil carbamoil)- 5- metil- 2- aza- biciclo [3.1.0] hex- 2- il]- 2 - oxo- etil}- 1H- pirazolo [3,4- c] piridina- 3- carboxílico	(1,4) Rf (CH2Cl2/MeOH 9:1) = 0,5; 521,2 [M + H] +, 1041,5 [2M + H] +, 519,2 [MH]- , 1039,5 [2M- H]- ; tR (f): 1,49 min.
739		1- {2- [(2S,4R)- 2- (6- Bromo- piridin- 2- ilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indazol- 3- carboxílico amida del ácido	(1) Rf (CH2Cl2/MeOH 9:1) = 0,5; 489.2/491.1 [M + H] +, 487.1/489.3 [MH]- , tr (f): 1,56 min.
740		(6- bromo- piridin- 2- il)- amida del ácido (1R, 3S, 5R)- 2- [2- (3- Acetil- pirazolo [4,3- c] piridin- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico	(1) Rf (CH2Cl2/MeOH 9:1) = 0,6; 483.1/485.2 [M + H] +, 965.3/697.3 [2M + H] +, 481.1/483.2 [MH]- , tr (f): 1,34 min.
741		amida del ácido 1- {2- [(1R,3S,5R)- 3- (6- Bromo- pirazin- 2- ilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indazol- 3- carboxílico	(1) Rf (CH2Cl2/MeOH 9:1) = 0,6; 501.2/503.2 [M + NH4] +, 482.1/484.1 [MH]- , tr (f): 1,51 min.

742		amida del ácido 1- {2- [(1R,3S,5R)- 3- (4- Bromo- tiazol- 2- ilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indazol- 3- carboxílico	(1) Rf (CH2Cl2/MeOH 9:1) = 0,5; 489.1/491.1 [M + H] +, 511.1/513.1 [M + Na] +, 487.1/489.1 [MH]- , tr (f): 1,59 min.
743		amida del ácido 1- {2- [(1R,3S,5R)- 3- (6- Bromo- piridin- 2- ilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 5,7- dimetil- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(1) Rf (CH2Cl2/MeOH 9:1) = 0,45; 512.2/514.2 [M + H] +, 510.2/512.2 [MH]- , tr (f): 1,25 min.
744		amida de ácido 1- {2- [(1R, 3S, 5R)- 3- (6- bromo- piridin- 2- ilcarbamoil)- 5- metil- 2- aza- biciclo [3.1.0] hex- 2- il]- 2 - oxo- etil}- 1H- indazol- 3- carboxílico	(1,4) Rf (CH2Cl2/MeOH 9:1) = 0,4; 497.2/499.2 [M + H] +, 495.2/497.2 [MH]- , tr (f): 1,82 min.
745		amida del ácido 1- {2- [(1R, 3S, 5R)- 3- (6- bromo- piridin- 2- ilcarbamoil)- 5- metil- 2- aza- biciclo [3.1.0] hex- 2- il]- 2 - oxo- etil} 5- metil- 1H- pirazolo- [3,4- c] piridina- 3- carboxílico	(1,4) Rf (CH2Cl2/MeOH 9:1) = 0,4; 512.2/514.2 [M + H] +, 510.1/512.2 [MH]- , 556.3/558.2 [M + HCOO]- ; tR (f): 1,37 min.
746		amida del ácido 1- {2- [(1R,2S,5S)- 2- (6- Bromo- piridin- 2- ilcarbamoil)- 3- aza- biciclo[3.1.0]hex- 3- il]- 2- oxo- etil}- 1H- indazol- 3- carboxílico	(1) Rf (CH2Cl2/MeOH 9:1) = 0,55; 483.1/485.1 [M + H] +, 481.1/483.1 [MH]- , 527.3/529.1 [M +

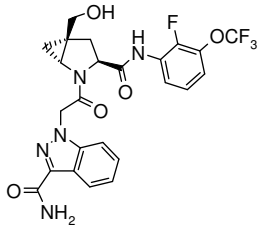
			HCOO]- ; tR (f): 1,74 min.
747		amida del ácido 1- {2- [(1R,3S,5R)- 3- (6- Bromo- piridin- 2- ilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 7- metil- 1H- pirazolo[3,4- c]piridina- 3- carboxílico	(1) Rf (CH2Cl2/MeOH 9:1) = 0,4; 498.2/500.2 [M + H] +, 496.7/498.4 [MH]- , tr (f): 1,26 min.
748		carboxílico del ácido (1R,3S,5R)- 2- {2- [3- Acetil- 5- (pirimidin- 2- ilmetoxi)- indazol- 1- il]- acetil}- 2- aza- biciclo[3.1.0]hexano- 3- (6- bromo- piridin- 2- il)- amida	(1) Rf (CH2Cl2/MeOH 9:1) = 0,75; 590.2/592.2 [M + H] +, 1179.5/1181.4 [2M + H] +, 588.3/590.4 [MH]- , tr (f): 1,80 min.
749		amida del ácido 1- {2- [(1R,3S,5R)- 3- (6- Bromo- piridin- 2- ilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 6- Cloro- 1H- indazol- 3- carboxílico	(1) Rf (CH2Cl2/MeOH 9:1) = 0,55; 517.1/519.1 [M + H] +, 515.1/517.1 [MH]- , 561.1/563.2 [M + HCOO]- ; tR (f): 1,88 min.
750		(6- bromo- piridin- 2- il)- amida del ácido (1R, 3S, 5R)- 2- [2- (3- acetil- pirrolo [2,3- b] piridin- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico	(1) Rf (CH2Cl2/MeOH 9:1) = 0,75; 482.1/484.2 [M + H] +, 480.1/482.1 [MH]- , 526.0/528.1 [M + HCOO]- ; tR (f): 1,75 min.

751		(6- bromo- piridin- 2- il)- amida del ácido (1R, 3S, 5R)- 2- [2- (3- acetil- pirrolo [3,2- c] piridin- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico	(1) Rf (CH2Cl2/MeOH 9:1) = 0,5; 482.1/484.2 [M + H] +, 480.0/482.1 [MH]- , 526.1/528.2 [M + HCOO]- ; tR (f): 1,27 min.
752		(6- bromo- piridin- 2- il)- amida del ácido (1R, 3S, 5R)- 2- [2- (5- Acetil- pirrolo [2,3- c] piridazin- 7- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico	(1) Rf (CH2Cl2/MeOH 9:1) = 0,55; 483.2/485.1 [M + H] +, 481.1/483.1 [MH]- , tr (f): 1,29 min.
753		amida del ácido 1- {2- [(1R,3S,5R)- 3- (6- Bromo- piridin- 2- ilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico	(1) Rf (CH2Cl2/MeOH 9:1) = 0,45; 482.1/484.1 [M + H] +, 499.2/501.2 [M + NH4] +, 480.1/482.1 [MH]- , tr (f): 1,64 min.
754		amida del ácido 1- {2- [(2S,3S,4S)- 2- (6- Bromo- piridin- 2- ilcarbamoil)- 4- fluoro- 3- metoxi- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indazol- 3- carboxílico	(1,5) 519.1/521.1 [M + H] +, 517.1/519.1 [MH]- , tr (f): 1,64 min.
755		amida del ácido 1- {2- [(2S,3S,4S)- 2- (3- Bromo- 2- fluoro- fenilcarbamoil)- 4- fluoro- 3- metoxi- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indazol- 3- carboxílico	(1,5) Rf (AcOEt) = 0,5; 553.2/555.2 [M + NH4] +, 534.2/536.1 [MH]- , 580.1/582.2 [M + HCOO]- ; tR (f): 1,76 min.

756		(6- bromo- piridin- 2- il)- amida del ácido (2S, 3S, 4S)- 1- [2- (3- Acetil- indazol- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico	(1,5)Rf (AcOEt) = 0,9;518.2/520.1 [M + H] + 516.1/518.1 [MH]- 562.2/564.2 [M + HCOO]- ; tR (F): 1,92 min.
757		(6- bromo- pirazin- 2- il)- amida del ácido (1R, 3S, 5R)- 2- [2- (3- Acetil- indazol- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico	(1)Rf (CH2Cl2/MeOH 9:1) = 0,85; 483.1/485.1 [M + H] +, 500.2/502.2 [M + NH4] +, 481.1/483.1 [MH]- , tr (f): 1,91 min.

(1) El derivado de ácido utilizado es el paso C se preparó como se describe en la parte A; (2) El derivado de amina utilizado en el paso A se preparó como se describe en la Parte C; (3) el paso C se efectúa utilizando T_3P y DIPEA como se describe en Esquema D8 Paso C; (4) El derivado de ácido utilizado en Paso A se preparó como se describe en la Parte B; (5) El compuesto del título se preparó de acuerdo con el procedimiento general descrito en el Esquema D11 los pasos B y C a partir del derivado de prolina sustituido preparado como se describe en la Parte B.

Ejemplo 758: amida de ácido 1- {2- [(1R,3S,5S)- 3- (2- Fluoro- 3- trifluorometoxi- fenilcarbamoil)- 5- hidroximetil- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indazol- 3- carboxílico



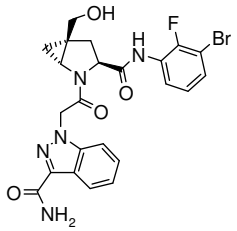
Una solución de éster (1R,3S,5S)- 2- [2- (3- carbamoil- indazol- 1- il)- acetil]- 3- (2- fluoro- 3- trifluorometoxi- fenilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 5- ilmetílico del ácido (3- carbamoil- indazol- 1- il)- acético (69,2 mg, 0,085 mmol) y NaOH (1 N, 188 µl, 0,19 mmol) en THF (0,45 ml) y agua (43 µl) se agitó a temperatura ambiente 1 h. Se añadieron agua y EtOAc, las capas se separaron y la capa acuosa se extrajo con EtOAc (x2). Los extractos orgánicos

combinados se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo bruto se purificó por HPLC preparativa (Waters Sunfire C18- DAB, 5 micras, 30x100 mm, eluyente: 20% a 100% CH_3CN en H_2O en 25 min, CH_3CN y H_2O que contiene 0.1% de TFA, flujo: 40 ml / min). Rf, la TLC (CH_2Cl_2/MeOH 9:1) = 0,45; EM (UPLC / MS): 536,4 [M + H] +, 553,3 [M + NH4] +, 558,2 [M + Na] +, 534,3 [MH]- , 580,3 [M + HCOO]- ; t_R (condiciones HPLC f): 1,82 min.

Éster metílico (1R,3S,5S)- 2- [2- (3- carbamoil- indazol- 1- il)- acetil]- 3- (2- fluoro- 3- trifluorometoxi- fenilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 5- il del ácido (3- carbamoil- indazol- 1- il)- acético

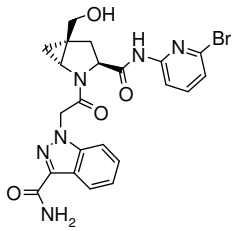
A una mezcla de ácido (3- carbamoil- indazol- 1- il)- acético (preparado como se describe en el Esquema A25, 41 mg, 0,18 mmol, 2 eq.), clorhidrato de (2- fluoro- 3- trifluorometoxi- fenil)- amida del ácido (1R, 3S, 5S)- 5- hidroximetil- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico (preparado como se describe en el Esquema B29, 51 mg, 0,09 mmol, 1 eq.), y HBTU (106 mg, 0,28 mmol) en DMF (0,45 ml) se añadió DIPEA (64 l, 0,37 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 30 min, después se vertió en agua y se extrajo con EtOAc (x2). Los extractos orgánicos combinados se lavaron con salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron. El material así obtenido se usó en la siguiente etapa sin purificación adicional. MS (UPLC / MS): 737,3 [M + H] +, 759,3 [M + Na] +, 735,2 [MH]- ; tR (condiciones HPLC f): 2,03 min.

Ejemplo 759: amida del ácido 1- {2- [(1R, 3S, 5S)- 3- (3- bromo- 2- fluoro- fenilcarbamoil)- 5- hidroximetil- 2- aza- biciclo [3.1.0] hex- 2- il]- 2- oxo- etil}- 1H- indazol- 3- carboxílico



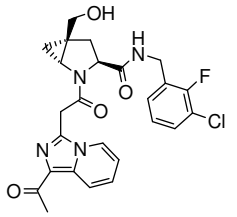
se preparó usando los protocolos descritos para la preparación del **Ejemplo 758** el uso a partir de 3- bromo- 2- fluoro- fenilamina. R_f, TLC (CH_2Cl_2/MeOH 9:1) = 0,45; EM (UPLC / MS): 547.2/549.2 [M + NH4] +, 552.2/554.1 [M + Na] +, 1081.3/1083.3 [2M + Na] + , 574.3/576.0 [M + HCOO]- , 1057.3/1059.3 [2M- H]- ; tR (condiciones HPLC f): 1,62 min.

Ejemplo 760: amida del ácido 1- {2- [(1R,3S,5S)- 3- (6- Bromo- piridin- 2- ilcarbamoil)- 5- hidroximetil- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indazol- 3- carboxílico



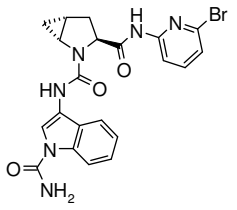
se preparó usando los protocolos descritos para la preparación del **Ejemplo 758** utilizando 6- bromo- piridin- 2- ilamina en lugar de 2- fluoro- 3- trifluorometoxi- fenilamina. Rf, TLC (CH_2Cl_2/MeOH 9:1) = 0,4; MS (UPLC / MS): 513.2/515.2 [M + H] +, 530.3/532.2 [M + NH4] +, 535.3/537.2 [M + Na] + ; tR (f) Condiciones HPLC: 1,47 min.

Ejemplo 761: 3- cloro- 2- fluoro- bencilamida del ácido (1R, 3S, 5S)- 2- [2- (1- Acetil- imidazo [1,5- a] piridin- 3- il)- acetil]- 5- hidroxi metil- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico



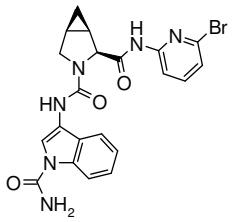
se preparó usando los protocolos descritos para la preparación del Ejemplo 758 a partir de éster terc- butílico del ácido (1R,3S,5S)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 5- hidroximetil- 2- aza- biciclo[3.1.0]- hexano- 2- carboxílico (preparado como se describe en el Esquema B28) y ácido (1- acetil- imidazo [1,5- a] piridin- 3- il)- acético (preparado como se describe en el Esquema A19). R_f, la TLC (CH_2Cl_2/MeOH 9:1) = 0,40; EM (UPLC / MS): 499.4/501.4 [M + H] +, 521.4/523.4 [M + Na] +, 543.5/545.5 [M + HCOO]- ; tr (f) Condiciones HPLC: 1,66 min.

Ejemplo 762: 3- [(6- bromo- piridin- 2- il)- amida] 2- [(- 1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 2 ,3- dicarboxílico



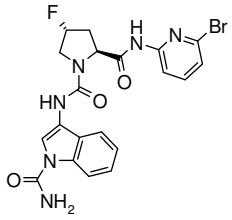
A una solución de (6- bromo- piridin- 2- il)- amida del ácido ((1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico (2 sal TFA, 40 mg, 0,08 mmol) y Et_3N (44 µl, 0,31 mmol) en THF (0,4 ml) se añadió una suspensión de amida de ácido 3- isocianato- indol- 1- carboxílico (25 mg, 0,08 mmol, preparado como se describe en el Esquema A1) en THF (0,8 ml). La solución resultante se agitó a temperatura ambiente bajo una atmósfera de nitrógeno durante 45 min, se concentró y se purificó por HPLC preparativa (Waters SunFire C18- ODB, 5 micras, 19x50 mm, 20- 100% CH_3CN/H_2O en 25 min, CH_3CN y H_2O que contiene TFA al 0,1% de flujo: 40 ml / min) para proporcionar el material deseado después de la neutralización (solución acuosa saturada de $NaHCO_3$) y la extracción de las fracciones purificadas (CH_2Cl_2) TLC, Rf (CH_2Cl_2/MeOH 9:1) = 0,45. ; MS (LC / MS): 483.1/485.2 [M + H] +, 965.3/967.3 [2M + H] +, 481.1/483.1 [MH]- ; tR (condiciones HPLC f): 1,83 min.

Ejemplo 763: 2- [(6- bromo- piridin- 2- il)- amida] 3- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1R,2S,5S)- 3- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico



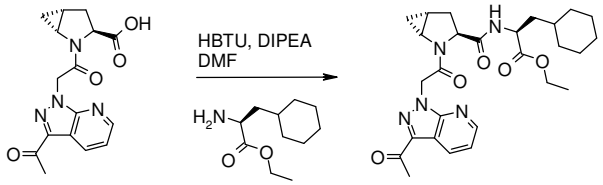
se preparó usando el protocolo descrito para la síntesis del **Ejemplo 762**; TLC, Rf (CH_2Cl_2/MeOH 9:1) = 0,55; 483.1/485.1 [M + H] +, 965.3/967.3 [2M + H] +, 481.1/483.2 [MH]- ; tR (condiciones HPLC f): 1,72 min.

Ejemplo 764: 2- [(6- bromo- piridin- 2- il)- amida] 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido ((2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico



se preparó utilizando el protocolo descrito para la síntesis del Ejemplo 762; TLC, Rf (CH_2Cl_2/MeOH 9:1) = 0,45; 489.1/491.1 [M + H] +, 506.1/508.2 [M + NH4] +, 487.1/489.1 [MH]- ; tR (condiciones HPLC f): 1,70 min.

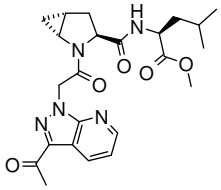
Esquema D12: el protocolo general descrito para la preparación de Ejemplo 765: éster etílico del ácido (S)- 2- ({(1R, 3S, 5R)- 2- [2- (3- Acetil- pirazolo [3,4- b] piridin- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carbonil}- amino)- 3- ciclohexil- propiónico

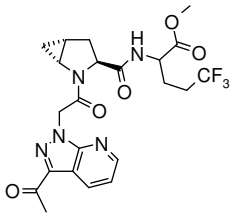
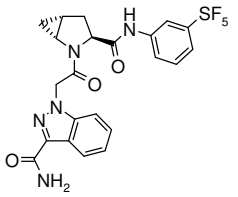


Ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirazolo[3,4- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico (20 mg, 0,061 mmol, preparado como se describe en el Esquema B30), éster etílico del ácido (S)- 2- amino- 3- ciclohexil- propanoico (17,3 mg, 0,073 mmol) y HBTU (34,7 mg, 0,091 mmol) en DMF (0,2 ml). Se añadió DIPEA (32 □l, 0,18 mmol) y la mezcla de reacción se agitó a 25 ° C durante 20 h. El material en bruto se purificó por HPLC preparativa (XBridge C18ODB, 5 m, 30x100, eluyente: CH_3CN al 20%/ H_2O al 80% a CH_3CN al 100% en 12 min, CH_3CN y H_2O que contiene 7,3 mM de NH_3, flujo de 45 ml / min). Las fracciones puras se combinaron y liofilizaron para proporcionar el material deseado como un polvo blanco. MS: 510,1 [M + H] +, 532,0 [M + Na] +; tR (condiciones HPLC l): 3,42 min.

Los ejemplos a continuación se prepararon de acuerdo a los procedimientos generales descritos en el Esquema D12 para el **Ejemplo 765** *utilizando precursores de síntesis comercialmente disponibles, si no se indica lo contrario:*

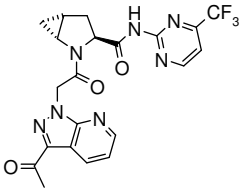
Tabla 11:

Ejemplo	Estructura	Nombre	Caracterización MS (LC / MS); tR (condiciones HPLC)
766		éster metílico del ácido (S)- 2- ({(1R, 3S, 5R)- 2- [2- (3- Acetil- pirazolo [3,4- b] piridin- 1- il)- acetil]- 2- aza- biciclo [3.1.0]	456,0 [M + H] +, 478,0 [M + Na] +; tR (l): 2,812 min.

		hexano- 3- carbonil}- amino)- 4- metil- pentanoico	
767		éster metílico del ácido 2- ({(1R, 3S, 5R)- 2- [2- (3- Acetil- pirazolo [3,4- b] piridin- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carbonil}- amino) 5,5,5- trifluoro- pentanoico	496,0 [M + H] +, 518,0 [M + Na] +; tR (l): 2,813 min.
768		amida del ácido 1- {2- [(1R, 3S, 5R)- 3- (3- pentafluoruro de azufre- fenil- fenilcarbamoil)- 2- aza- biciclo [3.1.0] hex- 2- il]- 2- oxo- etil} - 1H- indazol- 3- carboxílico	(1,2) 530 [M + H] +; tR (k): 3,45 min.

(1) La reacción se realizó a 40 ° C, (2) El derivado de ácido utilizado como material de partida se preparó de acuerdo con el Esquema B31.

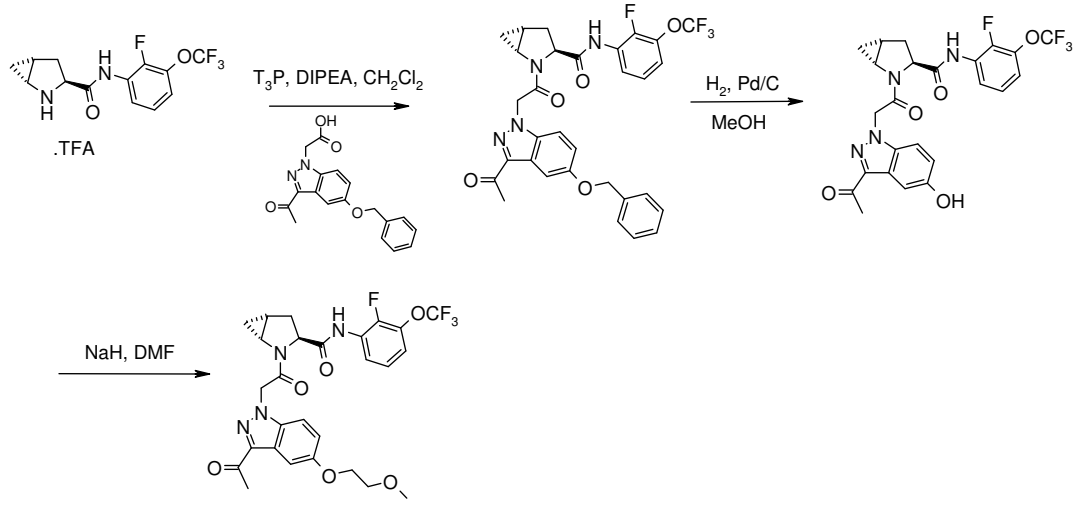
Ejemplo 769: (4- trifluorometil- pirimidin- 2- il)- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirazolo[3,4- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico



A una solución de ácido (1R,3S,5R)- 2- [2- (3- acetil- pirazolo[3,4- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico (50 mg, 0,15 mmol, preparado como se describe en la parte B) en CH_2Cl_2 (3 ml) se añadió 1- cloro- N, N, 2- trimetilprop- 1- en- 1- amina (81 mg, 0,609 mmol) a 0 ° C bajo atmósfera de nitrógeno. Después de agitar a 0 ° C durante 1 h, 4- (trifluorometil) pirimidin- 2- amina (27,3 mg, 0,17 mmol) seguido por DIPEA (0,053 ml, 0,305 mmol) se añadió y la mezcla se agitó a temperatura ambiente durante 16 h. La mezcla se concentró y el residuo se purificó por HPLC preparativa (Waters Sunfire C18- ODB, 5 um, 30x100mm, flujo: 40 ml / min, gradiente: 0 a 18,5 min 5% a 100% CH_3CN, 18,5 a 20 min 100% CH_3CN, CH_3CN y H_2O que contiene TFA al 0,1%).Las fracciones puras se combinaron, se neutralizaron con una solución acuosa saturada de Na_2CO_3, se extrajeron con

EtOAc, se secaron (Na_2SO_4), se filtraron y se concentraron. MS (UPLC- MS): 474,3 [M + H] +, 472,3 [MH]- ; tR (condiciones HPLC f): 1,81 min.

Esquema D13: protocolo general descrito para la preparación del Ejemplo 770: (2- fluoro- 3- trifluorometoxi- fenil)- amida del ácido (1R,3S,5R)- 2- {2- [3- Acetil- 5- (2- metoxi- etoxi)- indazol- 1- il]- acetil}- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico



A. (2- fluoro- 3- trifluorometoxi- fenil)- amida del ácido (1R, 3S, 5R)- 2- [2- (3- Acetil- 5- benciloxi- indazol- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico

A una solución de ácido (3- acetil- 5- benciloxi- indazol- 1- il)- acético (1,38 g, 4,30 moles, preparado como se describe en la Parte A), trifluoroacetato (2- fluoro- 3- trifluoro metoxi- fenil)- amida del ácido (1R, 3S, 5R)- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico (1,80 g, 4,30 mmol) y anhídrido propilfosfónico (50% en EtOAc, 3,80 ml, 6,46 mmol) en CH_2Cl_2 (40 ml) se añadió DIPEA (2,25 ml, 12,91 mmol) y la mezcla resultante se agitó a temperatura ambiente durante 2 h. La mezcla se concentró y el residuo en bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:00 a 0:1). MS (UPLC- MS): 611 [M + H] +; tR (condiciones HPLC f): 2,40 min.

B. (2- fluoro- 3- trifluorometoxi- fenil)- amida del ácido (1R, 3S, 5R)- 2- [2- (3- Acetil- 5- hidroxi- indazol- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico

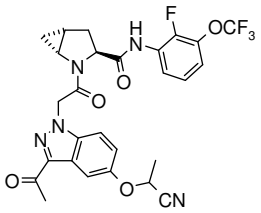
Una mezcla de (2- fluoro- 3- trifluorometoxi- fenil)- amida del ácido (1R, 3S, 5R)- 2- [2- (3- acetil- 5- benciloxi- indazol- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico (2,0 g, 3,28 mmol) y Pd / C (10%, 165 mg) en MeOH (40 ml) se agitó bajo una atmósfera de

H2 durante 1 h. La mezcla se filtró a través de una almohadilla de celite y se concentró. El producto se utilizó en la siguiente etapa sin purificación adicional. MS (UPLC- MS): 521 [M + H] +; tR (condiciones HPLC f): 2,02 min.

C. Ejemplo 770: (2- fluoro- 3- trifluorometoxi- fenil)- amida del ácido (1R, 3S, 5R)- 2- {2- [3- Acetil- 5- (2- metoxi- etoxi)- indazol- 1- il]- acetil}- 2- aza- biciclo [3.1 0,0] hexano- 3- carboxílico

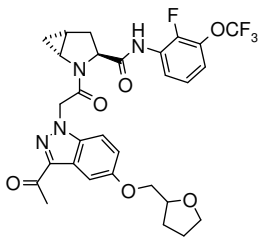
A una suspensión de hidruro de sodio (60% en aceite mineral, 4,8 mg, 0,121 mmol) en DMF (5 ml) a 0 º C se añadió (2- fluoro- 3- trifluorometoxi- fenil)- amida del ácido 1R, 3S, 5R)- 2- [2- (3- acetil- 5- hidroxi- indazol- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico (60 mg, 0,115 mmol). Después de agitar durante 5 min, 1- bromo- 2- metoxietano (0,016 ml, 0,173 mmol) se añadió y la mezcla de reacción se agitó a temperatura ambiente durante 16 h. La mezcla de reacción se inactivó con agua y se extrajo con EtOAc. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo bruto se purificó por HPLC preparativa (Waters Sunfire C18- ODB, 5 um, 30x100mm, flujo: 40 ml / min, gradiente: 0 a 18,5 min 5% a 100% CH_3CN, 18,5 a 20 min 100% CH_3CN, H_2O y CH_3CN que contiene TFA al 0,1%). La purificación adicional por cromatografía ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:00 a 0:1) proporcionó el compuesto del título .MS (UPLC- MS): 579,3. tR (f) Condiciones HPLC: 2,07 min.

Ejemplo 771: (2- fluoro- 3- trifluorometoxi- fenil)- amida del ácido (1R,3S,5R)- 2- {2- [3- Acetil- 5- (ciano- metil- metoxi)- indazol- 1- il]- acetil}- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico



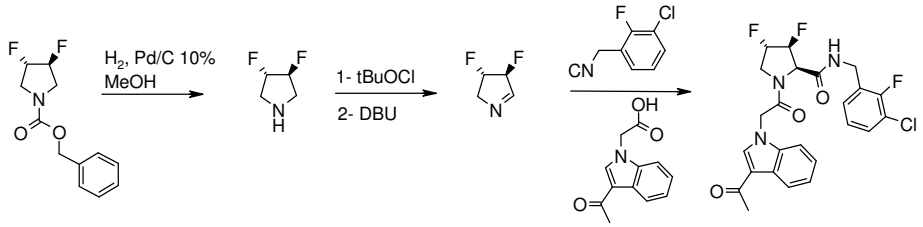
se preparó utilizando el protocolo descrito para la síntesis del Ejemplo 770 en el Esquema A13. El residuo bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (c- hexano/EtOAc 1:00 a 0:1). MS (UPLC- MS): 572,2 [MH]- ; tR (condiciones HPLC f): 2,15 min.

Ejemplo 772: (2- fluoro- 3- trifluorometoxi- fenil)- amida del ácido (1R,3S,5R)- 2- {2- [3- Acetil- 5- (tetrahidro- furan- 2- ilmetoxi)- indazol- 1- il]- acetil}- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico



se preparó utilizando el protocolo descrito para la síntesis del Ejemplo 770 en el Esquema D13 con el siguiente procedimiento para el Paso C. A una suspensión de hidruro de sodio (60% en aceite mineral, 4,8 mg, 0,121 mmol) en DMF (5 ml) a 0 º C se añadió (2- fluoro- 3- trifluorometoxi- fenil)- amida del ácido 1R, 3S, 5R)- 2- [2- (3- acetil- 5- hidroxi- indazol- 1- il)- acetil]- 2- aza- biciclo [3.1.0] hexano- 3- carboxílico (60 mg, 0,115 mmol). Después de agitar durante 5 min, se añadió 2- (bromometil) tetrahidrofurano (28,5 mg, 0,173 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 16 h. Se añadieron porciones adicionales de NaH (60% en aceite mineral, 4,6 mg, 0,115 mmol) y 2(bromometil) tetrahidrofurano (19,0 mg, 0,115 mmol) y la mezcla resultante se agitó a temperatura ambiente durante 16 h- . La mezcla de reacción se inactivó con agua y se extrajo con EtOAc. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo bruto se purificó por HPLC preparativa (Waters Sunfire C18- ODB, 5 um, 30x100mm, flujo: 40 ml / min, gradiente: 0 a 18,5 min 5% a 100% CH_3CN, 18,5 a 20 min 100% CH_3CN, H_2O y CH_3CN que contiene TFA al 0,1%).MS (UPLC- MS): 605,4. tR (f) Condiciones HPLC: 2,20 min.

<u>Esquema D14: protocolo general descrito para la preparación del Ejemplo 773: 3- cloro- 2- fluoro- bencilamida del ácido (2R, 3S, 4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 3,4- difluoro- pirrolidina- 2- carboxílico</u>



A. (3S, 4S)- 3,4- difluoro- pirrolidina

A una solución de éster bencilo del ácido (3S, 4S)- 3,4- difluoro- pirrolidina- 1- carboxílico (ACS Scientific Inc., n º de cat 6- 0.511, 3 g, 12,44 mmol) en MeOH (41 ml) se

añadió Pd / C al 10% (500 mg) y la solución se desgasificó 3 veces sustituyendo el aire por nitrógeno y, finalmente, el nitrógeno por hidrógeno. La mezcla de reacción se agitó adicionalmente en atmósfera de hidrógeno durante 3 días. Después de la terminación, la solución se desgasificó 3 veces sustituyendo el hidrógeno por nitrógeno y el catalizador se eliminó a través de una almohadilla de Celite. La solución resultante de (3S, 4S)- 3,4- difluoro- pirrolidina volátil en MeOH (aprox. 0,209 mol / L) se almacenó en la nevera y se utilizó sin tratamiento adicional en la siguiente etapa. Rf (EtOAc): 0.1.

B. (3S, 4S)- 3,4- difluoro- 3 ,4- dihidro- 2H- pirrol

A una solución de (3S, 4S)- 3,4- difluoro- pirrolidina (0,209 M en MeOH, 2,5 ml, 0,52 mmoles) en un matraz protegido con una lámina de aluminio a 0 º C bajo argón, se añadió tBuOCl (73 l, 0,52 mmoles). La mezcla de reacción se agitó a 0 ° C durante 1 h, hasta que la TLC (CH_2Cl_2/MeOH 9:1) indicó el consumo del material de partida. DBU (79 l, 0,52 mmol) y después se añadió a 0 ° C a la solución resultante de (3S, 4S)- 1- cloro- 3 ,4- difluoro- pirrolidina y la mezcla se dejó alcanzar la temperatura ambiente y se agitó adicionalmente durante 3 h. La solución así obtenida se utilizó en la siguiente etapa.

C. Ejemplo 773: 3- cloro- 2- fluoro- bencilamida del ácido (2R, 3S, 4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 3,4- difluoro- pirrolidina- 2- carboxílico

A la solución en bruto de (3S, 4S)- 3,4- difluoro- 3 ,4- dihidro- 2H- pirrol (0,52 mmol) en MeOH en atmósfera de argón se añadieron sucesivamente ácido (3- acetil- indol- 1- il)- acético (57 mg, 0,26 mmol) y 1- cloro- 2- fluoro- 3- (isocianometil)benceno (44 mg, 0,26 mmol) en MeOH (0,2 ml). La mezcla de reacción se agitó a temperatura ambiente durante 60 h y se vertió en una solución acuosa saturada de $NaHCO_3$ y se extrajo con CH_2Cl_2 (x2). Los extractos orgánicos combinados se secaron ($Na2SO_4$), se filtraron y se concentraron. El residuo bruto se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (columna Gold RediSep, 24 g, CH_2Cl_2 a CH_2Cl_2 / MeOH 95- 5), las fracciones que contenían el material deseado como una mezcla de 2 diastereoisómeros se concentraron y el residuo se purificó de nuevo por HPLC preparativa (Waters Sunfire C18- DAB, 5 micras, 30x100 mm, eluyente: 5% a 100% CH_3CN en H_2O en 25 min, CH_3CN y H_2O que contiene 0.1% TFA, flujo: 40 ml / min) para proporcionar 3- cloro- 2- fluoro- bencilamida del ácido (2S, 3S, 4S)- 1- [2- (3- acetil- indol- 1- il)- acetil]- 3,4- difluoro- pirrolidina- 2- carboxílico: Rf (EtOAc): 0,60; EM (UPLC): 492.2/494.2 [M + H] +, 536.2/538.2 [M + HCOO]- y 3- cloro- 2- fluoro- bencilamida del ácido (2R, 3S, 4S)- 1- [2- (3- acetil- indol- 1 ácido- acetil)- il]- 3,4- difluoro- pirrolidina- 2-

carboxílico; Rf (EtOAc): 0,50; EM (UPLC): 492.2/494.2 [M + H] + , 536.2/538.2 [M + HCOO]- ; tR (condiciones HPLC A): 3,37 min. La estereoquímica absoluta ha sido asignada provisionalmente con base en la comparación de espectros de ^{1}H- RMN y los resultados de la prueba en el ensayo biológico medida para ambos diastereoisómeros.

Datos de 1H RMN y HRMS para compuestos seleccionados:

Los espectros ^{1}H RMN se registraron utilizando Espectrometros Bruker Avance DPX 400 y II 600.

Ejemplo 1: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.65 (t, 1H), 8.35 (s, 1H), 8.27 (d, 1H), 8.00 (s, 1H), 7.74 (d, 1H), 7.34 - 7.54 (m, 4H), 7.26 (m, 1H), 7.08 - 7.21 (m, 2H), 5.51- 5.38 (m, 1H), 4.55 (t, 1H), 4.27 - 4.46 (m, 2H), 3.92 - 4.07 (m, 1H), 3.89- 3.96 (m, 1H), 2.5 (m, 1H), 1.97 - 2.19 (m, 1H).

Ejemplo 26: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.28 (m, 2H), 8.20 (s, 1H), 7.98 (s, 1H), 7.72 (d, 1H), 7.34 - 7.57 (m, 4H), 7.26 (t, 1H), 7.06 - 7.23 (m, 2H), 4.24 - 4.52 (m, 3H), 3.82 (dd, 1H), 3.69 (m, 1H), 3.53 (dd, 1H), 2.4 (m, 1H), 1.78 (m, 1H).

Ejemplo 73:HRMS: 497.2294 [M+H]+ (calculado 497.2296 para $C_{28}H_{28}N_6O_3$).

Ejemplo 107:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.19 - 8.34 (m, 2H), 7.98 (s, 2H), 7.69 - 7.86 (m, 4H), 7.64 (t, 1H), 7.41 (br.s, 2H), 7.26 (t, 1H), 7.18 (t, 1H), 5.44- 5.30 (m, 1H), 4.16 (m, 1H), 3.93 (m, 1H), 3.49 - 3.76 (m, 1H), 3.18 (m, 1H), 3.03 (m, 1H), 2.29 (m, 1H), 1.94 - 2.20 (m, 1H).

Ejemplo 124: HRMS: 476.1539 [M+H]+ (calculado 476.1540 para $C_{22}H_{20}F_3N_5O_4$), 498.1358 [M+Na]+ (calculado 498.1360 para $C_{22}H_{20}F_3N_5O_4Na$), 493.1805 [M+NH_4]+ (calculado 493.1806 para $C_{22}H_{20}F_3N_5O_4NH_4$); t_R (Condiciones HPLC a) 3.46 min.

Ejemplo 133: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.42 - 8.56 (m, 2H), 8.18 (d, 1H), 8.01 (s, 1H), 7.29 - 7.53 (m, 5H), 7.16 (t, 1H), 6.93 (dd, 1H), 4.75 (dd, 2H), 4.23 - 4.46 (m, 1H), 4.16 (dd, 1H), 3.81 (m, 1H), 3.71 (s, 3H), 2.34 (m, 1H), 2.10 (m, 1H), 1.80 (m, 1H), 0.84 (m, 1H), 0.56 (m, 1H).

Ejemplo 134:HRMS: 488.1539 [M+H]+ (calculado 488.1540 para $C_{23}H_{20}F_3N_5O_4$), 510.1358 [M+Na]+ (calculado 510.1360 para $C_{23}H_{20}F_3N_5O_4Na$), 505.1805 [M+NH_4]+ (calculado 505.1806 para $C_{23}H_{20}F_3N_5O_4NH_4$).

Ejemplo 136:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.38 - 8.54 (m, 2H), 8.17 (d, 1H), 7.99 (s, 1H), 7.46 (t, 1H), 7.25 - 7.42 (m, 4H), 7.16 (t, 1H), 6.89 (dd, 1H), 4.23 - 4.46 (m, 2H), 4.16 (dd, 1H), 3.83 (m, 1H), 3.78 (s, 3H), 2.33 (dd, 1H), 2.09 (m, 1H), 1.78 (m, 1H), 0.84 (m, 1H), 0.56 (m, 1H).

Ejemplo 141:HRMS: 488.1539 [M+H]+ (calculado 488.1540 para $C_{23}H_{20}F_3N_5O_4$), 510.1358 [M+Na]+ (calculado 510.1360 para $C_{23}H_{21}N_4O_4F_3Na$).

Ejemplo 148:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):10.07 (s, 1H), 8.64 (s, 1H), 8.27 (d, 1H), 8.00 (s, 2H), 7.80 (d, 1H), 7.49 - 7.59 (m, 1H), 7.38 (br.s, 2H), 7.11 - 7.30 (m, 4H), 4.18 (t, 1H), 3.88 - 3.97 (m, 1H), 2.29 - 2.41 (m, 1H), 2.08 - 2.21 (m, 1H), 1.74 - 1.88 (m, 1H), 0.77 - 0.89 (m, 1H), 0.50 - 0.65 (m, 1H).

Ejemplo 155: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.55 (m, 2H), 8.28 (d, 1H), 8.00 (s, 1H), 7.79 (d, 1H), 7.43 (br.s, 2H), 7.27 (t, 1H), 7.19 (t, 1H), 6.94 (d, 1H), 6.84 (d, 1H), 4.35 (m, 1H), 4.14 (dd, 1H), 3.80 (m, 1H), 2.30 (dd, 1H), 2.09 (m, 1H), 1.77 (m, 1H), 0.84 (m, 1H), 0.54 (m, 1H).

Ejemplo 158:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):10.16 (s, 1H), 8.68 (s, 1H), 8.29 (d, 1H), 8.01 (s, 1H), 7.92 (d, 1H), 7.80 (d, 1H), 7.70 (t, 1H), 7.40 (br.s, 2H), 7.23 - 7.32 (m, 1H), 7.20 (t, 1H), 6.99 (d, 1H), 4.38 (t, 1H), 3.93 (m, 1H), 2.68 (q, 2H), 2.39 (m, 1H), 2.19 (m, 1H), 1.80 (m, 1H), 1.22 (t, 3H), 0.84 (m, 1H), 0.54 (m, 1H).

Ejemplo 166:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.57 (s, 1H), 8.46 (t, 1H), 8.29 (d, 1H), 8.01 (s, 1H), 7.79 (d, 1H), 7.39 - 7.55 (m, 3H), 7.35 (t, 1H), 7.27 (m, 1H), 7.18 (m, 2H), 4.25 - 4.48 (m, 2H), 4.17 (dd, 1H), 3.83 (m, 1H), 2.33 (dd, 1H), 2.11 (m, 1H), 1.79 (m, 1H), 0.85 (m, 1H), 0.56 (m, 1H).

Ejemplo 170:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.49 (t, 1H), 8.25 (d, 1H), 8.10 (s, 1H), 7.97 (s, 1H), 7.72 (d, 1H), 7.36 - 7.54 (m, 3H), 7.33 (t, 1H), 7.23 (t, 1H), 7.12 (m, 2H), 4.20-4.49 (m, 3H), 3.69 (m, 1H), 3.53 (m, 1H), 2.13 (m, 1H), 1.73- 2.02 (m, 3H).

Ejemplo 175:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):9.98 (s, 1H), 8.68 (s, 1H), 8.29 (d, 1H), 7.91 - 8.04 (m, 2H), 7.80 (d, 1H), 7.43 (br.s, 2H), 7.24 - 7.36 (m, 3H), 7.20 (t, 1H), 4.40 (dd, 1H), 3.84 - 3.96 (m, 1H), 2.31 - 2.43 (m, 1H), 2.17 - 2.27 (m, 1H), 1.77 - 1.88 (m, 1H), 0.81 - 0.92 (m, 1H), 0.53 - 0.64 (m, 1H).

Ejemplo 176:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):9.88 (s, 1H), 8.68 (s, 1H), 8.29 (d, 1H), 8.01 (s, 1H), 7.88 (t, 1H), 7.80 (d, 1H), 7.43 (br.s, 2H), 7.16 - 7.37 (m, 4H), 4.35 - 4.44 (m, 1H), 3.87 - 3.95 (m, 1H), 2.32 - 2.43 (m, 1H), 2.16 - 2.27 (m, 1H), 1.78 - 1.87 (m, 1H), 0.82 - 0.91 (m, 1H), 0.55 - 0.63 (m, 1H).

Ejemplo 178:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.65 (br.s, 1H), 8.50 (br.s, 1H), 8.26 (d, 1H), 7.97 (br.s, 1H), 7.71 (d, 1H), 6.99 - 7.57 (m, 7H), 5.54 (br.s, 1H), 4.17 - 4.50 (m, 2H), 4.00 (br.s, 2H), 3.20 (br.s, 2H).

Ejemplo 181:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.65 (t, 1H), 8.34 (br.s, 1H), 8.27 (d, 1H), 8.00 (s, 1H), 7.76 (d, 1H), 7.41 - 7.55 (m, 3H), 7.37 (t, 1H), 7.26 (t, 1H), 7.04 - 7.21 (m,

2H), 5.36 (t, 1H), 4.59 (t, 1H), 4.37 - 4.49 (m, 1H), 4.21 - 4.37 (m, 1H), 3.81 - 3.94 (m, 1H), 3.53 - 3.81 (m, 3H), 2.34- 2.40 (m, 1H), 1.97 - 2.18 (m, 1H).

Ejemplo 183:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.56 (s, 1H), 8.45 (t, 1H), 8.28 (d, 1H), 8.02 (s, 1H), 7.80 (d, 1H), 7.44 (m, 2H), 7.22 - 7.38 (m, 5H), 7.18 (t, 1H), 4.30 (m, 1H), 4.17 (dd, 1H), 3.82 (m, 1H), 2.33 (dd, 1H), 2.12 (m, 1H), 1.78 (br.s, 1H), 0.86 (m, 1H), 0.56 (dt, 1H).

Ejemplo 184: ^{1}H RMN (400 MHz, DMSO- d_6): 8.54 (s, 1H), 8.47 (m, 1H), 8.28 (d, 1H), 8.01 (s, 1H), 7.81 (d, 1H), 7.47 (t, 1H), 7.44 (m, 2H), 7.36(t, 1H), 7.27 (t, 1H), 7.18 (t, 2H), 4.36 (m, 2H), 4.23 (m, 1H), 3.77 (m, 1H), 3,45 (d, 1H), 3.36 (d, 1H), 3.29 (s, 3H), 2.39 (dd, 1H), 2.10 (dd, 1H), 0.95 (m, 1H), 0.82 (m, 1H).

Ejemplo 186:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.47 (t, 1H), 8.27 (d, 1H), 8.12 (s, 1H), 7.99 (s, 1H), 7.73 (d, 1H), 7.34 - 7.52 (m, 4H), 7.26 (t, 1H), 7.09 - 7.20 (m, 2H), 4.59 (d, 1H), 4.27 - 4.47 (m, 2H), 4.11 - 4.19 (m, 1H), 3.72 - 3.82 (m, 1H), 3.50 - 3.61 (m, 1H), 3.34 (s, 3H), 2.03 - 2.23 (m, 2H).

Ejemplo 190: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.56 (t, 1H), 8.37 (s, 1H), 8.28 (d, 1H), 8.02 (s, 1H), 7.80 (d, 1H), 7.33 - 7.52 (m, 4H), 7.26 (t, 1H), 7.10 - 7.20 (m, 2H), 5.32 - 5.58 (m, 1H), 4.59 - 4.71 (m, 1H), 4.30 - 4.48 (m, 2H), 3.81 - 3.91 (m, 1H), 3.69 - 3.79 (m, 1H), 2.15 - 2.32 (m, 2H).

Ejemplo 194:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):10.63 (s, 1H), 8.68 (d, 1H), 8.45 (s, 1H), 8.39 - 8.43 (m, 2H), 8.26 (d, 1H), 7.97 (s, 1H), 7.76 (d, 1H), 7.41 (br.s, 2H), 7.25 (t, 1H), 7.17 (t, 1H), 5.51 (d, 1H), 4.55 - 4.68 (m, 1H), 3.74 - 4.14 (m, 2H), 2.53 - 2.64 (m, 1H), 2.04 - 2.28 (m, 1H).

Ejemplo 195:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.56 (s, 1H), 8.45 (t, 1H), 8.29 (d, 1H), 8.01 (s, 1H), 7.79 (d, 1H), 7.44 (br.s, 2H), 7.23 - 7.36 (m, 2H), 7.11 - 7.23 (m, 3H), 4.27 - 4.48 (m, 2H), 4.18 (dd, 1H), 3.81 (m, 1H), 2.33 (dd, 1H), 2.12 (m, 1H), 1.78 (m, 1H), 0.87 (m, 1H), 0.56 (m, 1H).

Ejemplo 200:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.52 (m, 1H), 8.23 (m, 2H), 7.97 (s, 1H), 7.75 (d, 1H), 7.28 - 7.51 (m, 4H), 7.22 (t, 1H), 7.04 - 7.18 (m, 2H), 4.32 - 4.50 (m, 2H), 4.18 - 4.32 (m, 1H), 3.96 (t, 1H), 3.80 (t, 1H), 3.61 (s, 3H), 3.31 (m, 2H), 2.08 (m, 1H).

Ejemplo 203:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.53 (s, 1H), 8.19 - 8.33 (m, 2H), 7.95 (s, 1H), 7.74 (d, 1H), 7.34 - 7.52 (m, 4H), 7.27 (t, 1H), 6.96 - 7.23 (m, 2H), 5.12 (m, 1H), 5.02 (t, 1H), 4.24 (dd, 1H), 3.79 (m, 1H), 3.58 (m, 2H), 2.21 - 2.31 (m, 1H), 2.07 - 2.17 (m, 1H), 1.77 (m, 1H), 0.85 (m, 1H), 0.53 (m, 1H).

Ejemplo 205: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.65 (t, 1H), 8.32 (s, 1H), 8.27 (d, 1H), 8.00 (s, 1H), 7.75 (d, 1H), 7.32 - 7.57 (m, 4H), 7.26 (t, 1H), 7.06 - 7.21 (m, 2H), 4.57 (t, 1H), 4.38 - 4.50 (m, 1H), 4.23 - 4.38 (m, 1H), 3.97 (dd, 1H), 3.61 - 3.80 (m, 1H), 2.4 (m, 1H), 1.86 - 2.14 (m, 1H), 1.57 (d, 3H).

Ejemplo 208: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.87 (t, 1H), 8.24 - 8.32 (m, 2H), 7.99 (s, 1H), 7.73 (d, 1H), 7.38 - 7.52 (m, 3H), 7.31 - 7.37 (m, 1H), 7.23 - 7.30 (m, 1H), 7.11 - 7.20 (m, 2H), 5.13 - 5.36 (m, 1H), 4.62 - 4.74 (m, 1H), 4.29 - 4.45 (m, 2H), 3.87 - 3.97 (m, 1H), 3.60 - 3.72 (m, 1H), 2.07 - 2.36 (m, 2H).

Ejemplo 210: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.41 (t, 1H), 8.27 (d, 1H), 8.14 (s, 1H), 7.98 (s, 1H), 7.74 (d, 1H), 7.45 (m, 4H), 7.25 (t, 1H), 7.15 (m, 2H), 4.37 - 4.49 (m, 2H), 4.25 - 4.37 (m, 1H), 3.93 (d, 1H), 3.64 (dd, 1H), 1.91 (m, 1H), 1.78 (m, 1H), 0.73 (q, 1H), 0.63 (m, 1H).

Ejemplo 213: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.24 - 8.33 (m, 2H), 8.08 (s, 1H), 7.99 (s, 1H), 7.73 (d, 1H), 7.53 (t, 1H), 7.37 - 7.48 (m, 3H), 7.26 (t, 1H), 7.16 (t, 1H), 7.08 (t, 1H), 5.35 (d, 1H), 4.30 - 4.52 (m, 4H), 3.74 - 3.84 (m, 1H), 3.50 - 3.60 (m, 1H), 1.96 - 2.16 (m, 2H).

Ejemplo 216: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.53 (s, 1H), 8.46 (t, 1H), 7.88 (m, 2H), 7.68 (d, 1H), 7.27 - 7.57 (m, 4H), 7.18 (t, 1H), 6.83 (dd, 1H), 4.22 - 4.47 (m, 2H), 4.16 (dd, 1H), 3.79 (m, 4H), 2.32 (m, 1H), 2.02 - 2.17 (m, 1H), 1.77 (m, 1H), 0.84 (m, 1H), 0.54 (m, 1H).

Ejemplo 218: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):10.00 (s, 1H), 8.68 (s, 1H), 8.29 (d, 1H), 8.17 - 8.25 (m, 1H), 8.00 (s, 1H), 7.80 (d, 1H), 7.34 - 7.57 (m, 4H), 7.23 - 7.31 (m, 1H), 7.16 - 7.23 (m, 1H), 4.34 - 4.46 (m, 1H), 3.85 - 3.95 (m, 1H), 2.31 - 2.43 (m, 1H), 2.19 - 2.29 (m, 1H), 1.77 - 1.88 (m, 1H), 0.81 - 0.92 (m, 1H), 0.55 - 0.64 (m, 1H).

Ejemplo 223: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm):8.52 (s, 1H), 8.34 (d, 1H), 8.27 (d, 1H), 7.95 (s, 1H), 7.74 (d, 1H), 7.48 - 7.41 (m, 4H), 7.27 (t, 1H), 7.22 - 7.16 (m, 2H), 5.19 (m, 1H), 4.18 (dd, 1H), 3.79 (m, 1H), 3,40 (2H under H_2O signal), 2.28 (dd, 1H), 2.10 – 2.04 (m, 1H), 1.92 –1.73 (m, 3H), 0.85 (m, 1H), 0.53 (m, 1H).

Ejemplo 237: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.71 (br.s, 1H), 8.48 (s, 2H), 8.35 (s, 1H), 8.26 (d, 1H), 8.02 (s, 1H), 7.88 (br.s, 1H), 7.75 (d, 1H), 7.42 (br.s, 2H), 7.26 (t, 1H), 7.16 (t, 1H), 5.27 - 5.66 (m, 1H), 4.53 (m, 1H), 4.37 (m, 2H), 4.01 (m, 1H), 3.73 - 3.93 (m, 1H), 2.08 - 2.24 (m, 1H), 1.94 - 2.08 (m, 1H).

Ejemplo 258: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.53 (s, 1H), 8.37 (t, 1H), 8.29 (d, 1H), 8.01 (s, 1H), 7.79 (d, 1H), 7.44 (br.s, 2H), 7.15 - 7.34 (m, 5H), 4.22 - 4.39 (m, 2H), 4.20 (dd, 1H), 3.81 (m, 1H), 2.31 (m, 1H), 2.13 (m, 1H), 1.77 (m, 1H), 0.85 (m, 1H), 0.54 (td, 1H).

Ejemplo 274:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):10.22 (br.s, 1H), 8.43 (br.s, 1H), 8.27 (d, 1H), 7.94 - 8.06 (m, 2H), 7.77 (d, 1H), 7.41 (br.s, 2H), 7.13 - 7.34 (m, 4H), 5.39 - 5.62 (m, 1H), 4.83 (t, 1H), 3.79 - 4.14 (m, 2H), 2.58 - 2.65 (m, 1H), 2.06 - 2.30 (m, 1H).

Ejemplo 285:HRMS: 446.2186 [M+H]+ (calculado 446.2187 para $C_{25}H_{27}N_5O_3F_3$), 468.2005 [M+Na]+ (calculado 468.2006 para $C_{25}H_{27}N_5O_3Na$); ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):9.83 (s, 1H), 8.62 (s, 1H), 8.29 (d, 1H), 8.02 (s, 1H), 7.81 (d, 1H), 7.53 (br. s, 1H), 7.47 (d, 1H), 7.38 (br. s, 2H), 7.12 - 7.31 (m, 3H), 6.93 (d, 1H), 4.23 (t, 1H), 3.93 (br. s, 1H), 2.85 (m, 1H), 2.35 (m, 1H), 2.20 (m, 1H), 1.82 (br. s, 1H), 1.20 (d, 6H), 0.86 (br. s, 1H), 0.58 (br. s, 1H).

Ejemplo 294:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.56 (s, 1H), 8.47 (t, 1H), 8.26 - 8.32 (m, 1H), 8.09 (s, 1H), 7.61 - 7.66 (m, 1H), 7.42 - 7.58 (m, 3H), 7.35 (t, 1H), 7.08 - 7.20 (m, 2H), 4.26 - 4.45 (m, 2H), 4.13 - 4.20 (m, 1H), 3.75 - 3.82 (m, 1H), 2.28 - 2.37 (m, 1H), 2.06 - 2.15 (m, 1H), 1.74 - 1.84 (m, 1H), 0.82 - 0.90 (m, 1H), 0.52 - 0.60 (m, 1H).

Ejemplo 298: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 10.22 (s, 1H), 8.33 (s, 1H), 8.15 (d, 1H), 7.93 - 8.05 (m, 2H), 7.22 - 7.41 (m, 5H), 6.83 - 6.91 (m, 1H), 5.39 - 5.62 (m, 1H), 4.83 (t, 1H), 3.80 - 4.13 (m, 2H), 3.78 (s, 3H), 2.54 - 2.66 (m, 1H), 2.07 - 2.29 (m, 1H).

Ejemplo 300:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.41 - 8.49 (m, 2H), 8.16 (d, 1H), 8.00 (s, 1H), 7.46 (m, 1H), 7.27 - 7.42 (m, 4H), 7.16 (t, 1H), 6.90 (dd, 1H), 4.24 - 4.45 (m, 2H), 4.16 (dd, 1H), 3.98 - 4.13 (m, 2H), 3.84 (m, 1H), 3.67 (t, 2H), 3.32 (s, 3H), 2.35 (m, 1H), 2.05 - 2.17 (m, 1H), 1.71 - 1.86 (m, 1H), 0.86 (m, 1H), 0.55 (m, 1H).

Ejemplo 302:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.49 (t, 1H), 8.27 (d, 1H), 7.99 (s, 1H), 7.58 (s, 1H), 7.34 – 7.52 (m, 4H), 7.19 - 7.32 (m, 2H), 7.11 (t, 1H), 6.85 (t, 1H), 4.67 - 4.85 (m, 1H), 4.28 - 4.50 (m, 2H), 2.14 - 2.32 (m, 1H), 1.83 - 1.98 (m, 2H), 1.70 - 1.82 (m, 1H), 1.58 (s, 3H), 1.44 (s, 3H).

Ejemplo 306: 1H RMN (400 MHz, DMSO- d_6) δ(ppm):8.56 (s, 1H), 8.45 (t, 1H), 8.21 (d, 1H), 8.01 (s, 1H), 7.69 (s, 1H), 7.40 - 7.54 (m, 3H), 7.34 (t, 1H), 7.11 - 7.21 (m, 2H), 4.27 - 4.45 (m, 2H), 4.18 (dd, 1H), 4.09 (q, 2H), 3.82 (m, 1H), 3.70 (s, 2H), 2.35 (m, 1H), 2.12 (m, 1H), 1.80 (m, 1H), 1.19 (t, 3H), 0.85 (m, 1H), 0.56 (m, 1H).

Ejemplo 312:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.50 (t, 1H), 8.27 (d, 1H), 8.18 (s, 1H), 7.99 (s, 1H), 7.77 (d, 1H), 7.31 - 7.53 (m, 4H), 7.25 (t, 1H), 7.14 (m, 2H), 4.76 (t, 1H), 4.35 - 4.49 (m, 2H), 4.30 (dd, 1H), 3.83 (t, 1H), 3.37 - 3.52 (m, 3H), 2.41 (m, 1H), 2.30 (m, 1H), 1.62 (m, 1H).

Ejemplo 315: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.55 (s, 1H), 8.46 (t, 1H), 8.22 (s, 1H), 7.98 (s, 1H), 7.72 (d, 1H), 7.41 - 7.55 (m, 3H), 7.35 (m, 1H), 7.17 (t, 1H), 7.08 (dd, 1H), 4.26 -

4.46 (m, 2H), 4.17 (dd, 1H), 4.09 (q, 2H), 3.80 (m, 1H), 3.75 (s, 2H), 2.28 - 2.34 (m, 1H), 2.10 (m, 1H), 1.78 (m, 1H), 1.19 (t, 3H), 0.85 (m, 1H), 0.56 (m, 1H).

Ejemplo 331:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.57 (t, 1H), 8.27 (d, 1H), 8.19 (s, 1H), 7.99 (s, 1H), 7.76 (d, 1H), 7.31 - 7.56 (m, 4H), 7.26 (t, 1H), 7.07 - 7.21 (m, 2H), 5.33 (d, 1H), 4.44 (dd, 1H), 4.26 - 4.40 (m, 3H), 3.76 (dd, 1H), 3.57 (dd, 1H), 2.30 - 2.42 (m, 1H), 1.82 - 1.94 (m, 1H).

Ejemplo 332:HRMS: 512.1350 [M+H]+ (calculado 512.1352 para $C_{22}H_{18}F_5N_5O_4$), 534.1169 [M+Na]+ (calculado 534.1171 para $C_{22}H_{18}F_5N_5O_4Na$), 529.1617 [M+NH_4]+ (calculado 529.1617 para $C_{22}H_{18}F_5N_5O_4NH_4$).

Ejemplo 333: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):10.31 (s, 1H), 8.59 - 8.69 (m, 1H), 8.43 (s, 1H), 8.26 (d, 1H), 7.98 (s, 1H), 7.90 - 7.96 (m, 1H), 7.76 (d, 1H), 7.30 - 7.51 (m, 2H), 7.25 (t, 1H), 7.17 (t, 1H), 5.50 (d, 1H), 4.83 (t, 1H), 4.31 (q, 2H), 3.77 - 4.12 (m, 2H), 2.53 - 2.66 (m, 1H), 2.09 - 2.30 (m, 1H), 1.30 (t, 3H).

Ejemplo 334:HRMS: 488.1539 [M+H]+ (calculado 488.1540 para $C_{23}H_{20}F_3N_5O_4$), 510.1358 [M+Na]+ (calculado 510.1360 para $C_{23}H_{20}F_3N_5O_4Na$). ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):10.22 (s, 1H),8.66 (s, 1H), 8.27 (d, 1H), 8.00 (s, 1H), 7.83 (s, 1H), 7.80 (d, 1H), 7.54 (d, 1H), 7.43 (t, 1H),7.40 (m, 2H), 7.26 (t, 1H), 7.19 (t, 1H), 7.03 (d, 1H), 4.18 (t, 1H), 3.95 (m, 1H), 2.30 (m, 1H), 2.10 (m, 1H), 1.80 (m, 1H), 0.83 (m, 1H), 0.59 (m, 1H).

Ejemplo 340:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):10.27 (s, 1H), 8.68 (s, 1H), 8.29 (d, 1H), 8.15 - 8.24 (m, 2H), 8.01 (s, 1H), 7.82 (d, 1H), 7.71 (s, 1H), 7.39 (br.s, 2H), 7.28 (t, 1H), 7.21 (t, 1H), 4.18 (t, 1H), 3.86 - 4.00 (m, 1H), 2.30 - 2.44 (m, 2H), 2.10 - 2.24 (m, 1H), 1.74 - 1.89 (m, 1H), 0.77 - 0.92 (m, 1H), 0.54 - 0.68 (m, 1H).

Ejemplo 343: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):10.32 - 10.48 (m, 1H), 8.51 - 8.59 (m, 1H), 8.48 (s, 1H), 8.25 (d, 1H), 7.97 (s, 1H), 7.86 - 7.92 (m, 1H), 7.77 (d, 2H), 7.40 (br.s, 2H), 7.23 (t, 1H), 7.15 (t, 1H), 5.48 (d, 1H), 4.87 (t, 1H), 3.76 - 4.12 (m, 2H), 2.54 - 2.65 (m, 1H), 2.03 - 2.29 (m, 1H).

Ejemplo 344: ^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 10.37 (s, 1H), 8.69 (s, 1H), 8.40 (s, 1H), 8.28 (d, 1H), 8.15 (s, 1H), 8.01 (s, 1H), 7.88 (s, 1H), 7.82 (d, 1H), 7.40 (br. s, 2H), 7.27 (t, 1H), 7.20 (t, 1H), 4.21 (t, 1H), 3.90 - 4.01 (m, 1H), 2.41 (dd, 1H), 2.19 (dt, 1H), 1.78 - 1.91 (m, 1H), 0.86 (dt, 1H), 0.58 - 0.68 (m, 1H).

Ejemplo 350:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.45 (t, 1H), 8.27 (d, 1H), 8.01 (s, 1H), 7.97 (s, 1H), 7.68 (d, 1H), 7.37 - 7.48 (m, 3H), 7.21 - 7.33 (m, 2H), 7.14 (t, 1H), 6.99 (br.s, 1H), 4.27 - 4.57 (m, 4H), 2.26 - 2.42 (m, 1H), 2.08 - 2.23 (m, 1H), 1.77 - 1.89 (m, 1H), 1.55 - 1.66 (m, 1H), 1.22 (d, 2H).

Ejemplo 358: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.53 (s, 1H), 8.39 - 8.45 (m, 1H), 8.28 (d, 1H), 8.00 (s, 1H), 7.81 (d, 1H), 7.31 - 7.54 (m, 4H), 7.27 (t, 1H), 7.17 (t, 2H), 4.29 - 4.44 (m, 2H), 4.17 - 4.26 (m, 1H), 3.69 (m, 1H), 3.49 – 3.44 (m, 2H under DMSO signal), 2.30 - 2.37 (m, 1H), 2.04 - 2.16 (m, 1H), 0.97 (m, 1H), 0.75 (m, 1H).

Ejemplo 359: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.6 (t, 1H), 8.26 (m, 2H), 7.97 (s, 1H), 7.75 (d, 1H), 7.45- 7.34 (m, 4H), 7.24 (t, 1H), 7.14 (m, 2H), 6.28 - 6.05 (tt, 1H), 4.46 - 4.27 (m, 3H), 3.89 (m, 1H), 3.65 (m,1H), 2.88 (m, 1H), 2.39 (m, 1H), 1.8 (m, 1H).

Ejemplo 362:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.80 (s, 1H), 8.75 (m, 1H), 8.27 (d, 1H), 7.98 (s, 1H), 7.66 (d, 1H), 7.41 - 7.56 (m, 3H), 7.37 (t, 1H), 7.25 (t, 1H), 7.03 - 7.22 (m, 3H), 4.72 (dd, 1H), 4.21 - 4.47 (m, 2H), 3.30 (m, 1H), 2.88 (dd, 1H).

Ejemplo 371: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):9.09 (br.s, 1H), 8.44 (m, 2H), 8.06 (d, 1H), 7.92 (s, 1H), 7.46 (t, 1H), 7.24 - 7.40 (m, 3H), 7.19 (t, 1H), 7.11 (d, 1H), 6.75 (dd, 1H), 4.24 - 4.47 (m, 2H), 4.16 (dd, 1H), 3.80 (m, 1H), 2.31 (dd, 1H), 2.00 - 2.20 (m, 1H), 1.77 (m, 1H), 0.85 (m, 1H), 0.54 (m, 1H).

Ejemplo 374: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):12.95 (br.s, 1H), 8.46 (m, 2H), 8.17 (d, 1H), 8.01 (s, 1H), 7.25 - 7.55 (m, 5H), 7.17 (t, 1H), 6.92 (dd, 1H), 4.66 (m, 2H), 4.27 - 4.43 (m, 2H), 4.17 (dd, 1H), 3.82 (m, 1H), 2.33 (dd, 1H), 2.10 (m, 1H), 1.78 (m, 1H), 0.86 (m, 1H), 0.55 (d, 1H).

Ejemplo 377: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.56 (s, 1H), 8.45 (t, 1H), 8.21 (d, 1H), 8.01 (s, 1H), 7.69 (s, 1H), 7.27 - 7.57 (m, 4H), 7.17 (m, 2H), 4.26 - 4.45 (m, 2H), 4.18 (dd, 1H), 3.83 (m, 1H), 3.62 (s, 2H), 2.31 - 2.37 (m, 1H), 2.04 - 2.17 (m, 1H), 1.78 (m, 1H), 0.85 (m, 1H), 0.55 (m, 1H).

Ejemplo 378: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):12.28 (br.s, 1H), 8.54 (s, 1H), 8.45 (t, 1H), 8.21 (s, 1H), 7.98 (s, 1H), 7.71 (d, 1H), 7.41 - 7.54 (m, 3H), 7.35 (t, 1H), 7.17 (t, 1H), 7.08 (dd, 1H), 4.27 - 4.45 (m, 2H), 4.17 (dd, 1H), 3.81 (m, 1H), 3.66 (s, 2H), 2.24 - 2.33 (m, 1H), 2.12 (m, 1H), 1.77 (m, 1H), 0.84 (m, 1H), 0.55 (m, 1H).

Ejemplo 379: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.48 (m, 2H), 8.16 (d, 1H), 8.00 (s, 1H), 7.46 (m, 1H), 7.24 - 7.42 (m, 4H), 7.17 (t, 1H), 6.90 (dd, 1H), 4.89 (t, 1H), 4.22 - 4.46 (m, 2H), 4.16 (dd, 1H), 3.99 (m, 2H), 3.84 (m, 1H), 3.74 (q, 2H), 2.34 (m, 1H), 2.10 (m, 1H), 1.73 (m, 1H), 0.85 (m, 1H), 0.55 (m, 1H).

Ejemplo 384:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.51 (s, 1H), 8.45 (t, 1H), 8.14 (s, 1H), 7.93 (s, 1H), 7.68 (d, 1H), 7.27 - 7.55 (m, 4H), 7.18 (t, 1H), 7.05 (dd, 1H), 4.65 (t, 1H), 4.25 - 4.46 (m, 2H), 4.17 (dd, 1H), 3.81 (m, 1H), 3.63 (m, 2H), 2.83 (t, 2H), 2.26 - 2.33 (m, 1H), 2.10 (m, 1H), 1.77 (m, 1H), 0.84 (m, 1H), 0.54 (m, 1H).

Ejemplo 385: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.39 - 8.53 (m, 2H), 8.17 (d, 1H), 7.98 (s, 1H), 7.63 (s, 1H), 7.46 (t, 1H), 7.27 - 7.40 (m, 3H), 7.09 - 7.21 (m, 2H), 4.65 (t, 1H), 4.26 - 4.45 (m, 2H), 4.17 (dd, 1H), 3.83 (m, 1H), 3.64 (m, 2H), 2.81 (t, 2H), 2.27 - 2.34 (m, 1H), 2.12 (m, 1H), 1.77 (m, 1H), 0.87 (m, 1H), 0.55 (m, 1H).

Ejemplo 387:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.46 (m, 2H), 8.16 (m, 2H), 7.99 (s, 1H), 7.46 (m, 1H), 7.25 - 7.41 (m, 3H), 7.15 (t, 1H), 6.89 (dd, 1H), 4.25 - 4.45 (m, 2H), 4.16 (dd, 1H), 3.96 - 4.12 (m, 2H), 3.84 (m, 1H), 2.59 - 2.72 (m, 2H), 2.34 (m, 1H), 2.24 (s, 6H), 2.11 (m, 1H), 1.71 - 1.83 (m, 1H), 0.84 (m, 1H), 0.55 (m, 1H).

Ejemplo 388: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.47 (m, 2H), 8.17 (s, 2H), 7.98 (s, 1H), 7.45 (t, 1H), 7.34 (m, 4H), 7.14 (t, 1H), 6.90 (dd, 1H), 4,36 (m, 3H), 4,16 (m, 1H), 4.24 (dd, 1H), 4,06 (m, 3H), 3.82 (m, 1H), 2,82 (m, 2H), 2,34 (m, 1H), 2,10 (m, 1H), 1,78 (m, 1H), 1,70 (m, 4H), 0,85 (m, 1H), 0,56 (m, 1H).

Ejemplo 392:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):9.28 (s, 1H), 8.43 (m, 2H), 7.78 (m, 2H), 7.56 (d, 1H), 7.47 (t, 1H), 7.35 (t, 1H), 7.30 (br.s, 2H), 7.18 (t, 1H), 6.66 (dd, 1H), 4.25 - 4.48 (m, 2H), 4.16 (m, 1H), 3.79 (m, 1H), 2.31 (dd, 1H), 2.03 - 2.13 (m, 1H), 1.70 - 1.83 (m, 1H), 0.85 (m, 1H), 0.52 (m, 1H).

Ejemplo 394: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.53 (s, 1H), 8.44 (t, 1H), 7.88 (s, 1H), 7.82 (d, 1H), 7.68 (d, 1H), 7.27 - 7.49 (m, 4H), 7.16 (t, 1H), 6.85 (dd, 1H), 4.79 (s, 2H), 4.22 - 4.45 (m, 2H), 4.14 (dd, 1H), 3.78 (m, 1H), 3.70 (s, 3H), 2.32 (m, 1H), 1.98 - 2.15 (m, 1H), 1.77 (m, 1H), 0.83 (m, 1H), 0.54 (m, 1H).

Ejemplo 395: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.52 (s, 1H), 8.45 (t, 1H), 7.88 (m, 2H), 7.68 (d, 1H), 7.26 - 7.55 (m, 4H), 7.18 (t, 1H), 6.84 (dd, 1H), 4.88 (br.s, 1H), 4.26 - 4.46 (m, 2H), 4.16 (dd, 1H), 4.00 (t, 2H), 3.70 - 3.85 (m, 3H), 2.32 (dd, 1H), 2.02 - 2.18 (m, 1H), 1.77 (m, 1H), 0.85 (m, 1H), 0.55 (m, 1H).

Ejemplo 396: HRMS: 494.1648 [M+H]+ (calculado 491.1649 para C22H21F3N6O4).

Ejemplo 409: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.57 (t, 1H), 8.28 (m, 3H), 8.02 (s, 1H), 7.8 (d, 1H), 7.4 (t, 2H), 7.3 (t, 1H), 7.2 (t, 1H), 7.15 (m, 2H), 4.7 (d, 1H), 4.4 (d, 2H), 3.94 (m, 2H), 3.0 (d, 2H), 2.4 (t, 1H), 2.3 (t, 1H).

Ejemplo 412: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.7 (t, 1H), 8.53 (s, 1H), 8.35 (d, 1H), 7.87 (m, 2H), 7.47 (t, 1H), 7.41 (t, 1H), 7.36 (t, 1H), 7.28 (t, 1H), 7.12 (t, 1H), 4.60 (t, 1H), 4.37 (m, 2H), 3.97 (dd, 1H), 3.80 (dd, 1H), 3.0 (dd, 2H), 2.61 (s, 3H), 2.45 (m, 1H), 2.07 (m, 1H).

Ejemplo 415: ^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 7.81 - 7.92 (m, 3H), 7.41 - 7.57 (m, 2H), 7.33 - 7.41 (m, 1H), 7.23 - 7.33 (m, 1H), 7.04 - 7.17 (m, 1H), 4.54 - 4.64 (m, 2H), 4.40 (dd, 2H), 4.09 - 4.17 (m, 1H), 3.94 - 3.66 (m, 2H), 2.61 (s, 3H).

Ejemplo 417: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.80 (t, 1H), 8.26 - 8.32 (m, 2H), 8.16 (br.s, 2H), 7.95 (s, 1H), 7.72 (d, 1H), 7.41 - 7.51 (m, 4H), 7.22 - 7.30 (m, 1H), 7.10 - 7.17 (m, 2H), 4.49 - 4.62 (m, 2H), 4.31 - 4.42 (m, 1H), 3.84 - 3.99 (m, 2H), 3.56 - 3.67 (m, 1H), 2.28 - 2.37 (m, 1H), 2.01 - 2.14 (m, 1H).

Ejemplo 430: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.88 (br. s, 1H), 8.23 - 8.32 (m, 1H), 8.15 (s, 1H), 7.97 (s, 1H), 7.73 (d, 1H), 7.37 - 7.51 (m, 2H), 7.24 (t, 1H), 7.09 - 7.18 (m, 2H), 4.90 (d, 1H), 4.57 (d, 1H), 4.29 - 4.47 (m, 2H), 3.81 - 3.88 (m, 1H), 3.51 - 3.64 (m, 1H).

Ejemplo 431: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.78 (br. s, 1H), 8.42 (s, 1H), 8.25 (d, 1H), 7.93 (s, 1H), 7.67 (d, 1H), 7.38 - 7.56 (m, 2H), 7.25 (t, 1H), 7.06 - 7.19 (m, 2H), 5.18 - 5.40 (m, 1H), 4.69 (d, 1H), 4.25 - 4.48 (m, 2H), 4.02 - 4.25 (m, 2H), 3.77 - 3.92 (m, 1H).

Ejemplo 432: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.80 (s, 1H), 8.54 (t, 1H), 8.27 (d, 1H), 8.03 (s, 1H), 7.60 (d, 1H), 7.37 - 7.54 (m, 3H), 7.34 (t, 1H), 7.27 (t, 1H), 7.06 - 7.23 (m, 2H), 5.43 (dd, 1H), 4.48 (t, 1H), 4.24 - 4.44 (m, 2H), 3.22 (m, 1H), 2.63 - 2.80 (m, 1H), 1.95 (m, 1H).

Ejemplo 446:^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.44 (t, 1H), 8.22 - 8.28 (m, 1H), 7.77 (s, 1H), 7.55 - 7.60 (m, 1H), 7.42 - 7.54 (m, 3H), 7.21 - 7.31 (m, 2H), 7.09 - 7.20 (m, 2H), 4.28 - 4.47 (m, 2H), 4.22 - 4.28 (m, 1H), 3.94 (s, 2H), 3.64 - 3.72 (m, 1H), 2.08 - 2.29 (m, 2H), 1.75 - 1.85 (m, 1H), 0.75 - 0.92 (m, 1H), 0.51 - 0.57 (m, 1H).

Ejemplo 452: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):8.46 (t, 1H), 8.13 (d, 1H), 7.74 (s, 1H), 7.33 - 7.54 (m, 3H), 7.28 (t, 1H), 7.03 - 7.19 (m, 2H), 6.87 (dd, 1H), 4.29 - 4.42 (m, 2H), 4.25 (dd, 1H), 3.90 (s, 2H), 3.75 (s, 3H), 3.68 (m, 1H), 2.19 - 2.31 (m, 1H), 2.04 - 2.19 (m, 1H), 1.78 (m, 1H), 0.94 (m, 1H), 0.54 (m, 1H).

Ejemplo 466: ^{1}H RMN (400 MHz, DMSO- d_6) δ (ppm): 8.40 - 8.82 (m, 1H), 8.11 - 8.37 (dd, 1H), 7.73 (s, 1H), 7.54- 7.55 (dd, 1H), 7.07- 7.46 (m, 8H), 4.90- 5.04 (m, 1H), 4.34- 4.47 (m, 3H), 4.08- 4.16 (m, 1H), 3.61- 3.87 (m, 4H)

Ejemplo 476: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):4:1 mezcla de rotámeros δ (ppm): 9.02 (t, 0.2H), 8.63 (t, 0.8H), 8.11 - 8.21 (m, 1H), 7.89 - 7.96 (m, 1H), 7.36 - 7.51 (m, 2H), 6.96 - 7.29 (m, 4H), 5.41 - 5.61 (m, 1H), 5.08 - 5.40 (m, 2H), 4.88 (t, 0.2H), 4.13 - 4.56 (m, 3.8H), 3.81 - 4.11 (m, 1H), 2.43 - 2.49 (m, 1H), 1.97 - 2.18 (m, 1H).

Ejemplo 483: ^{1}H RMN (400 MHz, DMSO- d_6): 8.51- 8.46 (m, 3H),8.35 (m, 1H),7.46 (m, 1H),7,31 (dd, 1H),7.21 (m, 1H), 7.09 (t, 1H),5,53 (d, 1H),5,37 (d, 1H),4.41- 4.27 (m, 3H),3.72 (m, 1H),2.47 (s, 3H),2,26 (m, 1H),2.19- 2.13 (m, 1H),1.89 (m, 1H),1.08 (m, 1H),0.75 (m, 1H).

Ejemplo 491: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):4:1 mezcla de rotámeros δ (ppm): 9.03 (t, 0.2H), 8.64 (t, 0.8H), 8.11 - 8.19 (m, 1H), 7.91 - 7.99 (m, 1H), 7.61 (m, 0.8H), 7.48 - 7.58 (br s, 1H), 7.34 - 7.48 (m, 1.2H), 7.11 - 7.28 (m, 2H), 6.97 (t, 1H), 5.43 - 5.63 (m, 1H), 5.09 - 5.43 (m, 2H), 4.89 (t, 0.2H), 4.10 - 4.59 (m, 3.8H), 3.83 - 4.05 (m, 0.8H), 3.42 - 3.59 (m, 0.2H), 2.71 - 2.85 (m, 0.2H), 2.42 - 2.47 (m, 0.8H), 1.98 - 2.27 (m, 1H).

Ejemplo 496: ^{1}H RMN (400 MHz, DMSO- d_6): 4:1 mezcla de rotámeros δ (ppm): 9.01 (t, 0.2H), 8.63 (t, 0.8H), 8.12 - 8.19 (m, 1H), 7.89 - 7.94 (m, 1H), 7.36 - 7.49 (m, 2H), 7.20 - 7.27 (m, 0.8H), 7.09 - 7.19 (m, 3H), 6.90 - 7.04 (m, 0.8H), 6.74 - 6.81 (m, 0.2H), 6.54 - 6.61 (m, 0.2H), 5.33 (d, 0.8H), 5.22 (d, 0.2H), 5.07 (d, 0.8H), 4.88 (t, 0.2H), 4.56 (d, 0.2H), 4.33 - 4.52 (m, 2H), 4.11 - 4.31 (m, 1.8H), 3.90 - 4.03 (m, 0.2H), 3.70 - 3.87 (m, 0.8H), 2.46 - 2.54 (m, 1H, overlapped by DMSO residual signal) 1.90 - 2.27 (m, 1H), 1.47 - 1.66 (m, 3H).

Ejemplo 497: ^{1}H RMN (400 MHz, DMSO- d_6): 4:1 mezcla de rotámeros δ (ppm): 9.02 (t, 0.2H), 8.82 (br. s, NH2) 8.63 (t, 0.8H), 7.83 - 7.90 (m, 1H), 7.66 (s, 1H), 7.12 - 7.51 (m, 3H), 7.02 (t, 1H), 6.72 - 6.80 (m, 1H), 5.39 - 5.58 (m, 0.8H), 5.00 - 5.37 (m, 2H), 4.86 (t, 0.2H), 4.23 - 4.62 (m, 3.4H), 4.09 - 4.22 (m, 0.8H), 3.81 - 4.05 (m, 0.8H), 3.78 (s, 3H), 2.71 - 2.85 (m, 0.2H), 1.97 - 2.26 (m, 0.8H), (protones NH_2 parcialmente intercambiados por deuterio).

Ejemplo 499: ^{1}H RMN (400 MHz, DMSO- d_6): 4:1 mezcla de rotámeros δ (ppm): 9.03 (t, 0.2H), 8.65 (t, 0.8H), 8.00 (d, 1H), 7.72 - 7.84 (m, 1H), 7.33 - 7.48 (m, 1H), 7.24 (t, 0.8H), 7.14 (t, 0.2H), 6.88 - 7.01 (m, 1.6H), 6.69 - 6.82 (m, 1.4H), 5.40 - 5.61 (m, 1H), 5.30 (d, 0.8H), 5.14 - 5.22 (m, 0.2H), 5.05 (d, 0.8H), 4.88 (t, 0.2H), 4.23 - 4.57 (m, 3.2H), 4.09 - 4.23 (m, 0.8H), 3.80 - 4.06 (m, 1H), 3.68 - 3.77 (m, 3H), 3.42 - 3.61 (m, 1H), 2.71 - 2.84 (m, 0.2H), 1.98 - 2.28 (m, 0.8H), (protones NH_2 intercambiados por deuterio).

Ejemplo 500: ^{1}H RMN (400 MHz, DMSO- d_6): 4:1 mezcla de rotámeros δ (ppm): 9.05 (t, 0.2H), 8.65 (t, 0.8H), 8.06 - 8.12 (m, 1H), 8.01 - 8.05 (m, 1H), 7.35 - 7.47 (m, 1.2H), 7.11 - 7.27 (m, 1H), 6.98 (d, 0.8H), 6.92 (t, 0.8H), 6.80 - 6.88 (m, 1.2H), 5.40 - 5.61 (m, 1H), 5.28 - 5.39 (m, 0.8H), 5.08 - 5.24 (m, 1H), 4.88 (t, 0.2H), 4.59 (d, 0.2H), 4.24 - 4.53 (m, 2.8H), 4.08 - 4.20 (m, 1H), 3.83 - 4.05 (m, 1H), 3.68 - 3.77 (m, 3H), 2.70 - 2.84 (m, 0.2H), 2.40 (s, 3H), 1.99 - 2.27 (m, 0.8H).

Ejemplo 505: ^{1}H RMN (400 MHz, DMSO- d_6) δ (ppm): 8.72 (t, 1H), 8.23 (s, 1H), 8.20 (m, 1H), 7.45 (m, 2H), 7.27 (t, 1H), 7.21 (m, 2H), 7.03 (t, 1H), 5.37 (d, 1H), 5.2 (m, 2H), 4.65 (d, 1H), 4.4 (dd, 1H), 4.3 (m, 3H), 4.1 (m, 2H), 3.4 (s, 3H), 2.42 (s, 3H).

Ejemplo 507: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):4:1 mezcla de rotámeros δ (ppm): 9.03 (t, 0.2H), 8.63 (t, 0.8H), 8.15 - 8.29 (m, 2H), 7.38 - 7.51 (m, 2H), 7.13 - 7.31 (m, 3.2H), 6.97 (t, 0.8H), 5.43 - 5.61 (m, 1H), 5.14 - 5.43 (m, 1.8H), 4.87 (t, 0.2H), 4.64 (d, 0.2H), 4.10 - 4.54 (m, 3.8H), 3.84 - 4.05 (m, 0.8H), 3.43 - 3.61 (m, 0.2H), 2.44 (s, 3H y m, 1H), 1.96 - 2.30 (m, 1H).

Ejemplo 508: ^{1}H RMN (400 MHz, DMSO- d_6): 4:1 mezcla de rotámeros δ (ppm): 9.02 (t, 0.2H), 8.62 (t, 0.8H), 8.12 - 8.22 (m, 1H), 7.75 - 7.83 (m, 1H), 7.30 - 7.53 (m, 7H), 7.24 (t, 0.8H), 7.16 (t, 0.2H), 7.10 (d, 0.2H), 6.96 - 7.03 (m, 0.8H), 6.88 - 6.96 (m, 1H), 5.41 - 5.61 (m, 0.8H), 5.27 - 5.41 (m, 1H), 5.19 - 5.26 (m, 0.2H), 5.09 - 5.19 (m, 2.8H), 4.85 (t, 0.2H), 4.59 (d, 0.2H), 4.22 - 4.51 (m, 2.8H), 4.07 - 4.21 (m, 0.8H), 3.80 - 4.05 (m, 1H), 3.43 - 3.60 (m, 0.2H), 3.35 (m, 1H, traslapando con señal residual de H_2O) 2.68 - 2.84 (m, 0.2H), 2.41 (s, 3H), 1.98 - 2.19 (m, 0.8H).

Ejemplo 510: ^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 8.49 (t, 1H), 8.31 (s, 1H), 8.16 - 8.24 (m, 1H), 7.41 - 7.55 (m, 2H), 7.15 - 7.28 (m, 3H), 7.04 (t, 1H), 5.39 (dd, 2H), 4.37 - 4.46 (m, 1H), 4.21 - 4.35 (m, 2H), 3.68 - 3.80 (m, 1H), 2.45 (s, 3H), 2.23 - 2.33 (m, 1H), 2.11 - 2.22 (m, 1H), 1.80 - 1.95 (m, 1H), 1.00 - 1.13 (m, 1H), 0.70 - 0.82 (m, 1H).

Ejemplo 514: 1H RMN (400 MHz, DMSO- d_6): 4:1 mezcla de rotámeros δ (ppm): 10.54 (s, 0.2H), 10.20 (s, 0.8H), 8.23 - 8.31 (m, 1H), 8.15 - 8.21 (m, 1H), 7.84 - 8.00 (m, 1H), 7.39 - 7.49 (m, 1H), 7.18 - 7.39 (m, 4H), 5.33 - 5.66 (m, 2H), 5.13 - 5.28 (m, 1H), 4.69 - 4.89 (m, 1H), 4.15 - 4.28 (m, 1H), 3.89 - 4.14 (m, 1H), 2.56 - 2.66 (m, 1H), 2.44 (s, 3H), 2.08 - 2.30 (m, 1H).

Ejemplo 515: ^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 10.31 (s, 1H), 8.27 - 8.41 (m, 2H), 8.18 (d, 1H), 8.04 - 8.11 (m, 1H), 7.88 (s, 1H), 7.52 (d, 1H), 7.10 - 7.32 (m, 2H), 5.45 (dd, 2H), 4.31 (dd, 1H), 3.86 (t, 1H), 2.44 (s, 3H), 2.32 - 2.40 (m, 1H), 2.21 - 2.32 (m, 1H), 1.83 - 2.02 (m, 1H), 0.98 - 1.13 (m, 1H), 0.73 - 0.89 (m, 1H).

Ejemplo 521: ^{1}H RMN (400 MHz, DMSO- d_6) δ (ppm): 3:1 mezcla de rotámeros 9.23 (t, 0.25H), 8.75 (t, 0.75H), 8.24 (s, 0.75H), 8.05 - 8.18 (m, 2.25H), 7.97 (m, 1H), 7.41 (m, 0.75H), 7.01 - 7.21 (m, 2.25H), 5.13 - 5.63 (m, 2.75H), 4.91 (t, 0.25H), 3.83 - 4.64 (m, 5H), 2.37 - 2.46 (m, 3H), 1.96 - 2.20 (m, 1H).

Ejemplo 524: ^{1}H RMN (400 MHz, DMSO- d_6): 9.35 (s, 1H), 8.50 (t, 1H),8.40 (s, 1H),8.32 (d, 1H),7.54 (d, 1H), 7.46 (m, 1H),7.19 (t, 1H),7.03 (t, 1H),5.53 (d, 1H),5.33 (d, 1H),4.43 (dd, 1H),4.31- 4.26 (m, 2H),3.71 (m, 1H),2.49 (s, 3H),2.34- 2.26 (m, 1H),2.20- 2.14 (m, 1H), 1.90 (m, 1H), 1.06 (m, 1H), 0.78 (m, 1H).

Ejemplo 525:^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 8.61 (t, 1H), 8.30 (s, 1H), 8.14 - 8.20 (m, 1H), 8.11 (dd, 1H), 7.97 - 8.02 (m, 1H), 7.41 - 7.51 (m, 1H), 7.18 (dd, 2H), 5.39 (dd, 2H), 4.39

- 4.46 (m, 2H), 4.33 (dd, 1H), 3.71 - 3.79 (m, 1H), 2.44 (s, 3H), 2.13 - 2.37 (m, 2H), 1.86 - 1.98 (m, 1H), 1.02 - 1.15 (m, 1H), 0.74 - 0.84 (m, 1H).

Ejemplo 526: ^{1}H RMN (400 MHz, DMSO- *d*$_6$): δ (ppm): 8.51 - 8.61 (m, 2H), 8.26 - 8.33 (m, 1H), 8.22 (s, 1H), 7.85 (dd, 1H), 7.37 - 7.44 (m, 1H), 7.16 (t, 1H), 6.91 (t, 1H), 5.63 (d, 1H), 5.40 (d, 1H), 4.38 - 4.47 (m, 1H), 4.24 - 4.33 (m, 2H), 3.67 - 3.91 (m, 4H), 2.47 (s, 3H), 2.26 - 2.35 (m, 1H), 2.13 - 2.22 (m, 1H), 1.85 - 1.96 (m, 1H), 1.04 - 1.13 (m, 1H), 0.73 - 0.80 (m, 1H).

Ejemplo 534: ^{1}H RMN (400 MHz, DMSO- *d*$_6$): 4:1 mezcla de rotámeros δ (ppm): 9.05 (t, 0.2H), 8.67 (t, 0.8H), 8.13 (s, 0.8H), 8.05 (m, 1.2H), 7.29 - 7.50 (m, 6.2H), 7.22 (t, 0.8H), 7.08 - 7.15 (m, 1H), 6.83 - 6.98 (m, 2H), 5.41 - 5.63 (m, 0.8H), 5.28 - 5.40 (m, 1H), 4.87 - 5.25 (m, 3.2H), 4.23 - 4.67 (m, 3H), 3.83 - 4.21 (m, 1.8H), 3.43 - 3.61 (m, 0.2H), 2.54 - 2.60 (m, 1H), 2.41 (s, 3H), 1.99 - 2.21 (m, 1H).

Ejemplo 536: ^{1}H RMN (400 MHz, DMSO- *d*$_6$): δ (ppm): 8.53 (t, 1H), 8.21 (s, 1H), 8.00 - 8.09 (m, 1H), 7.30 - 7.42 (m, 6H), 7.14 - 7.21 (m, 2H), 6.88 - 6.97 (m, 2H), 5.20 - 5.48 (m, 2H), 4.89 - 5.07 (m, 2H), 4.38 - 4.50 (m, 1H), 4.23 - 4.33 (m, 2H), 3.70 - 3.78 (m, 1H), 2.42 (s, 3H), 2.26 - 2.36 (m, 1H), 2.12 - 2.22 (m, 1H), 1.84 - 1.94 (m, 1H), 1.01 - 1.09 (m, 1H), 0.70 - 0.79 (m, 1H).

Ejemplo 542: ^{1}H RMN (400 MHz, DMSO- *d*$_6$): 4:1 mezcla de rotámeros δ (ppm): 9.05 (t, 0.2H), 8.66 (t, 0.8H), 8.38 - 8.46 (m, 1H), 8.28 (d, 1H), 7.95 - 8.20 (m, 1H), 7.84 (dd, 1H), 7.34 - 7.48 (m, 1.2H), 7.10 - 7.22 (m, 1H), 6.85 (t, 0.8H), 5.28 - 5.63 (m, 2.8H), 4.92 (t, 0.2H), 4.72 (d, 0.2H), 4.11 - 4.55 (m, 3.8H), 3.88 - 4.06 (m, 1H), 3.78 - 3.88 (m, 3H), 3.35 (m, 1H, traslapando con señal residual de H2O) 2.56 - 2.61 (m, 0.2H), 2.46 (s, 3H), 2.02 - 2.23 (m, 0.8H).

Ejemplo 545: ^{1}H RMN (400 MHz, DMSO- *d*$_6$): δ (ppm):8.51 (t, 1H), 8.27 - 8.33 (m, 1H), 8.12 (d, 1H), 7.40 - 7.50 (m, 2H), 7.10 - 7.23 (m, 2H), 6.96 - 7.09 (m, 1H), 5.46 (d, 1H), 5.29 (s, 1H), 4.36 - 4.50 (m, 1H), 4.22 - 4.36 (m, 2H), 3.56 - 3.78 (m, 5H), 2.44 (s, 3H), 2.24 - 2.37 (m, 1H), 2.12 - 2.22 (m, 1H), 1.84 - 1.95 (m, 1H), 1.26 (d, 1H), 1.02 - 1.10 (m, 1H), 0.73 - 0.80 (m, 1H).

Ejemplo 548: ^{1}H RMN (400 MHz, DMSO- *d*$_6$): 4:1 mezcla de rotámeros δ (ppm): 9.04 (t, 0.2H), 8.67 (t, 0.8H), 8.38 - 8.46 (m, 1H), 8.25 - 8.31 (m, 1H), 8.16 (s, 0.8H), 7.95 (s, 0.2H), 7.84 (d, 1H), 7.34 - 7.46 (m, 1.2H), 7.11 - 7.22 (m, 1H), 6.84 (t, 0.8H), 5.47 - 5.58 (m, 0.8H), 5.35 - 5.44 (m, 0.2H), 5.28 (d, 0.8H), 4.89 - 4.99 (m, 0.2H), 4.70 (d, 0.2H), 4.35 - 4.58 (m, 2H), 4.09 - 4.29 (m, 1.6H), 3.92 - 4.04 (m, 0.2H), 3.84 - 3.91 (m, 1H), 3.72 - 3.84 (m, 3H), 3.35 (m, 1H, traslapando con señal residual de H2O) 2.55 - 2.60 (m, 0.2H), 2.46 (s, 3H), 1.93 - 2.18 (m, 0.8H), 1.47 - 1.69 (m, 3H).

Ejemplo 549: ^{1}H RMN (400 MHz, DMSO- d_6): 4:1 mezcla de rotámeros δ (ppm):8.99 - 9.09 (m, 0.2H), 8.64 (t, 0.8H), 8.15 - 8.24 (m, 1H), 8.12 (d, 1H), 7.35 - 7.50 (m, 2H), 7.22 (t, 0.8H), 7.04 - 7.19 (m, 1.4H), 6.95 (t, 0.8H), 5.28 - 5.61 (m, 1.8H), 5.11 - 5.28 (m, 1H), 4.88 (t, 0.2H), 4.62 (d, 0.2H), 4.23 - 4.54 (m, 3H), 4.09 - 4.23 (m, 0.8H), 3.81 - 4.05 (m, 1H), 3.56 - 3.75 (m, 6H), 2.54 - 2.60 (m, 0.2H), 2.39 - 2.45 (m, 3H), 1.97 - 2.29 (m, 0.8H).

Ejemplo 550: ^{1}H RMN (400 MHz, DMSO- d_6): 8.90 (m, 1H),8.51 (t, 1H),8.49 (s, 1H),8.33 (d, 1H),8.06 (m, 1H), 7.45 (m, 1H),7.20 (m, 1H),7.06 (t, 1H),5.63 (d, 1H),5.42 (d, 1H),4.42 (dd, 1H),4.32- 4.28 (m, 2H),3.72 (m, 1H),2.48 (s, 3H),2.34- 2.26 (m, 1H),2.21- 2.14 (m, 1H), 1.90 (m, 1H), 1.08 (m, 1H), 0.81 (m, 1H).

Ejemplo 551: ^{1}H RMN (400 MHz, DMSO- d_6) δ (ppm): 3:1 mezcla de rotámeros 9.24 (d, 0.25H), 8.78 (d, 0.75H), 8.31 (s, 0.75H), 8.23 (s, 0.25H), 8.13 - 8.21 (m, 1H), 7.69 (s, 0.25H), 7.62 (s, 0.75H), 7.32 - 7.50 (m, 3H), 7.10 - 7.27 (m, 3.25H), 7.04 (d, 0.25H), 5.43 - 5.63 (m, 1H), 5.06 - 5.43 (m, 3H), 4.94 (t, 0.25H), 4.74 (d, 0.25H), 4.40 - 4.67 (m, 5H), 4.09 - 4.24 (m, 0.75H), 3.81 - 4.06 (m, 1.25H), 2.00 - 2.21 (m, 1H).

Ejemplo 556:^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 8.49 (t, 1H), 8.39 (s, 1H), 8.15 - 8.26 (m, 1H), 7.40 - 7.55 (m, 2H), 7.13 - 7.30 (m, 3H), 7.05 (t, 1H), 5.40 (dd, 2H), 4.55 (s, 2H), 4.36 - 4.45 (m, 1H), 4.20 - 4.35 (m, 2H), 3.67 - 3.78 (m, 1H), 2.23 - 2.32 (m, 1H), 2.12 - 2.21 (m, 1H), 1.81 - 1.95 (m, 1H), 1.06 (ddd, 1H), 0.71 - 0.82 (m, 1H).

Ejemplo 561:^{1}H RMN (400 MHz, DMSO- d_6) δ ppm: 4:1 mezcla de rotámeros 9.04 (t, 0.2H), 8.63 (t, 0.8H), 8.42 - 8.57 (m, 1H), 8.11 - 8.29 (m, 1H), 7.59 (d, 0.8H), 7.29 - 7.50 (m, 3.4H), 7.09 - 7.27 (m, 1H), 6.94 (t, 0.8H), 5.23 - 5.68 (m, 2.8H), 4.86 (t, 0.2H), 4.78 (d, 0.2H), 3.82 - 4.57 (m, 4.4H), 3.43 - 3.63 (m, 0.2H), 2.57 (d, 0.2H), 1.97 - 2.24 (m, 1H).

Ejemplo 563:^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 4:1 mezcla de rotámeros 9.03 (t, 0.2H), 8.63 (t, 0.8H), 8.34 (s, 0.8H), 8.29 (s, 0.2H), 8.20 (d, 1H), 7.34 - 7.51 (m, 2H), 7.11 - 7.30 (m, 3.2H), 6.98 (t, 0.8H), 5.14 - 5.63 (m, 2.8H), 4.87 (t, 0.2H), 4.64 (d, 0.2H), 4.54 (s, 2H), 3.79 - 4.52 (m, 4.8H), 1.97 - 2.20 (m, 1H).

Ejemplo 564:^{1}H RMN (400 MHz, DMSO- d_6) δ ppm 4:1 mezcla de rotámeros 9.02 (t, 0.2H), 8.62 (t, 0.8H), 8.34 (s, 0.8H), 8.29 (s, 0.2H), 8.14 - 8.25 (m, 1H), 7.51 - 7.62 (m, 1H), 7.38 - 7.50 (m, 1H), 7.17 - 7.31 (m, 3H), 7.10 (t, 0.2H), 6.91 (t, 0.8H), 5.11 - 5.65 (m, 2.8H), 4.87 (t, 0.2H), 4.63 (d, 0.2H), 4.54 (s, 2H), 3.82 - 4.51 (m, 4.8H), 1.97 - 2.21 (m, 1H).

Ejemplo 565: ^{1}H RMN (400 MHz, DMSO- d_6) δ (ppm): 4:1 mezcla de rotámeros 9.04 (t, 0.2H), 8.63 (t, 0.8H), 8.33 (s, 0.8H), 8.29 (s, 0.2H), 8.15 - 8.25 (m, 1H), 7.37 - 7.50 (m, 2H), 7.19 - 7.28 (m, 3H), 7.16 (t, 0.2H), 6.97 (t, 0.8H), 5.15 - 5.63 (m, 2.8H), 4.87 (t, 0.2H), 4.64 (d, 0.2H), 3.78 - 4.54 (m, 6.8H), 3.39 (s, 3H), 1.98 - 2.20 (m, 1H).

Ejemplo 568: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm):8.41 (d, 1H), 8.29 (s, 1H), 8.19 (m, 1H), 7.48 - 7.42 (m, 2H), 7.30 (t, 1H), 7.26 - 7.20 (m, 2H), 7.10 (t, 1H), 5.47 (d, 1H), 5.28 - 4.21 (m, 2H), 4.33 (dd, 1H), 3.72 (m, 1H), 3.48 (d, 1H), 3.33 (d, 1H), 3.22 (s, 3H), 2.43 (s, 3H), 2.27 - 2.22 (m, 1H), 2.18 - 2.12 (m, 1H), 1.87 (m, 1H), 1.05 (m, 1H), 0.73 (m, 1H).

Ejemplo 577: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):4:1 mezcla de rotámeros δ (ppm): 8.99 (t, 0.2H), 8.62 (t, 0.8H), 7.78 - 7.85 (m, 1H), 7.56 (m, 1H), 7.35 - 7.51 (m, 1.2H), 7.25 (t, 0.8H), 7.14 - 7.20 (m, 1H), 7.04 (t, 0.8H), 6.93 (d, 0.2H), 6.59 - 6.66 (m, 1H), 5.38 - 5.59 (m, 1H), 4.96 - 5.31 (m, 1.8H), 4.85 (t, 0.2H), 4.09 - 4.52 (m, 4H), 3.96 - 4.04 (m, 0.2H), 3.78 - 3.95 (m, 0.8H), 2.40 - 2.49 (m, 1H, pico residual de DMSO), 1.96 - 2.25 (m, 1H).

Ejemplo 578: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm):4:1 mezcla de rotámeros δ (ppm): 8.93 - 9.19 (m, 1H), 8.63 (t, 1H), 7.90 (d, 1H), 7.67 - 7.74 (m, 1H), 7.22 - 7.53 (m, 2H), 7.01 - 7.22 (m, 1H), 6.55 - 6.75 (m, 2H), 5.27 - 5.62 (m, 1H), 4.79 - 5.26 (m, 2H), 4.10 - 4.54 (m, 3.8H), 3.96 - 4.05 (m, 0.2H), 3.78 - 3.95 (m, 0.8H), 3.42 - 3.58 (m, 0.2H), 2.70 - 2.84 (m, 0.2H), 2.40 - 2.49 (m, 0.8H), 1.97 - 2.31 (m, 1H).

Ejemplo 579: ^{1}H RMN (400 MHz, DMSO- d_6): 4:1 mezcla de rotámeros δ (ppm): 8.96 - 9.10 (m, 1.2H), 8.63 (t, 0.8H), 8.05 - 8.14 (m, 1H), 7.57 - 7.64 (m, 1H), 7.36 - 7.51 (m, 1.2H), 7.11 - 7.29 (m, 1.8H), 6.95 - 7.05 (m, 1H), 6.67 (dd, 1H), 5.40 - 5.60 (m, 0.8H), 5.04 - 5.35 (m, 2H), 4.84 (t, 0.2H), 4.23 - 4.62 (m, 3H), 3.96 - 4.22 (m, 1H), 3.79 - 3.96 (m, 0.8H), 3.42 - 3.59 (m, 0.2H), 3.35 (m, 1H, traslapando con señal residual de H2O) 2.70 - 2.83 (m, 0.2H), 2.38 (s, 3H), 1.97 - 2.17 (m, 0.8H).

Ejemplo 580: ^{1}H RMN (400 MHz, DMSO- d_6): 4:1 mezcla de rotámeros δ (ppm): 8.59 - 9.06 (m, 1H), 8.06 - 8.15 (m, 1H), 7.57 - 7.64 (m, 1H), 7.33 - 7.51 (m, 1.2H), 7.13 - 7.30 (m, 1.8H), 6.94 - 7.07 (m, 1H), 6.67 (dd, 1H), 4.95 - 5.31 (m, 2H), 4.85 (t, 0.2H), 4.39 - 4.58 (m, 1.8H), 4.06 - 4.39 (m, 2H), 3.90 - 4.03 (m, 0.2H), 3.68 - 3.84 (m, 0.8H), 3.35 (m, 1H, traslapando con señal residual de H2O) 2.70 - 2.84 (m, 0.2H), 2.38 (s, 3H), 1.90 - 2.27 (m, 0.8H), 1.48 - 1.65 (m, 3H), (protón OH intercambiado por deuterio).

Ejemplo 581: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 8.48 (t, 1H), 8.18 (s, 1H), 7.61 (d, 1H), 7.43 - 7.51 (m, 1H), 7.17 - 7.30 (m, 2H), 7.07 (t, 1H), 6.69 (dd, 1H), 5.15 - 5.44 (m, 2H), 4.23 - 4.50 (m, 3H), 3.65 - 3.74 (m, 1H), 2.39 (s, 3H), 2.21 - 2.32 (m, 1H), 2.10 - 2.21 (m, 1H), 1.81 - 1.94 (m, 1H), 0.99 - 1.10 (m, 1H), 0.70 - 0.79 (m, 1H), (protón OH intercambiado por deuterio).

Ejemplo 582: ^{1}H RMN (400 MHz, DMSO- d_6): 4:1 mezcla de rotámeros δ (ppm):8.60 - 9.04 (m, 1H), 7.98 - 8.07 (m, 0.8H), 7.90 - 7.98 (m, 1H), 7.84 - 7.90 (m, 0.2H), 7.37 - 7.52 (m, 1.2H), 7.14 - 7.29 (m, 1H), 7.03 (t, 0.8H), 6.70 - 6.79 (m, 1.8H), 6.59 (d, 0.2H), 4.93 - 5.30 (m,

1.8H), 4.85 (t, 0.2H), 4.40 - 4.57 (m, 1.8H), 4.09 - 4.40 (m, 2H), 3.91 - 4.05 (m, 0.2H), 3.66 - 3.85 (m, 1H), 3.35 (m, 1H, traslapando con señal residual de H2O) 2.71 - 2.85 (m, 0.2H), 2.32 - 2.42 (m, 3H), 1.88 - 2.25 (m, 0.8H), 1.47 - 1.66 (m, 3H), (protón OH intercambiado por deuterio).

Ejemplo 583: ^{1}H RMN (400 MHz, DMSO- *d*$_6$): 4:1 mezcla de rotámeros δ (ppm): 9.18 - 9.36 (m, 1H), 9.00 (t, 0.2H), 8.63 (t, 0.8H), 7.89 - 8.17 (m, 2H), 7.37 - 7.53 (m, 1.2H), 7.22 - 7.31 (m, 0.8H), 6.99 - 7.21 (m, 1H), 6.58 - 6.82 (m, 2H), 5.40 - 5.61 (m, 0.8H), 5.27 (d, 1H), 4.98 - 5.20 (m, 1H), 4.85 (t, 0.2H), 4.23 - 4.58 (m, 3.2H), 4.09 - 4.23 (m, 0.8H), 3.78 - 4.07 (m, 1H), 3.35 (m, 1H, traslapando con señal residual de H_2O) 2.69 - 2.83 (m, 0.2H), 2.38 (s, 3H), 1.95 - 2.25 (m, 0.8H).

Ejemplo 584: ^{1}H RMN (400 MHz, DMSO- *d*$_6$): δ (ppm):8.51 (t, 1H), 8.10 (s, 1H), 7.87 - 8.00 (m, 1H), 7.45 (t, 1H), 7.23 (t, 1H), 7.10 (t, 1H), 6.69 - 6.85 (m, 2H), 5.08 - 5.42 (m, 2H), 4.23 - 4.53 (m, 3H), 3.64 - 3.78 (m, 1H), 2.39 (s, 3H), 2.21 - 2.31 (m, 1H), 2.11 - 2.21 (m, 1H), 1.83 - 1.94 (m, 1H), 1.01 - 1.11 (m, 1H), 0.69 - 0.77 (m, 1H), (protón OH intercambiado por deuterio).

Ejemplo 585: ^{1}H RMN (400 MHz, DMSO- *d*$_6$): 4:1 mezcla de rotámeros δ (ppm): 9.04 (t, 0.2H), 8.66 (t, 0.8H), 8.03 - 8.11 (m, 1H), 7.80 - 7.88 (m, 1H), 7.34 - 7.49 (m, 1.2H), 7.23 (t, 0.8H), 7.11 - 7.19 (m, 1H), 6.88 - 7.04 (m, 2H), 5.27 - 5.60 (m, 3.8H), 5.21 (d, 0.2H), 5.08 (d, 0.8H), 4.88 (t, 0.2H), 4.23 - 4.60 (m, 3.2H), 4.09 - 4.23 (m, 0.8H), 3.82 - 4.06 (m, 1H), 3.51 - 3.60 (m, 1H), 2.70 - 2.87 (m, 0.2H), 1.95 - 2.31 (m, 0.8H), (protones NH_2 intercambiados por deuterio).

Ejemplo 586: ^{1}H RMN (400 MHz, DMSO- *d*$_6$): 4:1 mezcla de rotámeros δ (ppm): 9.22 - 9.34 (m, 1H), 8.95 - 9.10 (m, 0.2H), 8.59 - 8.79 (m, 0.8H), 7.90 - 8.24 (m, 2H), 7.34 - 7.51 (m, 1.2H), 7.14 - 7.29 (m, 1.6H), 6.95 - 7.14 (m, 1.2H), 6.70 - 6.95 (m, 1H), 5.28 - 5.62 (m, 3H), 5.01 - 5.27 (m, 1H), 4.82 - 4.92 (m, 0.2H), 4.53 - 4.65 (m, 0.2H), 4.23 - 4.53 (m, 2.8H), 4.07 - 4.23 (m, 0.8H), 3.76 - 4.07 (m, 1H), 3.35 (m, 1H, traslapando con señal residual de H2O) 2.37 - 2.44 (m, 3H), 1.94 - 2.28 (m, 1H).

Ejemplo 587: ^{1}H RMN (400 MHz, DMSO- *d*$_6$): δ (ppm):8.51 (t, 1H), 8.23 (s, 1H), 8.02 - 8.14 (m, 1H), 7.33 - 7.46 (m, 1H), 7.10 - 7.25 (m, 2H), 6.89 - 7.05 (m, 2H), 5.37 - 5.53 (m, 2H), 5.20 - 5.35 (m, 2H), 4.34 - 4.54 (m, 1H), 4.21 - 4.34 (m, 2H), 3.67 - 3.78 (m, 1H), 2.40 - 2.45 (m, 3H), 2.26 - 2.37 (m, 1H), 2.11 - 2.23 (m, 1H), 1.90 (d, 1H), 1.00 - 1.15 (m, 1H), 0.73 - 0.86 (m, 1H).

Ejemplo 588: ^{1}H RMN (400 MHz, DMSO- *d*$_6$): 4:1 mezcla de rotámeros δ (ppm): 9.02 (t, 0.2H), 8.63 (t, 0.8H), 8.11 - 8.22 (m, 1H), 7.67 - 7.73 (m, 1H), 7.30 - 7.53 (m, 2H), 7.12 - 7.28

(m, 1H), 6.96 - 7.11 (m, 1H), 6.80 - 6.87 (m, 1H), 5.40 - 5.61 (m, 0.8H), 5.08 - 5.39 (m, 2H), 4.85 (t, 0.2H), 4.59 (d, 0.2H), 4.22 - 4.52 (m, 2.8H), 4.08 - 4.21 (m, 0.8H), 3.81 - 4.05 (m, 1H), 3.79 (s, 3H), 3.53 - 3.62 (m, 0.2H), 3.35 (m, 1H, traslapando con señal residual de H2O) 2.70 - 2.85 (m, 0.2H), 2.41 (s, 3H), 1.98 - 2.19 (m, 0.8H).

Ejemplo 589: ^{1}H RMN (400 MHz, DMSO- *d*$_6$): 4:1 mezcla de rotámeros δ (ppm): 8.58 - 9.07 (m, 2H), 8.14 - 8.24 (m, 1H), 7.98 (t, 1H), 7.76 - 7.82 (m, 1H), 7.66 (d, 1H), 7.35 - 7.51 (m, 3H), 7.09 - 7.28 (m, 1.2H), 6.92 - 7.03 (m, 1.8H), 5.41 - 5.63 (m, 1H), 5.10 - 5.40 (m, 3.8H), 4.85 (t, 0.2H), 4.59 (d, 0.2H), 4.22 - 4.52 (m, 2.8H), 4.08 - 4.20 (m, 1H), 3.80 - 4.05 (m, 1H), 2.40 (s, 3H), 1.96 - 2.27 (m, 1H).

Ejemplo 590: ^{1}H RMN (400 MHz, DMSO- *d*$_6$): 4:1 mezcla de rotámeros δ (ppm):8.58 - 9.05 (m, 3H), 8.11 - 8.19 (m, 1H), 7.68 - 7.72 (m, 1H), 7.41 - 7.49 (m, 2H), 7.32 - 7.40 (m, 1H), 7.13 - 7.27 (m, 1H), 6.95 - 7.11 (m, 1H), 6.91 (dd, 1H), 5.40 - 5.59 (m, 1H), 5.27 - 5.39 (m, 3H), 5.09 - 5.25 (m, 1H), 4.85 (t, 0.2H), 4.58 (d, 0.2H), 4.42 - 4.51 (m, 1H), 4.23 - 4.42 (m, 1.8H), 4.07 - 4.20 (m, 0.8H), 3.80 - 4.04 (m, 1H), 3.35 (m, 1H, traslapando con señal residual de H2O) 2.38 (s, 3H), 1.97 - 2.19 (m, 1H).

Ejemplo 592: ^{1}H RMN (400 MHz, DMSO- *d*$_6$): 4:1 mezcla de rotámeros δ(ppm): 9.02 (t, 0.2H), 8.65 (t, 0.8H), 8.02 (d, 1H), 7.78 - 7.84 (m, 1H), 7.34 - 7.49 (m, 1H), 7.11 - 7.27 (m, 1H), 6.91 - 7.02 (m, 1.8H), 6.81 (m, 1.2H), 5.25 - 5.60 (m, 1.8H), 5.18 (d, 0.2H), 5.04 (d, 0.8H), 4.87 (t, 0.2H), 4.53 - 4.76 (m, 2H), 4.24 - 4.52 (m, 3H), 4.08 - 4.23 (m, 0.8H), 3.81 - 4.06 (m, 1H), 3.69 (s, 3H), 3.42 - 3.59 (m, 0.2H), 2.71 - 2.85 (m, 0.2H), 1.97 - 2.18 (m, 0.8H). (protones NH_2 parcialmente intercambiados por deuterio).

Ejemplo 593: ^{1}H RMN (400 MHz, DMSO- *d*$_6$): 4:1 mezcla de rotámeros δ (ppm): 12.90 (br. s, 1H), 9.01 (t, 0.2H), 8.64 (t, 0.8H), 8.02 (d, 1H), 7.77 - 7.85 (m, 1H), 7.36 - 7.50 (m, 1H), 7.24 (t, 0.8H), 7.16 (t, 0.2H), 6.94 - 7.04 (m, 1.6H), 6.76 - 6.90 (m, 1.4H), 5.39 - 5.61 (m, 0.8H), 5.24 - 5.35 (m, 1H), 5.19 (d, 0.2H), 5.05 (d, 0.8H), 4.87 (t, 0.2H), 4.24 - 4.68 (m, 5H), 4.09 - 4.22 (m, 1H), 3.81 - 4.05 (m, 1H), 3.43 - 3.64 (m, 0.8H), 3.35 (m, 0.2 H, traslapando con señal residual de H2O)2.71 - 2.85 (m, 0.2H), 1.98 - 2.17 (m, 0.8H). (protones NH2 intercambiados por deuterio).

Ejemplo 595: ^{1}H RMN (400 MHz, DMSO- *d*$_6$): 4:1 mezcla de rotámeros δ (ppm): 12.29 (br. s, 1H), 9.05 (t, 0.2H), 8.64 (t, 0.8H), 8.15 - 8.22 (m, 1H), 8.11 (d, 1H), 7.35 - 7.49 (m, 2H), 7.23 (t, 0.8H), 7.09 - 7.19 (m, 1.4H), 6.95 (t, 0.8H), 5.41 - 5.63 (m, 1H), 5.38 (d, 0.8H), 5.22 - 5.33 (m, 0.2H), 5.16 (d, 0.8H), 4.88 (t, 0.2H), 4.61 (d, 0.2H), 4.23 - 4.53 (m, 3H), 4.10 - 4.22 (m, 0.8H), 3.81 - 4.06 (m, 1H), 3.48 - 3.64 (m, 2H), 3.35 (m, 1H, traslapando con señal residual de H2O) 2.70 - 2.84 (m, 0.2H), 2.42 (s, 3H), 1.98 - 2.27 (m, 0.8H).

Ejemplo 596: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 12.29 (br. s, 1H), 8.52 (t, 1H), 8.28 (s, 1H), 8.11 (d, 1H), 7.36 - 7.50 (m, 2H), 7.10 - 7.23 (m, 2H), 7.01 (t, 1H), 5.45 (d, 1H), 5.27 (d, 1H), 4.35 - 4.51 (m, 1H), 4.23 - 4.35 (m, 2H), 3.70 - 3.79 (m, 1H), 3.50 - 3.67 (m, 2H), 2.44 (s, 3H), 2.24 - 2.36 (m, 1H), 2.11 - 2.22 (m, 1H), 1.90 (q, 1H), 1.01 - 1.13 (m, 1H), 0.73 - 0.81 (m, 1H).

Ejemplo 597: ^{1}H RMN (400 MHz, DMSO- d_6): 85:15 mezcla de rotámeros δ (ppm): 12.77 (br. s, 1H), 9.06 (t, 0.15H), 8.68 (t, 0.85H), 8.36 - 8.46 (m, 1H), 8.26 (d, 1H), 8.18 (s, 0.85H), 7.98 (s, 0.15H), 7.83 (d, 1H), 7.36 - 7.49 (m, 1.15H), 7.10 - 7.27 (m, 1H), 6.92 (t, 0.85H), 5.24 - 5.64 (m, 2.85H), 4.92 (t, 0.15H), 4.72 (d, 0.15H), 4.11 - 4.55 (m, 3.85H), 3.86 - 4.06 (m, 1H), 3.35 (m, 1H, traslapando con señal residual de H2O) 2.55 - 2.60 (m, 0.15H), 2.46 (s, 3H), 2.00 - 2.20 (m, 0.85H).

Ejemplo 598: 1H RMN (400 MHz, DMSO- d_6): δ (ppm): 8.46 - 8.60 (m, 2H), 8.18 - 8.31 (m, 2H), 7.84 (dd, 1H), 7.42 (t, 1H), 7.19 (t, 1H), 6.98 (t, 1H), 5.61 (d, 1H), 5.38 (d, 1H), 4.35 - 4.45 (m, 1H), 4.23 - 4.35 (m, 2H), 3.74 - 3.82 (m, 1H), 2.47 (s, 3H), 2.24 - 2.35 (m, 1H), 2.11 - 2.22 (m, 1H), 1.85 - 1.94 (m, 1H), 1.04 - 1.13 (m, 1H), 0.73 - 0.81 (m, 1H).

Ejemplo 599: ^{1}H RMN (400 MHz, DMSO- d_6): 4:1 mezcla de rotámeros δ (ppm): 9.03 (t, 0.2H), 8.66 (t, 0.8H), 8.35 - 8.44 (m, 1H), 8.21 - 8.29 (m, 1H), 8.16 (s, 0.8H), 7.96 (s, 0.2H), 7.83 (d, 1H), 7.36 - 7.49 (m, 1.2H), 7.13 - 7.25 (m, 1H), 6.92 (t, 0.8H), 5.46 - 5.57 (m, 0.8H), 5.34 - 5.43 (m, 0.2H), 5.27 (d, 0.8H), 4.88 - 5.00 (m, 0.2H), 4.71 (d, 0.2H), 4.34 - 4.57 (m, 2H), 4.09 - 4.29 (m, 1.8H), 3.98 (dd, 1H), 3.73 - 3.91 (m, 0.8H), 3.40 - 3.48 (m, 0.2H), 2.55 - 2.60 (m, 0.2H), 2.46 (s, 3H), 1.93 - 2.27 (m, 0.8H), 1.47 - 1.67 (m, 3H), (COOH proton intercambiados por deuterio).

Ejemplo 604: ^{1}H RMN (400 MHz, DMSO- d_6): 4:1 mezcla de rotámeros δ (ppm): 9.04 (t, 0.2H), 8.65 (t, 0.8H), 8.14 - 8.21 (m, 1H), 8.10 - 8.14 (m, 1H), 7.38 - 7.47 (m, 2H), 7.14 - 7.26 (m, 2.2H), 6.97 (t, 0.8H), 5.43 - 5.61 (m, 0.8H), 5.39 (d, 0.8H), 5.12 - 5.32 (m, 1H), 4.88 (t, 0.2H), 4.63 (d, 0.2H), 4.52 - 4.59 (m, 2H), 4.34 - 4.52 (m, 2H), 4.11 - 4.32 (m, 2H), 3.83 - 4.06 (m, 1H), 3.35 (m, 1H, traslapando con señal residual de H2O) 2.42 (s, 3H), 1.98 - 2.27 (m, 1H).

Ejemplo 605: ^{1}H RMN (400 MHz, DMSO- d_6) δ (ppm): 3:1 mezcla de rotámeros 9.14 (t, 0.25H), 8.69 (t, 0.75H), 8.24 (s, 1H), 8.18 (d, 1.75H), 7.92 - 8.02 (m, 1.25H), 7.87 (m, 1H), 7.44 (m, 1H), 7.08 - 7.27 (m, 3H), 5.17 - 5.60 (m, 3.75H), 4.85 - 4.95 (t, 0.25H), 4.59 (d, 0.25H), 3.78 - 4.55 (m, 5.75H), 2.70 - 2.85 (m, 0.25H), 1.90 - 2.16 (m, 0.75H).

Ejemplo 615: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm):9.27 (s, 1H), 8.86 (s, 1H), 8.52 (d, 1H), 8.50 (m, 1H), 8.41 (d, 1H), 7.74 (d, 1H), 7.47 - 7.40 (m, 2H), 7.20 (t, 1H), 7.05 (t, 1H), 5.60 (d, 1H), 5.37 (d, 1H), 4.40 (dd, 1H), 3.32 - 4.26 (m, 2H), 3,73 (m, 1H), 3.25 (s, 3H), 3.02

(s, 3H), 2.49 (s, 3H), 2.34 – 2.26 (m, 1H), 2.20 –2.14 (m, 1H), 1.90 (m, 1H), 1.08 (m, 1H), 0.78 (m, 1H).

Ejemplo 617: ^{1}H RMN (400 MHz, DMSO- d_6): 85:15 mezcla de rotámeros δ (ppm): 9.06 (t, 0.15H), 8.70 (t, 0.85H), 8.33 - 8.44 (m, 2H), 8.25 (s, 0.85H), 8.09 (s, 0.15H), 7.85 (d, 1H), 7.38 - 7.49 (m, 0.15H), 7.28 - 7.35 (m, 0.85H), 7.11 - 7.22 (m, 1H), 6.81 (t, 1H), 5.42 - 5.65 (m, 1.85H), 5.27 - 5.42 (m, 1H), 4.93 (t, 0.15H), 4.75 (d, 0.15H), 4.11 - 4.58 (m, 3.85H), 3.89 - 4.09 (m, 1H), 2.54 - 2.62 (m, 0.15H), 2.48 (s, 3H), 2.00 - 2.29 (m, 0.85H).

Ejemplo 621: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm):8.51 (t, 1H), 8.34 (d, 1H), 8.18 (br. d, 1H), 7,46 (m, 1H), 7.35 (m, 1H), 7,22 (m, 1H), 7.08 (t, 1H), 6,95 (dt, 1H), 4,63 (d, 1H), 4.24 - 4.45 (m, 4H), 3,69 (m, 1H), 2,51 (s, 3H), 2,29 (m, 1H), 2,18 (m, 1H), 1,84 (m, 1H), 1,02 (m, 1H), 0,79 (m, 1H).

Ejemplo 628:^{1}H RMN (400 MHz, DMSO- d_6): 4:1 mezcla de rotámeros δ (ppm): 10.51 (s, 0.2H), 10.16 (s, 0.8H), 8.18 (m, 1H), 7.91 (m, 0.2H), 7.83 (m, 0.8H), 7.65 (m, 1H), 7.62 (d, 0.8H), 7.56 (d, 0.2H), 7.46- 7.22 (m, 5H), 5.66- 5.24 (m, 3H), 5.08 (d, 0.2H), 4.95 (d, 0.8 H), 4.56 (m, 0.2H), 4.33 (ddd, 0.8H), 4.24- 4.00 (m, 1.6H), 3.87- 3.60 (m, 0.4H), 3.47 (s, 0.6H), 3.43 (s, 2.4H).

Ejemplo 652: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 8.48 (br. s, 1H), 8.22 (d, 1H), 7.71 (d, 1H), 7.36 - 7.52 (m, 4H), 7.20 (t, 1H), 7.05 (t, 1H), 5.84 (d, 1H), 5.55 (d, 1H), 4.85 (s, 2H), 4.37 - 4.47 (m, 2H), 4.25 - 4.33 (m, 2H), 3.68 - 3.76 (m, 1H), 2.24 - 2.36 (m, 1H), 2.10 - 2.21 (m, 1H), 1.83 - 1.94 (m, 1H), 0.99 - 1.08 (m, 1H), 0.83 (m, 1H).

Ejemplo 657: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 9.17 (br. s, 1H), 8.65 (br. s, 1H), 8.38 (t, 1H), 8.07 (d, 1H), 7.85 (br. s, 1H), 7.56 (br. s, 1H), 7.46 (t, 1H), 7.22 (t, 1H), 6.99 - 7.15 (m, 1H), 5.76 (br. s, 2H), 5.45 (d, 1H), 4.38 (d, 1H), 4.28 (d, 1H), 4.15 - 4.24 (m, 1H), 4.02 - 4.12 (m, 1H).

Ejemplo 661: ^{1}H RMN (400 MHz, DMSO- d_6): 4:1 mezcla de rotámeros δ (ppm):8.99 (d, 0.8H), 8.92 (s, 0.2H), 8.63 (t, 1H), 7.90 (s, 1H), 7.77 (br. s, 1H), 7.48 - 7.55 (m, 1H), 7.40 - 7.48 (m, 1H), 7.17 - 7.29 (m, 1H), 7.04 (t, 1H), 5.53 - 5.80 (m, 1.8H), 5.43 - 5.50 (m, 0.2H), 5.30 - 5.41 (m, 0.4H), 5.19 - 5.27 (m, 0.2H), 5.01 - 5.13 (m, 0.4H), 4.66 (d, 0.8H), 4.51 - 4.60 (m, 0.2H), 4.34 - 4.49 (m, 1.2H), 4.09 - 4.32 (m, 2.6H), 3.95 - 4.09 (m, 0.8H), 3.56 - 3.86 (m, 0.4H), 3.39 (s, 3H), 2.61 (s, 3H).

Ejemplo 662: ^{1}H RMN (400 MHz, DMSO- d_6): 4:1 mezcla de rotámeros δ (ppm): 9.12 (d, 0.8H), 8.97 - 9.07 (m, 0.4H), 8.64 (br. s, 0.8H), 8.37 (d, 1H), 8.07 (dd, 1H), 7.84 (br. s, 1H), 7.56 (br. s, 1H), 7.40 - 7.52 (m, 1.2H), 7.18 - 7.30 (m, 1H), 7.05 (t, 0.8H), 5.57 - 5.81 (m, 1.6H), 5.47 (m, 0.4H), 5.34 (m, 0.4H), 5.17 - 5.28 (m, 0.2H), 5.05 - 5.17 (m, 0.4H), 4.67 (d,

0.8H), 4.50 - 4.62 (m, 0.2H), 4.35 - 4.49 (m, 1.2H), 4.11 - 4.32 (m, 2.8H), 3.99 - 4.10 (m, 0.8H), 3.64 - 3.83 (m, 0.2H), 3.40 (s, 3H).

Ejemplo 663: ^{1}H RMN (400 MHz, DMSO- d_6): 4:1 mezcla de rotámeros δ (ppm):9.43 (d, 0.8H), 8.99 (m, 0.2H), 8.62 (m, 1H), 8.39 - 8.48 (m, 1H), 7.89 (br. s, 1H), 7.63 (m, 1.8H), 7.40 - 7.55 (m, 1.2H), 7.17 - 7.30 (m, 1.2H), 7.04 (t, 0.8H), 5.55 - 5.71 (m, 1H), 5.43 - 5.54 (m, 1H), 5.20 - 5.41 (m, 0.6H), 4.90 - 5.13 (m, 0.4H), 4.65 (d, 0.8H), 4.50 - 4.60 (m, 0.2H), 4.35 - 4.48 (m, 1.2H), 4.08 - 4.32 (m, 2.8H), 3.96 - 4.08 (m, 0.8H), 3.61 - 3.85 (m, 0.2H), 3.39 (s, 3H).

Ejemplo 664: ^{1}H RMN (400 MHz, DMSO- d_6): 4:1 mezcla de rotámeros δ (ppm): 9.12 (s, 0.8H), 8.96 - 9.03 (m, 0.2H), 8.93 (s, 0.2H), 8.55 - 8.66 (m, 0.8H), 8.34 - 8.41 (m, 1H), 8.05 - 8.11 (m, 1H), 7.84 (br. s, 0.8H), 7.78 (br. s, 0.2H), 7.50 - 7.60 (m, 1H), 7.35 - 7.50 (m, 1.2H), 7.30 (t, 0.8H), 7.04 - 7.19 (m, 1H), 5.55 - 5.79 (m, 1.8H), 5.47 (m, 0.2H), 5.20 - 5.39 (m, 0.8H), 5.00 - 5.13 (m, 1.2H), 4.95 (d, 0.2H), 4.67 (d, 0.8H), 4.12 - 4.30 (m, 1.8H), 3.93 - 4.08 (m, 0.8H), 3.57 - 3.85 (m, 0.4H), 3.41 - 3.48 (m, 3H), 1.48 (d, 0.6H), 1.34 (d, 2.4H).

Ejemplo 668: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm):9.86 (s, 1H), 9.18 (s, 1H), 8.37 (d, 1H), 8.07 (d, 1H), 7,84 (m, 1H), 7.76 (t, 1H), 7.55 (m, 1H), 7.46 (t, 1H), 7.12 (t, 1H), 5.97 (d, 1H), 5.67 (d, 1H), 4.52 (m, 1H), 3.80 (m, 1H), 2.40- 2.20 (m, 2H), 1.93 (m, 1H), 1.05 (m, 1H), 0.83 (m, 1H).

Ejemplo 675: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm):9.14 (s, 1H), 8.50 (m, 1H), 8.38 (d, 1H), 8.08 (d, 1H), 7.84 (m, 1H), 7.55 (m, 1H), 7.45 (t, 1H), 7.21 (t, 1H), 7.07 (t, 1H), 5.88 (d, 1H), 5.57 (d, 1H), 4.41 - 4.24 (m, 3H), 3,48 (m, 1H), 2,44 (dd, 3H), 1.93 (dd, 1H), 1.28 (s, 3H), 1.01- 0.96 (m, 2H).

Ejemplo 684: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 9.79 (br. s, 1H), 9.19 (s, 1H), 8.37 (d, 1H), 8.08 (dd, 1H), 7.81 - 8.01 (m, 2H), 7.37 - 7.66 (m, 3H), 7.11 - 7.37 (m, 4H), 5.98 (d, 1H), 5.67 (d, 1H), 4.55 (dd, 1H), 3.75 - 3.89 (m, 1H), 2.21 - 2.41 (m, 2H), 1.87 - 2.01 (m, 1H), 0.98 - 1.13 (m, 1H), 0.82 (m, 1H).

Ejemplo 685: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 9.79 (br. s, 1H), 9.28 (s, 1H), 8.40 (d, 1H), 8.15 (d, 1H), 7.91 (t, 2H), 7.53 - 7.70 (m, 2H), 7.32 - 7.53 (m, 3H), 7.24 (t, 1H), 6.97 - 7.14 (m, 1H), 6.00 (d, 1H), 5.69 (d, 1H), 4.56 (dd, 1H), 3.75 - 3.86 (m, 1H), 2.23 - 2.40 (m, 2H), 1.85 - 2.01 (m, 1H), 0.94 - 1.13 (m, 1H), 0.82 (td, 1H).

Ejemplo 686: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 9.81 (br. s, 1H), 8.58 (m, 1H), 8.19 (d, 1H), 7.81 - 8.03 (m, 2H), 7.48 - 7.73 (m, 3H), 7.23 - 7.47 (m, 4H), 5.82 (d, 1H), 5.51 (d, 1H), 4.54 (dd, 1H), 3.76 - 3.84 (m, 1H), 2.32 (m, 2H), 1.86 - 1.98 (m, 1H), 1.00 - 1.10 (m, 1H), 0.71 - 0.81 (m, 1H).

Ejemplo 688: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 9.81 (br. s, 1H), 9.22 (s, 1H), 8.64 (dd, 1H), 8.38 (d, 1H), 8.02 - 8.19 (m, 2H), 7.82 - 8.02 (m, 2H), 7.46 - 7.63 (m, 2H), 7.27 (t, 1H), 7.18 - 7.23 (m, 1H), 5.99 (d, 1H), 5.68 (d, 1H), 4.55 (dd, 1H), 3.75 - 3.91 (m, 1H), 2.19 - 2.41 (m, 2H), 1.84 - 2.03 (m, 1H), 0.96 - 1.17 (m, 1H), 0.75 - 0.90 (m, 1H).

Ejemplo 690: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 8.42 - 8.51 (m, 1H), 7.52 (br. s, 2H), 7.46 (t, 1H), 7.28 (br. s, 1H), 7.20 (t, 1H), 7.11 (s, 1H), 7.06 (t, 1H), 5.62 (d, 1H), 5.35 (d, 1H), 4.37 - 4.47 (m, 1H), 4.22 - 4.35 (m, 3H), 3.63 - 3.71 (m, 1H), 2.21 - 2.32 (m, 1H), 2.09 - 2.20 (m, 1H), 1.81 - 1.92 (m, 1H), 0.97 - 1.06 (m, 1H), 0.67 - 0.76 (m, 1H).

Ejemplo 693: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 8.40 - 8.48 (m, 1H), 8.24 (d, 1H), 8.08 (d, 1H), 7.89 - 7.98 (m, 1H), 7.58 (br. s, 1H), 7.37 - 7.44 (m, 1H), 7.27 (t, 1H), 6.98 (t, 1H), 6.00 (d, 1H), 5.72 (d, 1H), 5.04 (m, 1H), 4.29 (dd, 1H), 3.74 - 3.81 (m, 1H), 2.78 (s, 3H), 2.29 (dd, 1H), 2.09 - 2.20 (m, 1H), 1.84 - 1.97 (m, 1H), 1.33 (d, 3H), 1.01 - 1.11 (m, 1H), 0.68 (m, 1H).

Ejemplo 694: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm):8.48 (t, 1H), 8.24 (d, 1H), 8.08 (d, 1H), 7.90 (br. s, 1H), 7.61 (br. s, 1H), 7.45 (t, 1H), 7.21 (t, 1H), 7.06 (t, 1H), 6.02 (d, 1H), 5.75 (d, 1H), 4.20 - 4.40 (m, 3H), 3.71 - 3.85 (m, 1H), 2.84 (s, 3H), 2.31 (dd, 1H), 2.14 (m, 1H), 1.83 - 2.01 (m, 1H), 0.99 - 1.16 (m, 1H), 0.62 - 0.80 (m, 1H).

Ejemplo 695: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 8.47 (br. s, 1H), 8.00 (br. s, 1H), 7.88 (br. s, 1H), 7.61 (br. s, 1H), 7.45 (t, 1H), 7.21 (t, 1H), 7.02 - 7.12 (m, 1H), 6.01 (d, 1H), 5.73 (d, 1H), 4.22 - 4.40 (m, 3H), 3.73 - 3.82 (m, 1H), 2.85 (s, 3H), 2.62 (s, 3H), 2.31 (dd, 1H), 2.07 - 2.19 (m, 1H), 1.85 - 1.96 (m, 1H), 1.00 - 1.12 (m, 1H), 0.64 - 0.76 (m, 1H).

Ejemplo 696: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm):8.36 - 8.50 (m, 1H), 7.96 (m, 1H), 7.63 (br. s, 1H), 7.40 (t, 1H), 7.27 (t, 1H), 6.98 (t, 1H), 6.02 (d, 1H), 5.71 (d, 1H), 4.97 - 5.13 (m, 1H), 4.28 (dd, 1H), 3.72 - 3.83 (m, 1H), 2.82 (s, 3H), 2.60 - 2.72 (m, 3H), 2.21 - 2.39 (m, 1H), 2.07 - 2.19 (m, 1H), 1.83 - 1.97 (m, 1H), 1.33 (d, 3H), 1.01 - 1.13 (m, 1H), 0.62 - 0.76 (m, 1H).

Ejemplo 697: ^{1}H RMN (400 MHz, DMSO- d_6): 4:1 mezcla de rotámeros δ (ppm): 9.09 (s, 0.8H), 9.01 (br. s, 0.2H), 8.59 - 8.69 (m, 1H), 7.89 - 8.00 (m, 1H), 7.81 (br. s, 1H), 7.48 - 7.59 (m, 1.2H), 7.38 - 7.48 (m, 1H), 7.18 - 7.30 (m, 1H), 7.04 (t, 0.8H), 5.56 - 5.80 (m, 1.8H), 5.20 - 5.52 (m, 0.8H), 5.10 (m, 0.4H), 4.66 (d, 0.8H), 4.50 - 4.61 (m, 0.2H), 4.33 - 4.49 (m, 1.4H), 3.97 - 4.33 (m, 3.4H), 3.60 - 3.86 (m, 0.2H), 3.39 (s, 3H), 2.92 (m, 2H), 1.20 - 1.40 (m, 3H).

Ejemplo 702: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 9.14 (s, 1H), 8.30 - 8.47 (m, 2H), 8.07 (m, 1H), 7.88 (br. s, 1H), 7.53 (br. s, 1H), 7.35 - 7.46 (m, 1H), 7.28 (t, 1H), 6.94 - 7.16 (m, 1H), 5.90 (d, 1H), 5.62 (d, 1H), 5.06 (quin, 1H), 4.30 (dd, 1H), 3.57 - 3.78 (m, 1H), 2.20 - 2.36

(m, 1H), 2.06 - 2.20 (m, 1H), 1.76 - 1.99 (m, 1H), 1.33 (d, 3H), 0.94 - 1.10 (m, 1H), 0.70 - 0.84 (m, 1H).

Ejemplo 703: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 9.16 (s, 1H), 8.45 - 8.54 (m, 1H), 8.38 (d, 1H), 8.08 (dd, 1H), 7.85 (br. s, 1H), 7.55 (br. s, 1H), 7.45 (t, 1H), 7.20 (t, 1H), 7.07 (t, 1H), 5.92 (d, 1H), 5.63 (d, 1H), 4.36 - 4.51 (m, 1H), 4.25 - 4.33 (m, 2H), 3.68 - 3.75 (m, 1H), 2.24 - 2.37 (m, 1H), 2.10 - 2.22 (m, 1H), 1.84 - 1.95 (m, 1H), 1.00 - 1.10 (m, 1H), 0.80 (m, 1H).

Ejemplo 705: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 8.99 (br. s, 1H), 8.40 - 8.54 (m, 1H), 8.02 (s, 2H), 7.88 (br. s, 1H), 7.61 (br. s, 1H), 7.36 - 7.53 (m, 1H), 7.17 - 7.28 (m, 1H), 7.04 - 7.17 (m, 1H), 5.75 (d, 1H), 5.45 (d, 1H), 4.24 - 4.48 (m, 3H), 3.58 - 3.71 (m, 1H), 2.21 - 2.32 (m, 1H), 2.10 - 2.21 (m, 1H), 1.82 - 1.93 (m, 1H), 0.97 - 1.07 (m, 1H), 0.82 (m, 1H).

Ejemplo 706: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 8.98 (s, 1H), 8.39 (m, 1H), 8.01 (d, 2H), 7.90 (br. s, 1H), 7.58 (br. s, 1H), 7.36 - 7.49 (m, 1H), 7.29 (t, 1H), 7.06 - 7.19 (m, 1H), 5.73 (d, 1H), 5.43 (d, 1H), 5.06 (quin, 1H), 4.28 (dd, 1H), 3.60 - 3.69 (m, 1H), 2.24 (m, 1H), 2.12 (m, 1H), 1.80 - 1.92 (m, 1H), 1.34 (d, 3H), 0.95 - 1.05 (m, 1H), 0.76 - 0.86 (m, 1H).

Ejemplo 707: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 9.96 (br. s, 1H), 8.19 (d, 1H), 7.78 - 7.88 (m, 1H), 7.65 (d, 2H), 7.21 - 7.49 (m, 5H), 5.81 (d, 1H), 5.51 (d, 1H), 4.50 (dd, 1H), 3.78 - 3.85 (m, 1H), 2.22 - 2.39 (m, 2H), 1.92 (m, 1H), 1.04 (dt, 1H), 0.77 (m, 1H).

Ejemplo 708: ^{1}H RMN (400 MHz, DMSO- d_6): 9:1 mezcla de rotámeros δ (ppm): 10.52 (s, 0.1H), 10.19 (s, 0.9H), 8.12 - 8.25 (m, 1H), 7.84 - 7.98 (m, 1H), 7.63 (d, 2H), 7.34 - 7.47 (m, 2H), 7.20 - 7.34 (m, 3H), 5.54 - 5.75 (m, 2H), 5.38 - 5.54 (m, 0.9H), 4.96 - 5.27 (m, 0.2H), 4.73 (t, 0.9H), 4.16 - 4.33 (m, 1H), 4.00 (dd, 1H), 3.91 (m, 1H), 2.56 - 2.65 (m, 1H), 2.04 - 2.31 (m, 1H).

Ejemplo 709: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 9.97 (d, 1H), 9.49 (s, 1H), 8.50 (d, 1 H), 7.99 (br. s, 1H), 7.79 - 7.86 (m, 2H), 7.69 (br. s, 1H), 7.22 - 7.37 (m, 2H), 5.90 (d, 1H), 5.59 (d, 1H), 4.51 (dd, 1H), 3.76 - 3.83 (m, 1H), 2.21 - 2.39 (m, 2H), 1.89 - 1.98 (m, 1H), 0.99 - 1.09 (m, 1H), 0.79 (m, 1H).

Ejemplo 712: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 9.97 (br. s, 1H), 9.17 (br. s, 1H), 7.99 (s, 1H), 7.79 - 7.89 (m, 2H), 7.57 (br. s, 1H), 7.23 - 7.38 (m, 2H), 5.97 (d, 1H), 5.65 (d, 1H), 4.51 (dd, 1H), 3.76 - 3.86 (m, 1H), 2.93 (q, 2H), 2.23 - 2.41 (m, 2H), 1.87 - 1.99 (m, 1H), 1.30 (t, 3H), 1.01 - 1.11 (m, 1H), 0.82 (td, 1H).

Ejemplo 716: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 10.01 (br. s, 1H), 8.24 (d, 1H), 8.09 (d, 1H), 7.80 - 7.99 (m, 2H), 7.61 (br. s, 1H), 7.21 - 7.36 (m, 2H), 6.11 (d, 1H), 5.76 (d, 1 H), 4.52 (dd, 1H), 3.81 - 3.93 (m, 1H), 2.90 (s, 3H), 2.39 (m, 1H), 2.21 - 2.33 (m, 1H), 1.90 - 2.03**Ejemplo 717**: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 10.01 (br. s, 1H), 7.96 (m, 1H),

7.69 - 7.91 (m, 2H), 7.59 (br. s, 1H), 7.16 - 7.39 (m, 2H), 6.09 (d, 1H), 5.72 (d, 1H), 4.51 (dd, 1H), 3.73 - 3.98 (m, 1H), 2.88 (s, 3H), 2.59 (s, 3H), 2.31 - 2.45 (m, 1H), 2.20 - 2.31 (m, 1H), 1.95 (dt, 1H), 1.02 - 1.13 (m, 1H), 0.68 - 0.78 (m, 1H).

Ejemplo 718: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 9.95 (br. s, 1H), 8.85 (d, 2H), 7.78 - 7.87 (m, 1H), 7.64 (d, 1H), 7.57 (s, 1H), 7.47 (t, 1H), 7.17 - 7.37 (m, 3H), 5.88 (d, 1H), 5.55 (d, 1H), 5.36 (s, 2H), 4.51 (dd, 1H), 3.77 - 3.86 (m, 1H), 2.58 (s, 3H), 2.23 - 2.37 (m, 2H), 1.84 - 1.97 (m, 1H), 0.95 - 1.09 (m, 1H), 0.74 - 0.89 (m, 1H).

Ejemplo 719: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm):9.96 (br. s, 1H), 8.93 - 9.08 (m, 1H), 7.92 (d, 1H), 7.70 - 7.86 (m, 2H), 7.49 (br. s, 1H), 7.19 - 7.39 (m, 2H), 5.90 (d, 1H), 5.60 (d, 1H), 4.50 (dd, 1H), 3.74 - 3.85 (m, 1H), 2.15 - 2.42 (m, 3H), 1.84 - 2.03 (m, 1H), 0.99 - 1.09 (m, 1H), 0.89 - 0.99 (m, 4H), 0.76 - 0.84 (m, 1H).

Ejemplo 721: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 10.63 (br. s, 1H), 9.29 (s, 1H), 8.40 (d, 1H), 8.05 - 8.23 (m, 2H), 7.82 - 8.02 (m, 2H), 7.44 - 7.71 (m, 2H), 7.15 - 7.33 (m, 3H), 6.02 (d, 1H), 5.69 (d, 1H), 4.43 - 4.60 (m, 1H), 3.72 - 3.93 (m, 1H), 2.20 - 2.38 (m, 2H), 1.87 - 1.97 (m, 1H), 1.00 - 1.08 (m, 1H), 0.75 - 0.84 (m, 1H).

Ejemplo 723: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 9.98 (br. s, 1H), 9.25 (br. s, 1H), 8.09 (br. s, 1H), 7.90 (br. s, 1H), 7.78 - 7.87 (m, 1H), 7.61 (br. s, 1H), 7.22 - 7.39 (m, 2 H), 5.99 (d, 1H), 5.67 (d, 1H), 4.51 (dd, 1H), 3.76 - 3.86 (m, 1H), 2.67 (s, 3H), 2.21 - 2.41 (m, 2H), 1.88 - 1.99 (m, 1H), 1.05 (dt, 1H), 0.82 (m, 1H).

Ejemplo 724: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 9.98 (br. s, 1H), 9.22 (s, 1H), 8.39 (d, 1H), 8.11 (d, 1H), 7.77 - 7.93 (m, 2H), 7.47 - 7.67 (m, 1H), 7.22 - 7.36 (m, 2H), 5.99 (d, 1H), 5.68 (d, 1H), 4.52 (dd, 1H), 3.76 - 3.86 (m, 1H), 2.21 - 2.40 (m, 2H), 1.87 - 1.99 (m, 1H), 1.01 - 1.10 (m, 1H), 0.83 (m, 1H).

Ejemplo 726: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm): 9.98 (br. s, 1H), 9.08 (s, 1H), 8.10 (s, 1H), 7.78 - 7.90 (m, 2H), 7.57 (br. s, 1H), 7.22 - 7.36 (m, 2H), 5.79 (d, 1H), 5.47 (d, 1H), 4.50 (m, 1H), 3.60 - 3.83 (m, 1H), 2.44 (s, 3H), 2.21 - 2.38 (m, 2H), 1.91 (m, 1H), 0.97 - 1.07 (m, 1H), 0.80 - 0.90 (m, 1H).

Ejemplo 727: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm):10.77 (m, 1H), 8.18 (d, 1H), 8.03 (d, 1H), 7.72 (t, 1H), 7,70 (m, 1H), 7.65 (d, 1H), 7.43 (t, 1H), 7.40 (m, 1H), 7.33 (d, 1H), 7.27 (t, 1H), 5.82 (d, 1H), 5.50 (d, 1H), 4.45 (m, 1H), 3.80 (m, 1H), 2.32 (m, 1H), 2.21 (m, 1H), 1.90 (m, 1H), 1.01 (m, 1H), 0.75 (m, 1H).

Ejemplo 731: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm):9.86 (m, 1H), 8.19 (d, 1H), 7.74 (br. t, 1H), 7.67 (m, 1H), 7.66 (d, 1H), 7.45 (br. t, 1H), 7.39 (m, 1H), 7.34 (br. t, 1H), 7.28 (td, 1H),

5.81 (d, 1H), 5.51 (d, 1H), 4.50 (dd, 1H), 3.80 (m, 1H), 2.30 (m, 2H), 1.92 (m, 1H), 1.04 (m, 1H), 0.77 (m, 1H).

Ejemplo 741: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm):11.14 (br.s, 1H), 9.27 (s, 1H), 8.55 (s, 1H), 8.18 (d, 1H), 7.68 (m, 1H), 7.66 (d, 1H), 7.45 (t, 1H), 7.38 (m, 1H), 7.27 (t, 1H), 5.83 (d, 1H), 5.51 (d, 1H), 4.47 (m, 1H), 3.83 (m, 1H), 2.32- 2.37 (m, 1H), 2.22- 2.28 (m, 1H), 1.91 (m, 1H), 1.01 (m, 1H), 0.77 (m, 1H).

Ejemplo 744: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm):10.77 (m, 1H), 8.18 (d, 1H), 8.04 (d, 1H), 7.72 (t, 1H), 7.67 (m, 1H), 7.64 (d, 1H), 7.44 (t, 1H), 7.37 (m, 1H), 7.33 (d, 1H), 7.26 (t, 1H), 5.78 (d, 1H), 5.44 (d, 1H), 4.40 (m, 1H), 3.59 (m, 1H), 2.46 (dd, 1H), 1.98 (dd, 1H), 1.90 (m, 1H), 1.30 (s, 3H), 0.96 (br. t, 1H), 0.90 (dd, 1H).

Ejemplo 746: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm): 90:10 mezcla de rotámeros, solamente se describe el rotamero principal: δ (ppm): 10.85 (s, 1H), 8.16 (d, 1H), 8.01 (d, 1H), 7.70 (t, 1H), 7.64 (d, 1H), 7.62 (m, 1H), 7.43 (t, 1H), 7.37 (m, 1H), 7.31 (d, 1H), 7.25 (t, 1H), 5.44 (s, 2H), 4.62 (br. d, 1H), 4.00 (dd, 1H), 3.87 (d, 1H), 1.99 (m, 1H), 1.87 (m, 1H), 0.78 (m, 1H), 0.73 (m, 1H).

Ejemplo 754: ^{1}H RMN (400 MHz, DMSO- d_6) δ(ppm): 85:15 mezcla de rotámeros, solamente se describe el rotamero principal: δ (ppm): 10.98 (m, 1H), 8.17 (d, 1H), 8.03 (d, 1H), 7.72 (t, 1H), 7.64 (d, 1H), 7.63 (m, 1H), 7.44 (t, 1H), 7.38 (m, 1H), 7.34 (d, 1H), 7.26 (t, 1H), 5.63 (d, 1H), 5.51 (d, 1H), 5.50- 5.34 (m, 1H), 4.90 (m, 1H), 4.33 (m, 1H), 4.23 - 4.03 (m, 2H), 3.41 (s, 3H).

Ejemplo 762: ^{1}H RMN (400 MHz, DMSO- d_6): δ (ppm):10.68 (m, 1H), 8.65 (m, 1H), 8.28 (d, 1H), 8.10 (d, 1H), 8.00 (s, 1H), 7.80 (d, 1H), 7.75 (t, 1H), 7.38 (m, 2H), 7.35 (d, 1H), 7.27 (t, 1H), 7.20 (t, 1H), 4.35 (t, 1H), 3.93 (m, 1H), 2.38 (dd, 1H), 2.17 (m, 1H), 1.80 (m, 1H), 0.85 (m, 1H), 0.55 (m, 1H).

Ejemplo 770:^{1}H RMN (400 MHz, DMSO- d_6): 4:1 mezcla de rotámeros δ (ppm): 9.95 (s, 1H), 7.81 (m, 1H), 7.63 (d, 1H), 7.56 (d, 1H), 7.30 (m, 1H), 7.27 (m, 1H), 7.14 (dd, 1H), 5.89- 5.52 (AB system, 2H), 4.50 (dd, 1H), 4.14 (m, 2H), 3.80 (m, 1H), 3.70 (m, 2H), 3.32 (s, 3H), 2.59 (s, 3H), 2.29 (m, 2H), 1.91 (m, 1H), 1.02 (m, 1H), 0.81 (m, 1H).

Ejemplo 773:^{1}H RMN (600 MHz, DMSO- d_6) δ(ppm): 85:15 mezcla de rotámeros δ (ppm): 9.15 (t, 0.15H), 8.72 (t, 0.85H), 8.32 (s, 0.15H), 8.23 (s, 0.85H), 8.19 - 8.20 (m, 1H), 7.48 - 7.49 (m, 1H), 7.44 (m, 0.85H), 7.41 (m, 0.15H), 7.20 - 7.23 (m, 2H), 7.18 (t, 0.15H), 7.01 (t, 0.85H), 5.75 (m, 0.15H), 5.67 (m, 0.15H), 5.61 (m, 0.85H), 5.52 (m, 1H), 5.45 (d, 0.85H), 5.28 (d, 0.15H),5.22 (d, 0.85H), 4.72 (m, 1H), 4.54 (m, 0.3H), 4.43 (dd, 0.85H), 4.31 (dd, 0.85H), 4.08- 4.25 (m, 1.70H), 4.01 (m, 0.15H), 3.70 (m, 0.15H), 2.43 (s, 3H).

Datos de Inhibición de Factor D utilizando el Método 1 para determinar el IC_{50} s.

Ejemplo	IC_{50} (nM)	Ejemplo	IC_{50} (nM)	Ejemplo	IC_{50} (nM)
1	7	**31**	12150	**61**	7100
2	25	**32**	3350	**62**	85
3	450	**33**	24050	**63**	11400
4	3980	**34**	90	**64**	22450
5	30	**35**	2850	**65**	13100
6	2100	**36**	3250	**66**	65
7	32	**37**	22000	**67**	22200
8	9	**38**	6300	**68**	15100
9	250	**39**	1050	**69**	1050
10	604	**40**	11150	**70**	2575
11	7	**41**	3200	**71**	2900
12	11135	**42**	2850	**72**	7000
13	139	**43**	7750	**73**	325
14	55	**44**	2600	**74**	3650
15	1100	**45**	22500	**75**	12550
16	94	**46**	22800	**76**	15650
17	4048	**47**	8950	**77**	14550
18	815	**48**	7500	**78**	10400
19	10	**49**	900	**79**	6000
20	1126	**50**	21600	**80**	14950
21	31	**51**	8500	**81**	4750
22	191	**52**	400	**82**	24750
23	1850	**53**	1750	**83**	2250
24	1700	**54**	1850	**84**	6000
25	6750	**55**	125	**85**	11350
26	25	**56**	1950	**86**	14300
27	8300	**57**	1350	**87**	4650
28	2525	**58**	350	**88**	6800
29	588	**59**	6400	**89**	7700
30	2700	**60**	800	**90**	1150

91	2950	**124**	500	**157**	850
92	8650	**125**	5100	**158**	80
93	4000	**126**	100	**159**	55
94	10950	**127**	3	**160**	1400
95	1350	**128**	2000	**161**	987
96	8050	**129**	4	**162**	5
97	900	**130**	54	**163**	100
98	1850	**131**	4600	**164**	400
99	23250	**132**	18	**165**	140
100	17550	**133**	6	**166**	3
101	15200	**134**	500	**167**	108
102	567	**135**	59	**168**	250
103	550	**136**	17900	**169**	268
104	1487	**137**	300	**170**	30
105	800	**138**	9	**171**	200
106	700	**139**	1500	**172**	1050
107	75	**140**	18300	**173**	111
108	55	**141**	650	**174**	35
109	2700	**142**	19	**175**	10
110	20	**143**	350	**176**	30
111	60	**144**	15	**177**	85
112	550	**145**	300	**178**	6
113	1150	**146**	9	**179**	400
114	500	**147**	120	**180**	650
115	1536	**148**	45	**181**	20
116	1150	**149**	10800	**182**	63
117	11850	**150**	25	**183**	20
118	17500	**151**	9323	**184**	9
119	4800	**152**	4400	**185**	550
120	3200	**153**	55	**186**	20
121	1250	**154**	1367	**187**	22200
122	150	**155**	20	**188**	1067
123	2930	**156**	150	**189**	942

190	20	**223**	12	**256**	4000
191	48	**224**	700	**257**	3950
192	17750	**225**	350	**258**	78
193	160	**226**	417	**259**	25
194	93	**227**	800	**260**	200
195	14	**228**	100	**261**	75
196	700	**229**	29	**262**	200
197	100	**230**	2550	**263**	400
198	357	**231**	103	**264**	10
199	8650	**232**	989	**265**	83
200	25	**233**	850	**266**	1625
201	20	**234**	150	**267**	83
202	450	**235**	80	**268**	8
203	6	**236**	8	**269**	1600
204	7	**237**	70	**270**	54
205	14	**238**	650	**271**	629
206	187	**239**	52	**272**	271
207	321	**240**	141	**273**	2263
208	29	**241**	250	**274**	14
209	1900	**242**	200	**275**	30
210	22	**243**	200	**276**	1310
211	1319	**244**	17	**277**	627
212	10	**245**	1046	**278**	350
213	12	**246**	2000	**279**	2900
214	1572	**247**	400	**280**	250
215	386	**248**	119	**281**	18
216	65	**249**	1425	**282**	3675
217	41	**250**	549	**283**	900
218	24	**251**	325	**284**	286
219	1850	**252**	114	**285**	55
220	233	**253**	1068	**286**	2650
221	23	**254**	150	**287**	112
222	137	**255**	434	**288**	1100

289	555	**322**	348	**355**	104
290	15783	**323**	902	**356**	480
291	3250	**324**	4250	**357**	389
292	3	**325**	2250	**358**	8
293	35	**326**	7151	**359**	250
294	5	**327**	1700	**360**	1000
295	150	**328**	102	**361**	25
296	218	**329**	181	**362**	5
297	350	**330**	250	**363**	9250
298	7	**331**	35	**364**	900
299	1800	**332**	450	**365**	45
300	4	**333**	47	**366**	3250
301	95	**334**	53	**367**	7950
302	75	**335**	550	**368**	66
303	8	**336**	750	**369**	850
304	653	**337**	250	**370**	95
305	1354	**338**	18900	**371**	3
306	4	**339**	65	**372**	45
307	13300	**340**	29	**373**	1
308	127	**341**	95	**374**	3
309	550	**342**	55	**375**	2
310	475	**343**	30	**376**	247
311	70	**344**	68	**377**	20
312	115	**345**	800	**378**	24
313	1300	**346**	69	**379**	5
314	20	**347**	677	**380**	17
315	13	**348**	200	**381**	57
316	3100	**349**	150	**382**	184
317	2800	**350**	85	**383**	4
318	3	**351**	600	**384**	32
319	548	**352**	200	**385**	7
320	7	**353**	252	**386**	8
321	85	**354**	1664	**387**	57

388	28	**421**	9300	**454**	103
389	30	**422**	888	**455**	767
390	38	**423**	780	**456**	85
391	30	**424**	68	**457**	107
392	7	**425**	1232	**458**	169
393	7	**426**	436	**459**	211
394	70	**427**	665	**460**	20
395	25	**428**	478	**461**	6250
396	667	**429**	1036	**462**	75
397	3161	**430**	58	**463**	3114
398	3050	**431**	31	**464**	254
399	1600	**432**	7	**465**	1589
400	3950	**433**	1789	**466**	43
401	1050	**434**	35	**467**	47
402	300	**435**	250	**468**	350
403	1000	**436**	150	**469**	3350
404	1000	**437**	107	**470**	250
405	295	**438**	924	**471**	89
406	150	**439**	1250	**472**	255
407	1050	**440**	1050	**473**	463
408	1400	**441**	5625	**474**	95
409	25	**442**	850	**475**	350
410	15	**443**	4468	**476**	33
411	26	**444**	243	**477**	628
412	14	**445**	580	**478**	258
413	101	**446**	16	**479**	89
414	311	**447**	739	**480**	33
415	48	**448**	26	**481**	22
416	315	**449**	51	**482**	188
417	40	**450**	25	**483**	60
418	168	**451**	90	**484**	358
419	476	**452**	15	**485**	15
420	1150	**453**	13	**486**	2450

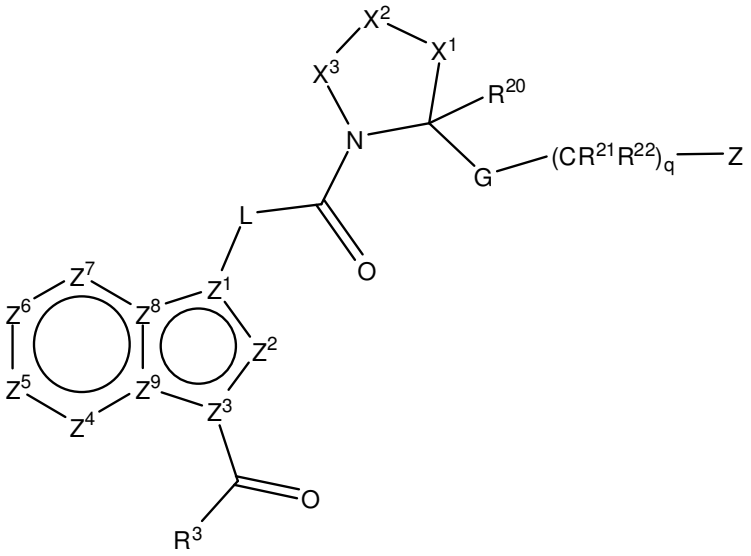
487	13	**520**	22	**553**	5297
488	250	**521**	37	**554**	44
489	124	**522**	415	**555**	2272
490	214	**523**	51	**556**	25
491	28	**524**	64	**557**	134
492	237	**525**	36	**558**	1986
493	108	**526**	54	**559**	15700
494	50	**527**	483	**560**	141
495	19	**528**	75	**561**	14
496	176	**529**	186	**562**	804
497	128	**530**	72	**563**	42
498	692	**531**	11	**564**	13
499	36	**532**	223	**565**	369
500	36	**533**	34	**566**	436
501	471	**534**	51	**567**	293
502	449	**535**	62	**568**	121
503	115	**536**	121	**569**	13
504	57	**537**	609	**570**	27
505	14	**538**	911	**571**	99
506	331	**539**	31	**572**	284
507	16	**540**	236	**573**	865
508	12	**541**	91	**574**	217
509	58	**542**	19	**575**	843
510	16	**543**	245	**576**	400
511	71	**544**	1110	**577**	71
512	411	**545**	113	**578**	50
513	193	**546**	10	**579**	39
514	95	**547**	38	**580**	252
515	268	**548**	363	**581**	60
516	8	**549**	69	**582**	134
517	1456	**550**	33	**583**	25
518	41	**551**	899	**584**	38
519	722	**552**	40	**585**	17

586	132	**619**	14	**652**	19
587	79	**620**	17	**653**	47
588	31	**621**	19	**654**	18
589	237	**622**	5595	**655**	91
590	10	**623**	24	**656**	358
591	109	**624**	26	**657**	78
592	115	**625**	19	**658**	24
593	56	**626**	36	**659**	25
594	85	**627**	16	**660**	16
595	41	**628**	38	**661**	10
596	95	**629**	17	**662**	13
597	14	**630**	36	**663**	36
598	14	**631**	11	**664**	24
599	46	**632**	18	**665**	58
600	14	**633**	55	**666**	6
601	110	**634**	53	**667**	16
602	227	**635**	18	**668**	19
603	1613	**636**	13	**669**	10
604	37	**637**	9	**670**	90
605	54	**638**	5	**671**	77
606	14	**639**	62	**672**	178
607	28	**640**	8	**673**	157
608	1835	**641**	32	**674**	75
609	1559	**642**	15	**675**	23
610	45	**643**	25	**676**	11
611	141	**644**	79	**677**	10
612	3433	**645**	132	**678**	40
613	215	**646**	12	**679**	134
614	245	**647**	16	**680**	16
615	42	**648**	17	**681**	19
616	123	**649**	441	**682**	12
617	28	**650**	22	**683**	48
618	39	**651**	21	**684**	27

685	5	**715**	27	**745**	5
686	30	**716**	46	**746**	7
687	98	**717**	31	**747**	13
688	10	**718**	24	**748**	4
689	156	**719**	13	**749**	4
690	34	**720**	140	**750**	34
691	68	**721**	98	**751**	81
692	3	**722**	20	**752**	95
693	6	**723**	90	**753**	66
694	17	**724**	61	**754**	5
695	15	**725**	18	**755**	17
696	101	**726**	169	**756**	7
697	3	**727**	9	**757**	3
698	29	**728**	8	**758**	64
699	118	**729**	62	**759**	9
700	6	**730**	143	**760**	12
701	15	**731**	53	**761**	70
702	10	**732**	44	**762**	5
703	10	**733**	25	**763**	14
704	23	**734**	4	**764**	4
705	21	**735**	3	**765**	211
706	45	**736**	18	**766**	216
707	88	**737**	36	**767**	346
708	54	**738**	93	**768**	146
709	144	**739**	23	**769**	378
710	52	**740**	13	**770**	9
711	71	**741**	5	**771**	8
712	38	**742**	37	**772**	7
713	260	**743**	5	**773**	28
714	300	**744**	4		

REIVINDICACIONES

1. Un compuesto de la fórmula I:



(I)

o una sal farmacéuticamente aceptable del mismo, en donde

Z^1 es C y L es un residuo divalente seleccionado del grupo que consta de –N(H)– y –C(H)(R^1)–, o

Z^1 es N y L es CH_2;

R^1 es hidrógeno, hidróxilo, o amino;

Z^2 es C(R^2) o N;

Z^3 es C o N,

Z^4 es C(R^4) o N;

Z^5 es C(R^5) o N, o un N- óxido del mismo;

Z^6 es C(R^6) o N, o un N- óxido del mismo;

Z^7 es C(R^7) o N, o un N- óxido del mismo;

Z^8 es C o N;

Z^9 es C o N;

en donde uno de Z^1, Z^3, Z^8 y Z^9 es N y tres de Z^1, Z^3, Z^8 y Z^9 son C;

en donde 0, 1, o 2 o 3 de Z^2, Z^4, Z^5, Z^6 y Z^7 son N;

R^2 es hidrógeno o C_1- C_6alquilo;

R^3 se selecciona del grupo que consta de hidrógeno, C_1- C_4alquilo, hidroxiC_1- C_4alquilo, C_1- C_4alcoxiC_1- C_4alquilo, haloC_1- C_4alquilo, amino o metilamino;

R^4 se selecciona del grupo que consta de hidrógeno, halógeno, y C_1- C_6alquilo;

R^5 y R^6 se seleccionan independientemente del grupo que consta de hidrógeno, halógeno, hidróxilo, NR^8R^9, ciano, CO_2H, $CONR^{10}R^{11}$ SO_2C_1- C_6alquilo, SO_2NH_2, $SO_2NR^{10}R^{11}$, C_1- C_6alcoxicarbonilo, - $C(NR^{10})NR^8R^9$, C_1- C_6alquilo, haloC_1- C_6alquilo, C_2- C_6alquenilo, C_1- C_6alcoxilo, haloC_1- C_6alcoxilo, y C_2- C_6alqueniloxilo, en donde cada alquilo, alquenilo, alcoxilo y alqueniloxilo es sustituido o no sustituido con hasta 4 sustituyentes independientemente seleccionados a partir de halógeno, hidróxilo, ciano, tetrazol, C_1- C_4alcoxilo, C_1- C_4haloalcoxilo, CO_2H, C_1- C_6alcoxicarbonilo, $C(O)NR^{10}R^{11}$, NR^8R^9, fenilo opcionalmente sustituido, heterociclo opcionalmente sustituido que tiene 4 a 7 átomos de anillo y 1, 2, o 3 heteroátomos de anillo seleccionados a partir de N, O o S, heteroarilo opcionalmente sustituido que tiene 5 o 6 átomos de anillo y 1, 2 o 3 heteroátomos de anillo seleccionados a partir de N, O o S, y en donde los sustituyentes opcionales de fenilo, heterociclo o heteroarilo se seleccionan a partir de halógeno, hidróxilo, C_1- C_4alquilo, C_1- C_4alcoxilo y CO_2H;

R^5 y $R^{6,}$ tomados en combinación con los átomos a los que están unidos, forman un ciclo que tiene 4 a 7 átomos de anillo y 0, 1 o 2 átomos N, O o S de anillo adicionales;

R^7 se selecciona del grupo que consta de hidrógeno, halógeno, C_1- C_6alquilo, C_1- C_6alcoxilo, haloC_1- C_6alquilo, haloC_1- C_6alcoxilo C_1- C_6alcoxicarbonilo, CO_2H y $C(O)NR^{10}R^{11}$;

R^8 y R^9 se seleccionan independientemente del grupo que consta de hidrógeno, y C_1- C_6alquilo, haloC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, hidroxiC_1- C_6alquilo, o NR^8R^9, tomados en combinación, forman un heterociclo que tiene 4 a 7 átomos de anillo y 0 o 1 átomos N, O o S de anillo adicionales, dicho heterociclo se sustituye por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de C_1- C_4alquilo, halógeno, hidróxilo, C_1- C_4alcoxilo;

R^{10} y R^{11}, son cada uno independientemente seleccionados del grupo que consta de hidrógeno y C_1- C_6alquilo, haloC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, o hidroxiC_1- C_6alquilo;

X^1 es $CR^{14}R^{15}$ o azufre;

X^2 es $CR^{16}R^{17}$, oxigeno, azufre, N(H) o N(C_1- C_6alquilo), en donde al menos uno entre X^1 y X^2 es carbono; o

X^1 y X^2, en combinación, forman una olefina de la fórmula $–C(R^{16})=C(H)-$ o $–C(R^{16})=C(C_1$- C_4alquilo)- , en donde el $C(R^{16})$ está fijado a X^3;

X^3 es $(CR^{18}R^{19})_m$ o N(H) en donde m es 0,1 o 2, en donde X^3 es $CR^{18}R^{19}$ o $(CR^{18}R^{19})_2$ cuando cualquiera X^1 o X^2 es azufre o X^2 es oxigeno; o

X^2 y X^3, tomados en combinación, son –N=C(H)– o –N=C(C_1- C_4alquil)– en los cuales el C(H) o C(C_1- C_4alquilo) está fijado a X^1;

R^{14} se selecciona del grupo que consta de hidrógeno, halógeno, hidróxilo, amino y C_1-C_6alquilo;

R^{15}se selecciona a partir del grupo que consta de hidrógeno, hidróxilo, halógeno, C_1-C_6alquilo, haloC_1- C_6alquilo, C_2- C_6alquenilo, C_2- C_6alquinilo, C_1- C_6alcoxilo, haloC_1-C_6alcoxilo, NR^8R^9, N(H)C(O)C_1- C_6alquilo, N(H)C(O)OC_1- C_6alquilo y OC(O)$NR^{10}R^{11}$ cada uno de los sustituyentes de alquilo, alcoxilo, alquenilo, y alquinilo pueden ser sustituidos por 0, 1, o 2 grupos independientemente seleccionados en cada ocurrencia a partir del grupo que consta de halógeno, hidróxilo, C_1- C_6alquilo, C_1- C_6alcoxilo, y NR^8R^9;

R^{16} es hidrógeno, halógeno, hidróxilo, azida, ciano, COOH, C_1- C_6alcoxicarbonilo, C_1-C_6alquilo, C_1- C_6alcoxilo, C_1- C_6haloalquilo, C_1- C_6haloalcoxilo, NR^8R^9, N(H)C(O)C_1-C_6alquilo, hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, o C_1- C_6alquilo sustituido por NR^8R^9, N(H)C(O)H o N(H)C(O)(C_1- C_4alquil);

R^{17} es hidrógeno, halógeno, hidróxilo, ciano, C_1- C_6alquilo, C_1- C_6alcoxilo, hidroxiC_1-C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, haloC_1- C_6alquilo, o C_1- C_6haloalcoxilo;

R^{18} se selecciona del grupo que consta de hidrógeno, fenilo y C_1- C_6alquilo, tal grupo alquilo es sustituido o no sustituido por hidróxilo, amino, azida, y NHC(O)C_1- C_6alquilo;

R^{19} y R^{20} son cada uno independientemente seleccionados a partir de hidrógeno y C_1-C_6alquilo; o

$CR^{16}R^{17}$, tomados en combinación forman un carbocilo espirocíclico de 3 a 6 miembros que se sustituye por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de halógeno y metilo; o

R^{16} y R^{17}, tomados en combinación, forman un metilideno exocíclico (=CH_2);

R^{15} y R^{16} tomados en combinación forman un anillo de epóxido o un sistema de anillo carbocíclico de 3 a 6 miembros cuyo anillo carbocíclico es sustituido por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de halógeno, metilo, etilo, hidroxiC_1-C_4alquilo, C_1- C_6alcoxiC_1- C_4alquilo, C_1- C_4alcoxicarbonilo, CO_2H, y C_1- C_4alquilo sustituido por NR^8R^9;

R^{16} y R^{18} o R^{17} y R^{19}, tomados en combinación, forman un sistema de anillo carbocíclico de 3 miembros fusionado que se sustituye por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de halógeno, metilo, etilo, hidroxiC_1-C_4alquilo, C_1- C_6alcoxiC_1- C_4alquilo, C_1- C_4alcoxicarbonilo, CO_2H, y C_1- C_4alquilo sustituido por NR^8R^9; o

R^{14} y R^{20} tomados en combinación forman un sistema de 3 anillos carbocíclicos fusionados;

R^{14} y R^{19} tomados en combinación forman un enlazador de alquileno de 1 a 3 carbonos;

R^{17} y R^{20} tomados en combinación forman un enlazador de alquileno de 1 a 3 carbonos;

G es un residuo divalente seleccionados a partir de C(O)- N(H), CH_2- N(H)–$S(O)_2$–, CH_2–N(H)–C(O), CH_2- N(H)- C(O)- O, CH_2N(H), CH_2- N(H)- C(O)- N(H), CH_2- N(H)- C(O)- N(Me), CH_2N(H)- $S(O)_2$- N(H)- , y CH_2N(H)- $S(O)_2$- N(Me)- , en donde el residuo más a la derecha está fijado a $–(CR^{21}R^{22})_q$;

q es 0, 1, 2, 3 o 4;

R^{21} se selecciona independientemente en cada ocurrencia a partir del grupo que consta de hidrógeno, hidróxilo, halógeno, C_1- C_6alquilo, haloC_1- C_6alquilo, cianoC_1- C_4alquilo, fenilo, CO_2H, C_1- C_6alcoxilo carbonilo, $C(O)NH_2$, hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, C_1- C_6alquilo sustituido por NR^8R^9, imidazoilC_1- C_6alquilo, heterocicloC_1- C_6alquilo, donde el heterociclo se selecciona a partir de azetidinilo, pirrolidinilo, piperidinilo, morfolinilo, 1- oxa- 6- aza- espiro[3.3]heptano, 2- oxa- 6- aza- espiro[3.3]heptano, piperazinilo, 1,6- diaza- espiro[3.3]heptano, y 2,6- diaza- espiro[3.3]heptano cada uno de los cuales es opcionalmente sustituido por 1 o 2 sustituyentes seleccionados a partir de flúor, hidróxilo, C_1- C_4alquilo o C_1- C_4alcoxilo;

R^{22} se selecciona independientemente en cada ocurrencia a partir de hidrógeno o C_1- C_6alquilo; o

Cuando q es 1, 2, 3 o 4, R^{21} y un sustituyente de R^{22}, tomados en combinación con los átomos de carbono a los que están unidos, forman un carbociclo de 3 a 6 miembros o heterociclo de 3 a 6 miembros que tiene un oxigeno o nitrógeno de anillo; o

cuando q es 2, 3 o 4, dos residuos R^{21} o R^{22}, localizados en átomos de carbono adyacentes, forman, junto con los átomos de carbono a los que están unidos, un carbociclo de 3 a 6 miembros; y

Z es C_1- C_6alquilo, C_1- C_6haloalquilo, fenilo, fenoxilo, naftilo, naftiloxilo, C_3- C_7cicloalquilo, indanilo, un heterociclo monocíclico o bicíclico saturado o parcialmente insaturado de 5, 6, 9 o 10 miembros que tiene 1, 2, o 3 heteroátomos de anillo seleccionados a partir de N, O, o S, o un heteroarilo o heteroariloxilo de 5 o 6 miembros, tal heteroarilo tiene 1 o 2 heteroátomos de anillo seleccionados a partir de N, O o S siempre que el anillo no tenga 2 átomos O o S, cada residuo es sustituido o no sustituido por 1, 2, 3, o 4 sustituyentes que se seleccionan independientemente del grupo que consta de C_1- C_6alquilo sustituido o no sustituido, C_3- C_7cicloalquilo, C_1- C_6haloalquilo, halógeno, SF_5, CN, hidróxilo, CO_2H,

tetrazolilo, $C(O)R^{25}$, $S(O)_2R^{26}$, C_1- C_6alcoxilo sustituido o no sustituido, haloC_1- C_6alcoxilo, fenoxilo, $NR^{23}R^{24}$, $CH_2NR^{23}R^{24}$, heteroarilo sustituido o no sustituido de 5 o 6 miembros y fenilo sustituido o no sustituido, tal fenilo y heteroarilo sustituido tiene 1 o 2 sustituyentes independientemente seleccionados del grupo que consta de ciano, halo, C_1- C_6alquilo o C_1- C_6haloalquilo, OH, COOH, COR^{25}, $S(O)_2R^{26}$, amino, y CH_2NH_2, y tal alquilo o alcoxilo sustituido tiene un sustituyente seleccionado a partir de hidróxilo, C_1- C_4alcoxilo, ciano, CO_2H, tetrazol o $NR^{23}R^{24}$;

R^{23} es hidrógeno o C_1- C_6alquilo;

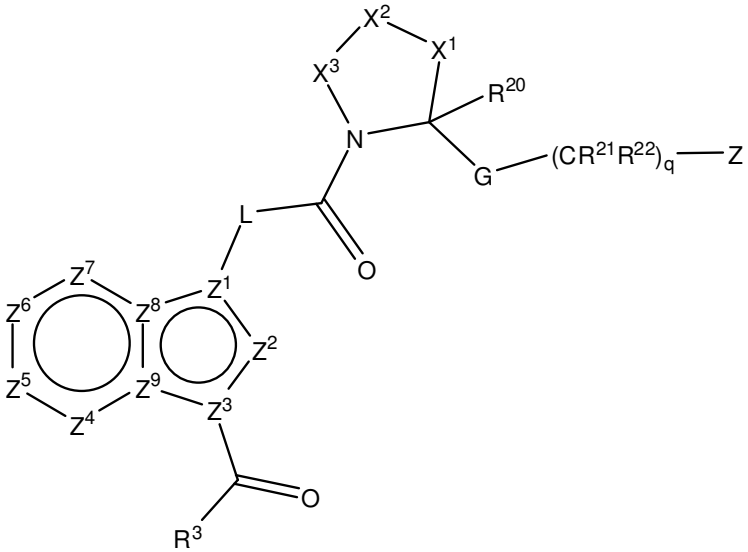
R^{24} es hidrógeno, C_1- C_6alquilo, hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, aminoC_1- C_6alquilo, mono- y di- C_1- C_6alquilaminoC_1- C_6alquilo; o

$NR^{23}R^{24}$, tomados en combinación forman un heterociclo de 4, 5 o 6 miembros que tiene 0 o 1 heteroátomos de anillo adicionales seleccionados del grupo que consta de N, O o S, y que se sustituye por 0, 1 o 2 sustituyentes independientemente seleccionados a partir de flúor, hidróxilo, C_1- C_4alquilo o C_1- C_4alcoxilo;

R^{25} se selecciona independientemente en cada ocurrencia a partir del grupo que consta de C_1- C_6alcoxilo y $NR^{23}R^{24}$; y

R^{26} se selecciona del grupo que consta de amino, hidróxilo, C_1- C_6alquilo, y, mono- y di- C_1- C_6alquilamino.

2. Un compuesto de la fórmula I:



(I)

o una sal farmacéuticamente aceptable del mismo, en donde

Z^1 es C y L es un residuo divalente seleccionado del grupo que consta de –N(H)– y –C(H)(R^1)–, o

Z^1 es N y L es CH_2;

R^1 es hidrógeno, hidróxilo, o amino;

Z^2 es C(R^2) o N;

Z^3 es C o N,

Z^4 es C(R^4) o N;

Z^5 es C(R^5) o N, o un N- óxido del mismo;

Z^6 es C(R^6) o N, o un N- óxido del mismo;

Z^7 es C(R^7) o N, o un N- óxido del mismo;

Z^8 es C o N;

Z^9 es C o N;

en donde uno de Z^1, Z^3, Z^8 y Z^9 es N y tres de Z^1, Z^3, Z^8 y Z^9 son C;

en donde 0, 1, o 2 o 3 de Z^2, Z^4, Z^5, Z^6 y Z^7 son N;

R^2 es hidrógeno o C_1- C_6alquilo;

R^3 se selecciona del grupo que consta de hidrógeno, C_1- C_4alquilo, hidroxiC_1- C_4alquilo, C_1- C_4alcoxiC_1- C_4alquilo, haloC_1- C_4alquilo, amino o metilamino;

R^4 se selecciona del grupo que consta de hidrógeno, halógeno, y C_1- C_6alquilo;

R^5 y R^6 se seleccionan independientemente del grupo que consta de hidrógeno, halógeno, hidróxilo, NR^8R^9, ciano, CO_2H, $CONR^{10}R^{11}$$SO_2C_1$- C_6alquilo, SO_2NH_2, $SO_2NR^{10}R^{11}$, C_1- C_6alcoxicarbonilo, - $C(NR^{10})NR^8R^9$, C_1- C_6alquilo, haloC_1- C_6alquilo, C_2- C_6alquenilo, C_1- C_6alcoxilo, haloC_1- C_6alcoxilo, y C_2- C_6alqueniloxilo, en donde cada alquilo, alquenilo, alcoxilo y alqueniloxilo es sustituido o no sustituido con hasta 4 sustituyentes independientemente seleccionados a partir de halógeno, hidróxilo, tetrazol, C_1- C_4alcoxilo, C_1- C_4haloalcoxilo, CO_2H, C_1- C_6alcoxicarbonilo, $C(O)NR^{10}R^{11}$, NR^8R^9, fenilo opcionalmente sustituido, heterociclo que tiene 4 a 7 átomos de anillo y 1, 2, o 3 heteroátomos de anillo seleccionados a partir de N, O o S, heteroarilo que tiene 5 o 6 átomos de anillo y 1 o 2 heteroátomos de anillo seleccionados a partir de N, O o S, y en donde sustituyentes opcionales de fenilo se seleccionan a partir de halógeno, hidróxilo, C_1- C_4alquilo, C_1- C_4alcoxilo y CO_2H;

R^5 y $R^{6,}$ tomados en combinación con los átomos a los que están unidos, forman un ciclo que tiene 4 a 7 átomos de anillo y 0, 1 o 2 átomos N, O o S de anillo adicionales;

R^7 se selecciona del grupo que consta de hidrógeno, halógeno, C_1- C_6alquilo, C_1- C_6alcoxilo, haloC- C_6alquilo, haloC- C_6alcoxilo C_1- C_6alcoxicarbonilo, CO_2H y $C(O)NR^{10}R^{11}$;

R^8 y R^9 se seleccionan independientemente del grupo que consta de hidrógeno, y C_1- C_6alquilo, haloC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, hidroxiC_1- C_6alquilo, o NR^8R^9, tomados en combinación, forman a heterociclo que tiene 4 a 7 átomos de anillo y 0 o 1 átomos N, O o S de anillo adicionales, dicho heterociclo se sustituye por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de C_1- C_4alquilo, halógeno, hidróxilo, C_1- C_4alcoxilo;

R^{10} y R^{11}, son cada uno independientemente seleccionados del grupo que consta de hidrógeno y C_1- C_6alquilo, haloC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, o hidroxiC_1- C_6alquilo;

X^1 es $CR^{14}R^{15}$ o azufre;

X^2 es $CR^{16}R^{17}$, oxigeno, azufre, N(H) o N(C_1- C_6alquil), en donde al menos uno entre X^1 y X^2 es carbono; o

X^1 y X^2, en combinación, forman una olefina de la fórmula –$C(R^{16})$=C(H)- o –$C(R^{16})$=C(C_1- C_4alquilo)- , en donde el $C(R^{16})$ está fijado a X^3;

X^3 es $(CR^{18}R^{19})_m$ o N(H)en donde m es 0,1 o 2, en donde X^3 es $CR^{18}R^{19}$ o $(CR^{18}R^{19})_2$ cuando cualquiera X^1 o X^2 es azufre o X^2 es oxigeno; o

X^2 y X^3, tomados en combinación, son –N=C(H)– o –N=C(C_1- C_4alquil)– en los cuales el C(H) o C(C_1- C_4alquil) está fijado a X^1;

R^{14} se selecciona del grupo que consta de hidrógeno, halógeno, hidróxilo, amino y C_1- C_6alquilo;

R^{15}se selecciona a partir del grupo que consta de hidrógeno, hidróxilo, halógeno, C_1- C_6alquilo, haloC_1- C_6alquilo, C_2- C_6alquenilo, C_2- C_6alquinilo, C_1- C_6alcoxilo, haloC_1- C_6alcoxilo, NR^8R^9, N(H)C(O)C_1- C_6alquilo, N(H)C(O)OC_1- C_6alquilo y OC(O)$NR^{10}R^{11}$ cada uno entre sustituyentes de alquilo, alcoxilo, alquenilo, y alquinilo pueden ser sustituidos por 0, 1, o 2 grupos independientemente seleccionados en cada ocurrencia a partir del grupo que consta de halógeno, hidróxilo, C_1- C_6alquilo, C_1- C_6alcoxilo, y NR^8R^9;

R^{16} es hidrógeno, halógeno, hidróxilo, azida, ciano, COOH, C_1- C_6alcoxicarbonilo, C_1- C_6alquilo, C_1- C_6alcoxilo, C_1- C_6haloalquilo, C_1- C_6haloalcoxilo, NR^8R^9, N(H)C(O)C_1- C_6alquilo, hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, o C_1- C_6alquilo sustituido por NR^8R^9, N(H)C(O)H o N(H)C(O)(C_1- C_4alquilo);

R^{17} es hidrógeno, halógeno, hidróxilo, ciano, C_1- C_6alquilo, C_1- C_6alcoxilo,hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, haloC_1- C_6alquilo, o C_1- C_6haloalcoxilo;

R^{18} se selecciona del grupo que consta de hidrógeno, fenilo y C_1- C_6alquilo, tal grupo alquilo es sustituido o no sustituido por hidróxilo, amino, azida, y NHC(O)C_1- C_6alquilo;

R^{19} y R^{20} son cada uno independientemente seleccionados a partir de hidrógeno y C_1- C_6alquilo; o

$CR^{16}R^{17}$, tomados en combinación forman un carbocilo espirocíclico de 3 a 6 miembros que se sustituye por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de halógeno y metilo; o

R^{16} y R^{17}, tomados en combinación, forman un metilideno exocíclico (=CH_2);

R^{15} y R^{16} tomados en combinación forman un anillo de epóxido o un sistema de anillo carbocíclico de 3 a 6 miembros cuyo anillo carbocíclico es sustituido por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de halógeno, metilo, etilo, hidroxiC_1- C_4alquilo, C_1- C_6alcoxiC_1- C_4alquilo, C_1- C_4alcoxicarbonilo, CO_2H, y C_1- C_4alquilo sustituido por NR^8R^9; o

R^{16} y R^{18}or R^{17} y R^{19}, tomados en combinación, forman un sistema de anillo carbocíclico de 3 miembros fusionados que se sustituye por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de halógeno, metilo, etilo, hidroxiC_1- C_4alquilo, C_1- C_6alcoxiC_1- C_4alquilo, C_1- C_4alcoxicarbonilo, CO_2H, y C_1- C_4alquilo sustituido por NR^8R^9; o

R^{14} y R^{20} tomados en combinación forman un sistema de 3 anillos carbocíclicos fusionados;

R^{14} y R^{19} tomados en combinación forman un enlazador de alquileno de 1 a 3 carbonos;

$R^{17}$and R^{20} tomados en combinación forman un enlazador de alquileno de 1 a 3 carbonos;

G es un residuo divalente seleccionado a partir de C(O)- N(H), CH_2- N(H)–$S(O)_2$–, CH_2–N(H)–C(O), CH_2- N(H)- C(O)- O, CH_2N(H), CH_2- N(H)- C(O)- N(H), CH_2- N(H)- C(O)- N(Me), CH_2N(H)- $S(O)_2$- N(H)- , y CH_2N(H)- $S(O)_2$- N(Me)- , en donde el residuo más a la derecha está fijado a –$(CR^{21}R^{22})_q$;

q es 0, 1, 2, 3 o 4;

R^{21} se selecciona independientemente en cada ocurrencia a partir del grupo que consta de hidrógeno, hidróxilo, halógeno, C_1- C_6alquilo, haloC_1- C_6alquilo, fenilo, CO_2H, C_1- C_6alcoxilo carbonilo, $C(O)NH_2$, hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, C_1- C_6alquilo sustituido por NR^8R^9,imidazoilC_1- C_6alquilo heterocicl$o C_1$- C_6alquilo, donde el heterociclo se selecciona a partir de azetidinilo, pirrolidinilo, piperidinilo, morfolinilo, 1- oxa- 6- aza- espiro[3.3]heptano, 2- oxa- 6- aza- espiro[3.3]heptano, piperazinilo, 1,6- diaza- espiro[3.3]heptano, y 2,6- diaza- espiro[3.3]heptano cada uno de los cuales se sustituye

opcionalmente por 1 o 2 sustituyentes seleccionados a partir de flúor, hidróxilo, C_1- C_4alquilo o C_1- C_4alcoxilo;

R^{22} se selecciona independientemente en cada ocurrencia a partir de hidrógeno o C_1- C_6alquilo; o

Cuando q es 1, 2, 3 o 4, R^{21} y un sustituyente de R^{22}, tomados en combinación con los átomos de carbono a los que están unidos, forman un carbociclo de 3 a 6 miembros o heterociclo de 3 a 6 miembros que tiene un oxigeno o nitrógeno de anillo; o

cuando q es 2, 3 o 4, dos residuos R^{21}o R^{22}, localizados en átomos de carbono adyacentes, forman, junto con los átomos de carbono a los que están unidos, un carbociclo de 3 a 6 miembros; y

Z es C_1- C_6alquilo, C_1- C_6haloalquilo, fenilo, fenoxilo, naftilo, naftiloxilo, C_3- C_7cicloalquilo, indanilo, un heterociclo monocíclico o bicíclico saturado o parcialmente insaturado de 5, 6, 9 o 10 miembros que tiene 1, 2, o 3 heteroátomos de anillo seleccionados a partir de N, O, o S, o un heteroarilo o heteroariloxilo de 5 o 6 miembros, tal heteroarilo tiene 1 o 2 heteroátomos de anillo seleccionados a partir de N, O o S siempre que el anillo no tenga 2 átomos O o S, cada residuo es sustituido o no sustituido por 1, 2, 3, o 4 sustituyentes que se seleccionan independientemente del grupo que consta de C_1- C_6alquilo sustituido o no sustituido, C_1- C_6haloalquilo, halógeno, CN, hidróxilo, CO_2H, tetrazolilo, $C(O)R^{25}$, $S(O)_2R^{26}$, C_1- C_6alcoxilo sustituido o no sustituido, haloC_1- C_6alcoxilo, fenoxilo, $NR^{23}R^{24}$, $CH_2NR^{23}R^{24}$, heteroarilo de 5 o 6 miembros y fenilo sustituido o no sustituido, tal fenilo sustituido tiene1 o 2 sustituyentes independientemente seleccionados del grupo que consta de ciano, halo, C_1- C_6alquilo o C_1- C_6haloalquilo, OH, COOH, COR^{25}, $S(O)_2R^{26}$, amino, y CH_2NH_2, y tal alquilo o alcoxilo sustituido tiene un sustituyente seleccionado a partir de hidróxilo, C_1- C_4alcoxilo, ciano, CO_2H, tetrazol o $NR^{23}R^{24}$;

R^{23} es hidrógeno o C_1- C_6alquilo;

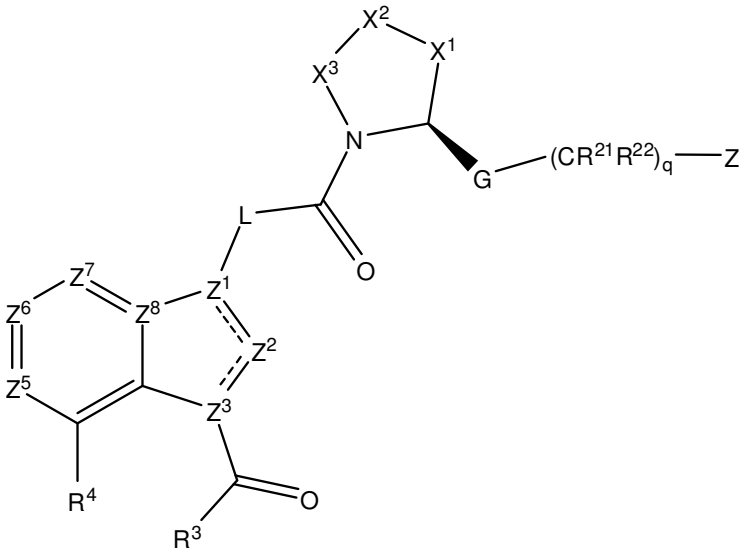
R^{24} es hidrógeno, C_1- C_6alquilo, hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, aminoC_1- C_6alquilo, mono- y di- C_1- C_6alquilaminoC_1- C_6alquilo; o

$NR^{23}R^{24}$, tomados en combinación forman un heterociclo de 4, 5 o 6 miembros que tiene 0 o 1 heteroátomos de anillo adicionales seleccionados del grupo que consta de N, O o S, y que se sustituye por 0, 1 o 2 sustituyentes independientemente seleccionados a partir de flúor, hidróxilo, C_1- C_4alquilo o C_1- C_4alcoxilo;

R^{25} se selecciona independientemente en cada ocurrencia a partir del grupo que consta de C_1- C_6alcoxilo y $NR^{23}R^{24}$; y

R^{26} se selecciona del grupo que consta de amino, hidróxilo, C_1- C_6alquilo, y, mono- y di- C_1- C_6alquilamino.

3. El compuesto de la reivindicacion 1 o reivindicación 2, o una sal del mismo, que se representa por la fórmula (II)



(II)

en donde:

Z^2 es CH o N;

X^1 es CHR^{15} o S;

X^2 es $CR^{16}R^{17}$ o S, en donde al menos uno entre X^1 y X^2 no es azufre;

X^3 es $CR^{18}R^{19}$or N(H);

R^{15}se selecciona a partir del grupo que consta de hidrógeno, hidróxilo, halógeno, C_1- C_6alquilo, haloC_1- C_6alquilo, C_1- C_6alcoxilo, haloC_1- C_6alcoxilo, NR^8R^9,N(H)C(O)C_1- C_4alquilo, N(H)C(O)OC_1- C_4alquilo y OC(O)$NR^{10}R^{11}$, cada alquilo y alcoxilo pueden ser sustituidos por 0, 1, o 2 grupos independientemente seleccionados en cada ocurrencia a partir del grupo que consta de hidróxilo, C_1- C_6alquilo, C_1- C_6alcoxilo, y NR^8R^9;

R^{16} es hidrógeno, halógeno, hidróxilo, amino, ciano, C_1- C_4alquilo, C_1- C_4alcoxilo, C_1- C_4haloalquilo, C_1- C_4haloalcoxilo, heterocicloC_0- C_4alquilo, NR^8R^9, N(H)C(O)C_1- C_4alquilo, hidroxiC_1- C_4alquilo, C_1- C_4alcoxiC_1- C_4alquilo o C_1- C_4alquilo sustituido por NR^8R^9;

R^{17} es hidrógeno, halógeno, hidróxilo, C_1- C_4alquilo, hidroxiC_1- C_4alquilo o C_1- C_2alcoxiC_1- C_4alquilo;

R^{18} se selecciona del grupo que consta de hidrógeno, fenilo y C_1- C_6alquilo, tal grupo alquilo es sustituido o no sustituido por hidróxilo, amino, NHC(O)C_1- C_6alquilo, amida o mono- o di- C_1- C_4alquil- amida;

R^{19} es hidrógeno; o

$CR^{16}R^{17}$, tomados en combinación, forman un carbocilo espirocíclico de 3 a 6 miembros; o

R^{15} y R^{16}, tomados en combinación, forman un anillo de ciclopropilo que se sustituye por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de halógeno, metilo, etilo, hidroximetilo, hidroxietilo, metoximetilo; o

R^{17} y R^{19} tomados en combinación forman un anillo de ciclopropilo.

4. El compuesto de cualquiera de las reivindicaciones 1- 3, en los que X^1 es CHR^{15}; y R^{15} es hidrógeno, flúor, hidróxilo, amino, C_1- C_4alquilo, C_1- C_6alcoxilo, OCH_2CH_2OMe, o C_2- C_4alcoxilo sustituido por NR^8R^9;

X^2 es $CR^{16}R^{17}$;

R^{16} es hidrógeno, halógeno, hidróxilo, C_1- C_4alquilo, C_1- C_4alcoxilo, C_1- C_4haloalquilo, C_1- C_4haloalcoxilo, NR^8R^9, hidroxiC_1- C_4alquilo, C_1- C_4alcoxiC_1- C_4alquilo, C_1- C_4alquilo sustituido por NR^8R^9 o C_2- C_4alcoxilo sustituido por NR^8R^9;

R^{17} es hidrógeno, halógeno, hidroxi o C_1- C_4alquilo; o

R^{15} y R^{16} tomados en combinación forman un anillo de ciclopropilo; o

R^{17} y R^{19} tomados en combinación forman un anillo de ciclopropilo.

5. El compuesto de cualquiera de las reivindicaciones 1- 3, en lo que

X^1 es S; y X^2 y X^3 son CH_2; o

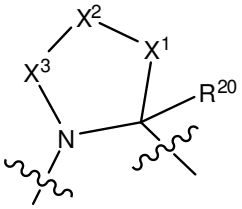
X^1 es CHR^{15}, en donde R^{15} es hidrógeno, flúor, metilo, hidróxilo, metoxilo, etoxilo, metoxietoxilo, C_2- C_4alcoxilo sustituido por NR^8R^9or amino; X^3 es CH_2; y X^2 es $CR^{16}R^{17}$, en donde R^{16} es flúor, amino, hidroximetilo, metoximetilo, aminometilo o metilo y R^{17} es hidrógeno o flúor; o

X^1 es CHR^{15}, X^2 es $CR^{16}R^{17}$, y X^3 es CHR^{19}, en donde R^{17} y R^{19}, tomados en combinación forman un anillo de ciclopropilo,y R^{16} es hidrógeno, hidroximetilo, o metoximetilo, y R^{15} es hidrógeno; o

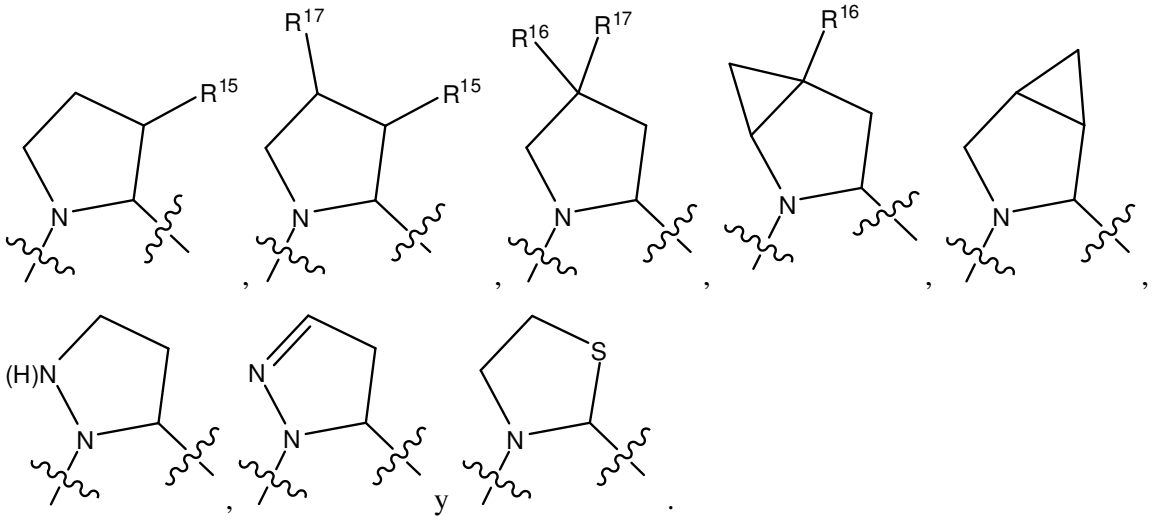
X^1 es CHR^{15}, X^2 es $CR^{16}R^{17}$, y X^3 es CHR^{19}, en donde R^{15} y R^{16}, tomados en combinación forman un anillo de ciclopropilo, R^{17} y R^{19} son hidrógeno; o

X^1 y X^2 son CH_2, y X^3 es N(H).

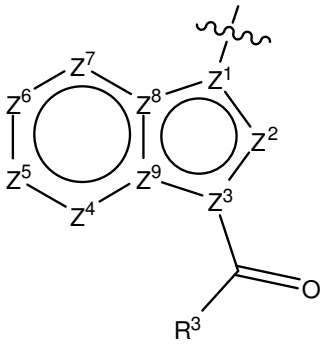
6. El compuesto de cualquiera de las reivindicaciones 1- 3, en donde el anillo heterocíclico de la fórmula:



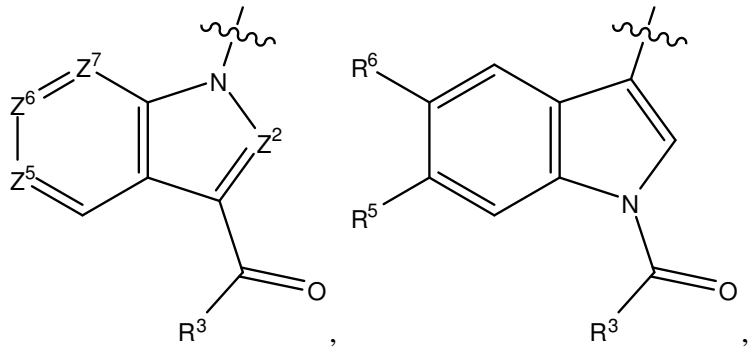
se selecciona del grupo que consta de:

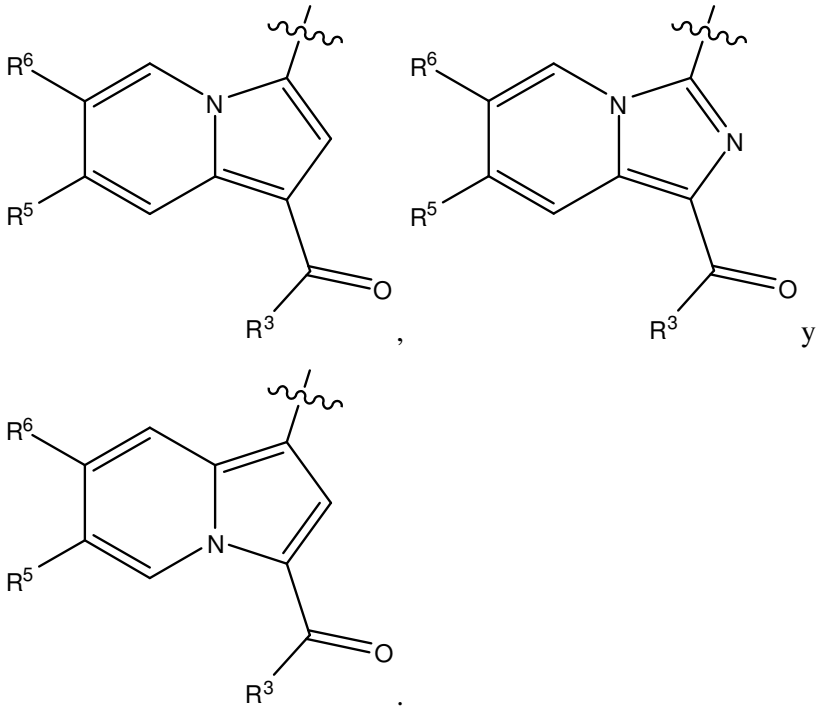


7. El compuesto de la reivindicación 1 o 2, en donde el anillo bicíclico de la fórmula:



se selecciona del grupo que consta de:





8. El compuesto de cualquiera de las reivindicaciones anteriores en las que L es –N(H)– o –CH_2–.

9. El compuesto de cualquiera de las reivindicaciones anteriores en las que G es –C(O)-N(H)–.

10. El compuesto de cualquiera de las reivindicaciones anteriores en las que q es 0 o 1;

R^{21} se selecciona del grupo que consta de hidrógeno, C_1- C_6alquilo, hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo y C_1- C_6alquilo sustituido por NR^8R^9;

R^{22} es hidrógeno; o

$CR^{21}R^{22}$, tomados en combinación, forman un anillo de ciclopropilo;

Z es fenilo, piridilo, oxalilo, isoxalilo, tiazolilo, pirazolilo, tienilo, cada uno de los cuales es sustituido o no sustituido por 1, 2 o 3 sustituyentes, cada uno de los cuales se selecciona independientemente del grupo que consta de:
halógeno, hidróxilo, C_1- C_4alquilo, C_1- C_4alcoxilo, haloC_1- C_4alquilo, haloC_1- C_4alcoxilo, $NR^{23}R^{24}$, CO_2H, $C(O)NR^{23}R^{24}$, CO_2(C_1- C_4alquil), tetrazol, piperidinilo, piperazinilo, morfolino, y alquilo sustituido por C_1- C_4alcoxilo o $NR^{23}R^{24}$.

11. El compuesto de cualquiera de las reivindicaciones anteriores en las que q es 0 o 1;

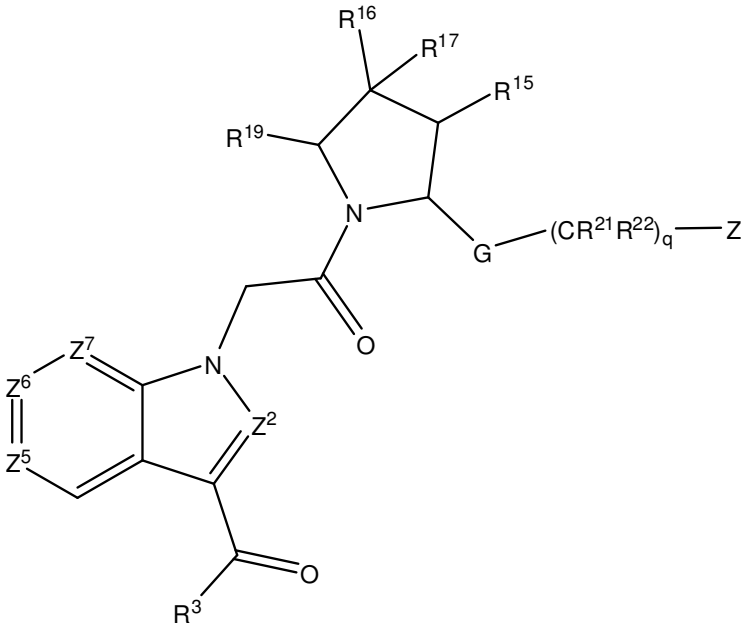
R^{21} se selecciona del grupo que consta de hidrógeno, C_1- C_6alquilo, hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, aminoC_1- C_6alquilo, y mono- y di- C_1- C_4alquilaminoC_1- C_6alquilo, en donde el residuo de alquilo es sustituido por 0 o 1 heterociclos que tiene 4, 5 o 6 átomos de anillo, un átomo de nitrógeno de anillo y 0 o 1 heteroátomos de anillo adicionales seleccionados a partir de N, O o S, tal heterociclo es sustituido por 0 o 1 sustituyentes seleccionados a partir de flúor o metoxilo;

R^{22} es hidrógeno; o

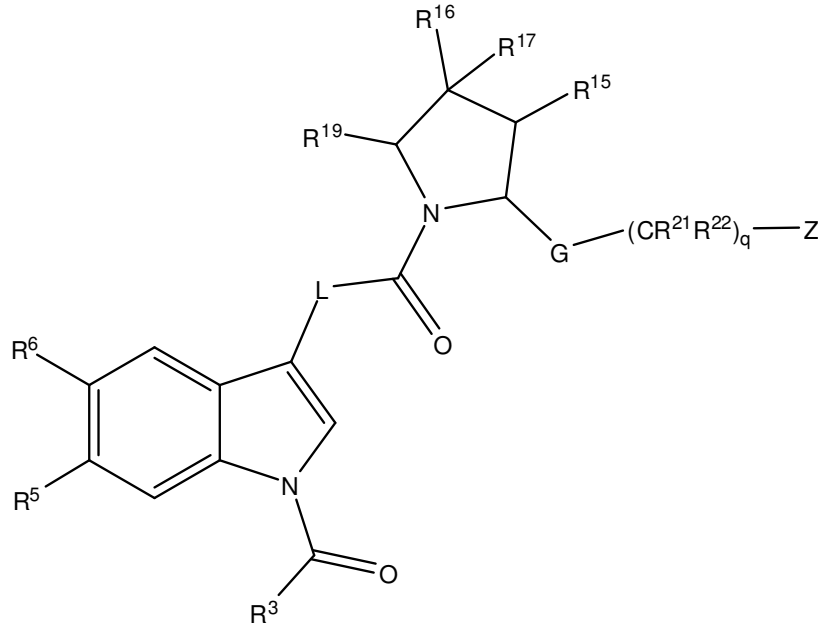
$CR^{21}R^{22}$, tomados en combinación, forman un anillo de ciclopropilo; y

Z es fenilo que es sustituido o no sustituido por 1, 2, o 3 sustituyentes, cada uno de los cuales se selecciona independientemente del grupo que consta de halógeno, hidróxilo, C_1- C_4alquilo, C_1- C_4alcoxilo, haloC_1- C_4alquilo, haloC_1- C_4alcoxilo, CO_2H, tetrazol,heterociclo, $C(O)NH_2$, $CO_2(C_1$- C_4alquil), amino, y mono- y di- C_1- C_4alquilamino, en donde cada residuo N- alquilo es sustituido por 0 o 1 residuos seleccionados del grupo que consta de hidróxilo, C_1- C_4alcoxilo, C_1- C_4alcoxilo, amino, o mono- o di- C_1- C_2alquilamino y cada heterociclo se selecciona a partir de heterociclos de 5 o 6 miembros que tiene 1 o 2 heteroátomos de anillo seleccionados a partir de N, O o S y dicho heterociclo se sustituye por 0 o 1 sustituyentes seleccionados a partir de halógeno, C_1- C_4alquilo o C_1- C_4alcoxilo.

12. El compuesto de cualquiera de las reivindicaciones 1- 3, en las cuales el compuesto se representa por una de las fórmulas (III), (IV) o (V):

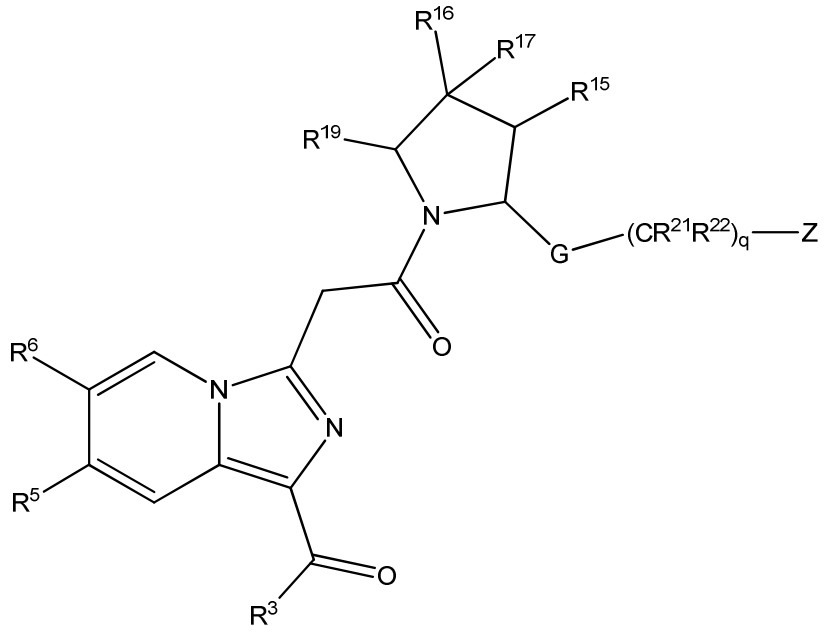


(III)



(IV)

o



(V)

en donde

Z^2 es CH o N;

Z^5 es CR^5 o N;

Z^6 es CR^6 o N;

Z^7 es CH, $C(CH_3)$ o N, en donde 0 o 1 o 2 de Z^5, Z^6 y Z^7 es N;

R^3 es hidrógeno, metilo, etilo, iPr, amino, hidroximetilo, CH2OMe, o mono- , di- y triflúormetilo, NHMe;

R^5 es hidrógeno, halógeno, C_1- C_4alquilo, C_1- C_4alcoxilo, C_2- C_4alquenilo, C_2- C_4alqueniloxilo, hidróxilo, CO_2H, tetrazol , C_1- C_4alcoxicarbonilo, ciano, en donde cada grupo alquilo o alcoxilo es sustituido o no sustituido por hasta 5 átomos de halógeno y por 0 o 1 sustituyentes adicionales seleccionados del grupo que consta de hidróxilo, tetrazol,C_1- C_4alcoxilo, CO_2H, C_1- C_4alcoxicarbonilo, fenilo opcionalmente sustituido, piridilo y pirimidinilo, y en donde el fenilo es sustituido o no sustituido por 1 o 2 sustituyentes independientemente seleccionados a partir de halógeno, hidróxilo, metilo, metoxi y CO_2H;

R^6 es hidrógeno, halógeno, C_1- C_4alquilo, C_1- C_4alcoxilo, C_2- C_4alquenilo, C_2- C_4alqueniloxilo, hidróxilo, CO_2H, C_1- C_4alcoxicarbonilo, ciano, en donde cada grupo alquilo o alcoxilo es sustituido o no sustituido por hasta 5 átomos de halógeno y por 0 o 1 sustituyentes adicionales seleccionados del grupo que consta de hidróxilo, $NR^{10}R^{11}$, tetrazol, ciano, imidazolilo, C_1- C_4alcoxilo, CO_2H, C_1- C_4alcoxicarbonilo, fenilo opcionalmente sustituido, pirrolilo, morfolino, piperidino, piperazino, y piridilo, y en donde el fenilo es sustituido o no sustituido por 1 o 2 sustituyentes independientemente seleccionados a partir de halógeno, hidróxilo, metilo, metoxilo, mono- y dimetilo amino, y CO_2H;

L es CH_2 o NH ;

R^{15} es hidrógeno, flúor, metilo, hidróxilo, metoxilo, etoxilo y OCH_2CH_2OMe, $OCH_2CH_2N(CH_3)_2$, amino o OCH_2CH_2pirrolilo

R^{16} es hidrógeno, flúor, metilo, amino, hidroximetilo, metoximetilo, o aminometilo;

R^{17} es hidrógeno, flúor o metilo;

R^{19} es hidrógeno o R^{19} y R^{17}, tomados en combinación, forman un anillo de ciclopropilo; o

R^{15} y R^{16}, tomados en combinación, forman un anillo de ciclopropilo;

G es - C(O)N(H)- ; y

q es 0, 1, o 2;

R^{21} es hidrógeno, metilo, o etilo, tal metilo y etilo son sustituidos o no sustituidos por hidróxilo, metoxilo, amino, mono- o di- metilamino, morfolinometilo, azetidinometilo opcionalmente sustituido, tal anillo de azetidino es sustituido por 0 o 1 flúor o metoxilo; o

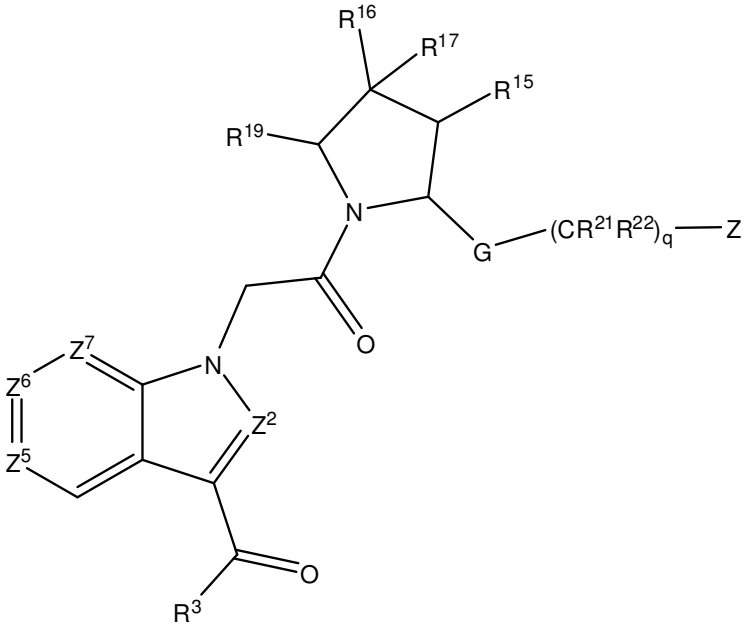
R^{22} es hidrógeno;

$CR^{21}R^{22}$, tomados en combinación, forman un anillo de ciclopropano; o

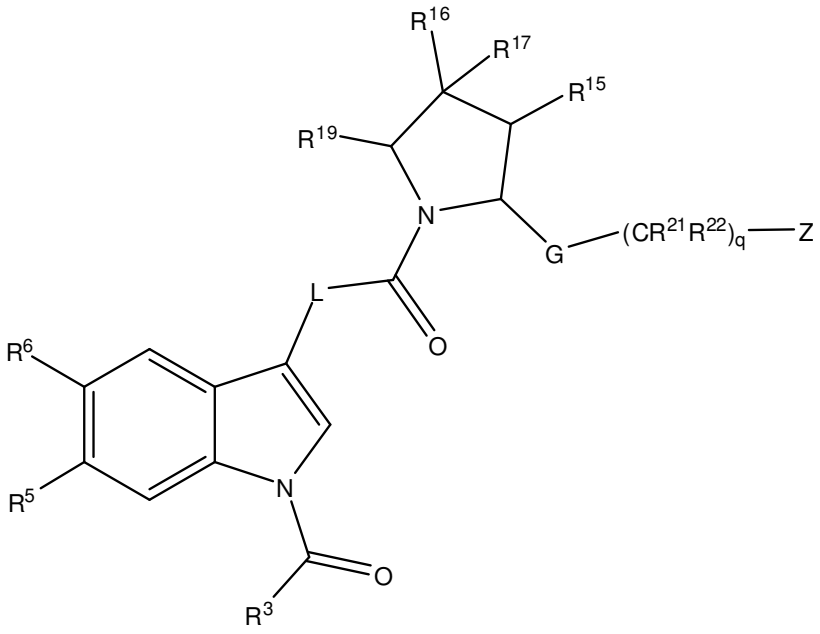
cuando q es 2, $CR^{21}R^{22}CR^{21}R^{22}$, tomados en combinación forman a anillo cis- o trans de ciclopropano;

Z es fenilo, piridilo, o tienilo, cada uno de los cuales es sustituido o no sustituido por 1, 2, o 3 residuos seleccionados independientemente en cada ocurrencia a partir del grupo que consta de halógeno, metilo, metoxilo, hidróxilo, trifluorometilo, trifluorometoxilo, CO_2H, tetrazol, y $NR^{23}R^{24}$.

13. El compuesto de la reivindicación 1, en la cual el compuesto se representa por una de las fórmulas (IIIb) o (IVb):



(IIIb)



(IVb)

en donde

Z^2 es CH o N;

Z^5 es CR^5 o N;

Z^6 es CR^6 o N; o un N- óxido del mismo

Z^7 es CH, $C(CH_3)$ o N, en donde 0 o 1 o 2 de Z^5, Z^6 y Z^7 es N;

R^3 es hidrógeno, metilo, etilo, iPr, amino, hidroximetilo, CH2OMe, o mono- , di- y trifluorometilo, NHMe;

R^5 es hidrógeno, halógeno, C_1- C_4alquilo, C_1- C_4alcoxilo, C_2- C_4alquenilo, C_2- C_4alqueniloxilo, hidróxilo, CO_2H, tetrazol , C_1- C_4alcoxicarbonilo, ciano, en donde cada grupo alquilo o alcoxilo es sustituido o no sustituido con hasta 5 átomos de halógeno y con 0 o 1 sustituyentes adicionales seleccionados del grupo que consta de hidróxilo, ciano, tetrazol, C_1- C_4alcoxilo, CO_2H, C_1- C_4alcoxicarbonilo, tetrahidrofuranilo, fenilo opcionalmente sustituido, piridilo y pirimidinilo, y en donde el fenilo es sustituido o no sustituido por 1 o 2 sustituyentes independientemente seleccionados a partir de halógeno, hidróxilo, metilo, metoxi y CO_2H;

R^6 es hidrógeno, halógeno, C_1- C_4alquilo, C_1- C_4alcoxilo, C_2- C_4alquenilo, C_2- C_4alqueniloxilo, hidróxilo, CO_2H, C_1- C_4alcoxicarbonilo, ciano, en donde cada grupo alquilo o alcoxilo es sustituido o no sustituido con hasta 5 átomos de halógeno y con 0 o 1 sustituyentes adicionales seleccionados del grupo que consta de hidróxilo, $NR^{10}R^{11}$, tetrazol, ciano, imidazolilo, C_1- C_4alcoxilo, CO_2H, C_1- C_4alcoxicarbonilo, fenilo opcionalmente sustituido, pirrolilo, morfolino, piperidino, piperazino, y piridilo, y en donde el fenilo es sustituido o no sustituido por 1 o 2 sustituyentes independientemente seleccionados a partir de halógeno, hidróxilo, metilo, metoxilo, mono- y dimetilo amino, y CO_2H;

L es CH_2 o NH ;

R^{15} es hidrógeno, flúor, metilo, hidróxilo, metoxilo, etoxilo y OCH_2CH_2OMe, $OCH_2CH_2N(CH_3)_2$, amino o OCH_2CH_2pirrolilo

R^{16} es hidrógeno, flúor, metilo, amino, hidroximetilo, metoximetilo, o aminometilo;

R^{17} es hidrógeno, flúor o metilo;

R^{19} es hidrógeno o R^{19} y R^{17}, tomados en combinación, forman un anillo de ciclopropilo; o

R^{15} y R^{16}, tomados en combinación, forman un anillo de ciclopropilo;

G es - C(O)N(H)- ; y

q es 0 o 1;

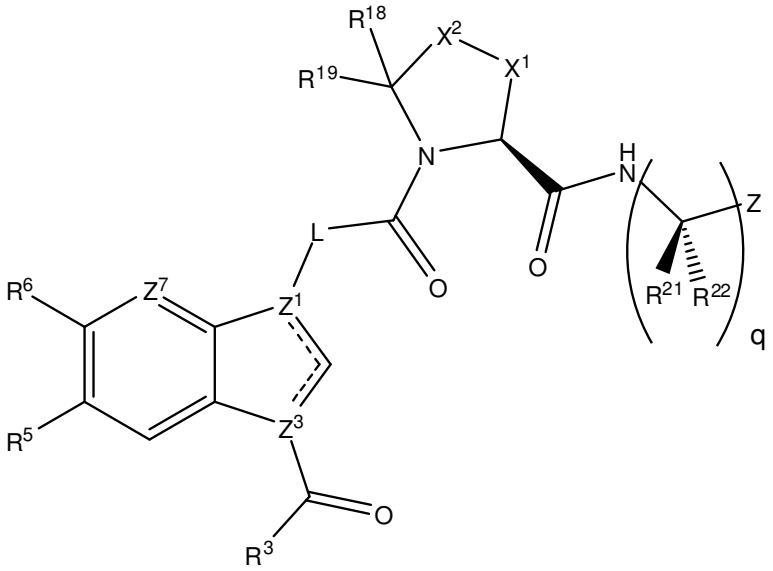
R^{21} es hidrógeno, metilo, o etilo, tal metilo y etilo son sustituidos o no sustituidos por hidróxilo, metoxilo, ciano, amino, mono- o di- metilamino, morfolinometilo, azetidinometilo opcionalmente sustituido, tal anillo de azetidino es sustituido por 0 o 1 flúor o metoxilo; o

R^{22} es hidrógeno;

$CR^{21}R^{22}$, tomados en combinación, forman un anillo de ciclopropano;

Z es fenilo, piridilo, pirazinilo o tienilo, cada uno de los cuales es sustituido o no sustituido por 1, 2, o 3 residuos seleccionados independientemente en cada ocurrencia del grupo que consta de halógeno, metilo, etilo, isopropilo, ciclopropilo, metoxilo, hidróxilo, trifluorometilo, di o trifluorometoxilo, SF_5, CO_2H, tetrazol, y $NR^{23}R^{24}$, fenilo sustituido o no sustituido y piridinilo sustituido o no sustituido, tal fenilo y piridinilo susituido tiene 1 o 2 sustituyentes independientemente seleccionados del grupo que consta de halógeno y metilo.

14. El compuesto de cualquiera de las reivindicaciones 1- 3, o una sal del mismo, que se representa por la fórmula (VI):



(VI)

en donde

q es 0, 1 o 2;

R^{21} es hidrógeno;

R^{22} es hidrógeno, metilo, o etilo, tal metilo y etilo son sustituidos o no sustituidos por hidróxilo, metoxilo, amino, o mono- o di- metilo amino; o

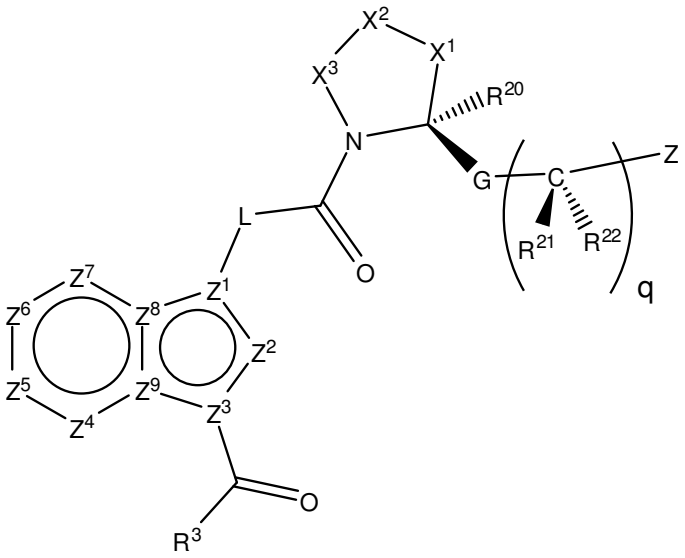
$CR^{21}R^{22}$, tomados en combinación, forman un anillo de ciclopropano;

cuando q es 2, $CR^{21}R^{22}CR^{21}R^{22}$, tomados en combinación forman un anillo cis- o trans de ciclopropano;

Z es fenilo que es sustituido o no sustituido por 1, 2, o 3 residuos seleccionados del grupo que consta de flúor, cloro, bromo, metilo, triflúormetilo, metoxilo, triflúormetoxilo, $NR^{23}R^{24}$, tetrazol o CO_2H; o

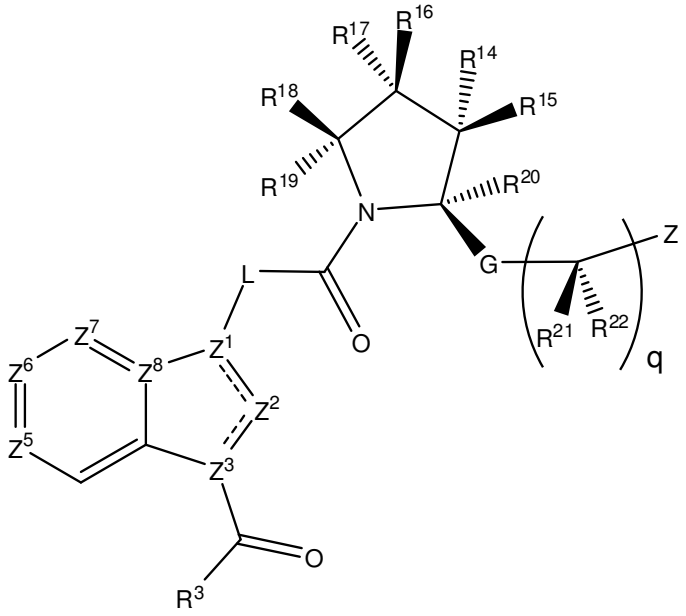
Z es piridilo o tienilo, cada uno de los cuales es sustituido o no sustituido por 1 o 2 sustituyentes seleccionado del grupo que consta de flúor, cloro, bromo, metilo, triflúormetilo, metoxilo, o trifluorometoxilo.

15. El compuesto de la reivindicación 1 o reivindicación 2, o una sal del mismo, que se representa por la fórmula (VI):



(VI).

16. Un compuesto que se representa por la fórmula



(VII): (VII),

o una sal farmacéuticamente aceptable del mismo, en donde

L es un residuo divalente seleccionado del grupo que consta de –N(H)– y –C(H)(R^1)–,

R^1 es hidrógeno, hidróxilo, o amino;

Z^1 es C o N;

Z^2 es C(H) o N;

Z^3 es C o N,

Z^5 es C(R^5), N o un N óxido del mismo;

Z^6 es C(R^6), N o un N óxido del mismo;

Z^7 es C(R^7), N o un N óxido del mismo;

Z^8 es C o N

en donde uno de Z^1 y Z^3 es N y el otro es C;

en donde 0, 1, 2 o 3 de Z^2, Z^5, Z^6, Z^7y Z^8 son N;

R^3 se selecciona del grupo que consta de hidrógeno, C_1- C_4alquilo, hidroxiC_1- C_4alquilo, C_1- C_4alcoxiC_1- C_4alquilo, haloC_1- C_4alquilo, amino o metilamino;

R^5 y R^6 se seleccionan independientemente del grupo que consta de hidrógeno, halógeno, hidróxilo, NR^8R^9, ciano, CO_2H, $CONR^{10}R^{11}$ SO_2C_1- C_6alquilo, y $SO_2NR^{10}R^{11}$, C_1- C_6alcoxicarbonilo, $C(NR^8)NR^8R^9$, C_1- C_6alquilo, haloC_1- C_6alquilo, C_2- C_6alquenilo, C_1-

C_6alcoxilo, haloC_1- C_6alcoxilo, C_2- C_6alqueniloxilo, en donde cada alquilo, alquenilo, alcoxilo y alqueniloxilo es sustituido o no sustituido con hasta 4 sustituyentes independientemente seleccionados a partir de halógeno, hidróxilo, tetrazol, C_1- C_4alcoxilo, C_1- C_4haloalcoxilo, CO_2H, C_1- C_6alcoxicarbonilo, $C(O)NR^{10}R^{11}$, NR^8R^9 fenilo opcionalmente sustituido, heterociclo que tiene 4 a 7 átomos de anillo y 1, 2, o 3 heteroátomos de anillo seleccionados a partir de N, O o S, heteroarilo que tiene 5 o 6 átomos de anillo y 1 o 2 heteroátomos de anillo seleccionados a partir de N, O o S, y en donde sustituyentes opcionales de fenilo se seleccionan a partir de halógeno, hidróxilo, C_1- C_4alquilo, C_1- C_4alcoxilo y CO_2H;

R^5 y $R^{6,}$ tomados en combinación con los átomos a los que están unidos, forman un ciclo que tiene 4 a 7 átomos de anillo y 0 o 1 átomos cíclicos de N, O o S adicionales;

R^7 se selecciona del grupo que consta de hidrógeno, halógeno, C_1- C_6alquilo, C_1- C_6alcoxilo, haloC- C_6alquilo, haloC- C_6alcoxilo C_1- C_6alcoxicarbonilo, CO_2H y $C(O)NR^{10}R^{11}$;

R^8 y R^9 se seleccionan independientemente del grupo que consta de hidrógeno, y C_1- C_6alquilo, haloC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, hidroxiC_1- C_6alquilo, o NR^8R^9, tomados en combinación, forman un heterociclo que tiene 4 a 7 átomos de anillo y 0 o 1 átomos N, O o S de anillo adicionales, dicho heterociclo se sustituye por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de C_1- C_4alquilo, halógeno, hidróxilo, C_1- C_4alcoxilo;

R^8 y R^9 se seleccionan independientemente del grupo que consta de hidrógeno, y C_1- C_6alquilo, haloC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, hidroxiC_1- C_6alquilo, o NR^8R^9, tomados en combinación, forman un heterociclo que tiene 4 a 7 átomos de anillo y 0 o 1 átomos N, O o S de anillo adicionales, dicho heterociclo se sustituye por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de C_1- C_4alquilo, halógeno, hidróxilo, C_1- C_4alcoxilo;

R^{10} y R^{11}, son cada uno independientemente seleccionados del grupo que consta de hidrógeno y C_1- C_6alquilo, haloC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, o hidroxiC_1- C_6alquilo;

R^{14} se selecciona del grupo que consta de hidrógeno, halógeno, hidróxilo, amino y C_1- C_6alquilo;

R^{15}se selecciona a partir del grupo que consta de hidrógeno, hidróxilo, halógeno, C_1- C_6alquilo, haloC_1- C_6alquilo, C_2- C_6alquenilo, C_2- C_6alquinilo, C_1- C_6alcoxilo, haloC_1- C_6alcoxilo, NR^8R^9, N(H)C(O)C_1- C_6alquilo, N(H)C(O)OC_1- C_6alquilo y $OC(O)NR^{10}R^{11}$ cada uno de los sustituyentes de alquilo, alcoxilo, alquenilo, y alquinilo pueden ser sustituidos por 0,

1, o 2) grupos independientemente seleccionados en cada ocurrencia a partir del grupo que consta de halógeno, hidróxilo, C_1- C_6alquilo, C_1- C_6alcoxilo, y $NR^{10}R^{11}$;

R^{16} es hidrógeno, halógeno, hidróxilo, azida, ciano, COOH, C_1- C_6alcoxicarbonilo, C_1- C_6alquilo, C_1- C_6alcoxilo, C_1- C_6haloalquilo, C_1- C_6haloalcoxilo, NR^8R^9, $N(H)C(O)C_1$- C_6alquilo, hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, o C_1- C_6alquilo sustituido por NR^8R^9, N(H)C(O)H o $N(H)C(O)(C_1$- C_4alquilo);

R^{17} es hidrógeno, halógeno, hidróxilo, C_1- C_6alquilo, C_1- C_4alcoxilo, hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, o C_1- C_6haloalcoxilo;

R^{18} se selecciona del grupo que consta de hidrógeno, fenilo y C_1- C_6alquilo, tal grupo alquilo es sustituido o no sustituido por hidróxilo, amino, azida, y $NHC(O)C_1$- C_6alquilo;

R^{19} y R^{20} son cada uno independientemente seleccionados a partir de hidrógeno y C_1- C_6alquilo; o

$CR^{16}R^{17}$, tomados en combinación, forman un carbocilo espirocíclico de 3 a 6 miembros que se sustituye por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de halógeno y metilo; o

R^{16} y R^{17}, tomados en combinación, forman un metilideno exocíclico (=CH_2);

R^{15} y R^{16}or R^{14} y R^{17} tomados en combinación forman un anillo de epoxido o un sistema de anillo carbocíclico de 3 a 6 miembros cuyo anillo carbocíclico es sustituido por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de halógeno, metilo, etilo, hidroxiC_1- C_4alquilo, C_1- C_6alcoxiC_1- C_4alquilo, C_1- C_4alcoxicarbonilo, CO_2H, y C_1- C_4alquilo sustituido por NR^8R^9; o

R^{17} y R^{19} o R^{16} y R^{18}, tomados en combinación, forman un sistema de anillo carbocíclico de 3 miembros fusionado que se sustituye por 0, 1, o 2 sustituyentes independientemente seleccionados del grupo que consta de halógeno, metilo, etilo, hidroxiC_1- C_4alquilo, C_1- C_4alcoxicarbonilo, CO_2H, y C_1- C_4alquilo sustituido por NH^8R^9; o

R^{14} y R^{20} tomados en combinación forman un sistema de 3 anillos carbocíclicos fusionados;

R^{14} y R^{19}, tomados en combinación, forman un enlazador de alquileno de 1 a 3 carbonos;o

R^{17} y R^{20}, tomados en combinación, forman un enlazador de alquileno de 1 a 3 carbonos;

G es un residuo divalente seleccionado a partir de C(O)- N(H), CH_2- $N(H)–S(O)_2–$, $CH_2–N(H)–C(O)$, CH_2- N(H)- C(O)- O, $CH_2N(H)$, CH_2- N(H)- C(O)- N(H), CH_2- N(H)- C(O)-

N(Me), $CH_2N(H)$- $S(O)_2$- N(H)- , y $CH_2N(H)$- $S(O)_2$- N(Me)- , en donde el residuo más a la derecha está fijado a $-(CR^{21}R^{22})_q$;

q es 0, 1, 2, 3 o 4;

R^{21} se selecciona independientemente en cada ocurrencia a partir del grupo que consta de hidrógeno, hidróxilo, halógeno, C_1- C_6alquilo, haloC_1- C_6alquilo, fenilo, CO_2H, C_1- C_6alcoxilo carbonilo, $C(O)NH_2$, hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, C_1- C_6alquilo sustituido por NR^8R^9, imidazoilC_1- C_6alquilo heterocicloC_1- C_6alquilo, donde el heterociclo se selecciona a partir de azetidinilo, pirrolidinilo, piperidinilo, morfolinilo, 1- oxa- 6- aza- espiro[3.3]heptano, 2- oxa- 6- aza- espiro[3.3]heptano, piperazinilo, 1,6- diaza- espiro[3.3]heptano, y 2,6- diaza- espiro[3.3]heptano cada uno de los cuales se sustituye opcionalmente por 1 o 2 sustituyentes seleccionados a partir de flúor, hidróxilo, C_1- C_4alquilo o C_1- C_4alcoxilo;

R^{22} se selecciona independientemente en cada ocurrencia a partir de hidrógeno o C_1- C_6alquilo; o

cuando q es 1, 2, 3 o 4, R^{21} y un sustituyente R^{22}, tomados en combinación con los átomos de carbono a los que están unidos, forman un carbociclo de 3 a 6 miembros o heterociclo de 3 a 6 miembros que tiene un oxigeno o nitrógeno cíclico; o

cuando q es 2, 3 o 4, dos residuos de R^{21} o R^{22}, localizados en átomos de carbono adyacentes, forman, junto con los átomos de carbono a los que están unidos, un carbociclo de 3 a 6 miembros; y

Z es C_1- C_6alquilo, C_1- C_6haloalquilo, fenilo, fenoxilo, naftilo, naftiloxilo, C_3- C_7cicloalquilo, indanilo, un heterociclo monocíclico o bicíclico saturado o parcialmente insaturado de 5, 6, 9 o 10 miembros que tiene 1, 2, o 3 heteroátomos de anillo seleccionados a partir de N, O, o S, o un heteroarilo o heteroariloxilo de 5 o 6 miembros, tal heteroarilo tiene 1 o 2 heteroátomos de anillo seleccionados a partir de N, O o S siempre que el anillo no tenga 2 átomos O o S, cada residuo es sustituido o no sustituido por 1, 2, 3, o 4 sustituyentes que se seleccionan independientemente del grupo que consta de C_1- C_6alquilo sustituido o no sustituido, C_1- C_6haloalquilo, halógeno, CN, hidróxilo, CO_2H, tetrazolilo, $C(O)R^{25}$, $S(O)_2R^{26}$, C_1- C_6alcoxilo sustituido o no sustituido, haloC_1- C_6alcoxilo, fenoxilo, $NR^{23}R^{24}$, $CH_2NR^{23}R^{24}$, heteroarilo de 5 o 6 miembros y fenilo sustituido o no sustituido, tal fenilo sustituido tiene 1 o 2 sustituyentes independientemente seleccionados del grupo que consta de ciano, halo, C_1- C_6alquilo o C_1- C_6haloalquilo, OH, COOH, COR^{25}, $S(O)_2R^{26}$, amino, y CH_2NH_2, y tal alquilo o alcoxilo sustituido tiene un sustituyente seleccionado a partir de hidróxilo, C_1- C_4alcoxilo, ciano, CO_2H, tetrazol o $NR^{23}R^{24}$;

R^{23} es hidrógeno o C_1- C_6alquilo;

R^{24} es hidrógeno, C_1- C_6alquilo, hidroxiC_1- C_6alquilo, C_1- C_6alcoxiC_1- C_6alquilo, aminoC_1- C_6alquilo, mono- y di- C_1- C_6alquilaminoC_1- C_6alquilo; o

$NR^{23}R^{24}$, tomados en combinación forman un heterociclo de 4, 5 o 6 miembros que tiene 0 o 1 heteroátomos de anillo adicionales seleccionados del grupo que consta de N, O o S, y que se sustituye por 0, 1 o 2 sustituyentes independientemente seleccionados a partir de flúor, hidróxilo, C_1- C_4alquilo o C_1- C_4alcoxilo;

R^{25} se selecciona independientemente en cada ocurrencia a partir del grupo que consta de C_1- C_6alcoxilo y $NR^{23}R^{24}$; y

R^{26} se selecciona del grupo que consta de amino, hidróxilo, C_1- C_6alquilo, y, mono- y di- C_1- C_6alquilamino.

17. Un compuesto de la reivindicación 1 o reivindicación 2, dicho compuesto se selecciona del grupo que consta de:

1- [(1- carbamoil- 1H- indol- 3- il)- amida]2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

2- bencilamida 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1 - [(1 - carbamoil- 1H- indol- 3- il)- amida]- 2- [(piridin- 3- ilmetil)- amida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1 - [(1 - carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- 5- {[(2- metoxi- etil)- metil- amino]- metil}- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1 - [(1 - carbamoil- 1H- indol- 3- il)- amida]- 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida} del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1 - [(1 - carbamoil- 1H- indol- 3- il)- amida]- 2- [(piridin- 4- ilmetil)- amida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1 - [(1 - carbamoil- 1H- indol- 3- il)- amida]- 2- [3- cloro- 2- fluoro- 5- (4- metil- piperazin- 1- il)- bencilamida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1 - [(1 - carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- hidroxi- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [3- cloro- 2- fluoro- 5- (4- metil- piperazin- 1- ilmetil)- bencilamida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(5- cloro- tiofen- 2- ilmetil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 5- dietilamino- metil- 2- fluoro- bencil- amida) del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [((S)- 2- hidroxi- 1- fenil- etil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (2,3- difluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;
ester terc- butilo del ácido (2S,3S)- 2- {[(2S,4R)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- 3- metil- pentanoico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [3- cloro- 2- fluoro- 5- (4- metoxi- piperidin- 1- il)- bencilamida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 5- {[(2- dimetilamino- etil)- metil- amino]- metil}- 2- fluoro- bencilamida del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- 5- morfolin- 4- ilmetil- bencilamida) del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- 5- morfolin- 4- il- bencilamida) del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [3- cloro- 2- fluoro- 5- (4- metoxi- piperidin- 1- ilrnetil)- bencilamida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {3- cloro- 2- fluoro- 5- [(2- metoxi- etil)- metil- arnino]- bencilamida} del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {3- cloro- 5- [(2- dimetilamino- etilamino)- metil]- 2- fluoro- bencilamida} del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;
Ácido 2- ({[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- metil)- benzoico;
Ácido 2- ({[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 3- carbonil]- amino}- metil)- benzoico;
Ácido (2S,3S)- 2- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- 3- metil- pentanoico;

1- [(1- carbamoil- 1- H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1- H- indol- 3- il)- amida]- 2- fenilamida del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

2- bencilamida 1- [(1- carbamoil- 1- H- indol- 3- il)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico como una sal formiato;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- metil- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- trifluorometil- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- fluoro- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- ciano- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

2- (3- bromo- bencilamida)- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- hidroxi- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

(2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico acid 1- [(1- carbamoil- 1H- indol- 3- il)- amida]

2- (3- metoxi- bencilamida);

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- trifluorometoxi- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- fenoxi- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

2- [(bifenil- 3- ilmetil)- amida]- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico como una sal de formiato;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- pirrol- 1- il- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [3- (5- cloro- tiofen- 2- il)- bencilamida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(5'- cloro- [2,2']bitiofenil- 5- ilmetil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (4- metil- bencilamida) del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (4- cloro- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (4- trifluorometil- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (4- trifluorometoxi- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico.
2- (4- hidroxi- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (2- hidroxi- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (2- fluoro- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxilico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (2- cloro- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;
2- [(bifenil- 2- ilmetil)- amida]- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (2,3- difluoro- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (5- cloro- 2- metoxi- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1- H- indol- 3- il)- amida]- 2- (3- cloro- 4- metoxi- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (5- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 4- fluoro- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- metil- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (5- cloro- 2- metil- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 4- metil- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3,5- dicloro- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3,4- dicloro- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2,6- difluoro- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(naftalen- 2- ilmetil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(naftalen- 1- ilmetil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(5- metil- tiazol- 2- ilmetil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(5- cloro- tiofen- 2- ilmetil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(4- metil- piridin- 2- ilmetil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {[(S)- 1- (3- cloro- fenil)- etil]- amida} del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico como una sal formiato;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {[(R)- 1- (3- cloro- fenil)- etil]- amida}del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico como una sal formiato;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {[1- (3,5- dicloro- fenil)- 2- hidroxi- etil]- amida} del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {[1- (3- cloro- fenil)- 3- hidroxi- propil]- amida} del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(1- fenil- ciclopropil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

2- benzhydril- amida 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico como una sal de formiato;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- ciclohexilmetil- amida del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [((1R,2S)- 2- hidroxi- ciclohexilmetil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [((1S,2S)- 2- hidroxi- ciclohexilmetil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- ciclohexilamida del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3,4,5,6- tetrahydro- 2H- [1,2']bipiridinil- 3- il)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(6- cloro- indan- 1- il)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(6- cloro- croman- 4- il)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (fenetil- amida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(2- hidroxi- 2- fenil- etil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [((1R,2S)- 2- fenil- ciclopropil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [((R)- 2- fenil- propil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [((S)- 2- fenil- propil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {[2- (3- cloro- fenil)- etil]- amida} del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1Hindol- 3- il)- amida]- 2- {[2- (2- cloro- fenil)- etil]- amida} del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1Hindol- 3- il)- amida]- 2- {[2- (2- fluoro- fenil)- etil]- amida} del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1Hindol- 3- il)- amida]- 2- {[2- (3- fluoro- fenil)- etil]- amida} del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {[2- (3- cloro- 5- fluoro- fenil)- etil]- amida} del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(2- fenoxi- etil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

Ester metilo del ácido (2S,3S)- 2- {[(2S,4S)- 4- amino- 1- (1- carbarnoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- 3- metil- pentanoico;

Ester metilo del ácido (S)- 2- {[(2S,4S)- 4- Amino- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- pentanoico;
Ester metilo del ácido (R)- 2- {[(2S,4S)- 4- amino- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- 3- metil- butírico;
Ester metilo del ácido (S)- 2- {[(2S,4S)- 4- amino- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- 4- metil- pentanoico;
Ester metilo del ácido (S)- 2- {[(2S,4S)- 4- Amino- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- 3- terc- butoxi- propionico;
Ester metilo del ácido (S)- 2- {[(2S,4S)- 4- amino- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- 3- fenil- propionico;
Ester metilo del ácido (S)- {[(2S,4S)- 4- amino- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- fenil- acético;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [((1S,2S)- 1- carbamoil- 2- metil- butil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- etil- bencilamida) del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [((1S,2S)- 1- hidroximetil- 2- metil- butil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- isopropil- fenil)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

2- bifenil- 3- ilamida- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- amino- pirrolidina- 1,2- dicarboxílico;

Amida del ácido 3- {[(2S,4R)- 2- (bencenosulfonilamino- metil)- 4- fluoro- pirrolidina- 1- carbonil]- amino}- indol- 1- carboxílico;

Amida del ácdio 3- ({(2S,4R)- 4- fluoro- 2- [(3- fluoro- bencenosulfonilamino)- metil]- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico;

Amida del ácido 3- ({(2S,4R)- 4- fluoro- 2- [(3- cloro- bencenosulfonilamino)- metil]- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico;

Amida del ácido 3- ({(2S,4R)- 4- fluoro- 2- [(3- bromo- bencenosulfonilamino)- metil]- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico;

Amida del ácido 3- ({(2S,4R)- 4- fluoro- 2- [(3- trifluorometoxi- bencenosulfonilamino)- metil]- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico;

Amida del ácido 3- ({(2S,4R)- 2- [(3- cloro- 2- fluoro- bencenosulfonilamino)- metil]- 4- fluoro- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico;

Amida del ácido 3- ({(2S,4R)- 2- [(5- cloro- tiofeno- 2- sulfonilamino)- metil]- 4- fluoro- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico;

Amida del ácido 3- ({(S)- 2- [(3- Cloro- bencenosulfonilamino)- metil]- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico;

Amida del ácido 3- {[(2S,4R)- 4- fluoro- 2- (fenilacetilamino- metil)- pirrolidina- 1- carbonil]- amino}- indol- 1- carboxílico;

Ester fenilo del ácido [(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidin- 2- ilmetil]- carbámico;

Ester 3- cloro- 2- fluoro- fenilo del ácido [(1R,3S,5R)- 2- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 3- ilmetil]- carbámico;

Amida del ácido 3- ({(2S,4R)- 2- [(3- cloro- 2- fluoro- bencilamino)- metil]- 4- fluoro- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico;

Amida del ácido 3- ({(S)- 2- [(3- trifluorometoxi- fenilamino)- metil]- pirrolidina- 1- carbonil}- amino)- indol- 1- carboxílico;

Amida del ácido 1- {2- oxo- 2- [(S)- 2- (3- trifluorometoxi- 3- carboxílico;

(3- trifluorometoxi- fenil)- amida del ácido (S)- 1- [2- (1- acetil- 1H- indol- 3- il)- acetil]- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (1- acetil- 1H- indol- 3- il)- 2- amino- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;

1- [(3- carbamoil- indolizin- 1- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico;

1- [(3- carbamoil- indolizin- 1- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- indolizin- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- ciano- pirrolidina- 1,2 dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R)- 3- metil- pirrolidina- 1,2- dicarboxílico;

Ester terc- butilo del ácido (1- carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 6- il)- acético;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- Metoxi- pirrolidina- 1,2- dicarboxílico;

2- [(1- acetil- 1H- indol- 3- il)- amida]- 3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2hidroxi- etil]- amida} del ácido (1R,3S,5R)- 2- azabiciclo[3.1.0]hexano- 2,3- dicarboxílico;

3- (3- cloro- 2- fluoro- bencilamida) 2- [(1- metilcarbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- azabiciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- hidroxi- pirrolidina- 1,2- dicarboxílico;

1- {[1- carbamoil- 5- (2- metoxi- etoxi)- 1H- indol- 3- il]- amida} 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- 4- metil- pirrolidina- 1,2- dicarboxílico;

Ester metilo del ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- iloxi)- acético;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- [(3- trifluorometoxi- fenil)- amida] del ácido (1S,3S,5S)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (1S,2S,5R)- 3- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- (3- cloro- 2- fluoro- bencilamida) del ácido 2- aza- biciclo[2.1.1]hexano- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- metil- pirrolidina- 1,2- dicarboxílico;

2- (3- bromo- 2- fluoro- bencilamida)- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,5R)- 5- (acetilamino- metil)- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (R)- Pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (1S,2S,5R)- 3- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(2- fluoro- trifluorometoxi- fenil)- amida] del ácido (S)- tiazolidina- 2,3- dicarboxílico;

Ester metilo del ácido 3- cloro- 5- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- benzoico;

Ácido 3- ({[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- metil)- 5- cloro- 4- fluoro- benzoico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- 2,5- Dihidro- pirrola- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,2S,5S)- 6- oxa- 3- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- trifluorometil- pirrolidina- 1,2- dicarboxílico;

3- [(3- bromo- fenil)- amida]- 2- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1 R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 1- (3- cloro- 2- fluoro- bencilamida) del ácido (1S,5R)- 2- aza- biciclo[3.1.0]hexano- 1,2- dicarboxílico;

2- [(3- bromo- fenil)- amida] 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 4- [(3- trifluorometoxi- fenil)- amida] del ácido (R)- 2,2- dimetil- tiazolidina- 3,4- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(4'- ciano- bifenil- 3- il)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico;

Ester metilo del ácido 3- Bromo- 5- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- benzoico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [3- cloro- 5- (2- dimetilamino- etilcarba- moil)- 2- fluoro- bencilamida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- [(5- cloro- tiofen- 2- ilmetil)- amida] del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

Ester metilo del ácido bromo- 4- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- benzoico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- metil- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(6- etil- piridin- 2- il)- amida] del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

Ácido bromo- 5- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- benzoico;

2- [(4- tert- butil- tiazol- 2- il)- amida]- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (S)- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 4- [(3- trifluorometoxi- fenil)- amida] del ácido (R)- tiazolidina- 3,4- dicarboxílico;

2- {[1- carbamoil- 5- (2- metoxi- etoxi)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(6- etil- piridin- 2- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- hidroxi- 4- metil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- bromo- 4- metil- piridin- 3- il)- amida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

(1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico acid 2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida);

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (1R,2S,5S)- 3- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- [(5- bromo- 2- metil- piridin- 3- il)- amida] 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;
3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (2,3- difluoro- bencilamida) del ácido (S)- tiazolidina- 2,3- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- pirrolidina- 1,2- dicarboxílico;
2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- [(5- bromo- piridin- 3- il)- amida] del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- [(3- fluoro- piridin- 2- il)- amida] del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- (2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- azabiciclo[3.1.0]hexano- 2,3- dicarboxílico;
3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (S)- tiazolidina- 2,3- dicarboxílico;
2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- [(2- fluoro- 3- trifluorometoxi- fenil)- amida] del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- [(3- cloro- 2- fluoro- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (2S,3R)- 3- Hidroxi- pirrolidina- 1,2- dicarboxílico;
3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- tiazolidina- 2,3- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,5R)- 5- azidometil- pirrolidina- 1,2- dicarboxílico;
5- [(1- carbamoil- 1H- indol- 3- il)- amida]- 6- (3- cloro- bencilamida) del ácido (S)- 5- aza- espiro[2.4]heptano- 5,6- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- fluoro- 4- hidroximetil- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- metil- pirrolidina- 1,2- dicarboxílico;
2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- (3- cloro- bencilamida) del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5S)- 5- metoximetil- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- [(3- fluoro- piridin- 4- il)- amida] del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R)- 3- metoxi- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Piperidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(2- fluoro- 3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- ciano- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2R,3S,4R)- 4- dimetilamino- 3- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2R,3R)- 3- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- 2- metil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(5- cloro- piridin- 3- il)- amida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(5- bromo- piridin- 3- il)- amida] del ácido (2S,4R)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 23- (2,3- difluoro- bencilamida) del ácido (1R,3S,5R)- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Hidroxi- 4- hidroximetil- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (1S,2S,5R)- 6- Oxa- 3- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

Éster metilo del ácido 3- Bromo- 5- {[(S)- 3- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- tiazolidina- 2- carbonil]- amino}- benzoico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(2- metil- 5- fenil- 2H- pirazol- 3- il)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

Éster metilo del ácido (3S,5S)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- 5- (3- cloro- 2- fluoro- bencilcarbamoil)- pirrolidina- 3- carboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 5- (3- cloro- 2- fluoro- bencilamida) del ácido 4,5- Dihidro- pirazol- 1,5- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Hidroxi- 4- hidroximetil- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi-etil]- amida} del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3S,4S)- 4- Fluoro- 3- metoxi- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- 4- metil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3S,4S)- 3- Acetilamino- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi-etil]- amida} del ácido (1S,2S,5R)- 3- Azabiciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2R,3S)- 3- Fluoro- pirrolidina- 1,2- dicarboxílico;

H(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- 4- morfolin- 4- ilmetil- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,2S,5S)- 3- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2R,3S,4R)- 4- Acetilamino- 3- fluoro- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida} del ácido (1R,2S,5S)- 3- Azabiciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R)- 3- Hidroxi- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1S,3S,5R)- 5- Metoximetil- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- fluoro- piridin- 3- ilmetil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 6- metoxi- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

3- {[(S)- 1- (3- bromo- fenil)- 2- hidroxi- etil]- amida} 2- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- Azabiciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(2- fluoro- 3- trifluorometil- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

Éster metilo del ácido 3- {[(S)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- pirrolidina- 2- carbonil]- amino}- benzoico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- Piperidina- 1,2- dicarboxílico;

carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- (Acetilamino- metil)- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (2- fluoro- 3- trifluorometil- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- {[(R)- 1- (3- cloro- 2- fluoro- fenil)- 3- hidroxi- propil]- amida} del ácido (1R,3S,5R)- 2- Azabiciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (2,3- difluoro- 4- metoxi- bencilamida) del ácido (S)- Tiazolidina- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)amida] 3- [(piridin- 3- ilmetil)- amida] del ácido (1R,3S,5R)- 2Azabiciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,3S)- 3- Metil- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(5- cloro- piridin- 3- ilmetil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(R)- 1- (3- cloro- 2- fluoro- fenil)- 3- hidroxi-propil]- amida} del ácido (2S,4R)- 4- Fluoro- 4- metil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- fluoro- piridin- 4- ilmetil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi-etil]- amida} del ácido (1R,2S,5S)- 3- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- fluoro- 2- trifluorometil- piridin- 4- ilmetil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- sulfamoil- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(3- difluorometoxi- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (2,3- difluoro- 5- metoxi- bencilamida) del ácido (S)- Tiazolidina- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi-etil]- amida} del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- cloro- piridin- 3- ilmetil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(6- etil- piridin- 2- il)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi-etil]- amida} del ácido (2S,4R)- 4- Fluoro- 4- metil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- 5- metilcarbamoil-bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Fluoro- 4- fluorometil- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(3- fluoro- piridin- 2- ilmetil)- amida] del ácido 1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
H(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Fluoro- 4- morfolin- 4- ilmetil- pirrolidina- 1,2- dicarboxílico;
Éster metilo del ácido 3- ({[(2S,4R)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- metil)- 5- cloro- 4- fluoro- benzoico;
3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etil]- amida} del ácido (1S,2S,5R)- 3- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
Ácido {[(2S,4R)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- (3- cloro- fenil)- acético;
2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(5- cloro- piridin- 3- il)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- dimetilamino- etil]- amida} del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- Hidroxi- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [3- cloro- 2- fluoro- 5- (morfolina- 4- carbonil)- bencilamida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;
2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(3- metoxi- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 5- dietilamino- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;
3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida} del ácido (S)- Tiazolidina- 2,3- dicarboxílico;
2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(3- cloro- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [3- cloro- 2- fluoro- 5- (3- metoxi- Azetidina- 1- carbonil)- bencilamida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- Ciano- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (2S,3S)- 3- Hidroxi- pirrolidina- 1,2- dicarboxílico;
3- bencilamida 2- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- cloro- tiofen- 2- ilmetil)- amida] del ácido (2S,3R)- 3- Hidroxi- pirrolidina- 1,2- dicarboxílico;

1- [(1- acetil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Hidroximetil- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- (2- fluoro- 3- trifluorometil- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (2,3- difluoro- 6- metoxi- bencilamida) del ácido (S)- Tiazolidina- 2,3- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(2- cloro- tiazol- 5- ilmetil)- amida] del ácido (S)- Tiazolidina- 2,3- dicarboxílico;

3- [(1- carbamoil- 5- fluoro- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- Tiazolidina- 2,3- dicarboxílico;

3- (3- cloro- 2- fluoro- bencilamida) 2- [(1- metilcarbamoil- 1H- indol- 3- il)- amida] del ácido (1 R,3S,5S)- 5- Hidroximetil- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- 4- Metileno- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Tiazolidina- 2,3- dicarboxílico;

2- [(5- alliloxi- 1- carbamoil- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 6- metil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etil]- amida} 2- [(1- metilcarbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- acetil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

Éster metilo del ácido 3- Bromo- 5- {[(1R,3S,5R)- 2- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 3- carbonil]- amino}- benzoico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida del ácido (2S,5R)- 5- Fenil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(2- fluoro- 3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

2- [(1- acetil- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5S)- 5- Hidroximetil- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

Éster metilo del ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- trifluorometoxi- fenilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 6- iloxi)- acético;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 5- dimetilcarbamoil- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;
Ácido 2- Bromo- 4- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- benzoico;
2- [(5- tert- butil- 2- metil- 2H- pirazol- 3- il)- amida] 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;
1- [(6- alliloxi- 1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;
2- [(1- acetil- 1H- indol- 3- il)- amida] 3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- dimetilamino- etil]- amida} del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
1- [(1- metilcarbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(2- cloro- tiazol- 5- ilmetil)- amida] del ácido (2S,3R)- 3- Hidroxi- pirrolidina- 1,2- dicarboxílico;
3- (3- cloro- 2- fluoro- bencilamida) 2- [(1- metilcarbamoil- 1H- indol- 3- il)- amida] del ácido (1 R,3S,5S)- 5- Metoximetil- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(3- isopropil- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
1- [(6- bromo- 1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;
3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida}2- [(1- metilcarbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- Azabiciclo[3.1.0]hexano- 2,3- dicarboxílico;
1- [(1- carbamoil- 6- etil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;
3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- dimetilamino- etil]- amida} 2- [(1- metilcarbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
1- [(1- carbamoil- 6- trifluorometil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 6- cloro- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 5- metoxi- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- cloro- tiofen- 2- ilmetil)- amida] del ácido (S)- Tiazolidina- 2,3- dicarboxílico;

2- [(1- carbamoil- 5- fluoro- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(2- cloro- tiazol- 5- ilmetil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(S)- 1- (3- cloro- fenil)- 2,2,2- trifluoro- etil]- amida} del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 6- fluoro- 1H- indol- 3- il)- amida] 3- [(3- trifluorometoxi- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 5- metoxi- 1H- indol- 3- il)- amida] 2- [(2- fluoro- 3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Azetidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 5- metoxi- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- 4,4- Difluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- 5,5- Dimetil- pirrolidina- 1,2- dicarboxílico;

1- {[1- carbamoil- 5- (2- metoxi- etoxi)- 1H- indol- 3- il]- amida} 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- fluoro- 4- metil- piridin- 2- ilmetil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- trifluorometil- piridin- 3- ilmetil)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

Éster etílico del ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- il)- acético;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 1- [(3- trifluorometoxi- fenil)- amida] del ácido (1S,5R)- 2- Aza- biciclo[3.1.0]hexano- 1,2- dicarboxílico;

1- [(1- carbamoil- 6- difluorometoxi- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(2- metoxi- piridin- 4- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- cloro- piridin- 3- il)- amida] del ácido (S)- Tiazolidina- 2,3- dicarboxílico;

2- [(6- alliloxi- 1- carbamoil- 1H- indol- 3- il)- amida] 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Hidroximetil- pirrolidina- 1,2- dicarboxílico;

1- [(6- benciloxi- 1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- dimetilamino- etil]- amida} del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

Éster etílico del ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 6- il)- acético;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- Metoxi- pirrolidina- 1,2- dicarboxílico;

2- [(2- tert- butil- piridin- 4- il)- amida] 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

Éster metilo del ácido (1- Carbamoil- 3- {[(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil- pirrolidina- 1- carbonil]- amino}- 1H- indol- 5- iloxi)- acético;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {[(R)- 1- (3- cloro- fenil)- 2,2,2- trifluoro- etil]- amida} del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- {[(S)- 1- (3- cloro- fenil)- 2- hidroxi- etil]- amida} del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

3- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(5- bromo- piridin- 3- il)- amida] del ácido (S)- Tiazolidina- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [3- cloro- 2- fluoro- 5- (4- metil- piperazina- 1- carbonil)- bencilamida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- fluoro- piridin- 4- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- carbamoil- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- metanosulfonil- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(6- cloro- croman- 4- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico (mezcla de 2 diastereoisómeros);

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- fluoro- piridin- 2- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

H(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Dimetilaminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- {3- cloro- 5- [(2- dimetilamino- etil)- metil- amino]- 2- fluoro- bencilamida} del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

3- [(3- tert- butil- fenil)- amida] 2- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1 R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Hidroxi- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- 4,4- Difluoro- pirrolidina- 1,2- dicarboxílico;

Éster etílico del ácido 3- Bromo- 5- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- 4- fluoro- benzoico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida] 3- [(3- trifluorometoxi- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(5- alliloxi- 1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,5R)- 5- Metil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,5S)- 5- Metil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [(3- trifluoromtoxi- fenil)- amida] del ácido (2S,5R)- 5- Etil- pirrolidina- 1,2- dicarboxílico;

Ácido 3- Cloro- 5- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- benzoico;

Ácido 3- Bromo- 5- {[(1R,3S,5R)- 2- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 3- carbonil]- amino}- benzoico;

Ácido 3- Bromo- 5- {[(S)- 3- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- tiazolidina- 2- carbonil]- amino}- benzoico;

Ácido 3- Bromo- 5- {[(1R,3S,5R)- 2- (1- carbamoil- 5- metoxi- 1H- indol- 3- ilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 3- carbonil]- amino}- benzoico;

Ácido 3- Bromo- 5- {[(2S,4R)- 1- (1- carbamoil- 1H- indol- 3- ilcarbamoil)- 4- fluoro- pirrolidina- 2- carbonil]- amino}- 4- fluoro- benzoico;

3- {[3- bromo- 5- (1H- tetrazol- 5- il)- fenil]- amida} 2- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1 R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

3- {[3- bromo- 5- (1- tert- butil- 1H- tetrazol- 5- il)- fenil]- amida} 2- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida] 2- [3- cloro- 2- fluoro- 5- (1H- tetrazol- 5- il)- bencilamida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

2- [5- (1 - tert- butil- 1H- tetrazol- 5- il)- 3- cloro- 2- fluoro- bencilamida] 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (2R,3S)- 3- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (2R,3R)- 3- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,5R)- 5- Metil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,5R)- 5- Etil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Hidroximetil- pirrolidina- 1,2- dicarboxílico;

Éster metilo del ácido (3S,5S)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- 5- (3- cloro- 2,6- difluoro- bencilcarbamoil)- pirrolidina- 3- carboxílico;

Ácido (3S,5S)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- 5- (3- cloro- 2,6- difluoro- bencilcarbamoil)- pirrolidina- 3- carboxílico;

2- (3- bromo- 2- fluoro- bencilamida)1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- Hidroximetil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Fluoro- 4- hidroximetil- pirrolidina- 1,2- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1S,3S,5R)- 5- Hidroximetil- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- [(1- carbamoil- 1H- indol- 3- il)- amida]- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5S)- 5- Hidroximetil- 2- aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Difluorometil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,5R)- 5- Hidroximetil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]5- (3- cloro- bencilamida) del ácido 4,5- Dihidro- pirazol- 1,5- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]5- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- 4,5- Dihidro- pirazol- 1,5- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]5- (3- cloro- 2- fluoro- bencilamida) del ácido (R)- 4,5- Dihidro- pirazol- 1,5- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {[(R)- 1- (3- cloro- 2- fluoro- fenil)- etil]- amida} del ácido (2S,3R)- 3- Hidroxi- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- etil]- amida} del ácido (2S,3R)- 3- Hidroxi- pirrolidina- 1,2- dicarboxílico;

1- {[1- (2- hidroxi- acetil)- 1H- indol- 3- il]- amida}- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

1- [(1- acetil- 6- ciano- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;

1- [(1- acetil- 6- difluorometoxi- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 6- hidroxi- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 5- hidroxi- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;
2- [(1- carbamoil- 5- hidroxi- 1H- indol- 3- il)- amida]- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
2- [(1- carbamoil- 5- hidroxi- 1H- indol- 3- il)- amida]- 3- (2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
2- [(1- carbamoil- 5- cianometoxi- 1H- indol- 3- il)- amida]- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
Ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- iloxi)- acético;
Ácido (1- Carbamoil- 3- {[(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil- pirrolidina- 1- carbonil]- amino}- 1H- indol- 5- iloxi)- acético;
Ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 6- iloxi)- acético;
Ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- il)- acético;
Ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 6- il)- acético;
2- {[1- carbamoil- 5- (2- hidroxi- etoxi)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
3- {[1- carbamoil- 5- (2- hidroxi- etoxi)- 1H- indol- 3- il]- amida}- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- Tiazolidina- 2,3- dicarboxílico;
2- {[1- carbamoil- 5- (2- hidroxi- etoxi)- 1H- indol- 3- il]- amida}- 3- [(3- trifluorometoxi- fenil)- amida] del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
3- {[1- carbamoil- 5- (2- hidroxi- etoxi)- 1H- indol- 3- il]- amida} 2- (3- cloro- 2- fluoro- bencilamida) del ácido (1S,2S,5R)- 3- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
1- {[1- carbamoil- 5- (2- hidroxi- etoxi)- 1H- indol- 3- il]- amida}- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- 4- metil- pirrolidina- 1,2- dicarboxílico;
2- {[1- carbamoil- 6- (2- hidroxi- etil)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- {[1- carbamoil- 5- (2- hidroxi- etil)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
2- {[1- carbamoil- 5- (2- hidroxi- 2- metil- propoxi)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
2- {[1- carbamoil- 5- (2- dimetilamino- etoxi)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;

2- {[1- carbamoil- 5- (2- pirrolidin- 1- il- etoxi)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
2- {[1- carbamoil- 5- (2- imidazol- 1- il- etoxi)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
Ester terc- butilo del ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- iloxi)- acético;
Ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 5- iloxi)- acético;
2- [(1- carbamoil- 6- hidroxi- 1H- indol- 3- il)- amida]- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
1- [(1- carbamoil- 6- hidroxi- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;
Ester metilo del ácido (1- Carbamoil- 3- {[(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hexano- 2- carbonil]- amino}- 1H- indol- 6- iloxi)- acético;
2- {[1- carbamoil- 6- (2- hidroxi- etoxi)- 1H- indol- 3- il]- amida}- 3- (3- cloro- 2- fluoro- bencilamida) del ácido (1R,3S,5R)- 2- Aza- biciclo[3.1.0]hexano- 2,3- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3S,4R)- 4- Amino- 3- metoxi- pirrolidina- 1,2- dicarboxílico;
1- [(6- benciloxi- 1- carbamoil- 1H- indol- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido
(2S,4S)- 4- Amino- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (S)- Piperazina- 1,2- dicarboxílico;
2- [(4'- aminometil- bifenil- 3- il)- amida]- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;
2- [(4'- aminometil- 2'- fluoro- bifenil- 3- il)- amida]- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,5R)- 5- Aminometil- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4R)- 4- Aminometil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- Aminometil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Aminometil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Dimetilaminometil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Aminometil- 4- hidroxi- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4R)- 4- Aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Fluoro- 4- formilaminometil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2,6- difluoro- bencilamida) del ácido (2S,4S)- 4- Aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- acetil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

2- {[(S)- 1- (3- bromo- fenil)- 2- fluoro- etil]- amida}- 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4S)- 4- Aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- trifluorometoxi- fenil)- amida] del ácido (2S,4S)- 4- Aminometil- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- acetil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3S,4S)- 3- Amino- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R,4S)- 4- Amino- 3- hidroxi- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R)- 3- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- acetil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R)- 3- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- {[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2,2,2- trifluoro- etil]- amida} del ácido (2S,3R)- 3- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3S)- 3- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- bencilamida) del ácido (2S,3S)- 3- Amino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R)- 3- Acetilamino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3R)- 3- (2- Metoxi- etilamino)- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Fluoro- 4- metilaminometil- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Metilamino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- (2- Metoxi- etilamino)- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,4S)- 4- Dimetilamino- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- (3- cloro- 2- fluoro- bencilamida) del ácido (S)- 4,4- Dimetoxi- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3S,4R)- 4- Amino- 3- hidroxi- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2R,3S,4R)- 4- Amino- 3- fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluorobencilamida) del ácido (2S,3S,4S)- 3- Amino- 4- fluoro- pirrolidina- 1,2- dicarboxílico;

Amida del ácido 3- {2- [(S)- 5- (3- Cloro- 2- fluoro- bencilcarbamoil)- pirazolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico;

Amida del ácido 3- {2- [(R)- 5- (3- Cloro- 2- fluoro- bencilcarbamoil)- pirazolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]5- (3- cloro- bencilamida) del ácido Pirazolidina- 1,5- dicarboxílico;

Ester metilo del ácido (3S,5S)- 1- (1- Carbamoil- 1H- indol- 3- ilcarbamoil)- 5- (2- fluoro- 3- trifluorometoxi- fenilcarbamoil)- pirrolidina- 3- carboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2,6- difluoro- bencilamida) del ácido (2S,4S)- 4- Hidroximetil- pirrolidina- 1,2- dicarboxílico;

2- [(3- bromo- 5- carbamoil- fenil)- amida] 1- [(1- carbamoil- 1H- indol- 3- il)- amida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [3- cloro- 2- fluoro- 5- (2- metoxi- etilcarbamoil)- bencilamida] del ácido (2S,4R)- 4- Fluoro- pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- isopropil- isoxazol- 5- il)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;
1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- [(3- fenil- isoxazol- 5- il)- amida] del ácido (S)- Pirrolidina- 1,2- dicarboxílico;
Amida del ácido 3- {2- [(S)- 2- (3- trifluorometoxi- fenilcarbamoil)- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico;

Amida del ácido 3- {2- [(2S,4R)- 4- Fluoro- 2- (2- fluoro- 3- trifluorometoxi- fenilcarbamoil)- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- (2- {(1S,2S,5R)- 2- [(S)- 1- (3- Cloro- 2- fluoro- fenil)- 2- hidroxi- etilcarbamoil]- 3- azabiciclo[3.1.0]hex- 3- il}- 2- oxo- etil)- indol- 1- carboxílico;
Amida del ácido 3- {2- [(2S,3R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 3- hidroxi- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- {2- [(2S,4S)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- dimetilaminometil- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- (2- {(2S,4R)- 2- [(R)- 1- (3- Cloro- 2- fluoro- fenil)- 3- hidroxi- propilcarbamoil]- 4- fluoro- 4- metil- pirrolidin- 1- il}- 2- oxo- etil)- indol- 1- carboxílico;
Amida del ácido 3- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- (2- {(1R,3S,5R)- 3- [(S)- 1- (3- Cloro- 2- fluoro- fenil)- 2- hidroxi- etil carbamoil]- 2- aza- biciclo[3.1.0]hex- 2- il}- 2- oxo- etil)- indol- 1- carboxílico;
Amida del ácido 3- {2- [(S)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- Tiazolidin- 3- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- hidroximetil- pirrolidin- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 5- metoxi- indol- 1- carboxílico;
Amida del ácido 3- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 5- (2- hidroxi- etoxi)- indol- 1- carboxílico;
Amida del ácido 3- {2- [(1R,3S,5S)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 5- metoximetil- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 5- (2- Hidroxi- etoxi)- 3- {2- oxo- 2- [(1R,3S,5R)- 3- (3- trifluorometoxi- fenilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- etil}- indol- 1- carboxílico;
Amida del ácido 3- (2- {(1R,3S,5R)- 3- [(5- Cloro- tiofen- 2- ilmetil)- carbamoil]- 2- aza- biciclo[3.1.0]hex- il}- 2- oxo- etil)- indol- 1- carboxílico;
Amida del ácido 3- (2- {(1R,3S,5R)- 3- [(R)- 1- (3- Cloro- 2- fluoro- fenil)- 3- hidroxi- propilcarbamoil]- 2- azabiciclo[3.1.0]hex- 2- il}- 2- oxo- etil)- indol- 1- carboxílico;
Amida del ácido 3- (2- {(1R,3S,5R)- 3- [(S)- 1- (3- Cloro- 2- fluoro- fenil)- 2- dimetilamino- etilcarbamoil]- 2- aza- biciclo[3.1.0]hex- 2- il}- 2- oxo- etil)- indol- 1- carboxílico;

Amida del ácido 3- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil-pirrolidin- 1- il]- 2- oxo- etil}- 5- (2- hidroxi- etoxi)- indol- 1- carboxílico;
Amida del ácido 3- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 5- fluoro- indol- 1- carboxílico;
Amida del ácido 3- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza-biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 2- metil- indol- 1- carboxílico;
Amida del ácido 3- {2- [(S)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- Tiazolidin- 3- il]- 2- oxo- etil}- 5- (2- hidroxi- etoxi)- indol- 1- carboxílico;
Amida del ácido 3- (2- {(1R,2S,5S)- 2- [(S)- 1- (3- Cloro- 2- fluoro- fenil)- 2- hidroxi-etilcarbamoil]- 3- azabiciclo[3.1.0]hex- 3- il}- 2- oxo- etil)- indol- 1- carboxílico;
Amida del ácido 3- (2- {(1R,3S,5R)- 3- [(S)- 1- (3- Cloro- 2- fluoro- fenil)- 2- metoxi-etilcarbamoil]- 2- aza- biciclo[3.1.0]hex- 2- il}- 2- oxo- etil)- indol- 1- carboxílico;
Amida del ácido 3- {2- [(1 S,2S,5R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 3- aza-biciclo[3.1.0]hex- 3- il]- 2- oxo- etil}- 5- (2- hidroxi- etoxi)- indol- 1- carboxílico;
Amida del ácido 3- {2- [(2S,3S,4S)- 3- Amino- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4-fluoro- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- {2- [(1R,3S,5S)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 5- hidroximetil-2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- {2- [(2S,4S)- 4- Amino- 2- (3- cloro- 2- fluoro- bencilcarbamoil)-pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- {2- [5- (3- Cloro- bencilcarbamoil)- pirazolidin- 1- il]- 2- oxo- etil}- indol-1- carboxílico;
Amida del ácido 3- {2- [(2S,4S)- 4- Aminometil- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4-fluoro- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- {2- [(2S,4S)- 4- Aminometil- 2- (3- cloro- 2,6- difluoro- bencilcarbamoil)-4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- indol- 1- carboxílico;
Amida del ácido 3- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza-biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 5- (2- dimetilamino- etoxi)- indol- 1- carboxílico;
Ácido (1- Carbamoil- 3- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza-biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 6- il)- acético;
Amida del ácido 3- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza-biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 6- (2- hidroxi- etil)- indol- 1- carboxílico;
Amida del ácido 1- {2- [(1R,3S,5R)- 3- (3- Cloro- 2- fluoro- bencilcarbamoil)- 2- aza-biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;

Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;
Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 7- metoxi- 1H- indol- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- piperidina- 2- carboxílico;
Amida del ácido 6- Bromo- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 5- fluoro- 1H- indol- 3- carboxílico;
Ester metilo del ácido 3- [({(1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carbonil}- amino)- metil]- 5- cloro- 4- fluoro- benzoico;
Amida del ácido 1- {2- [(2S,4R)- 2- (3- Bromo- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
(5- cloro- tiofen- 2- ilmetil)- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- 5- metoxi- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico;
Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- fenilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- 6- metoxi- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico;
Amida del ácido 5- Cloro- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;
Amida del ácido 7- Cloro- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5S)- 2- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 5- metoximetil- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
Amida del ácido 6- Cloro- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;
Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 5,6- difluoro- 1H- indol- 3- carboxílico;

Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 6- trifluorometoxi- 1H- indol- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- 5- metoxi- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- {2- [3- (2,2,2- Trifluoro- acetil)- indol- 1- il]- acetil}- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;
Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- metoxi- 1H- indol- 3- carboxílico;
3- cloro- 5- ciano- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;
Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- metoxi- 1H- indol- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 6- metoxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (S)- 1- [2- (3- Acetil- 5- metoxi- indol- 1- il)- acetil]- piperidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- pirrolo[3,2- c]piridin- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico;
Amida del ácido 5- Benciloxi- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- oxo- etil}- 1H- indol- 3- carboxílico;
[(R)- 1- (3- cloro- 2- fluoro- fenil)- 3- hidroxi- propil]- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,2S,5S)- 3- [2- (3- Acetil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 3- aza- biciclo[3.1.0]hexano- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 5- benciloxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 6- trifluorometoxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;

cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,4S)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[2.2.1]heptane- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (S)- 3- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- Tiazolidina- 2- carboxílico;
(2- fluoro- 3- trifluorometoxi- fenil)- amida del ácido (2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;
[3- bromo- 5- (2H- tetrazol- 5- il)- fenil]- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
3- bromo- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;
Amida del ácido 1- {2- [(2S,4R)- 4- Fluoro- 2- (2- fluoro- 3- trifluorometil- fenilcarbamoil)- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;
[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido (2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;
metilamida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- 5- (1H- tetrazol- 5- il)- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;
[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- dimetilamino- etil]- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
Ester metilo del ácido 3- [({(2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carbonil}- amino)- metil]- 5- cloro- 4- fluoro- benzoico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[3,2- c]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
3- cloro- 2- fluoro- 5- (1H- tetrazol- 5- il)- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
Ester metilo del ácido 3- Acetil- 1- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- il]- 2- oxo- etil}- 1H- indol- 6- carboxílico;

Cloro- 5- ciano- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 6- difluorometoxi- 1H- indol- 3- carboxílico;
Amida del ácido 6- Benciloxi- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 6- cloro- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- 6- ciano- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etil]- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 6- benciloxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;
[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etil]- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- 6- benciloxi- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,2S,5S)- 3- [2- (3- Acetil- pirrolo[3,2- c]piridin- 1- il)- acetil]- 3- aza- biciclo[3.1.0]hexano- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,2S,5S)- 3- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 3- aza- biciclo[3.1.0]hexano- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 5- trifluorometoxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;
Ester metilo del ácido 3- Acetil- 1- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 5- carboxílico;
Ester metilo del ácido 3- Acetil- 1- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluorobencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 7- carboxílico;
Ester metilo del ácido 3- Acetil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 4- Fluoro- 1- {2- [3- (2- hidroxi- acetil)- indol- 1- il]- acetil}- ;4- metil- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (1S,2S,5R)- 3- [2- (3- Acetil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 3- aza- biciclo[3.1.0]hexano- 2- carboxílico;
Ester metilo del ácido (3- Acetil- 1- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza- biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 6- il)- acético;
3- bromo- 2- fluoro- bencilamida del ácido (2S,4R)- 4- Fluoro- 1- {2- [3- (2,2,2- trifluoro- acetil)- indol- 1- il]- acetil}- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;
Ester metilo del ácido 3- Acetil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- carboxílico;
Ester metilo del ácido (3- Acetil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- il)- acético;
3- cloro- 2- fluorobencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
[(S)- 1- (3- bromo- fenil)- 2- fluoro- etil]- amida del ácido (2S,4R)- 4- Fluoro- 1- {2- [3- (2- hidroxi- acetil)- indol- 1- il]- acetil}- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- pirrolo[2,3- c]piridin- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[3,2- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 4- Fluoro- 4- metil- 1- {2- [3- (2,2,2- trifluoro- acetil)- indol- 1- il]- acetil}- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2R,3S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- dimetilamino- 3- fluoro- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- {2- [3- (2- Hidroxi- acetil)- indol- 1- il]- acetil}- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
[(R)- 1- (3- cloro- 2- fluoro- fenil)- 3- hidroxi- propil]- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
(3- trifluorometoxi- fenil)- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
(3- trifluorometoxi- fenil)- amida del ácido (S)- 1- [2- (3- Formil- indol- 1- il)- acetil]- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 4- Fluoro- 1- [2- (3- formil- 5- metoxi- indol- 1- il)- acetil]- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 4- Fluoro- 1- {2- [3- (2,2,2- trifluoro-acetil)- indol- 1- il]- acetil}- pirrolidina- 2- carboxílico;
(2- fluoro- 3- trifluorometoxi- fenil)- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[2,3-b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 4- Fluoro- 1- {2- [3- (2- hidroxi- acetil)-indol- 1- il]- acetil}- pirrolidina- 2- carboxílico;
3- bromo- 2- fluoro- bencilamida del ácido (2S,4R)- 4- Fluoro- 1- {2- [3- (2- hidroxi- acetil)-indol- 1- il]- acetil}- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 4- Fluoro- 1- {2- [3- (2- metoxi- acetil)-indol- 1- il]- acetil}- pirrolidina- 2- carboxílico;
Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4-hidroximetil- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;
Amida del ácido 1- {2- [(S)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- Tiazolidin- 3- il]- 2-oxo- etil}- 1H- indol- 3- carboxílico;
[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- metoxi- etil]- amida del ácido (1R,3S,5R)- 2- [2- (3-Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4-fluoro- 3- etoxi- pirrolidina- 2- carboxílico;
[(R)- 1- (3- cloro- 2- fluoro- fenil)- etil]- amida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- indol- 1-il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico;
[(S)- 1- (3- cloro- 2- fluoro- fenil)- etil]- amida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- indol- 1-il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico;
[1- (3- cloro- fenil)- ciclopropil]- amida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- indol- 1- il)-acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico;
[1- (4- cloro- fenil)- ciclopropil]- amida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- indol- 1- il)-acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico;
Amida del ácido 1- {2- [(2S,3S,4S)- 3- Amino- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4-fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 3-amino- 4- fluoro- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2R,3S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4-amino- 3- fluoro- pirrolidina- 2- carboxílico;
Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro-pirrolidin- 1- il]- 2- oxo- etil}- hidroxi- 1H- indol- 3- carboxílico;

Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- hidroxi- 1H- indol- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 5- hidroxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 5- hidroxi- indol- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- 5- hidroxi- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 6- hidroxi- indol- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 6- hidroxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- 6- hidroxi- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 6- (1H- tetrazol- 5- ilmetoxi)- 1H- indol- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- {2- [3- Acetil- 6- (1H- tetrazol- 5- ilmetoxi)- indol- 1- il]- acetil}- 4- fluoro- irrolidina- carboxílico;
Cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 5- metoxi- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- {2- [3- Acetil- 5- (piridin- 2- ilmetoxi)- indol- 1- il]- acetil}- 4- fluoro- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- {2- [3- Acetil- 5- (pirimidin- 2- ilmetoxi)- indol- 1- il]- acetil}- 4- fluoro- pirrolidina- 2- carboxílico;
Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 6- (2- metoxi- etoxi)- 1H- indol- 3- carboxílico;
Ester metilo del ácido (3- Carbamoil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- iloxi)- acético;
Ácido (3- Carbamoil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- iloxi)- acético;
Amida del ácido 1- {2- [(2S,4R)- 2- (3- Cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 6- (2- hidroxi- etoxi)- 1H- indol- 3- carboxílico;
Ácido (3- Acetil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- il)- acético;

Ácido (3- Acetil- 1- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza-biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 6- il)- acético;

Ácido 3- Acetil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- pirrolidin-1- il]- 2- oxo- etil}- 1H- indol- 6- carboxílico;

Ácido 3- Acetil- 1- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza-biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 6- carboxílico;

Ácido 3- Acetil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro- 4- metil-pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- carboxílico;

1- [(1- carbamoil- 1H- indol- 3- il)- amida]- 2- (3- cloro- 2- fluoro- bencilamida) del ácido (2S,3S,4S)- 4- Fluoro- 3- metoxi- pirrolidina- 1,2- dicarboxílico;

Ácido acetil- 1- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza-biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 7- carboxílico;

Ácido (3- Acetil- 1- {2- [(2S,4R)- 2- (3- cloro- 2- fluoro- bencilcarbamoil)- 4- fluoro-pirrolidin- 1- il]- 2- oxo- etil}- 1H- indol- 6- iloximetil)- benzoico;

Ácido 3- acetil- 1- {2- [(1R,3S,5R)- 3- (3- cloro- 2- fluoro- bencilcarbamoil)- 2- aza-biciclo[3.1.0]hex- 2- il]- 2- oxo- etil}- 1H- indol- 5- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- [2- (3- Acetil- 6- hidroximetil- indol- 1-il)- acetil]- 4- fluoro- pirrolidina- 2- carboxílico;

Ácido 3- [({(2S,4R)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- pirrolidina- 2- carbonil}-amino)- metil]- 5- cloro- 4- fluoro- benzoico;

Ácido 3- [({(1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3-carbonil}- amino)- metil]- 5- cloro- 4- fluoro- benzoico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4-aminometil- 4- fluoro- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4-metilamino- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (2S,4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- (2-metoxi- etilamino)- pirrolidina- 2- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5S)- 2- [2- (3- Acetil- pirrolo[2,3- b]piridin-1- il)- acetil]- 5- hidroximetil- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5S)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 5-hidroximetil- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;

[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2hidroxi- etil]- amida del ácido (1S,2S,5R)- 3- [2- (3-Acetil- indol- 1- il)- acetil]- 3- aza- biciclo[3.1.0]hexano- 2- carboxílico;

[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido (1R,3S,5R)- 2- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
[(S)- 1- (3- cloro- 2- fluoro- fenil)- 2- hidroxi- etil]- amida del ácido (2S,4R)- 1- [2- (3- Acetil- pirrolo[2,3- b]piridin- 1- il)- acetil]- 4- fluoro- 4- metil- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- {2- [3- Acetil- 5- (N,N- dimetil- carbamimidoil)- indol- 1- il]- acetil}- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- {2- [3- Acetil- 6- (N,N- dimetil- carbamimidoil)- indol- 1- il]- acetil}- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,4R)- 1- {2- [3- Acetil- 6- (1H- tetrazol- 5- il)- indol- 1- il]- acetil}- 4- fluoro- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- {2- [3- Acetil- 6- (1H- tetrazol- 5- il)- indol- 1- il]- acetil}- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- d3- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (2S,3S,4S)- 1- [2- (3- Acetil- indol- 1- il)- acetil]- 4- fluoro- 3- metoxi- d3- pirrolidina- 2- carboxílico;
3- cloro- 2- fluoro- bencilamida del ácido (1R,3S,5R)- 2- [2- (1- Acetil- imidazo[1,5- a]piridin- 3- il)- acetil]- 2- aza- biciclo[3.1.0]hexano- 3- carboxílico; y
Éster 3- cloro- 2- fluoro- fenilo del ácido {(1R,3S,5R)- 2- [2- (3- Acetil- indol- 1- il)- acetil]- 2- aza- biciclo[3.1.0]hex- 3- ilmetil}- carbamico.

18. Una composition farmacéutica que comprende uno o más vehículos farmacéuticamente aceptables y una cantidad terapéuticamente efectiva de un compuesto de cualquiera de las reivindicaciones 1- 17.

19. Una combinación, en particular una combinación farmacéutica, que comprende una cantidad terapéuticamente efectiva del compuesto según cualquiera de las reivindicaciones 1- 17 y un segundo agente terapéuticamente activo.

20. Un método de modular la actividad de la vía alternativa de complemento en un sujeto, en donde el método comprende administrar al sujeto una cantidad terapéuticamente efectiva del compuesto según cualquiera de las reivindicaciones 1- 17.

21. Un método de tratar un trastorno o enfermedad en un sujeto mediada por la activación del complemento, en particular mediada por la activación de la vía alternativa de

complemento, en donde el método comprende administrar al sujeto una cantidad terapéuticamente efectiva del compuesto según cualquiera de las reivindicaciones 1- 17.

22. El método de la reivindicación 20, en el que la enfermedad o trastorno se selecciona de entre el grupo que consiste de degeneración macular relacionada con la edad, atrofia geográfica, retinopatía diabética, uveítis, retinitis pigmentosa, edema macular, uveítis de Behcet, coroiditis multifocal, síndrome de Vogt- Koyangi- Harada, uveítis intermedia, retinocorioditis tipo perdigón, oftalmía simpática, penfigoide ocular cicatricial, pénfigo ocular, neuropatía óptica isquémica no artértica, inflamación post- operatoria, oclusión de la vena retiniana, trastornos neurológicos, esclerosis múltiple, accidente cerebrovascular, síndrome de Guillain Barré, lesión cerebral traumática, enfermedad de Parkinson, trastornos de la activación inapropiada o indeseable del complemento, complicaciones de hemodiálisis, rechazo hiperagudo de aloinjertos, rechazo de xenoinjertos, toxicidad inducida por interleucina-2durante terapia con IL- 2, trastornos inflamatorios, inflamación de enfermedades autoinmunes, enfermedad de Crohn, síndrome de dificultad respiratoria del adulto, miocarditis, condiciones de reperfusión post- isquémica, infarto de miocardio, angioplastia con balón, síndrome pos bomba en bypass cardiopulmonar o bypass renal, aterosclerosis, hemodiálisis, isquemia renal, reperfusión arterial mesentérica después de reconstrucción aórtica, enfermedad infecciosa o sepsis, trastornos complejos inmunes y enfermedades autoinmunes, artritis reumatoide, lupus eritematoso sistémico (LES), nefritis por LES, nefritis proliferativa, fibrosis hepática, anemia hemolítica, miastenia gravis, regeneración de tejidos y regeneración neuronal,, disnea, hemoptisis, SDRA, asma, enfermedad pulmonar obstructiva crónica (EPOC), enfisema, embolias pulmonares e infartos, neumonía, enfermedades fibrogénicas del polvo, fibrosis pulmonar, asma, alergia, broncoconstricción, neumonitis por hipersensibilidad, enfermedades parasitarias, el síndrome de Goodpasture, vasculitis pulmonar, vasculitis pauciinmune, inflamación asociada a inmune compleja, síndrome antifosfolípido, glomerulonefritis y obesidad.

23. Un método de tratar degeneración macular relacionada con la edad que comprende administrar a un sujeto que lo necesita una cantidad efectiva de una composición que comprende un compuesto de cualquiera de las reivindicaciones 1 a 17.

24. Un compuesto según cualquiera de las reivindicaciones 1- 17, para utilizar como un medicamento.

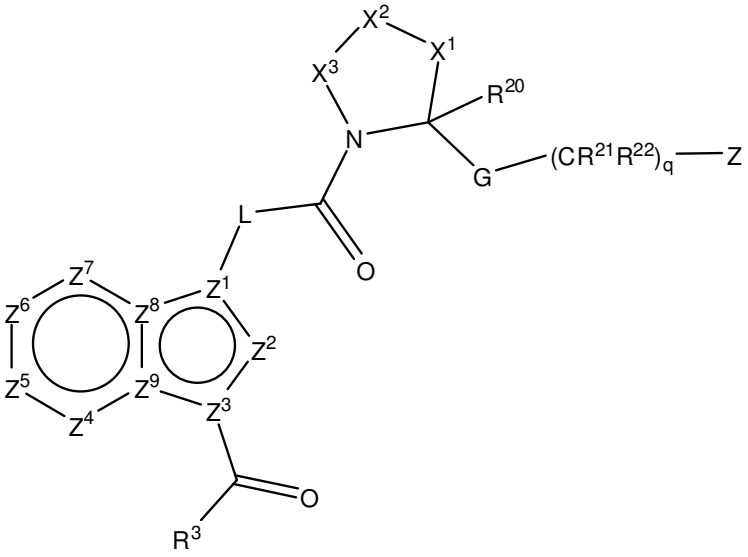
25. El uso de un compuesto compuesto según cualquiera de las reivindicaciones 1-17 en la fabricación de un medicamento para el tratamiento de un trastorno o enfermedad en un sujeto mediada por la activación de complemento o activation de la vía alternativa de complemento**.**

26. El uso de un compuesto según cualquiera de las reivindicaciones 1- 17, para el tratamiento de degeneración macular relacionada con la edad.

27. Un compuesto seleccionado del grupo que consta de 3- amino- 1H- indol- 1-carboxamida, 3- isocianato- 1H- indol- 1- carboxamida, 1- (3- isocianato- 1H- indol- 1-il)etanona, 3- isocianato- N- metil- 1H- indol- 1- carboxamida y sales de los mismos.

Resumen

La presente invención proporciona un compuesto de la fórmula I:



(I)

un método para la fabricación de los compuestos de la invención, y sus usos terapéuticos. La presente invención proporciona además una combinación de agentes farmacológicamente activos y una composición farmacéutica.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

VON SPRECHER, Georg
Novartis Pharma AG
Patent Department
CH-4002 Basel
SUISSE

Date of mailing *(day/month/year)*
06 July 2012 (06.07.2012)

Applicant's or agent's file reference
54497-WO-PCT

IMPORTANT NOTIFICATION

International application No.
PCT/EP2012/050005

International filing date *(day/month/year)*
02 January 2012 (02.01.2012)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address
ROGEL, Olivier
Novartis Pharma AG
Postfach
CH-4002 Basel
Switzerland

State of Nationality: FR
State of Residence: CH
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address
STARK-ROGEL, Véronique
4 rue des Loriots
68220 Hésingue
France

State of Nationality: FR
State of Residence: FR
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

3. Further observations, if necessary:
The person identified in Box 2 has been recorded as applicant for the United States of America only (as heiress of the deceased applicant indicated in Box 1).

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 54497-WO-PCT	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/EP2012/050005	International filing date *(day/month/year)* 02/01/2012	(Earliest) Priority Date *(day/month/year)* 04/01/2011
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 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established by this Authority to read as follows:

   INDOLE COMPOUNDS OR ANALOGUES THEREOF USEFUL FOR THE TREATMENT OF AGE-RELATED MACULAR DEGENERATION (AMD)

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/050005

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D403/12 C07D403/14 C07D405/14 C07D409/14
C07D417/12 C07D417/14 C07D471/04 A61K31/403 A61K31/407
A61K31/416 A61P27/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/106980 A2 (PFIZER [US]; BUCHLER INGRID PRICE [US]; HAYES MICHAEL JOSEPH [US]; HEG) 3 September 2009 (2009-09-03) page 2; compound I page 62, paragraph 6 partial structures; page 22 - page 25 examples 390-393	1-27
A	WO 2010/020675 A1 (NOVARTIS AG [CH]; ASTEX THERAPEUTICS LTD [GB]; BESONG GILBERT [GB]; BR) 25 February 2010 (2010-02-25) page 4; compound I page 21, paragraph 1 page 117; example 58 page 118; example 51	1-27

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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"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
21 March 2012	29/03/2012

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, Fax: (+31-70) 340-3016	Hoepfner, Wolfgang

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/050005

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		WO 2010020675 A1	25-02-2010