SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-123611- -00000-0000

Fecha: 2011-09-21 16:56:50 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 694

Fecha: 2011-09-21 16:56:50 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 687

# Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

# SOLICITUD
# PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** _____

54. **TÍTULO** INHIBIDORES DEL VIRUS DE LA HEPATITIS C.

51. **CLASIFICACIÓN INTERNACIONAL** _____

71. **SOLICITANTE** BRISTOL-MYERS SQUIBB COMPANY.

**DOMICILIO** ESTADOS UNIDOS DE AMÉRICA.

74. **APODERADO** ALVARO CORREA ORDOÑEZ.

22. **BOGOTÁ, D.C.,** SEPTIEMBRE 21, 2011.

(FORMA P-10)

**PETITORIO**

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-123611- -00000-0000

Fecha: 2011-09-21 16:56:50 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 694

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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 687

Industria y Comercio
SUPERINTENDENCIA

# FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
# PCT
## ENTRADA EN FASE NACIONAL

**(1) SOLICITUD DE :**

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

[X] Capítulo I. [ ] Capítulo II.

**(2) SOLICITANTE (71)**

Nombre: **BRISTOL-MYERS SQUIBB COMPANY**

Dirección: P.O. Box 4000 Route 206 and ProvinceLine Road Princeton, New Jersey 08543-4000 (US)

Nacionalidad o Domicilio: **Estados Unidos de América**

Lugar de Constitución:

Teléfono: Fax:

E-Mail

**IDENTIFICACION**

C.C. [ ] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número

**(3) REPRESENTANTE O APODERADO**

Nombre: ALVARO CORREA ORDOÑEZ

Dirección: Avenida 82 No. 10-62 Piso 5

Teléfono: 6341500 Fax: 3762211

E-Mail: alvaro.correa@bakermckenzie.com

**IDENTIFICACION**

C.C. [X] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número 79.143.366 Usaquén TP 20281

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de propiedad Industrial, sirvase indicar el número de radicación (del poder).

**(4) INVENTOR (ES) (72)**

Nombre: BENDER, John A.; HEWAWASAM, Piyasena; KADOW, John F.; LOPEZ, Omar D.; MEANWELL, Nicholas A.; NGUYEN, Van N.; ROMINE, Jeffrey Lee; SNYDER, Lawrence B.; ST. LAURENT, Denis R.; WANG, Gan; XU, Ningning; BELEMA, Makonen.

Dirección: P.O. Box 4000 Route 206 and ProvinceLine Road Princeton, New Jersey 08543-4000 (US)

Nacionalidad o Domicilio: Estados Unidos de América

**(5) PCT (85)**

Solicitud Internacional No. **PCT/US2010/028456** Fecha **24/03/2010**

Publicación Internacional No. **WO/2010/117635** Fecha **14/10/2010**

**(6) Título (54)** **INHIBIDORES DEL VIRUS DE LA HEPATITIS C**

**(7) Clasificación Internacional (51)** **C07D 403/04, A61K 31/4178 , A61P 31/14, C07D 403/14, C07D 405/14.**

**(8) Prioridad** SI [X] NO [ ]

| (33) País de Origen | (32) Fecha | (31) Número de Solicitud |
|---|---|---|
| US | 30/03/2009 | 61/164,531 |
| US | 23/03/2010 | 12/729,940 |

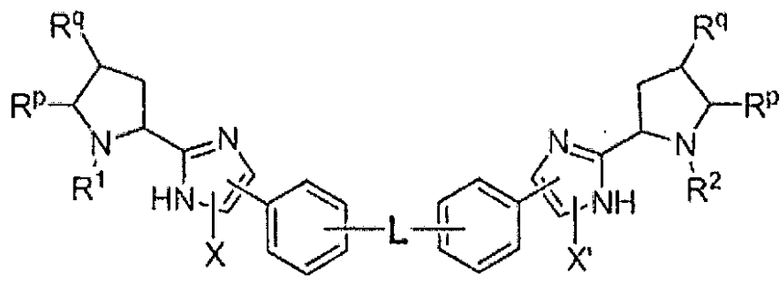
**(9) Comprobante de pago No.** 11-0085021, 11-0087573, 11-0087574, 11-0082427, 11-0082444, 11-0079819 **Fecha** 31/08/2011, 07/09/2011, 07/09/2011, 25/08/2011, 25/08/2011, 18/08/2011

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

(10) 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. *Ver Poder radicado bajo el número 08.129.399*
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [ ] Arte final 12 x 12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: Extractos

(11) FIGURA CARATERISTICA




(I)

(12) Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

C.C. 79.143.366 de Usaquén T.P. 20.281

Instrucciones para la presentación de los anexos, ver reverso de esta página

Recibos de Pago

2011/014 3

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

Industria y Comercio
SUPERINTENDENCIA

**RECIBO DE CAJA**

**No. 11 - 0085021**

Bogotá D.C., Agosto 31 de 2011 - 16:33:02

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

| TIPO PAGO | BANCO | CUENTA | No. PAGO | FECHA PAGO | VR.PAGO |
|---|---|---|---|---|---|
| CONSIGNACION | BANCO DE BOGOTA | 062754387 | 413165900 | 30/08/2011 | 43.398.000.00 |

*** Conceptos Pagados ***

| CANT. | RENTISTICO | CONCEPTO | Vr.UNDITARIO | Vr.CONCEPTO |
|---|---|---|---|---|
| 1 | 50005-01-01 SOLICITUDES | 1 TRAMITES DE SOL. DE PATENTE DE INVENCION | 571.000.00 | 571.000.00 |
| | | | | $571.000.00 |

**SON: **QUINIENTOS SETENTA Y UN MIL PESOS MONEDA CORRIENTE*****

Responsable: _____
******

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
**No. 11-123611- -00000-0000**
Fecha: 2011-09-21 16:56:50 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 694

Fecha: 2011-09-21 16:56:50 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 687

2011/014

4

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

Industria y Comercio
SUPERINTENDENCIA

**RECIBO DE CAJA**

**No. 11 - 0087573**

Bogotá D.C., Septiembre 07 de 2011 - 16:53:10

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

| TIPO PAGO | BANCO | CUENTA | No. PAGO | FECHA PAGO | VR PAGO |
|---|---|---|---|---|---|
| CONSIGNACION | BANCO DE BOGOTA | 062754387 | 325037790 | 07/09/2011 | 52.925.000.00 |

*** Conceptos Pagados ***

| CANT | RENTISTICO | CONCEPTO | Vr.UNDITARIO | Vr.CONCEPTO |
|---|---|---|---|---|
| 1 | 50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL | 99 OTROS SERVCIOS ADMINISTRATIVOS | 6.000.00 | 6.000.00 |
| | | | | $6.000.00 |

**SON: **SEIS MIL PESOS MONEDA CORRIENTE*****

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

**No. 11-123611- -00000-0000**

Fecha: 2011-09-21 16:56:50 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 694

**No. 11-123611- -00000-0000**

Fecha: 2011-09-21 16:56:50 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 687

2011/014 5

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

Industria y Comercio
SUPERINTENDENCIA

**RECIBO DE CAJA**

**No. 11 - 0087574**

Bogotá D.C., Septiembre 07 de 2011 - 16:53:10

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

| TIPO PAGO | BANCO | CUENTA | No. PAGO | FECHA PAGO | VR.PAGO |
|---|---|---|---|---|---|
| CONSIGNACION | BANCO DE BOGOTA | 062754387 | 325037790 | 07/09/2011 | 52.925.000.00 |

*** Conceptos Pagados ***

| CANT. | RENTISTICO | CONCEPTO | Vr.UNDITARIO | Vr.CONCEPTO |
|---|---|---|---|---|
| 1 | 50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL | 99 OTROS SERVCIOS ADMINISTRATIVOS | 6.000.00 | 6.000.00 |
| | | | | $6.000.00 |

**SON: **SEIS MIL PESOS MONEDA CORRIENTE*****

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

**No. 11-123611- -00000-0000**
Fecha: 2011-09-21 16:56:50 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 694

**No. 11-123611- -00000-0000**
Fecha: 2011-09-21 16:58:50 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 687

2011/013 6

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

Industria y Comercio
SUPERINTENDENCIA

**RECIBO DE CAJA**

**No. 11 - 0082427**

Bogotá D.C., Agosto 25 de 2011 - 06:44:36

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

| TIPO PAGO | BANCO | CUENTA | No. PAGO | FECHA PAGO | VR PAGO |
|---|---|---|---|---|---|
| CONSIGNACION | BANCO DE BOGOTA | 062754387 | 412132932 | 23/08/2011 | 27.000.00 |

*** Conceptos Pagados ***

| CANT. | RENTISTICO | CONCEPTO | Vr UNDITARIO | Vr CONCEPTO |
|---|---|---|---|---|
| 1 | 50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL | 54 INFORMACION DETALLADA DE UN TRAMITE | 27.000.00 | 27.000.00 |
| | | | | $27.000.00 |

**SON: **VEINTISIETE MIL PESOS MONEDA CORRIENTE*****

Responsable: _____
-***-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
**No. 11-123611- -00000-0000**
Fecha: 2011-09-21 16:56:50 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 694

**No. 11-123611- -00000-0000**
Fecha: 2011-09-21 16:56:50 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 687

2011/013

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

Industria y Comercio
SUPERINTENDENCIA

**RECIBO DE CAJA**

**No. 11 - 0082444**

Bogotá D.C., Agosto 25 de 2011 - 06:44:36

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

| TIPO PAGO | BANCO | CUENTA | No. PAGO | FECHA PAGO | VR PAGO |
|---|---|---|---|---|---|
| CONSIGNACION | BANCO DE BOGOTA | 062754387 | 412132932 | 23/08/2011 | 86.000.00 |

*** Conceptos Pagados ***

| CANT | RENTISTICO | CONCEPTO | Vr.UNDITARIO | Vr.CONCEPTO |
|---|---|---|---|---|
| 1 | 50005-01-08 PRORROGA DE TERMINOS | 1608 N.CREACION PRORROGA DE TERMINOS O PLAZO ADICIONAL | 86.000.00 | 86.000.00 |
| | | | | $86.000.00 |

**SON: **OCHENTA Y SEIS MIL PESOS MONEDA CORRIENTE*****

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

**No. 11-123611- -00000-0000**

Fecha: 2011-09-21 16:56:50 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 694

**No. 11-123611- -00000-0000**

Fecha: 2011-09-21 16:56:50 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 687

2011/0138

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

Industria y Comercio
SUPERINTENDENCIA

**RECIBO DE CAJA**

**No. 11 - 0079819**

Bogotá D.C., Agosto 18 de 2011 - 16:59:22

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

| TIPO PAGO | BANCO | CUENTA | No. PAGO | FECHA PAGO | VR PAGO |
|---|---|---|---|---|---|
| CONSIGNACION | BANCO DE BOGOTA | 062754387 | 411692035 | 17/08/2011 | 82.279.000.00 |

*** Conceptos Pagados ***

| CANT. | RENTISTICO | CONCEPTO | Vr.UNDITARIO | Vr.CONCEPTO |
|---|---|---|---|---|
| 1 | 50005-01-03 | CAMBIO DE MODALIDAD Y MODIFICACIONES N.CREACION CORRECCION A SOLICITUD EN TRAMITE / MODOFICA | 118.000.00 | 118.000.00 |
| | | | | $118.000.00 |

**SON: **CIENTO DIECIOCHO MIL PESOS MONEDA CORRIENTE*****

Responsable: _____
*****

Recibo de Caja ~~Aplicado~~ al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
**No. 11-123611- -00000-0000**
Fecha: 2011-09-21 16:56:50 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
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Fecha: 2011-09-21 16:56:50 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 687

Extractos

Industria y Comercio
SUPERINTENDENCIA

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**
**DIVISION DE NUEVAS CREACIONES**
**TARJETA ARCHIVO PROPIETARIOS**

PATENTE DE INVENCION ___ PCT X MODELO DE UTILIDAD ___ DISEÑO INDUSTRIAL ___

(21) N° de solicitud:
(22) Fecha de solicitud:
(51) Clasificación Internacional :

(71)Solicitante(s) BRISTOL-MYERS SQUIBB COMPANY

(72) Inventor(es) BENDER, John A.; HEWAWASAM, Piyasena; KADOW, John F.; LOPEZ, Omar D.; MEANWELL, Nicholas A.; NGUYEN, Van N.; ROMINE, Jeffrey Lee; SNYDER, Lawrence B.; ST. LAURENT, Denis R.; WANG, Gan; XU, Ningning; BELEMA, Makonen.

(74) Apoderado: ALVARO CORREA ORDOÑEZ

| (30) Prioridad | (31) *No. Prioridad* | 32) *Fecha* | (33) *País* |
|---|---|---|---|
| | 61/164,531 | 30/03/2009 | US |
| | 12/729,940 | 23/03/2010 | US |

(85) Fecha inicio fase nacional: 30/10/2011
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 24/03/2010
No. de solicitud PCT/US2010/028456

(87) Publicación internacional
Fecha: 14.10.2010
N° publicación: WO/2010/117635

(54) Titulo: INHIBIDORES DEL VIRUS DE LA HEPATITIS C

Industria y Comercio
SUPERINTENDENCIA

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**
**DIVISION DE NUEVAS CREACIONES**
**TARJETA ARCHIVO TEMATICO**

SUPERINTENDENCIA PATENTE DE INVENCION ___ PCT _X_ MODELO DE UTILIDAD ___ DISEÑO INDUSTRIAL ___

(21) N° de solicitud: (22) Fecha de solicitud:
(51) Clasificación Internacional :

(71)Solicitante(s) BRISTOL-MYERS SQUIBB COMPANY

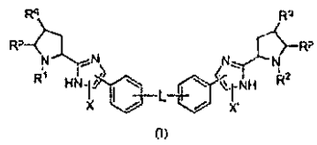
(72) Inventor(es) BENDER, John A.; HEWAWASAM, Piyasena; KADOW, John F.; LOPEZ, Omar D.; MEANWELL, Nicholas A.; NGUYEN, Van N.; ROMINE, Jeffrey Lee; SNYDER, Lawrence B.; ST. LAURENT, Denis R.; WANG, Gan; XU, Ningning; BELEMA, Makonen.

(74) Apoderado: ALVARO CORREA ORDOÑEZ

| (30) Prioridad | (31) *No. Prioridad* | 32) *Fecha* | (33) *País* |
|---|---|---|---|
| | 61/164,531 | 30/03/2009 | US |
| | 12/729,940 | 23/03/2010 | US |

(85) Fecha límite inicio fase nacional: 30/10/2011
(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud: 24/03/2010
No. de solicitud PCT/US2010/028456

(87) Publicación internacional:
Fecha: 14/10/2010
No. Publicación : WO/2010/117635

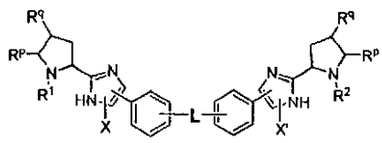


(I)

(54) Titulo:

INHIBIDORES DEL VIRUS DE LA HEPATITIS C

(57) Resumen:
La presente divulgación se refiere a compuestos novedosos de la Fórmula (I) tal como se definen en la memoria descriptiva y a las composiciones que comprenden dichos compuestos novedosos. Estos compuestos son agentes antivirales útiles, especialmente para inhibir la función de la proteína NS5A codificada por el virus de la hepatitis C (VHC). Por lo tanto, la divulgación también se refiere a un procedimiento de tratamiento de enfermedades o afecciones relacionadas con VHC mediante el uso de estos compuestos novedosos o de una composición que comprende dichos compuestos novedosos.



(I)

CONTINUA AL RESPALDO ...

Industria y Comercio
SUPERINTENDENCIA

# SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
## DIVISION DE NUEVAS CREACIONES
### EXTRACTO PARA PUBLICACIÓN
### SOLICITUD DE PATENTE DE INVENCION

(21) N° de solicitud:

22) Fecha de solicitud:

| (30) Prioridad | (31) *No. Prioridad* | 32) *Fecha* | (33) *País* |
|---|---|---|---|
| | 61/164,531 | 30/03/2009 | US |
| | 12/729,940 | 23/03/2010 | US |

(51) Int Cl:

(71)Solicitante(s) **BRISTOL-MYERS SQUIBB COMPANY**

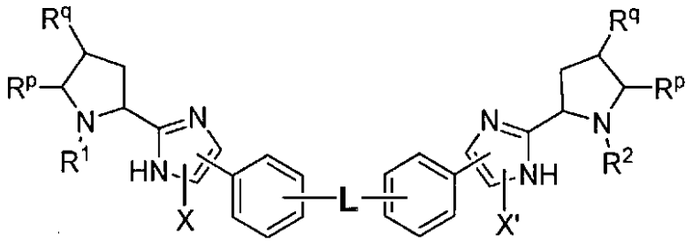
(72) Inventor(es) BENDER, John A.; HEWAWASAM, Piyasena; KADOW, John F.; LOPEZ, Omar D.; MEANWELL, Nicholas A.; NGUYEN, Van N.; ROMINE, Jeffrey Lee; SNYDER, Lawrence B.; ST. LAURENT, Denis R.; WANG, Gan; XU, Ningning; BELEMA, Makonen.

(74) Apoderado: **ALVARO CORREA ORDOÑEZ**

(54) Titulo: INHIBIDORES DEL VIRUS DE LA HEPATITIS C


Resumen:

La presente divulgación se refiere a compuestos novedosos de la Fórmula (I) tal como se definen en la memoria descriptiva y a las composiciones que comprenden dichos compuestos novedosos. Estos compuestos son agentes antivirales útiles, especialmente para inhibir la función de la proteína NS5A codificada por el virus de la hepatitis C (VHC). Por lo tanto, la divulgación también se refiere a un procedimiento de tratamiento de enfermedades o afecciones relacionadas con VHC mediante el uso de estos compuestos novedosos o de una composición que comprende dichos compuestos novedosos.


(I)

Documentos Solicitud
Internacional

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 October 2010 (14.10.2010)

PCT

(10) International Publication Number
WO 2010/117635 A1

(51) International Patent Classification:
*C07D 403/04* (2006.01) *A61K 31/4178* (2006.01)
*C07D 403/14* (2006.01) *A61P 31/14* (2006.01)
*C07D 405/14* (2006.01)

(21) International Application Number:
PCT/US2010/028456

(22) International Filing Date:
24 March 2010 (24.03.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/164,531 30 March 2009 (30.03.2009) US
12/729,940 23 March 2010 (23.03.2010) US

(71) Applicant *(for all designated States except US)*: **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; P.O. Box 4000, Route 206 and ProvinceLine Road, Princeton, New Jersey 08543-4000 (US).

(72) Inventors; and

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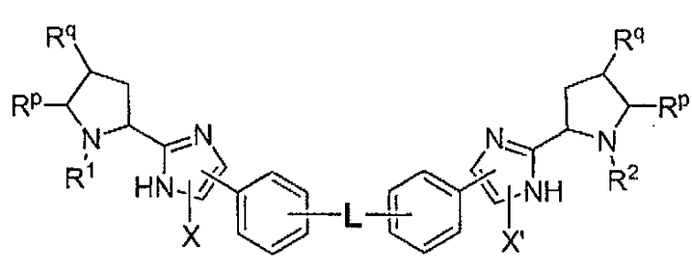
(74) Agents: **MINGO, Pamela A.** et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, New Jersey 08543-4000 (US).

(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, RO, RS, RU, 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.

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*[Continued on next page]*

(54) Title: HEPATITIS C VIRUS INHIBITORS



(I)

(57) Abstract: This disclosure concerns novel compounds of Formula (I) as defined in the specification and compositions comprising such novel compounds. These compounds are useful antiviral agents, especially in inhibiting the function of the NS5A protein encoded by Hepatitis C virus (HCV). Thus, the disclosure also concerns a method of treating HCV related diseases or conditions by use of these novel compounds or a composition comprising such novel compounds.

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# HEPATITIS C VIRUS INHIBITORS

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial Number 61/164,531 filed March 30, 2009.

## FIELD OF THE DISCLOSURE

The present disclosure is generally directed to antiviral compounds, and more specifically directed to compounds which can inhibit the function of the NS5A protein encoded by Hepatitis C virus (HCV), compositions comprising such compounds, and methods for inhibiting the function of the NS5A protein.

## BACKGROUND OF THE DISCLOSURE

HCV is a major human pathogen, infecting an estimated 170 million persons worldwide - roughly five times the number infected by human immunodeficiency virus type 1. A substantial fraction of these HCV infected individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma.

The current standard of care for HCV, which employs a combination of pegylated-interferon and ribavirin, has a non-optimal success rate in achieving sustained viral response and causes numerous side effects. Thus, there is a clear and long-felt need to develop effective therapies to address this undermet medical need.

HCV is a positive-stranded RNA virus. Based on a comparison of the deduced amino acid sequence and the extensive similarity in the 5' untranslated region, HCV has been classified as a separate genus in the Flaviviridae family. All members of the Flaviviridae family have enveloped virions that contain a positive stranded RNA genome encoding all known virus-specific proteins via translation of a single, uninterrupted, open reading frame.

Considerable heterogeneity is found within the nucleotide and encoded amino acid sequence throughout the HCV genome due to the high error rate of the encoded RNA dependent RNA polymerase which lacks a proof-reading capability. At least six major genotypes have been characterized, and more than 50 subtypes have been

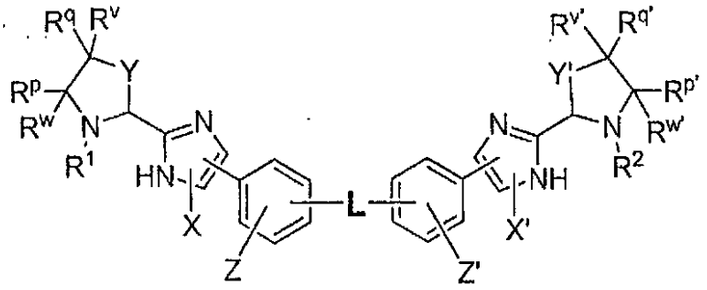
described with distribution worldwide. The clinical significance of the genetic heterogeneity of HCV has demonstrated a propensity for mutations to arise during monotherapy treatment, thus additional treatment options for use are desired. The possible modulator effect of genotypes on pathogenesis and therapy remains elusive.

The single strand HCV RNA genome is approximately 9500 nucleotides in length and has a single open reading frame (ORF) encoding a single large polyprotein of about 3000 amino acids. In infected cells, this polyprotein is cleaved at multiple sites by cellular and viral proteases to produce the structural and non-structural (NS) proteins. In the case of HCV, the generation of mature non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) is effected by two viral proteases. The first one is believed to be a metalloprotease and cleaves at the NS2-NS3 junction; the second one is a serine protease contained within the N-terminal region of NS3 (also referred to herein as NS3 protease) and mediates all the subsequent cleavages downstream of NS3, both in cis, at the NS3-NS4A cleavage site, and in trans, for the remaining NS4A-NS4B, NS4B-NS5A, NS5A-NS5B sites. The NS4A protein appears to serve multiple functions by both acting as a cofactor for the NS3 protease and assisting in the membrane localization of NS3 and other viral replicase components. The formation of a NS3-NS4A complex is necessary for proper protease activity resulting in increased proteolytic efficiency of the cleavage events. The NS3 protein also exhibits nucleoside triphosphatase and RNA helicase activities. NS5B (also referred to herein as HCV polymerase) is a RNA-dependent RNA polymerase that is involved in the replication of HCV with other HCV proteins, including NS5A, in a replicase complex.

Compounds useful for treating HCV-infected patients are desired which selectively inhibit HCV viral replication. In particular, compounds which are effective to inhibit the function of the NS5A protein are desired. The HCV NS5A protein is described, for example, in the following references: S. L. Tan, et al., *Virology*, 284:1-12 (2001); K.-J. Park, et al., *J. Biol. Chem.*, 30711-30718 (2003); T. L. Tellinghuisen, et al., *Nature*, **435**, 374 (2005); R. A. Love, et al., *J. Virol*, **83**,

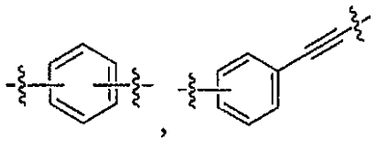
4395 (2009); N. Appel, et al., *J. Biol. Chem.*, **281**, 9833 (2006); L. Huang, *J. Biol. Chem.*, **280**, 36417 (2005); C. Rice, et al., WO2006093867.

The present disclosure provides compounds which selectively inhibit HCV viral replication, as characterized by Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

L is selected from –O–, $-CH_2CH_2-$, –CH=CH–, –C≡C–, $-OCH_2-$, $-CH_2O-$, $-CH_2OCH_2-$,  , and  ;

X is hydrogen (H) or halogen and Z is hydrogen; or

X and Z, together with the carbon atoms to which they are attached, form a five- to eight-membered aromatic or non-aromatic fused ring optionally containing one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the five- to eight-membered ring is optionally substituted with one, two, or three substitutents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylsulfonyl, aryl, arylalkyl, arylsulfonyl, carboxy, formyl, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, $(NR^aR^b)$alkyl, $(NR^aR^b)$carbonyl, oxo, and spirocycle;

X' is hydrogen (H) or halogen and Z' is hydrogen; or

X' and Z', together with the carbon atoms to which they are attached, form a five- to eight-membered aromatic or non-aromatic fused ring optionally containing one or two heteroatoms independently selected from nitrogen,

oxygen, and sulfur; wherein the five- to eight-membered ring is optionally substituted with one, two, or three substitutents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylsulfonyl, aryl, arylalkyl, arylsulfonyl, carboxy, formyl, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, $(NR^aR^b)$alkyl, $(NR^aR^b)$carbonyl, oxo, and spirocycle;

Y and Y' are each independently $-CH_2-$, $-CH_2CH_2-$, or $-CH_2O-$, wherein the $-CH_2O-$ is drawn such that the oxygen atom is bound to the carbon atom substituted with $R^v$ and $R^q$ or $R^{v'}$ and $R^{q'}$;

$R^p$ is hydrogen or $C_1$ to $C_4$ alkyl;

$R^q$ is hydrogen, alkyl, or halo; or

$R^p$ and $R^q$, together with the carbon atoms to which they are attached, form a cycloalkyl ring;

$R^v$ is selected from hydrogen, alkyl, halo, and hydroxy; or

$R^v$ and $R^q$, together with the carbon atom to which they are attached, form an ethylenyl group or a cycloalkyl ring;

$R^{p'}$ is hydrogen or $C_1$ to $C_4$ alkyl;

$R^{q'}$ is hydrogen, alkyl, or halo; or

$R^{p'}$ and $R^{q'}$, together with the carbon atoms to which they are attached, form a cycloalkyl ring;

$R^{v'}$ are independently selected from hydrogen, alkyl, halo, and hydroxy; or

$R^{v'}$ and $R^{q'}$, together with the carbon atom to which they are attached, form an ethylenyl group or a cycloalkyl ring;

$R^w$ and $R^{w'}$ are independently selected from hydrogen and alkyl;

$R^1$ is hydrogen or $-C(O)R^x$;

$R^2$ is hydrogen or $-C(O)R^y$;

$R^x$ and $R^y$ are independently selected from cycloalkyl, heteroaryl, heterocyclyl, alkoxy, and alkyl, said alkyl being substituted by one or more substituents independently selected from aryl, alkenyl, cycloalkyl, heterocyclyl, heteroaryl, $-OR^3$, $-C(O)OR^4$, $-NR^aR^b$, and $-C(O)NR^cR^d$, wherein any said aryl and heteroaryl may optionally be substituted with one or more substituents independently selected from alkenyl, alkyl, haloalkyl,

arylalkyl, heterocyclyl, heterocyclylalkyl, halogen, cyano, nitro, -C(O)OR$^4$, -OR$^5$, -NR$^a$R$^b$, (NR$^a$R$^b$)alkyl, and (MeO)(HO)P(O)O-, and

wherein any said cycloalkyl and heterocyclyl may optionally be fused onto an aromatic ring and may optionally be substituted with one or more substituents independently selected from alkyl, hydroxyl, halogen, aryl, -NR$^a$R$^b$, oxo, and -C(O)OR$^4$;

R$^3$ is hydrogen, alkyl, or arylalkyl;

R$^4$ is alkyl or arylalkyl;

R$^5$ is hydrogen, alkyl, or arylalkyl;

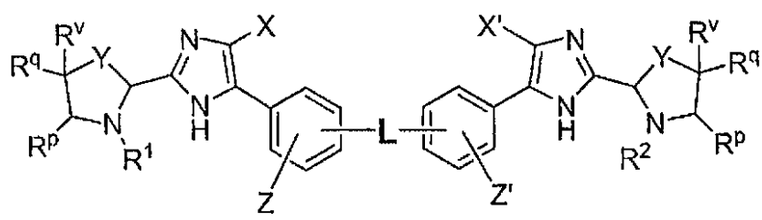
R$^a$ and R$^b$ are independently selected from hydrogen, alkyl, cycloalkyl, arylalkyl, heteroaryl, -C(O)R$^6$, -C(O)OR$^7$, –C(O)NR$^c$R$^d$, and (NR$^c$R$^d$)alkyl, or alternatively, R$^a$ and R$^b$, together with the nitrogen atom to which they are attached, form a five- or six-membered ring or bridged bicyclic ring structure, wherein said five- or six-membered ring or bridged bicyclic ring structure optionally may contain one or two additional heteroatoms independently selected from nitrogen, oxygen, and sulfur and may contain one, two, or three substituents independently selected from $C_1$ to $C_6$ alkyl, $C_1$ to $C_4$ haloalkyl, aryl, hydroxyl, $C_1$ to $C_6$ alkoxy, $C_1$ to $C_4$ haloalkoxy, and halogen;

R$^6$ is alkyl;

R$^7$ is alkyl, arylalkyl, cycloalkyl, or haloalkyl; and

R$^c$ and R$^d$ are independently selected from hydrogen, alkyl, arylalkyl, and cycloalkyl.

In a first embodiment of the first aspect the present disclosure provides a compound of Formula (I) further characterized by Formula (Ia):



(Ia),

or a pharmaceutically acceptable salt or a tautomer thereof, wherein:

X is hydrogen or chloro (Cl) and Z is hydrogen; or

X and Z, together with the carbon atoms to which they are attached, form a six-membered aromatic or non-aromatic fused ring;

X' is hydrogen or chloro (Cl) and Z' is hydrogen; or

X' and Z', together with the carbon atoms to which they are attached, form a six-membered aromatic or non-aromatic fused ring;

Y is $-CH_2-$, $-CH_2CH_2-$, or $-CH_2O-$, wherein the $-CH_2O-$ is drawn such that the oxygen atom is bound to the carbon atom substituted with $R^v$ and $R^q$;

$R^p$ is hydrogen or $C_1$ to $C_4$ alkyl;

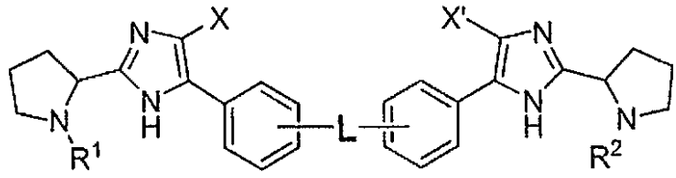
$R^q$ is hydrogen, alkyl, or halo; or

$R^p$ and $R^q$, together with the carbon atoms to which they are attached, form a cycloalkyll ring; and

$R^v$ is selected from hydrogen, alkyl, halo, and hydroxy; or

$R^v$ and $R^q$, together with the carbon atom to which they are attached, form an ethylenyl group or a cycloalkyl ring.

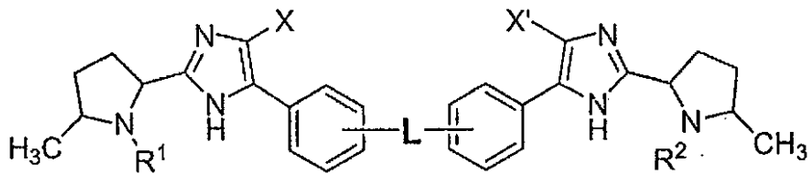
In a second embodiment of the first aspect the present disclosure provides a compound of Formula (I) further characterized by Formula (Ib):



(Ib),

or a pharmaceutically acceptable salt or a tautomer thereof.

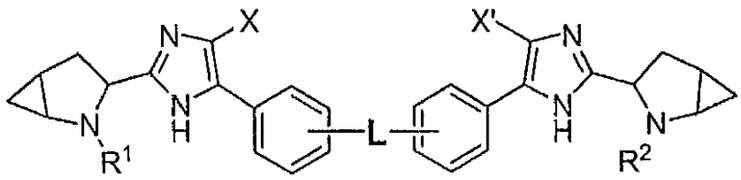
In a third embodiment of the first aspect the present disclosure provides a compound of Formula (I) further characterized by Formula (Ic):



(Ic),

or a pharmaceutically acceptable salt or a tautomer thereof.

In a fourth embodiment of the first aspect the present disclosure provides a compound of Formula (I) further characterized by Formula (Id):



(Id),

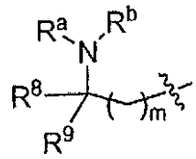
or a pharmaceutically acceptable salt or a tautomer thereof.

In a fifth embodiment of the first aspect the present disclosure provides a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein:

$R^1$ is $-C(O)R^x$;

$R^2$ is $-C(O)R^y$;

$R^x$ and $R^y$ are independently alkyl substituted by at least one $-NR^aR^b$, characterized by Formula (A):



(A),

wherein:

m is 0 or 1;

$R^8$ is hydrogen or alkyl;

$R^9$ is selected from hydrogen, cycloalkyl, aryl, heteroaryl, heterocyclyl, and alkyl optionally substituted with a substituent selected from aryl, alkenyl, cycloalkyl, heterocyclyl, heteroaryl, heterobicyclyl, $-OR^3$, $-C(O)OR^4$, $-NR^aR^b$, and $-C(O)NR^cR^d$,

wherein any said aryl and heteroaryl may optionally be substituted with one or more substituents independently selected from alkyl, haloalkyl, arylalkyl, heterocyclyl, heterocyclylalkyl, halogen, cyano, nitro, $-C(O)OR^4$, $-OR^5$, $-NR^aR^b$, $(NR^aR^b)$alkyl, and (MeO)(HO)P(O)O-, and

wherein any said cycloalkyl and heterocyclyl may optionally be fused onto an aromatic ring and may optionally be substituted with one or more substituents

independently selected from alkyl, hydroxyl, halogen, aryl, $-NR^aR^b$, oxo, and $-C(O)OR^4$; and

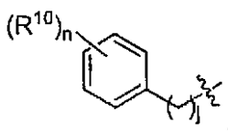
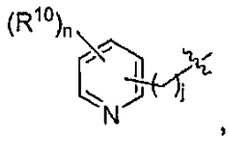
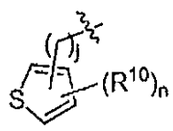
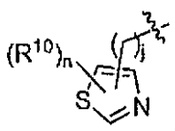
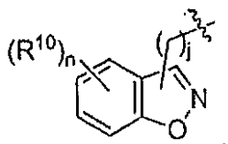
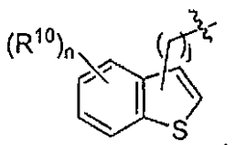
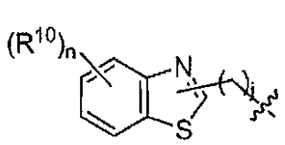
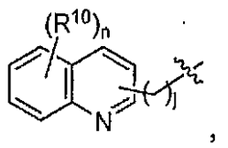
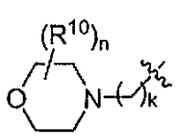
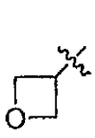
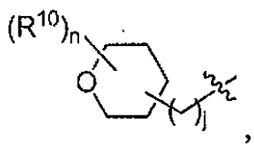
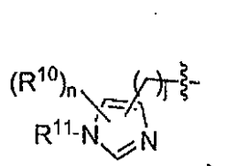
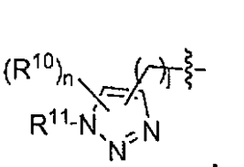
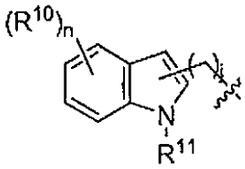
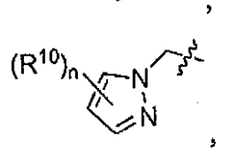
$R^3$, $R^4$, $R^5$, $R^a$, $R^b$, $R^c$, and $R^d$ are defined as in Formula (I).

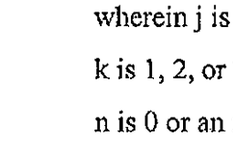
In a sixth embodiment of the first aspect the present disclosure provides a compound of Formula (Ia) or a pharmaceutically acceptable salt thereof, wherein

m is 0;

$R^8$ is hydrogen or $C_1$ to $C_4$ alkyl;

$R^9$ is selected from hydrogen, $C_1$ to $C_6$ alkyl optionally substituted with $-OR^{12}$, $C_3$ to $C_6$ cycloalkyl, allyl, $-CH_2C(O)NR^cR^d$, $(NR^cR^d)$alkyl,

wherein j is 0 or 1;

k is 1, 2, or 3;

n is 0 or an integer selected from 1 through 4;

each $R^{10}$ is independently hydrogen, $C_1$ to $C_4$ alkyl, $C_1$ to $C_4$ haloalkyl, halogen, nitro, -OBn, or (MeO)(OH)P(O)O-;

$R^{11}$ is hydrogen, $C_1$ to $C_4$ alkyl, or benzyl;

$R^{12}$ is hydrogen, $C_1$ to $C_4$ alkyl, or benzyl;

$R^a$ is hydrogen or $C_1$ to $C_4$ alkyl;

$R^b$ is $C_1$ to $C_4$ alkyl, $C_3$ to $C_6$ cycloalkyl, benzyl, 3-pyridyl, pyrimidin-5-yl, acetyl, $-C(O)OR^7$, or $-C(O)NR^cR^d$;

$R^7$ is $C_1$ to $C_4$ alkyl or $C_1$ to $C_4$ haloalkyl;

$R^c$ is hydrogen or $C_1$ to $C_4$ alkyl; and

$R^d$ is hydrogen, $C_1$ to $C_4$ alkyl, or $C_3$ to $C_6$ cycloalkyl.

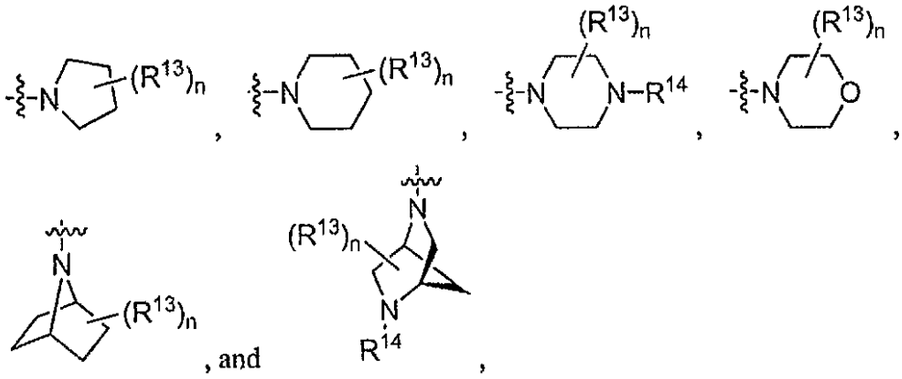
In a seventh embodiment of the first aspect the present disclosure provides a compound of Formula (Ia) or a pharmaceutically acceptable salt thereof, wherein

m is 0;

$R^8$ is hydrogen;

$R^9$ is phenyl optionally substituted with one up to five substituents independently selected from $C_1$ to $C_6$ alkyl, $C_1$ to $C_4$ haloalkyl, halogen, $C_1$ to $C_6$ alkoxy, hydroxyl, cyano, and nitro; and

$NR^aR^b$ is a heterocyclyl or heterobicyclyl group selected from:



wherein n is 0, 1, or 2;

each $R^{13}$ is independently selected from $C_1$ to $C_6$ alkyl, phenyl, trifluoromethyl, halogen, hydroxyl, methoxy, and oxo; and

$R^{14}$ is $C_1$ to $C_6$ alkyl, phenyl, benzyl, or $-C(O)OR^{15}$ group, wherein $R^{15}$ is $C_1$ to $C_4$ alkyl, phenyl, or benzyl.

In an eighth embodiment of the first aspect the present disclosure provides a compound of Formula (Ia) or a pharmaceutically acceptable salt thereof, wherein

m is 1;

$R^8$ is hydrogen;

$R^9$ is $C_1$ to $C_6$ alkyl, arylalkyl, or heteroarylalkyl;

$R^a$ is hydrogen; and

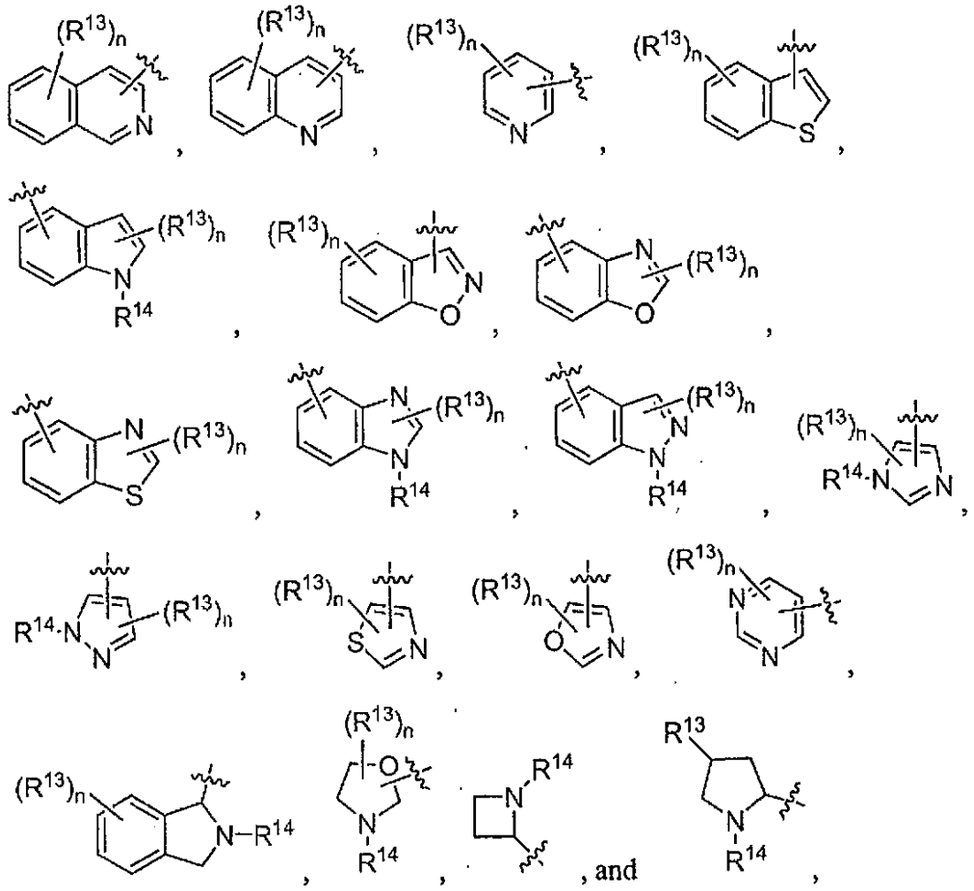
$R^b$ is $-C(O)OR^7$, wherein $R^7$ is $C_1$ to $C_6$ alkyl.

In a ninth embodiment of the first aspect the present disclosure provides a compound of Formula (Ia) or a pharmaceutically acceptable salt thereof, wherein

$R^1$ is $-C(O)R^x$;

$R^2$ is $-C(O)R^y$;

$R^x$ and $R^y$ are heteroaryl or heterocyclyl independently selected from:



wherein n is 0 or an integer selected from 1 through 4;

each $R^{13}$ is independently selected from hydrogen, $C_1$ to $C_6$ alkyl, $C_1$ to $C_4$ haloalkyl, phenyl, benzyl, $C_1$ to $C_6$ alkoxy, $C_1$ to $C_4$ haloalkoxy, heterocyclyl, halogen, $NR^cR^d$, hydroxyl, cyano, and oxo, where $R^c$ and $R^d$ are independently hydrogen or $C_1$ to $C_4$ alkyl; and

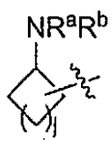
$R^{14}$ is hydrogen (H), $C_1$ to $C_6$ alkyl, benzyl, or $-C(O)OR^4$, wherein $R^4$ is $C_1$ to $C_6$ alkyl.

In a tenth embodiment of the first aspect the present disclosure provides a compound of Formula (Ia) or a pharmaceutically acceptable salt thereof, wherein

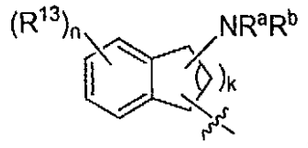
$R^1$ is $-C(O)R^x$;

$R^2$ is $-C(O)R^y$;

$R^x$ and $R^y$ are cycloalkyl independently selected from:




and




,

wherein

j is 0, 1, 2, or 3;

k is 0, 1, or 2;

n is 0 or an integer selected from 1 through 4;

each $R^{13}$ is independently selected from hydrogen, $C_1$ to $C_6$ alkyl, $C_1$ to $C_4$ haloalkyl, $C_1$ to $C_6$ alkoxy, halogen, hydroxyl, cyano, and nitro; and

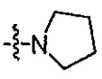
$R^a$ and $R^b$ are each independently hydrogen, $C_1$ to $C_6$ alkyl, or $-C(O)OR^7$, wherein $R^7$ is $C_1$ to $C_6$ alkyl.

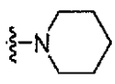
In an eleventh embodiment of the first aspect the present disclosure provides a compound of Formula (Ia) or a pharmaceutically acceptable salt thereof, wherein

$R^1$ is $-C(O)R^x$;

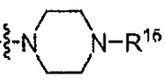
$R^2$ is $-C(O)R^y$;

$R^x$ and $R^y$ are independently arylalkyl, wherein aryl part of said arylalkyl may optionally be substituted with $(NR^aR^b)$alkyl; and

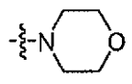
$R^a$ and $R^b$ are independently hydrogen, $C_1$ to $C_6$ alkyl, or benzyl, or alternatively, $R^a$ and $R^b$, together with the nitrogen atom to which they are attached, form a five- or six-membered ring selected from  ,




,



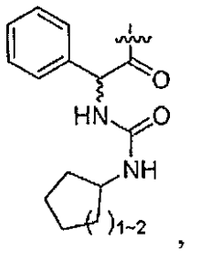
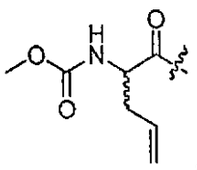
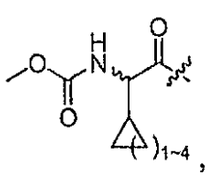
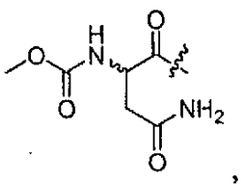
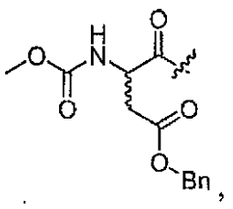
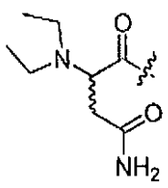
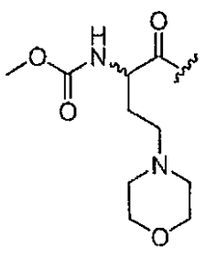
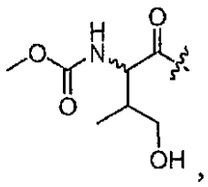
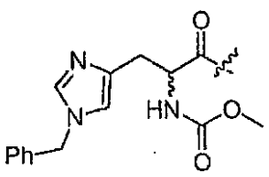
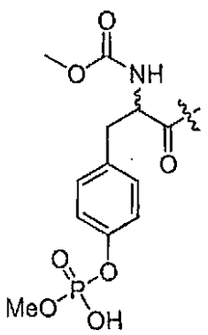
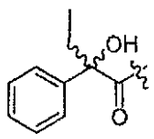
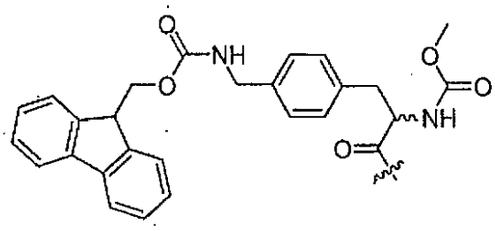

, and




, wherein $R^{15}$ is hydrogen, $C_1$ to $C_6$ alkyl, or benzyl.

In a twelfth embodiment of the first aspect the present disclosure provides a compound of Formula (Ia) or a pharmaceutically acceptable salt thereof, wherein

$R^1$ and $R^2$ are the same and are selected from the group consisting of:


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wherein a squiggle bond ( ~~~ ) in the structure indicates that a stereogenic center to which the bond is attached can take either (R)- or (S)- configuration so long as chemical bonding principles are not violated.

In a thirteenth embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein

$R^1$ is $-C(O)R^x$;

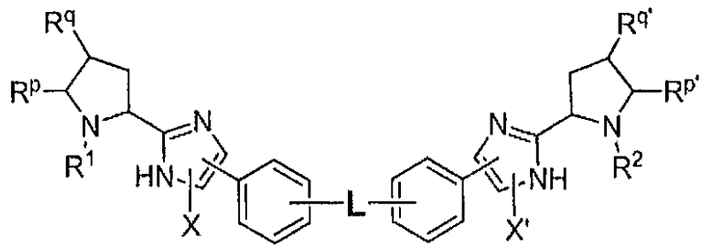
$R^2$ is $-C(O)R^y$; and

$R^x$ and $R^y$ are both t-butoxy.

In a fourteenth embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein

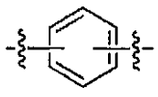
$R^1$ and $R^2$ are both hydrogen.

In a second aspect the present disclosure provides a compound of Formula (II):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

L is selected from –O–, $–CH_2CH_2–$, –CH=CH–, –C≡C–, $–OCH_2–$, $-CH_2O–$, $-CH_2OCH_2–$,  , and  ;

X and X′ are independently hydrogen (H) or halogen;

$R^p$ is hydrogen or $C_1$ to $C_4$ alkyl, and $R^q$ is hydrogen, or alternatively, $R^p$ and $R^q$, together with the carbon atoms to which they are attached, form a cyclopropyl ring;

$R^{p'}$ is hydrogen or $C_1$ to $C_4$ alkyl, and $R^{q'}$ is hydrogen, or alternatively, $R^{p'}$ and $R^{q'}$, together with the carbon atoms to which they are attached, form a cyclopropyl ring;

$R^1$ is hydrogen or $–C(O)R^x$;

$R^2$ is hydrogen or $–C(O)R^y$;

$R^x$ and $R^y$ are independently selected from cycloalkyl, heteroaryl, heterocyclyl, alkoxy, and alkyl, said alkyl being substituted by one or more substituents independently selected from aryl, alkenyl, cycloalkyl, heterocyclyl, heteroaryl, $-OR^3$, $-C(O)OR^4$, $-NR^aR^b$, and $-C(O)NR^cR^d$,

wherein any said aryl and heteroaryl may optionally be substituted with one or more substituents independently selected from alkyl, haloalkyl, arylalkyl, heterocyclyl, heterocyclylalkyl, halogen, cyano, nitro, -C(O)OR$^4$, -OR$^5$, -NR$^a$R$^b$, (NR$^a$R$^b$)alkyl, and (MeO)(HO)P(O)O-, and

wherein any said cycloalkyl and heterocyclyl may optionally be fused onto an aromatic ring and may optionally be substituted with one or more substituents independently selected from alkyl, hydroxyl, halogen, aryl, -NR$^a$R$^b$, oxo, and -C(O)OR$^4$;

R$^3$ is hydrogen, alkyl, or arylalkyl;

R$^4$ is alkyl or arylalkyl;

R$^5$ is hydrogen, alkyl, or arylalkyl;

R$^a$ and R$^b$ are independently selected from hydrogen, alkyl, cycloalkyl, arylalkyl, heteroaryl, -C(O)R$^6$, -C(O)OR$^7$, –C(O)NR$^c$R$^d$, and (NR$^c$R$^d$)alkyl, or alternatively, R$^a$ and R$^b$, together with the nitrogen atom to which they are attached, form a five- or six-membered ring or bridged bicyclic ring structure, wherein said five- or six-membered ring or bridged bicyclic ring structure optionally may contain one or two additional heteroatoms independently selected from nitrogen, oxygen, and sulfur and may contain one, two, or three substituents independently selected from $C_1$ to $C_6$ alkyl, $C_1$ to $C_4$ haloalkyl, aryl, hydroxyl, $C_1$ to $C_6$ alkoxy, $C_1$ to $C_4$ haloalkoxy, and halogen;

R$^6$ is alkyl;

R$^7$ is alkyl, arylalkyl, or haloalkyl; and

R$^c$ and R$^d$ are independently selected from hydrogen, alkyl, arylalkyl, and cycloalkyl.

In a third aspect the present disclosure provides a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, wherein Formula (I) is defined according to any of the embodiments described above in the first aspect of the present disclosure.

In a first embodiment of the third aspect the composition further comprises at least one additional compound having anti-HCV activity.

In a second embodiment of the third aspect at least one of the additional compounds is an interferon or a ribavirin.

In a third embodiment of the third aspect the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

In a fourth embodiment of the third aspect the present disclosure provides a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, and at least one additional compound having anti-HCV activity, wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5′-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

In a fifth embodiment of the third aspect the present disclosure provides a composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, and at least one additional compound having anti-HCV activity, wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

In a fourth aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein Formula (I) is defined according to any of the embodiments described above in the first aspect of the present disclosure.

In a first embodiment of the fourth aspect the method further comprises administering at least one additional compound having anti-HCV activity prior to, after or simultaneously with the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In a second embodiment of the fourth aspect at least one of the additional compounds is an interferon or a ribavirin.

In a third embodiment of the fourth aspect the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

In a fourth embodiment of the fourth aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one additional compound having anti-HCV activity prior to, after or simultaneously with the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

In a fifth embodiment of the fourth aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one additional compound having anti-HCV activity prior to, after or simultaneously with the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

The compounds of the present disclosure can be effective to inhibit the function of the HCV NS5A protein. In particular, the compounds of the present disclosure can be effective to inhibit the HCV 1b genotype or multiple genotypes of HCV.

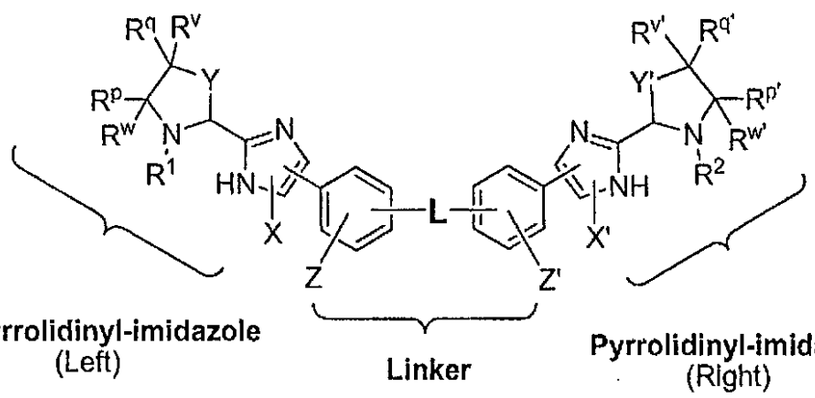
Therefore, this disclosure also encompasses: (1) compositions comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier; and (2) a method of treating an HCV infection in

a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

Other aspects of the present disclosure may include suitable combinations of embodiments disclosed herein.

Yet other aspects and embodiments may be found in the description provided herein. The description of the present disclosure herein should be construed in congruity with the laws and principals of chemical bonding. In some instances it may be necessary to remove a hydrogen atom in order to accommodate a substituent at any given location.

Certain features of the structure of Formula (I) are further illustrated below:

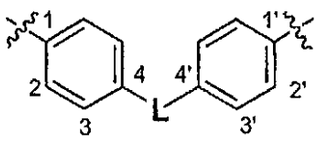



(I).

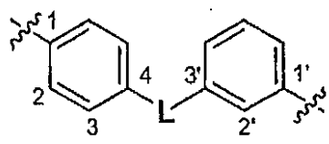
In Formula (I), as depicted above, the "pyrrolidinyl-imidazole" moiety on the left side of the "linker" is independent from the "pyrrolidinyl-imidazole" moiety on the right side of the linker group in respect to, *e.g.*, (1) tautomer form of imidazole ring, (2) absolute configuration of the stereogenic centers on the pyrrolidine ring, and (3) substituents on the pyrrolidine nitrogen, *i.e.*, $R^1$ and $R^2$ are independent from each other, although in some circumstances they are preferably the same.

It should be understood that the depiction of a pyrrolidine moiety on the "left" side or on the "right" side is for illustration purpose only, which does not in any way limit the scope of the disclosure.

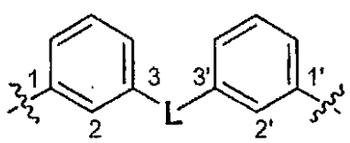
In the linker group of Formula (I), the linkage between "L" and the two benzene rings encompasses all the following combinations:



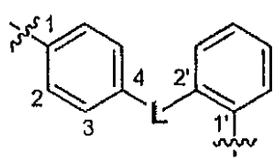

(para-para),



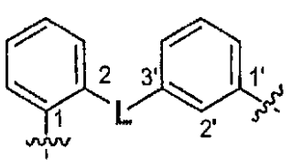

(para-meta),



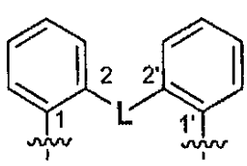

(meta-meta),




(para-ortho),

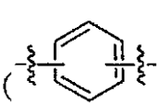


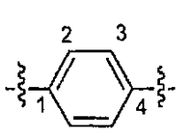

(meta-ortho), and



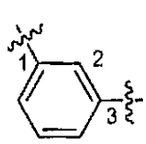

(ortho-ortho),

wherein the "para-para," "para-meta," and "meta-meta" linkages are preferred.

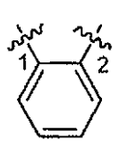
Likewise, in Formula (I), when L is a phenylene (  ) group, it can link to the adjacent two benzene rings by the following manners:




(para),



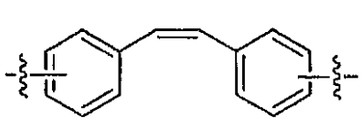

(meta), and



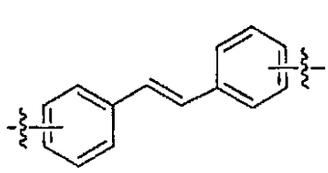

(ortho),

wherein the "para" and "meta" arrangements are preferred, and the "para" arrangement is the more preferred.

In Formula (I), when L is a vinylene (-CH=CH-) group, it can take either trans- or cis-configuration, as depicted below:

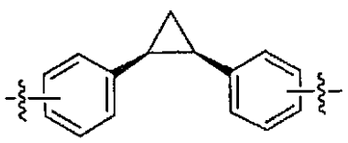
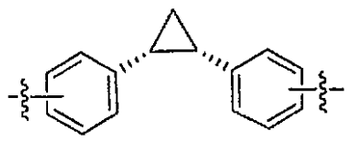
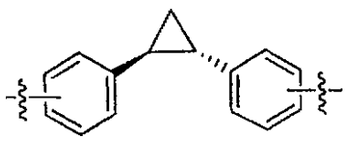
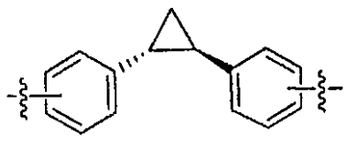


(cis-),

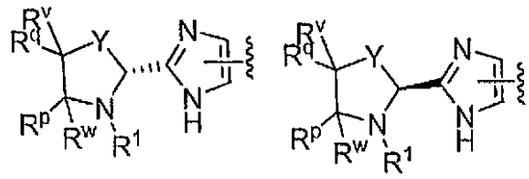


(trans-).

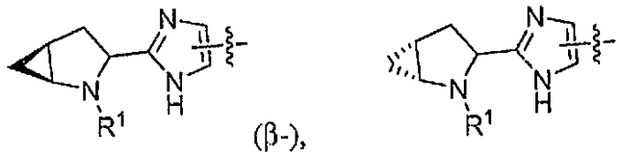
In Formula (I), when L is a cyclopropylene (  ) group, the two benzene substituents can be either trans- or cis- to each other, forming one of the following four configurations:


(cis-),

(cis-),

(trans-),

(trans-).

In a pyrrolidine ring of a pyrrolidinyl-imidazole moiety, the stereogenic carbon center to which the imidazole group is attached can take either (R)- or (S)- configuration as depicted below:

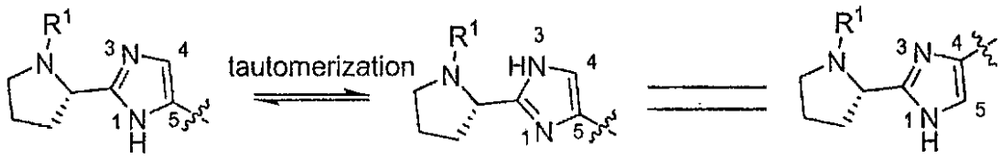

(R-) (S-)

When a cyclopropyl ring is fused onto a pyrrolidine ring of a pyrrolidinyl-imidazole moiety, *i.e.*, when ($R^p$, $R^q$) together is $-CH_2-$, the $CH_2$ group of the fused cyclopropyl ring can take either α- or β- position relative to the pyrrolidine ring, as depicted below:


(β-), (α-).

Thus, this disclosure is intended to cover all possible stereoisomers even when a single stereoisomer, or no stereochemistry, is described in a structure.

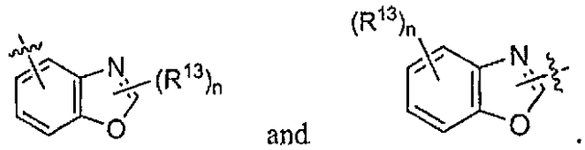
In Formula (I), the linkage between a benzene ring of the linker group and an imidazole ring of a pyrrolidinyl-imidazole moiety can take place in either the C-4 or the C-5 position (see below) of the imidazole ring. As a person of ordinary skill in the art would understand, due to tautomerization of the imidazole ring, a bonding of a benzene ring to the C-4 position may be equivalent to a bonding of the benzene ring to the C-5 position, as shown in the following equation:




The sample principle also applies to substituent X or X'.

Thus, this disclosure is intended to cover all possible tautomers even when a structure depicts only one of them.

In this disclosure, a floating bond (*e.g.*, $\overset{\xi}{\frown}$) or a floating substituent (*e.g.*, -$R^{13}$) on a structure indicates that the bond or substituent can attach to any available position of the structure by removal of a hydrogen from the available position. It should be understood that in a bicyclic or polycyclic ring structure, unless specifically defined otherwise, the position of a floating bond or a floating substituent does not limit the position of such bond or substituent to a specific ring. Thus, the following two substituents should be construed to be equivalent:




It should be understood that the compounds encompassed by the present disclosure are those that are suitably stable for use as pharmaceutical agent.

It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. For example, for substituent $(R^{10})_n$, when n is 2, each of the two $R^{10}$ groups may be the same or different.

All patents, patent applications, and literature references cited in the specification are herein incorporated by reference in their entirety. In the case of inconsistencies, the present disclosure, including definitions, will prevail.

## DEFINITIONS

Definitions have been provided above for each of the groups defined. In addition, the following definitions shall be used.

As used herein, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise.

Unless stated otherwise, all aryl, cycloalkyl, heteroaryl, and heterocyclyl groups of the present disclosure may be substituted as described in each of their respective definitions. For example, the aryl part of an arylalkyl group may be substituted as described in the definition of the term "aryl."

The term "acetyl," as used herein, refers to $-C(O)CH_3$.

The term "alkenyl," as used herein, refers to a monovalent, straight or branched hydrocarbon chain having one or more, preferably one to two, double bonds therein. The double bond of an alkenyl group can be unconjugated or conjugated to another unsaturated group. Suitable alkenyl groups include, but are not limited to, $C_2$ to $C_{10}$ alkenyl groups, such as vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, 4-(2-methyl-3-butene)-pentenyl. An alkenyl group can be unsubstituted or substituted with one or two suitable substituents.

The term "alkoxy," as used herein, refers to an alkyl group attached to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy group include, but are not limited to, methoxy ($CH_3O$-), ethoxy ($CH_3CH_2O$-), and t-butoxy ($(CH_3)_3CO$-).

The term "alkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkoxy groups.

The term "alkoxycarbonyl," as used herein, refers to an alkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "alkyl," as used herein, refers to a group derived from a straight or branched chain saturated hydrocarbon by removal of a hydrogen from one of the saturated carbons. The alkyl group preferably contains from one to ten carbon atoms. Representative examples of alkyl group include, but are not limited to, methyl, ethyl, isopropyl, and *tert*-butyl.

The term "alkylcarbonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a carbonyl group. Representative examples of alkylcarbonyl group include, but are not limited to, acetyl ($-C(O)CH_3$), propanoyl

(-C(O)$CH_2CH_3$), n-butyryl (-C(O)$CH_2CH_2CH_3$), and 2,2-dimethylpropanoyl or pivaloyl (-C(O)$C(CH_3)_3$).

The term "alkylsulfonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfonyl group.

The term "allyl," as used herein, refers to the $-CH_2CH=CH_2$ group.

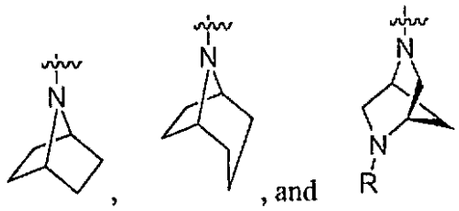
The term "aryl," as used herein, refers to a group derived from an aromatic carbocycle by removal of a hydrogen atom from an aromatic ring. The aryl group can be monocyclic, bicyclic or polycyclic, wherein in bicyclic or polycyclic aryl group, the aromatic carbocycle can be fused onto another four- to six-membered aromatic or non-aromatic carbocycle. Representative examples of aryl groups include, but are not limited to, phenyl, indanyl, indenyl, naphthyl, and 1,2,3,4-tetrahydronaphth-5-yl.

The term "arylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three aryl groups, wherein aryl part of the arylalkyl group may optionally be substituted by one to five substituents independently selected from $C_1$ to $C_6$ alkyl, $C_1$ to $C_4$ haloalkyl, $C_1$ to $C_6$ alkoxy, halogen, cyano, and nitro groups. Represented examples of arylalkyl include, but are not limited to, benzyl, 2-phenyl-1-ethyl ($PhCH_2CH_2$-), (naphth-1-yl)methyl, and (naphth-2-yl)methyl.

The term "arylsulfonyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a sulfonyl group.

The term "benzyl," as used herein, refers to a methyl group on which one of the hydrogen atoms is replaced by a phenyl group, wherein said phenyl group may optionally be substituted by one to five substituents independently selected from methyl, trifluoromethyl (-$CF_3$), methoxy (-$OCH_3$), halogen, and nitro (-$NO_2$). Representative examples of benzyl group include, but are not limited to, $PhCH_2$-, 4-MeO-$C_6H_4CH_2$-, and 2,4,6-tri-methyl-$C_6H_4CH_2$-.

The term "bridged bicyclic ring," as used herein, refers to a ring structure comprising a bridgehead between two of the ring members, wherein the ring and the bridgehead optionally may independently comprise one or more, preferably one to two, heteroatoms independently selected from nitrogen, oxygen, and sulfur. Illustrated examples of a bridged bicyclic ring structure include, but are not limited to:



The terms "Cap" and "cap," as used herein, refer to the group which is placed on the nitrogen atom of the pyrrolidine ring in the compounds of formula (I). It should be understood that "Cap" or "cap" can also refer to the reagent which is a precursor to the final "cap" in compounds of formula (I) and is used as one of the starting materials in the reaction to append a group on the pyrrolidine nitrogen that results in the final product, a compound which contains the functionalized pyrrolidine that will be present in the compound of formula (I).

The term "carbonyl," as used herein, refers to -C(O)-.

The term "carboxyl," or "carboxy," as used herein, refers to -CO2H.

The term "cyano," as used herein, refers to -CN.

The term "cycloalkyl," as used herein, refers to a group derived from a saturated carbocycle, having preferably three to eight carbon atoms, by removal of a hydrogen atom from the saturated carbocycle, wherein the saturated carbocycle can optionally be fused onto one or two other aromatic or nonaromatic carbocycles. Representative examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclopentyl, cyclohexyl, and 1,2,3,4-tetrahydronaphth-1-yl.

The term "formyl," as used herein, refers to -CHO.

The terms "halo" and "halogen," as used herein, refer to F, Cl, Br, or I.

The term "haloalkoxy," as used herein, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "haloalkyl," as used herein, refers to an alkyl group substituted by at least one halogen atom. The haloalkyl group can be an alkyl group of which all hydrogen atoms are substituted by halogens. Representative examples of haloalkyl include, but are not limited to, trifluoromethyl ($CF_3$-), 1-chloroethyl ($ClCH_2CH_2$-), and 2,2,2-trifluoroethyl ($CF_3CH_2$-).

The term "heteroaryl," as used herein, refers to group derived from a monocyclic, bicyclic, or polycyclic compound comprising at least one aromatic ring comprising

one or more, preferably one to three, heteroatoms independently selected from nitrogen, oxygen, and sulfur, by removal of a hydrogen atom from an aromatic ring thereof. As is well known to those skilled in the art, heteroaryl rings have less aromatic character than their all-carbon counterparts. Thus, for the purposes of the disclosure, a heteroaryl group need only have some degree of aromatic character. Illustrative examples of heteroaryl groups include, but are not limited to, pyridyl, pyridazinyl, pyrimidyl, pyrazyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3,)- and (1,2,4)-triazolyl, pyrazinyl, pyrimidinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, isoxazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, benzisoxazolyl, benzothiazolyl, benzothienyl, and pyrrolopyridinyl.

The term "heteroarylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three heteroaryl groups.

The term "heterobicyclyl," as used herein, refers to a ring structure comprising two fused or bridged rings that include carbon and one or more, preferably one to three, heteroatoms independently selected from nitrogen, oxygen, and sulfur. The heterobicyclic ring structure is a subset of heterocyclic ring and can be saturated or unsaturated. Examples of heterobicyclic ring structures include, but are not limited to, tropane, quinuclidine, and 7-azabicyclo[2.2.1]heptane.

The term "heterocyclyl," as used herein, refers to a group derived from a monocyclic, bicyclic, or polycyclic compound comprising at least one nonaromatic ring comprising one or more, preferably one to three, heteroatoms independently selected from nitrogen, oxygen, and sulfur, by removal of a hydrogen atom from the nonaromatic ring. The heterocyclyl group encompasses the heterobicyclyl group. The heterocyclyl groups of the present disclosure can be attached to the parent molecular moiety through a carbon atom or a nitrogen atom in the group. Examples of heterocyclyl groups include, but are not limited to, morpholinyl, oxazolidinyl, piperazinyl, piperidinyl, pyrrolidinyl, tetrahydrofuryl, thiomorpholinyl, and indolinyl.

The term "heterocyclylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three heterocyclyl groups.

The terms "hydroxy" or "hydroxyl," as used herein, refer to -OH.

The term "hydroxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three hydroxy groups.

The term "nitro," as used herein, refers to $-NO_2$.

The term "$-NR^aR^b$," as used herein, refers to two groups, $R^a$ and $R^b$, which are attached to the parent molecular moiety through a nitrogen atom, or alternatively $R^a$ and $R^b$, together with the nitrogen atom to which they are attached, form a 5- or 6-membered ring or a fused- or bridged-bicyclic ring structure optionally containing one, two, or three additional heteroatom independently selected from nitrogen, oxygen, and sulfur. The term "$-NR^cR^d$" is defined similarly.

The term "$(NR^aR^b)$alkyl," as used herein, refers to an alkyl group substituted with one, two, or three $-NR^aR^b$ groups. The term "$(NR^cR^d)$alkyl" is defined similarly.

The term "oxo," as used herein, refers to =O.

The term "sulfonyl," as used herein, refers to $-SO_2-$.

The term "trialkylsilyl," as used herein, refers to $-SiR_3$, wherein each R is $C_1$ to $C_4$ alkyl or phenyl. The three R groups may be the same or different. Representative examples of "trialkylsilyl" include, but are not limited to, trimethylsilyl (TMS), *tert*-butyldiphenylsilyl (TBDPS), *tert*-butyldimethylsilyl (TBS or TBDMS), and triisopropylsilyl (TIPS).

Asymmetric centers exist in the compounds of the present disclosure. These centers are designated by the symbols "R" or "S", depending on the configuration of substituents around the chiral carbon atom. It should be understood that the disclosure encompasses all stereochemical isomeric forms, or mixtures thereof, which possess the ability to inhibit NS5A. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, or direct separation of enantiomers on chiral chromatographic columns. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art.

Certain compounds of the present disclosure may also exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present disclosure includes each conformational isomer of these compounds and mixtures thereof.

The term "compounds of the present disclosure", and equivalent expressions, are meant to embrace compounds of Formula (I), and pharmaceutically acceptable enantiomers, diastereomers, and salts thereof. Similarly, references to intermediates are meant to embrace their salts where the context so permits.

The present disclosure is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon include $^{13}C$ and $^{14}C$. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed. Such compounds may have a variety of potential uses, for example as standards and reagents in determining biological activity. In the case of stable isotopes, such compounds may have the potential to favorably modify biological, pharmacological, or pharmacokinetic properties.

The compounds of the present disclosure can exist as pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present disclosure which are water or oil-soluble or dispersible, which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting a suitable nitrogen atom with a suitable acid. Representative acid addition

salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate; digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate, and undecanoate. Examples of acids which can be employed to form pharmaceutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric.

Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of pharmaceutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, N,N-dibenzylphenethylamine, and N,N'-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

When it is possible that, for use in therapy, therapeutically effective amounts of a compound of Formula (I), as well as pharmaceutically acceptable salts thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the disclosure further provides pharmaceutical compositions, which include therapeutically effective amounts of compounds of Formula (I) or pharmaceutically acceptable salts thereof, and one or more, preferably one to three, pharmaceutically acceptable carriers, diluents, or excipients. The term "therapeutically effective amount," as used herein, refers to the

total amount of each active component that is sufficient to show a meaningful patient benefit, *e.g.*, a sustained reduction in viral load. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially, or simultaneously. The compounds of Formula (I) and pharmaceutically acceptable salts thereof, are as described above. The carrier(s), diluent(s), or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the present disclosure there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, with one or more, preferably one to three, pharmaceutically acceptable carriers, diluents, or excipients. The term "pharmaceutically acceptable," as used herein, refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use. Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Dosage levels of between about 0.01 and about 250 milligram per kilogram ("mg/kg") body weight per day, preferably between about 0.05 and about 100 mg/kg body weight per day of the compounds of the present disclosure are typical in a monotherapy for the prevention and treatment of HCV mediated disease. Typically, the pharmaceutical compositions of this disclosure will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending on the condition being treated, the severity of the condition, the time of administration, the route of administration, the rate of excretion of the compound employed, the duration of treatment, and the age, gender, weight, and condition of the patient. Preferred unit

dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Generally, treatment is initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compound is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

When the compositions of this disclosure comprise a combination of a compound of the present disclosure and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent are usually present at dosage levels of between about 10 to 150%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual, or transdermal), vaginal, or parenteral (including subcutaneous, intracutaneous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional, intravenous, or intradermal injections or infusions) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s). Oral administration or administration by injection are preferred.

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example,

starch or mannitol. Flavoring, preservative, dispersing, and coloring agent can also be present.

Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate, or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate, or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, and the like. Lubricants used in these dosage forms include sodium oleate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, betonite, xanthan gum, and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant, and pressing into tablets. A powder mixture is prepared by mixing the compound, suitable comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelating, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or and absorption agent such as betonite, kaolin, or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage, or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc, or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present disclosure can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective

coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material, and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups, and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners, or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax, or the like.

The compounds of Formula (I), and pharmaceutically acceptable salts thereof, can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phopholipids, such as cholesterol, stearylamine, or phophatidylcholines.

The compounds of Formula (I) and pharmaceutically acceptable salts thereof may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in *Pharm. Res.*, 3(6):318 (1986).

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols, or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles, and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a course powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, *i.e.*, by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurized aerosols, nebulizers, or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, and soutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The term "patient" includes both human and other mammals.

The term "treating" refers to: (i) preventing a disease, disorder or condition from occurring in a patient that may be predisposed to the disease, disorder, and/or condition but has not yet been diagnosed as having it; (ii) inhibiting the disease, disorder, or condition, *i.e.*, arresting its development; and (iii) relieving the disease, disorder, or condition, *i.e.*, causing regression of the disease, disorder, and/or condition.

The compounds of the present disclosure can also be administered with a cyclosporin, for example, cyclosporin A. Cyclosporin A has been shown to be active against HCV in clinical trials (*Hepatology*, 38:1282 (2003); *Biochem. Biophys. Res. Commun.*, 313:42 (2004); *J. Gastroenterol.*, 38:567 (2003)).

Table 1 below lists some illustrative examples of compounds that can be administered with the compounds of this disclosure. The compounds of the disclosure can be administered with other anti-HCV activity compounds in

combination therapy, either jointly or separately, or by combining the compounds into a composition.

*Table 1*

| Brand Name | Physiological Class | Type of Inhibitor or Target | Source Company |
|---|---|---|---|
| NIM811<br>Debio-025 | | Cyclophilin inhibitors | Novartis Debiopharm |
| Zadaxin | | Immunomodulator | SciClone |
| Suvus | | Methylene blue | Bioenvision |
| Actilon (CPG10101) | | TLR9 agonist | Coley |
| Batabulin (T67) | Anticancer | β-Tubulin inhibitor | Tularik Inc., South San Francisco, CA |
| ISIS 14803 | Antiviral | Antisense | ISIS Pharmaceuticals Inc, Carlsbad, CA / Elan Pharmaceuticals Inc., New York, NY |
| Summetrel | Antiviral | Antiviral | Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA |
| GS-9132 (ACH-806) | Antiviral | HCV inhibitor | Achillion / Gilead |
| Pyrazolopyrimidine compounds and salts From WO 2005/047288 May 26, 2005 | Antiviral | HCV inhibitors | Arrow Therapeutics Ltd. |
| Levovirin | Antiviral | IMPDH inhibitor | Ribapharm Inc., Costa Mesa, CA |
| Merimepodib (VX-497) | Antiviral | IMPDH inhibitor | Vertex Pharmaceuticals Inc., Cambridge, MA |

| Brand Name | Physiological Class | Type of Inhibitor or Target | Source Company |
|---|---|---|---|
| XTL-6865 (XTL-002) | Antiviral | Monoclonal antibody | XTL Biopharmaceuticals Ltd., Rehovot, Israel |
| Telaprevir (VX-950, LY-570310) | Antiviral | NS3 serine protease inhibitor | Vertex Pharmaceuticals Inc., Cambridge, MA / Eli Lilly and Co., Inc., Indianapolis, IN |
| HCV-796 | Antiviral | NS5B replicase inhibitor | Wyeth / Viropharma |
| NM-283 | Antiviral | NS5B replicase inhibitor | Idenix / Novartis |
| GL-59728 | Antiviral | NS5B replicase inhibitor | Gene Labs / Novartis |
| GL-60667 | Antiviral | NS5B replicase inhibitor | Gene Labs / Novartis |
| 2'C MeA | Antiviral | NS5B replicase inhibitor | Gilead |
| PSI 6130 | Antiviral | NS5B replicase inhibitor | Roche |
| R1626 | Antiviral | NS5B replicase inhibitor | Roche |
| 2'C Methyl adenosine | Antiviral | NS5B replicase inhibitor | Merck |
| JTK-003 | Antiviral | RdRp inhibitor | Japan Tobacco Inc., Tokyo, Japan |
| Levovirin | Antiviral | Ribavirin | ICN Pharmaceuticals, Costa Mesa, CA |
| Ribavirin | Antiviral | Ribavirin | Schering-Plough Corporation, Kenilworth, NJ |

| Brand Name | Physiological Class | Type of Inhibitor or Target | Source Company |
|---|---|---|---|
| Viramidine | Antiviral | Ribavirin prodrug | Ribapharm Inc., Costa Mesa, CA |
| Heptazyme | Antiviral | Ribozyme | Ribozyme Pharmaceuticals Inc., Boulder, CO |
| BILN-2061 | Antiviral | Serine protease inhibitor | Boehringer Ingelheim Pharma KG, Ingelheim, Germany |
| SCH 503034 | Antiviral | Serine protease inhibitor | Schering-Plough |
| Zadazim | Immune modulator | Immune modulator | SciClone Pharmaceuticals Inc., San Mateo, CA |
| Ceplene | Immunomodulator | Immune modulator | Maxim Pharmaceuticals Inc., San Diego, CA |
| CELLCEPT® | Immunosuppressant | HCV IgG immunosuppressant | F. Hoffmann-La Roche LTD, Basel, Switzerland |
| Civacir | Immunosuppressant | HCV IgG immunosuppressant | Nabi Biopharmaceuticals Inc., Boca Raton, FL |
| Albuferon - α | Interferon | Albumin IFN-α2b | Human Genome Sciences Inc., Rockville, MD |
| Infergen A | Interferon | IFN alfacon-1 | InterMune Pharmaceuticals Inc., Brisbane, CA |
| Omega IFN | Interferon | IFN-ω | Intarcia Therapeutics |

| Brand Name | Physiological Class | Type of Inhibitor or Target | Source Company |
|---|---|---|---|
| IFN-β and EMZ701 | Interferon | IFN-β and EMZ701 | Transition Therapeutics Inc., Ontario, Canada |
| REBIF® | Interferon | IFN-β1a | Serono, Geneva, Switzerland |
| Roferon A | Interferon | IFN-α2a | F. Hoffmann-La Roche LTD, Basel, Switzerland |
| Intron A | Interferon | IFN-α2b | Schering-Plough Corporation, Kenilworth, NJ |
| Intron A and Zadaxin | Interferon | IFN-α2b/α1-thymosin | RegeneRx Biopharma. Inc., Bethesda, MD / SciClone Pharmaceuticals Inc, San Mateo, CA |
| Rebetron | Interferon | IFN-α2b / ribavirin | Schering-Plough Corporation, Kenilworth, NJ |
| Actimmune | Interferon | INF-γ | InterMune Inc., Brisbane, CA |
| Interferon-β | Interferon | Interferon-β-1a | Serono |
| Multiferon | Interferon | Long lasting IFN | Viragen / Valentis |
| Wellferon | Interferon | Lymphoblastoid IFN-αn1 | GlaxoSmithKline plc, Uxbridge, UK |
| Omniferon | Interferon | natural IFN-α | Viragen Inc., Plantation, FL |
| Pegasys | Interferon | PEGylated IFN-α2a | F. Hoffmann-La Roche LTD, Basel, Switzerland |

| Brand Name | Physiological Class | Type of Inhibitor or Target | Source Company |
|---|---|---|---|
| Pegasys and Ceplene | Interferon | PEGylated IFN-α2a/immune modulator | Maxim Pharmaceuticals Inc., San Diego, CA |
| Pegasys and Ribavirin | Interferon | PEGylated IFN-α2a/ribavirin | F. Hoffmann-La Roche LTD, Basel, Switzerland |
| PEG-Intron | Interferon | PEGylated IFN-α2b | Schering-Plough Corporation, Kenilworth, NJ |
| PEG-Intron / Ribavirin | Interferon | PEGylated IFN-α2b/ribavirin | Schering-Plough Corporation, Kenilworth, NJ |
| IP-501 | Liver protection | Antifibrotic | Indevus Pharmaceuticals Inc., Lexington, MA |
| IDN-6556 | Liver protection | Caspase inhibitor | Idun Pharmaceuticals Inc., San Diego, CA |
| ITMN-191 (R-7227) | Antiviral | Serine protease inhibitor | InterMune Pharmaceuticals Inc., Brisbane, CA |
| GL-59728 | Antiviral | NS5B replicase inhibitor | Genelabs |
| ANA-971 | Antiviral | TLR-7 agonist | Anadys |
| Boceprevir | Antiviral | Serine protease inhibitor | Schering-Plough |
| TMS-435 | Antiviral | Serine protease inhibitor | Tibotec BVBA, Mechelen, Belgium |
| BI-201335 | Antiviral | Serine protease inhibitor | Boehringer Ingelheim Pharma KG, Ingelheim, Germany |

| Brand Name | Physiological Class | Type of Inhibitor or Target | Source Company |
|---|---|---|---|
| MK-7009 | Antiviral | Serine protease inhibitor | Merck |
| PF-00868554 | Antiviral | Replicase inhibitor | Pfizer |
| ANA598 | Antiviral | Non-Nucleoside NS5B polymerase inhibitor | Anadys Pharmaceuticals, Inc., San Diego, CA, USA |
| IDX375 | Antiviral | Non-Nucleoside replicase inhibitor | Idenix Pharmaceuticals, Cambridge, MA, USA |
| BILB 1941 | Antiviral | NS5B polymerase inhibitor | Boehringer Ingelheim Canada Ltd R&D, Laval, QC, Canada |
| PSI-7851 | Antiviral | Nucleoside polymerase inhibitor | Pharmasset, Princeton, NJ, USA |
| VCH-759 | Antiviral | NS5B polymerase inhibitor | ViroChem Pharma |
| VCH-916 | Antiviral | NS5B polymerase inhibitor | ViroChem Pharma |
| GS-9190 | Antiviral | NS5B polymerase inhibitor | Gilead |
| Peg-interferon lamda | Antiviral | Interferon | ZymoGenetics / Bristol-Myers Squibb |

The compounds of the present disclosure may also be used as laboratory reagents. Compounds may be instrumental in providing research tools for designing of viral replication assays, validation of animal assay systems and structural biology studies to further enhance knowledge of the HCV disease mechanisms. Further, the compounds of the present disclosure are useful in establishing or determining the binding site of other antiviral compounds, for example, by competitive inhibition. The compounds of this disclosure may also be used to treat or prevent viral contamination of materials and therefore reduce the risk of viral infection of

laboratory or medical personnel or patients who come in contact with such materials, *e.g.*, blood, tissue, surgical instruments and garments, laboratory instruments and garments, and blood collection or transfusion apparatuses and materials.

This disclosure is intended to encompass compounds having Formula (I) when prepared by synthetic processes or by metabolic processes including those occurring in the human or animal body (*in vivo*) or processes occurring *in vitro*.

The abbreviations used in the present application, including particularly in the illustrative examples which follow, are well-known to those skilled in the art. Some of the abbreviations used are as follows: TFA for trifluoroacetic acid; min or min. or mins for minutes; MeCN or ACN for acetonitrile; LDA for lithium diisopropylamide; DMSO for dimethylsulfoxide; h or hr or hrs for hours; Boc or BOC for tert-butoxycarbonyl; HATU for O-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate; RT or Rt or rt for retention time or room temperature (context will dictate); Me for methyl; DMF for N,N-dimethylformamide; $Pd(Ph_3P)_4$ for tetrakistriphenyl phosphine palladium; MeOH for methanol; MeOD for $CD_4OD$; TEA for triethylamine; Ph for phenyl; TBDPS for tert-butyldiphenylsilyl; $Et_3N$ or TEA for triethylamine; DMAP for N,N-dimethylaminopyridine; EtOAc for ethyl acetate; TBAF for tetrabutylammonium fluoride; THF for tetrahydrofuran; DIEA or DIPEA or $iPr_2NEt$ for diisopropylethylamine; NCS for N-chlorosuccinimide; NBS for N-bromosuccinimide; DCM for dichloromethane; SEM for 2-(trimethylsilyl)ethoxymethyl; DCE for 1,2-dichloroethane; EDCI for 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene; $Pd(t\text{-}Bu_3P)_2$ for palladium bis(tributylphosphine); HMDS for hexamethyldisilazide; $TMSCHN_2$ for trimethylsilyldiazomethane; H-D-Ser-OBzl for D-serine benzyl ester; i-PrOH for isopropanol; LiHMDS for lithium hexamethyldisilazide; DIBAL or DIBALH for diisobutylaluminum hydride; TBDMS for tert-butyldimethylsilyl; CBz for carbobenzyloxy; Bn for benzyl; DEAD for diethyl azodicarboxylate; mCPBA for meta-chloroperoxybenzoic acid; TMSCN for trimethylsilyl cyanide; dppe for 1,5-Bis(diphenylphosphino) pentane; TMEDA for tetramethylethylenediamine; OAc for acetate; DMA for N,N-dimethylacetamide; and d for days.

The present disclosure will now be described in connection with certain embodiments which are not intended to limit its scope. On the contrary, the present disclosure covers all alternatives, modifications, and equivalents as can be included within the scope of the claims. Thus, the following examples, which include specific embodiments, will illustrate one practice of the present disclosure, it being understood that the examples are for the purposes of illustration of certain embodiments and are presented to provide what is believed to be the most useful and readily understood description of its procedures and conceptual aspects.

Starting materials can be obtained from commercial sources or prepared by well-established literature methods known to those of ordinary skill in the art.

## EXAMPLES

Unless noted otherwise, purity assessments were conducted on Shimadzu LC system, and retention time ($R_t$) determination and low resolution mass analysis were conducted on a Shimadzu LC system coupled with Waters MICROMASS® ZQ MS system. It should be noted that retention times may vary slightly between machines.

Condition 1

Column = PHENOMENEX®, C18, 3.0 X 50 mm, 10 µm

Start %B = 0

Final %B = 100

Gradient time = 2 min

Stop time = 3 min

Flow Rate = 4 mL/min

Wavelength = 220 nm

Solvent A = 0.1 % TFA in 10% methanol/90% water

Solvent B = 0.1 % TFA in 90% methanol/10% water

Condition 2

Column = XTERRA®, C18, 3.0 x 50 mm, S7

Start %B = 0

Final %B = 100

Gradient time = 2 min

Stop time = 3 min

Flow Rate = 5 mL/min

Wavelength = 220 nm

Solvent A = 0.2 % $H_3PO_4$ in 10% methanol/90% water

Solvent B = 0.2 % $H_3PO_4$ in 90% methanol/10% water

Condition 3

Column = PHENOMENEX®, C18, 3.0 X 50 mm, 10 µm

Start %B = 0

Final %B = 100

Gradient time = 3 min

Stop time = 4 min

Flow Rate = 4 mL/min

Wavelength = 220 nm

Solvent A = 0.1 % TFA in 10% methanol/90% water

Solvent B = 0.1 % TFA in 90% methanol/10% water

Condition 4

Column = XTERRA®, C18, 3.0 x 50 mm, S7

Start %B = 0

Final %B = 100

Gradient time = 10 min

Stop time = 11 min

Flow Rate = 5 mL/min

Wavelength = 220 nm

Solvent A = 0.2 % $H_3PO_4$ in 10% methanol/90% water

Solvent B = 0.2 % $H_3PO_4$ in 90% methanol/10% water

Condition 5

Column = PHENOMENEX®, C18, 3.0 X 50 mm, 10 µm

Start %B = 0

Final %B = 100

Gradient time = 4 min

Stop time = 5 min

Flow Rate = 4 mL/min

Wavelength = 220 nm

Solvent A = 0.1 % TFA in 10% methanol/90% water

Solvent B = 0.1 % TFA in 90% methanol/10% water

Condition 6

Column = Phenomenex-Luna, C18, 4.6 X 50 mm, S10

Start %B = 0

Final %B = 100

Gradient time = 3 min

Stop time = 4 min

Flow Rate = 4 mL/min

Wavelength = 220 nm

Solvent A = 0.1 % TFA in 10% methanol/90% water

Solvent B = 0.1 % TFA in 90% methanol/10% water

Condition 7

Column = Phenomenex-Luna, C18, 3.0X 50 mm, S10

Start %B = 0

Final %B = 100

Gradient time = 2 min

Stop time = 3 min

Flow Rate = 4 mL/min

Wavelength = 220 nm

Solvent A = 0.1 % TFA in 10% methanol/90% water

Solvent B = 0.1 % TFA in 90% methanol/10% water

Condition 9

Column = Waters Sunfire, C18, 4.6X150 mm, 3.5 µm

Start %B = 10

Final %B = 50

Gradient time = 20 min

Stop time = 25 min

Flow Rate = 1 mL/min

Wavelength = 220 & 254 nm

Slovent A = 0.1% TFA in 5% $CH_3CN$/95%$H_2O$

Solvent B = 0.1% TFA in 95% $CH_3CN$/5% $H_2O$

Condition 9a

Same as Condition 9 with the exception that Stop time = 35 min

Condition 9a.1

Column = Waters Sunfire, C18, 4.6X150 mm, 3.5 µm

Start %B = 30

Final %B = 100

Gradient time = 20 min

Stop time = 25 min

Flow Rate = 1 mL/min

Wavelength = 220 & 254 nm

Slovent A = 0.1% TFA in 5% $CH_3CN$/95%$H_2O$

Solvent B = 0.1% TFA in 95% $CH_3CN$/5% $H_2O$

Condition 10

Column = Waters Xbridge phenyl, C18, 4.6X150 mm, 3 µm

Start %B = 10

Final %B = 50

Gradient time = 20 min

Stop time = 25 min

Flow Rate = 1 mL/min

Wavelength = 220 & 254 nm

Slovent A = 0.1% TFA in 5% $CH_3CN$/95%$H_2O$

Solvent B = 0.1% TFA in 95% $CH_3CN$/5% $H_2O$

Condition 10a

Same as Condition 10 with the exception that Stop time = 35 min

Condition 10a.1

Column = Waters Xbridge phenyl, C18, 4.6X150 mm, 3 µm

Start %B = 40

Final %B = 100

Gradient time = 20 min

Stop time = 25 min

Flow Rate = 1 mL/min

Wavelength = 220 & 254 nm

Slovent A = 0.1% TFA in 5% $CH_3CN$/95%$H_2O$

Solvent B = 0.1% TFA in 95% $CH_3CN$/5% $H_2O$

Condition 10b

Column = Sunfire, C18, 3.0 X 150 mm, 3.5 µm

Start %B = 10

Final %B = 40

Gradient time = 15 min

Stop time = 18 min

Flow Rate = 1 mL/min

Wavelength 1 = 220 nm

Wavelength 2 = 254 nm

Solvent A = 0.1 % TFA in 5% MeCN/95% water

Solvent B = 0.1 % TFA in 95% MeCN/5% water

Condition 10c

Column = Xbridge Phenyl, C18, 3.0 X 150 mm, 3.5 µm

Start %B = 10

Final %B = 40

Gradient time = 15 min

Stop time = 18 min

Flow Rate = 1 mL/min

Wavelength 1 = 220 nm

Wavelength 2 = 254 nm

Solvent A = 0.1 % TFA in 5% MeCN/95% water

Solvent B = 0.1 % TFA in 95% MeCN/5% water

Condition 10d

Column = PHENOMENEX®-Luna, C18, 2.0 X 50 mm, 3 µm

Start %B = 0

Final %B = 100

Gradient time = 4 min

Stop time = 5 min

Flow Rate = 0.8 mL/min

Wavelength = 220 nm

Solvent A = 0.1 % TFA in 10% methanol/90% water

Solvent B = 0.1 % TFA in 90% methanol/10% water

Oven temp. = 40 °C

Condition 10e (Agilent 1200 series LC system)

Column = Xbridge phenyl, C18, 4.6X150 mm, 3.5 µm

Solvent A = Buffer: $CH_3CN$ (95:5)

Solvent B = Buffer: $CH_3CN$ (5:95)

Buffer = 0.05% TFA in $H_2O$ (pH 2.5, adjusted with dilute ammonia)

Start %B = 10

Final %B = 100

Gradient time = 12 min

Isocratic time = 3 min

Stop time = 23 min

Flow Rate = 1 mL/min

Wavelength = 220 & 254 nm

Condition 10f (Agilent LC-1200 series coupled with 6140 single quad. mass spectrometer, ESI +ve mode)

Column = Zorbax SB, C18, 4.6X50 mm, 5 µm

Slovent A = MeOH (10%) + 0.1% TFA in $H_2O$ (90%)

Solvent B = MeOH (90%) + 0.1% TFA in $H_2O$ (10%)

Start %B = 0

Final %B = 100

Gradient time = 3 min

Isocratic time = 1 min

Stop time = 5 min

Flow Rate = 5 mL/min

Wavelength = 220 nm

Condition 10g (Agilent LC-1200 series coupled with 6140 single quad. mass spectrometer, ESI +ve mode)

Column = Ascentis Express, C-8, 2.1X5 mm, 2.7 µm

Slovent A = $CH_3CN$ (2%) + 10 mM $NH_4COOH$ in $H_2O$ (98%)

Solvent B = $CH_3CN$ (98%) + 10 mM $NH_4COOH$ in $H_2O$ (2%)

Start %B = 0

Final %B = 100

Gradient time = 1.5 min

Isocratic time = 1.7 min

Stop time = 4 min

Flow Rate = 1 mL/min

Wavelength = 220 nm

Condition 10h

Column = PHENOMENEX®-Luna, C18, 4.6 X 30 mm, S10

Start %B = 0

Final %B = 100

Gradient time = 3 min

Stop time = 4 min

Flow Rate = 4 mL/min

Wavelength = 220 nm

Solvent A = 0.1 % TFA in 10% methanol/90% water

Solvent B = 0.1 % TFA in 90% methanol/10% water

Condition 11

Column = PHENOMENEX®-Luna, C18, 50X2 mm, 3µm

Start %B = 0

Final %B = 100

Gradient time = 4 min

Stop time = 5 min

Flow Rate = 0.8 mL/min

Wavelength = 220 nm

Solvent A = 5% methanol/95% water : 10 mM ammonium acetate

Solvent B = 95% methanol/5% water : 10 mM ammonium acetate

Oven temperature = 40 °C

Condition 12 (Waters Acquity HPLC with Waters PDA UV-Vis detection and Waters SQ MS-ESCI probe)

Column = Waters Acquity BEH, C18, 150 X 2.1 mm ID, 1.7 µm (at 35 °C)

Mobile phase A = 0.05% TFA in water

Mobile phase B = 0.05% TFA in acetonitrile

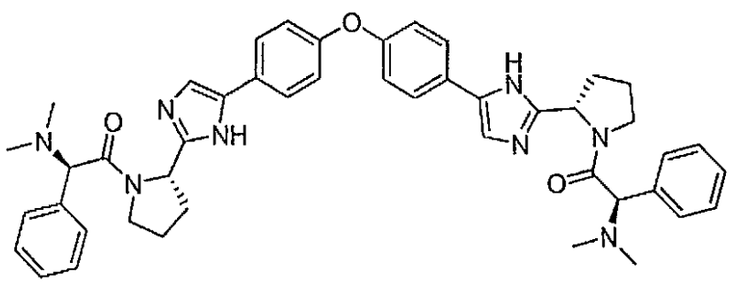
Solvent system: Hold 10%B: 0-1min; 10-98%B: 1-32min; Hold 98%B: 32-35 min; 98-10%B: 35-35.3 min; hold 10%B: 35.3-40 min

Flow rate = 0.35 ml/min

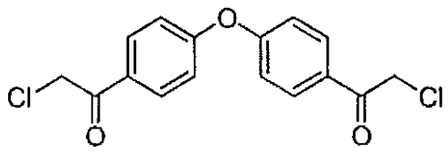
UV detection = 335 nm

## EXAMPLES

Example OL-1

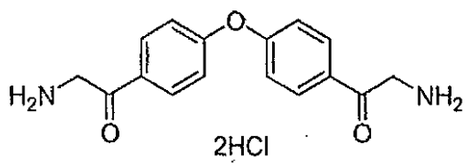


Example OL-1, step a



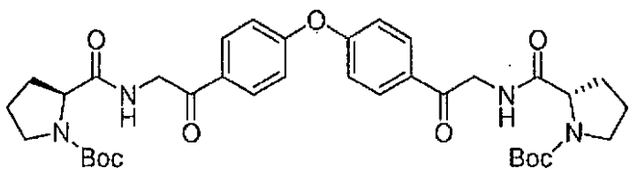
4,4'-Oxybis-(benzoic acid) dimethyl ester (1.5 g, 5.24 mmol) was added to a solution of chloroiodomethane (3.05 mL, 41.92 mmol) in tetrahydrofuran (50 mL) and the resulting solution was cooled to -78 °C. A 1.8M solution of LDA (29 mL, 52 mmol) in tetrahydrofuran was added dropwise and the resulting brown suspension was stirred at -78 °C for 15 min. A solution of glacial acetic acid in tetrahydrofuran (10 mL in 50 mL) was then added slowly and the brown mixture was stirred at -78 °C for 10 min. before allowing it to reach room temperature. The mixture was taken up in ethyl acetate and brine (1:1, 50 mL) and the organic layer was then separated, washed with a sat. solution of sodium bicarbonate and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was submitted to flash chromatography (silica gel; 15 % ethyl acetate/hexanes) to provide OL-1a as a pale brown solid (0.6 g). $^1H$ NMR (500 MHz, DMSO-$d_6$) δ ppm 5.17 (s, 4 H), 7.22 (d, J=8.85 Hz, 4 H), 8.06 (d, J=8.85 Hz, 4 H). LC (Cond. 2): RT = 1.53 minutes, 97% homogeneity index; LCMS: Anal. Calcd. For $(M-H)^+$ $C_{16}H_{11}Cl_2O_3$: 321.01; found: 321.30.

Example OL-1, step b




A mixture of OL-1a (0.6 g, 1.85 mmol) and sodium diformylamide (0.42 g, 4.45 mmol) in acetonitrile (20 mL) was heated to reflux for 4 h. The solvent was the removed under reduced pressure and the remaining residue was redissolved in a 5% HCl solution in ethanol (30 mL) and heated to reflux temperature for 2 h. The mixture was cooled in an ice-water bath and the resulting precipitate was filtered, washed with ethanol and ether and dried in vacuo. The recovered pale brow solid was used without further purification (0.66 g). $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 4.54 (s, 4 H), 7.25 (d, J=8.85 Hz, 4 H), 8.11 (d, J=8.55 Hz, 4 H), 8.52 (br. s, 6 H). LC (Cond. 1): RT = 1.24 min; LRMS: Anal. Calcd. For $(M+H)^+$ $C_{16}H_{17}N_2O_3$ 285.12; found: 285.19.

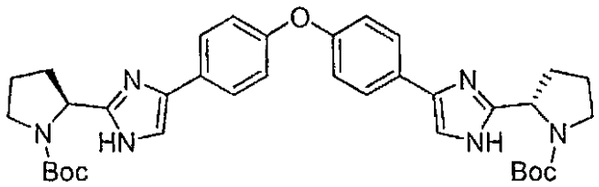
Example OL-1, step c




N,N-Diisopropylethylamine (1.13 mL, 6.47 mmol) was added dropwise, over 15 minutes, to a heterogeneous mixture of N-Boc-L-proline (0.8 g, 3.73 mmol), HATU (1.48 g, 3.88 mmol), OL-1b (0.66 g, 1.85 mmol) and dimethylformamide (15 mL), and stirred at ambient condition for 4 h. Most of the volatile components were removed in vacuo, and the resulting residue was partitioned between ethyl acetate (30 mL) and water (20 mL). The organic layer was washed with water (20 mL) and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. A silica gel mesh was prepared from the residue and submitted to flash chromatography (silica gel; 65-85 % ethyl acetate/ hexanes) to provide OL-1c as a pale brown solid (0.7 g). $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.39/1.34 (rotomers, s, 18 H), 1.70 - 1.91 (m, 6 H), 2.00 - 2.25 (m, J=8.55 Hz, 2 H), 3.22 - 3.33 (m, 2 H), 3.32 - 3.47 (m, J=10.68, 10.68 Hz, 2

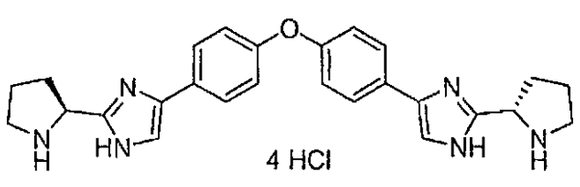
H), 4.08 - 4.26 (m, 2 H), 4.56 (ddd, J=36.93, 18.16, 5.34 Hz, 4 H), 7.19 (d, J=8.85 Hz, 4 H), 8.06 (d, J=7.93 Hz, 4 H), 8.11 - 8.24 (m, J=5.49 Hz, 2 H). LC (Cond. 1): RT = 2.55 min; LRMS: Anal. Calcd. for $(M+H)^+$ $C_{36}H_{47}N_4O_9$ 679.33; found: 679.44.

Example OL-1, step d




A mixture of OL-1c (0.7 g, 1.025 mmol) and ammonium acetate (0.79 g, 10 mmol) in xylenes (5 mL) was heated in a sealed tube at 140 °C for 1.2 hours under microwave radiation. The volatile component was removed in vacuo, and the residue was partitioned carefully between ethyl acetate and water, whereby enough saturated sodium bicarbonate solution was added so as to make the pH of the aqueous phase slightly basic after the shaking of the biphasic system. The layers were separated, and the aqueous layer was extracted with additional ethyl acetate. The combined organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting material submitted to a flash chromatography (silica gel; 15-25% acetone/dichloromethane) to provide OL-1d (0.13 g). $^1H$ NMR (500 MHz, DMSO-$d_6$) δ ppm 1.17/1.48 (rotomers, s, 18 H), 1.76 - 1.93 (m, 4 H), 1.93 - 2.06 (m, J=10.07 Hz, 2 H), 2.10 - 2.30 (m, 2 H), 3.32 - 3.39 (m, 2 H), 3.45 - 3.62 (m, 2 H), 4.69 - 4.80 (m, 1 H), 4.83 (d, J=7.02 Hz, 1 H), 6.97 (d, J=7.93 Hz, 4 H), 7.00 - 7.22 (m, 1 H), 7.40/7.62 (rotomers, m, 2 H), 7.73 (d, J=8.55 Hz, 3 H), 11.74/11.81/12.07 (rotomers, s, 2 H). LC (Cond. 2): RT = 1.53 minutes, 93% homogeneity index; LCMS: Anal. Calcd. for $(M+H)^+$ $C_{36}H_{44}N_6O_5$: 641.34; found: 641.50.

Example OL-1, step e

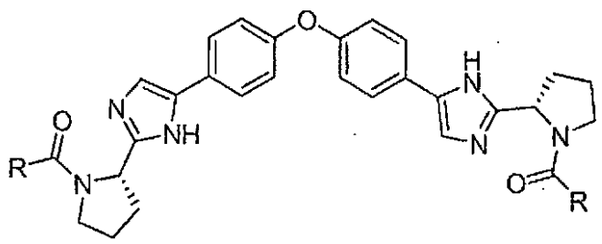


To a solution of OL-1d (0.13 g, 0.2 mmol) in 30 mL dichloromethane was added 1 mL of a 4.0M solution of HCl in dioxane. The reaction was stirred for 2 hours at room temperature and concentrated under reduced pressure. The resulting residue was redissolved in a minimum amount of methanol and the desired product was triturated with ether, filtered and dried in vacuo. A pale tan solid (0.11g) was recovered and used without further purification. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.92 - 2.07 (m, 2 H), 2.12 - 2.25 (m, 2 H), 2.37 - 2.47 (m, 4 H), 3.30 - 3.47 (m, 4 H), 4.90 - 5.02 (m, 2 H), 7.15 (d, J=8.55 Hz, 4 H), 7.91 (d, J=8.24 Hz, 4 H), 7.97 (s, 2 H), 9.74 (br. s, 2 H), 10.25 (br. s, 2 H). Note: the signal of the imidazole NH was too broad to assign a chemical shift. LC (Cond. 1): RT = 1.68 min; LRMS: Anal. Calcd. for $(M+H)^+$ $C_{26}H_{29}N_6O$ 441.24; found: 441.30.

Example OL-1

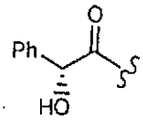
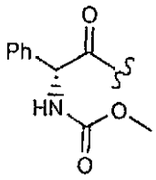
HATU (52 mg, 0.137 mmol) was added to a mixture of OL-1e (35 mg, 0.06 mmol), diisopropylethylamine (58 µL, 0.33 mmol) and Cap-1 (22 mg, 0.12 mmol) in dimethylformamide (3 mL), and the resulting mixture was stirred at ambient for 3 h. The volatile component was removed in vacuo, and the residue was purified by a reverse phase HPLC system (water/methanol/TFA) to provide the TFA salt of Example OL-1 as an off-white solid (32 mg). $^1$H NMR (500 MHz, DMSO-$D_6$) δ ppm 1.82 - 1.93 (m, 2 H), 1.94 - 2.08 (m, 4 H), 2.14 - 2.24 (m, 2 H), 2.29 - 2.40 (m, 4 H), 2.83 (s, 4 H), 2.97 - 3.07 (m, 4 H), 3.97 (t, J=8.24 Hz, 2 H), 4.89 - 5.20 (m, 2 H), 5.34 - 5.73 (m, 2 H), 7.00 - 7.22 (m, 6 H), 7.49 - 7.64 (m, 9 H), 7.70 - 7.89 (m, 5 H), 10.20 (br.s, 2 H). LC (Cond. 1): RT = 2.48 min; LRMS: Anal. Calcd. for $(M+H)^+$ $C_{46}H_{51}N_8O_3$ 763.41; found: 763.56; HRMS: Anal. Calcd. for $(M+H)^+$ $C_{46}H_{51}N_8O_3$ 763.4084; found: 763.4109.

Examples OL-2 and OL-3

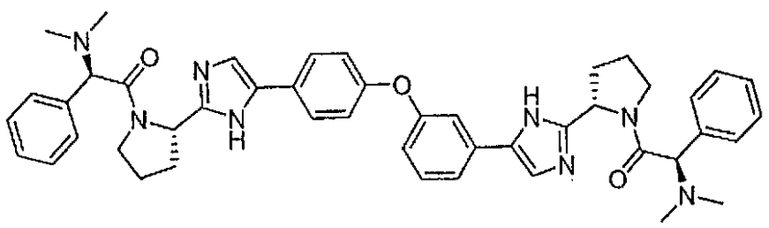


Examples OL-2 and OL-3 were prepared as TFA salts by substituting the respective acids for Cap-1 using the same method described for Example OL-1.

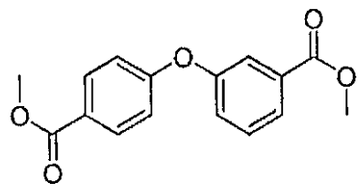
5

| Example |  Acid | RT (LC-Cond.); MS data |
|---|---|---|
| OL-2 |  Mandelic acid | RT = 2.92 min. LC (Cond. 2); LCMS: Anal. Calcd. For $(M+H)^+$ $C_{42}H_{41}N_6O_5$ 709.31; Found: 709.41; HRMS: Anal. Calcd. for: $C_{42}H_{41}N_6O_5$ 709.3138; Found: 709.3147 $(M+H)^+$ |
| OL-3 |  Cap-4 | RT = 3.65 min). LC (Cond. 2); LCMS: Anal. Calcd. for $(M+H)^+$ $C_{46}H_{47}N_8O_7$ 823.35; Found: 823.66; HRMS: Anal. Calcd. for $(M+H)^+$ $C_{46}H_{47}N_8O_7$ 823.3568; Found: 823.3574 |

Example OL-4

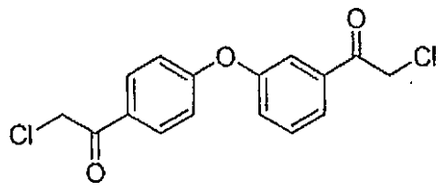


Example OL-4, step a



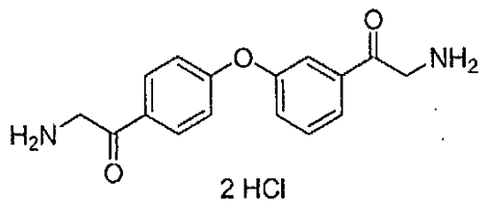
Methyl 3-bromobenzoate (5 g, 23.2 mmol), methyl 4-hydroxybenzoate (5.3 g, 34.87 mmol), cesium carbonate (15.12 g, 46.4 mmol), copper (I) iodide (0.44 g, 2.32 mmol) and N,N-dimethyl hydrochloride (0.97 g, 6.96 mmol) were combined in dioxane (100 ml) in a sealed tube and the resulting mixture was heated to 90 °C for 15 h. The solvent was removed under reduced pressure and the residue was taken up in ethyl acetate/water (1:1, 200 mL). The organic layer was washed with saturated aq. sodium carbonate, water and brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting material was purified by flash chromatography (silica gel, 5% ethyl acetate/hexanes) to provide OL-4a as a clear oil that solidified upon standing (5.8 g). $^1H$ NMR (500 MHz, DMSO-$d_6$) δ ppm 3.83 (s, 6 H), 7.10 (d, J=8.55 Hz, 2 H), 7.43 (dd, J=8.09, 2.59 Hz, 1 H), 7.56 (s, 1 H), 7.61 (t, J=7.93 Hz, 1 H), 7.81 (d, J=7.63 Hz, 1 H), 7.98 (d, J=8.55 Hz, 2 H). LC (Cond. 2): RT = 1.53 minutes; LCMS: Anal. Calcd. for $(M+1)^+$ $C_{16}H_{15}O_5$: 287.01; found: 287.23.

Example OL-4, step b



OL-4b was prepared from OL-4a, according to the same procedure used for the preparation of OL-1a. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ ppm 5.14 (s, 2 H), 5.20 (s, 2 H), 7.13 (d, J=8.85 Hz, 2 H), 7.43 - 7.49 (m, 1 H), 7.64 (t, J=8.09 Hz, 1 H), 7.66 - 7.68 (m, 1 H), 7.85 (d, J=7.93 Hz, 1 H), 8.02 (d, J=8.85 Hz, 2 H). LC (Cond. 1): RT = 1.51 min; LRMS: Anal. Calcd. for $(M+H)^+$ $C_{16}H_{13}Cl_2O_3$ 323.02; found: 323.07.

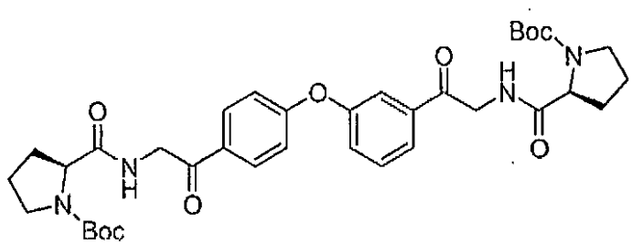
Example OL-4, step c




2 HCl

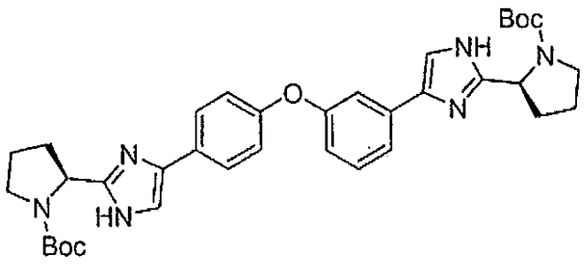
OL-4c was prepared from Example OL-4b, according to the same procedure used for the preparation of Example OL-1b. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm. 4.52 (s, 2 H), 4.56 (s, 2 H), 7.16 (d, J=8.85 Hz, 2 H), 7.51 (dd, J=8.24, 2.44 Hz, 1 H), 7.68 (t, J=7.93 Hz, 1 H), 7.71 - 7.75 (m, 1 H), 7.91 (d, J=7.63 Hz, 1 H), 8.07 (d, J=8.85 Hz, 2 H), 8.60 (s, 6 H). LC (Cond. 2): Anal. Calcd. for $C_{16}H_{17}N_2O_3$ $(M+H)^+$ 285.12; found: 285.15.

Example OL-4d



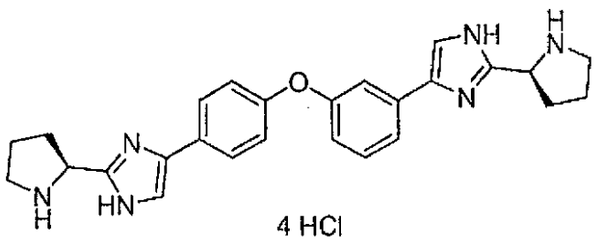

Example OL-4d was prepared from Example OL-4c, according to the same procedure used for the preparation of Example OL-1c. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.38/1.33 (rotomers, s, 18 H), 1.69 - 1.91 (m, 6 H), 1.95 - 2.19 (m, 2 H), 3.20 - 3.31 (m, 2 H), 3.32 - 3.47 (m, 2 H), 4.08 - 4.23 (m, 2 H), 4.43 - 4.68 (m, 4 H), 7.10 (d, J=8.55 Hz, 2 H), 7.42 (dd, J=8.09, 1.98 Hz, 1 H), 7.57 - 7.70 (m, 2 H), 7.86 (d, J=7.02 Hz, 1 H), 8.03 (d, J=7.93 Hz, 2 H), 8.08 - 8.24 (m, 2 H). LC (Cond. 1): RT = 2.53 min; LRMS: Anal. Calcd. for $C_{36}H_{47}N_4O_9$ $(M+H)^+$ 679.33; found: 679.42.

Example OL-4e




Example OL-4e was prepared from Example OL-4d, according to the same procedure used for the preparation of Example OL-1d. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.14/1.17 /1.38/1.40(rotomers, s, 18 H), 1.71 - 2.06 (m, 6 H), 2.09 - 2.28 (m, J=25.79, 13.89 Hz, 2 H), 3.31 - 3.40 (m, 2 H), 3.51 (s, 2 H), 4.65 - 4.89 (m, 2 H), 6.80 (t, J=8.39 Hz, 1 H), 6.91 - 7.10 (m, 2 H), 7.28 - 7.55 (m, 5 H), 7.58 - 7.80 (m, 2 H), 11.66 - 12.21 (m, 2 H). LC (Cond. 1): RT = 2.98 min; LRMS: Anal. Calcd. for $C_{36}H_{45}N_6O_5$ $(M+H)^+$ 641.34; found: 641.39.

Example OL-4f

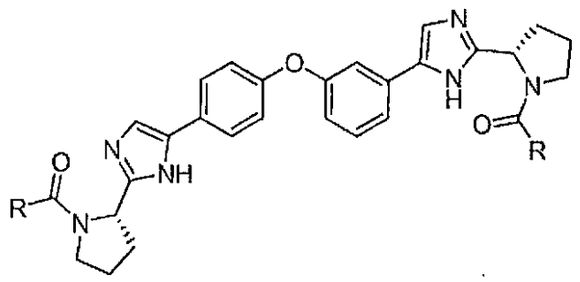



Example OL-4f was prepared from Example OL-4e, according to the same procedure used for the preparation of Example OL-1e. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.94 - 2.06 (m, 2 H), 2.09 - 2.23 (m, 2 H), 2.28 - 2.38 (m, 1 H), 2.37 - 2.47 (m, 3 H), 3.27 - 3.50 (m, 4 H), 4.90 (br. s, 1 H), 4.99 (br. s, 1 H), 7.00 (d, J=7.93 Hz, 1 H), 7.13 (d, J=8.55 Hz, 2 H), 7.49 (t, J=7.93 Hz, 1 H), 7.62 (s, 1 H), 7.69 (d, J=7.63 Hz, 1 H), 7.92 (d, J=8.55 Hz, 2 H), 7.99 (s, 2 H), 9.58 (br. s, 1 H), 9.84 (br. s, 1 H), 10.25 (br. d, J=22.28 Hz, 2 H). Note: the signal of the imidazole NH was too broad to assign a chemical shift. LC (Cond. 1): RT = 1.72 min; LRMS: Anal. Calcd. for $C_{26}H_{29}N_6O$ $(M+H)^+$ 441.24; found: 441.29.

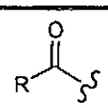
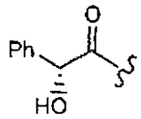
Example OL-4

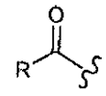
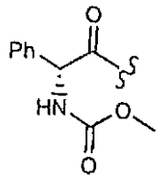
Example OL-4 was prepared from Example OL-4f according to the same procedure used for the preparation of Example OL-1. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.83 - 1.92 (m, 4 H), 1.95 - 2.09 (m, 8 H), 2.11 - 2.23 (m, 4 H), 2.75 - 2.88 (m, 2 H), 2.92 (s, 1 H), 2.96 - 3.12 (m, 2 H), 3.97 (t, J=8.39 Hz, 2 H), 5.14 (dd, J=17.70, 7.02 Hz, 2 H), 5.41 (s, 2 H), 6.91 - 7.11 (m, J=49.75 Hz, 2 H), 7.14 (d, J=7.93 Hz, 2 H), 7.44 - 7.68 (m, 12 H), 7.79 (d, J=8.54 Hz, 2 H), 7.84 - 8.02 (m, J=9.16 Hz, 2 H), 10.21 (s, 1 H). Note: the signal of the imidazole NH was too broad to assign a chemical shift. LC (Cond. 1): RT = 1.78 min; LRMS: Anal. Calcd. for $C_{46}H_{51}N_8O_3$ $(M+H)^+$ 763.41; found: 763.56. HRMS: Anal. Calcd. for $C_{46}H_{51}N_8O_3$ $(M+H)^+$ 763.4084; found: 763.4067.

Examples OL-5 and OL-6

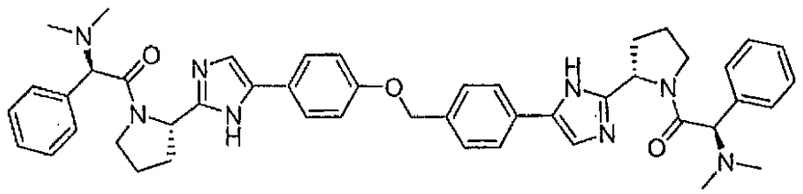


Examples OL-5 to OL-6 were prepared as TFA salts by substituting the respective acids for Cap-1 according to the same method described for Example OL-4.

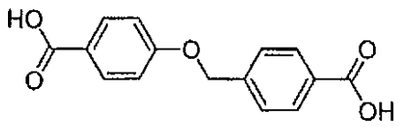
| Example |  Acid | RT (LC-Cond.); MS data |
|---|---|---|
| OL-5 |  Mandelic acid | RT = 1.78 min. LC (Cond. 2); LCMS: Anal. Calcd. for: $C_{42}H_{41}N_6O_5$ $(M+H)^+$ 709.31; Found: 709.42; HRMS: Anal. Calcd. for: $C_{42}H_{41}N_6O_5$ $(M+H)^+$ 709.3138; Found: 709.3130 |

| Example |  Acid | RT (LC-Cond.); MS data |
|---|---|---|
| OL-6 |  Cap-4 | RT = 1.96 min. LC (Cond. 2); LCMS: Anal. Calcd. for: $C_{46}H_{47}N_8O_7$ $(M+H)^+$ 823.36; Found: 823.51; HRMS: Anal. Calcd. for: $C_{46}H_{47}N_8O_7$ $(M+H)^+$ 823.3568; Found: 823.3588 |

Example OL-7

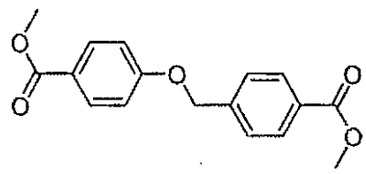


Example OL-7a



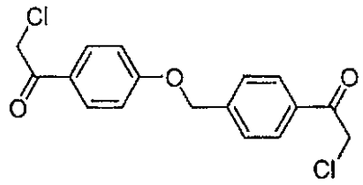
To a solution of 4-(chloromethyl)benzoic acid (8.53 g, 50 mmol) and sodium hydroxide (10 g, 0.25 mol) in water (40 mL) was added a solution of 4-hydroxybenzoic acid (6.9 g, 50 mmol) and sodium hydroxide (6 g, 0.15 mol) in water (50 mL). The resulting mixture was heated to reflux temperature for 15 h and, after cooling to room temperature, it was filtered and acidified with a solution of sulfuric acid in water (1:1, 200 mL). The resulting precipitate was filtered off, washed with water and dried in vacuo. The off-white solid (9.3 g) was used without further purification. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 5.27 (s, 1 H), 7.10 (d, J=8.85 Hz, 2 H), 7.56 (d, J=8.24 Hz, 2 H), 7.89 (d, J=8.85 Hz, 2 H), 7.96 (d, J=8.24 Hz, 2 H), 12.36 (br. s, 2 H). LC (Cond. 2), Note: The molecule did not ionize well in the LC/MS system and therefore an exact mass was not obtained.

Example OL-7b



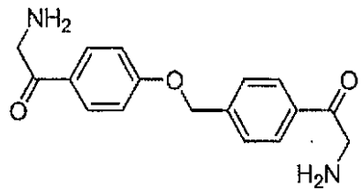
(Diazomethyl)trimethylsilane (15 mL, 30 mmol, 2 M in hexanes) was added dropwise to a suspension of Example OL-7a (2.04 g, 7.5 mmol) in methanol (30 mL) at 5 °C (ice-water bath). When the addition was complete, the cooling bath was removed and the mixture was stirred at ambient overnight. The solvent was removed under reduced pressure and the remaining residue was taken up in ethyl acetate, washed with water, sodium bicarbonate and brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting material was purified by flash chromatography (silica gel, 10% ethyl acetate/hexanes) to provide Example OL-7b as white solid (1.5 g). $^1H$ NMR (500 MHz, DMSO-$d_6$) δ ppm 3.80 (s, 3 H), 3.85 (s, 3 H), 5.29 (s, 2 H), 7.13 (d, J=8.85 Hz, 2 H), 7.59 (d, J=8.24 Hz, 2 H), 7.91 (d, J=9.16 Hz, 2 H), 7.98 (d, J=8.24 Hz, 2 H). LC (Cond. 1): RT = 2.56 min; LRMS: Anal. Calcd. for $C_{17}H_{16}O_5$ $(M+H)^+$ 301.11; found: 301.22.

Example OL-7c



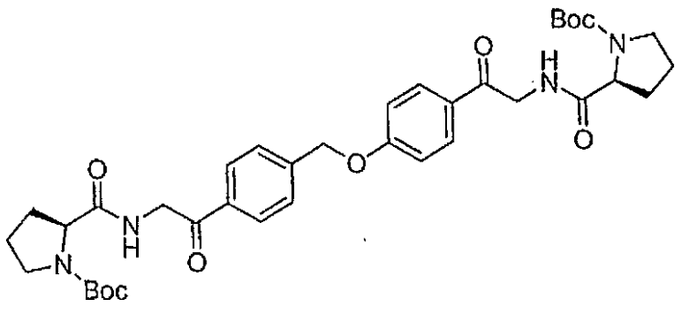
Example OL-7c was prepared from Example OL-7b, according to the same procedure used for the preparation of Example OL-1a. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ ppm 5.09 (s, 2 H), 5.18 (s, 2 H), 5.34 (s, 2 H), 7.15 (d, J=8.85 Hz, 2 H), 7.62 (d, J=8.55 Hz, 2 H), 7.95 (d, J=9.16 Hz, 2 H), 8.00 (d, J=8.55 Hz, 2 H). LC (Cond. 1): RT = 2.36 min; LRMS: Anal. Calcd. for $C_{17}H_{15}Cl_2O_3$ $(M+H)^+$ 337.04 found: 337.09.

Example OL-7d



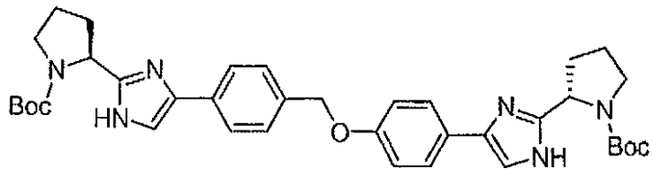
Example OL-7d was prepared from Example OL-7c, according to the same procedure used for the preparation of Example OL-1b. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 4.49 (s, 2 H), 4.57 (s, 2 H), 5.38 (s, 2 H), 7.19 (d, J=8.85 Hz, 2 H), 7.66 (d, J=8.24 Hz, 2 H), 8.00 (d, J=8.85 Hz, 2 H), 8.05 (d, J=8.24 Hz, 2 H), 8.45 (s, 6 H). LC (Cond. 1): RT = 1.26 min; LRMS: Anal. Calcd. for $C_{17}H_{19}Nl_2O_3$ $(M+H)^+$ 299.14 found: 299.19.

Example OL-7e



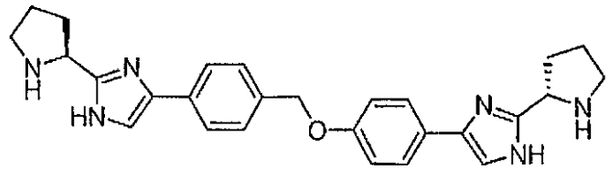
Example OL-7e was prepared from Example OL-7d, according to the same procedure used for the preparation of Example OL-1c. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.30 - 1.47 (m, 18 H), 1.65 - 1.89 (m, 6 H), 2.01 - 2.20 (m, 2 H), 3.24 - 3.34 (m, 2 H), 3.34 - 3.43 (m, 2 H), 4.09 - 4.25 (m, 2 H), 4.44 - 4.68 (m, 4 H), 5.33 (s, 2 H), 7.13 (d, J=8.85 Hz, 2 H), 7.60 (d, J=8.24 Hz, 2 H), 7.99 (dd, J=20.29, 8.09 Hz, 4 H), 8.04 - 8.22 (m, J=31.74 Hz, 2 H). LC (Cond. 2): RT = 1.53 minutes, 97% homogeneity index; LCMS: Anal. Calcd. for $C_{37}H_{49}N_4O_9$ $(M+1)^+$ 693.35; found: 693.32.

Example OL-7f



Example OL-7f was prepared from Example OL-7e, according to the same procedure used for the preparation of Example OL-1d. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.06 - 1.52 (m, 18 H), 1.69 - 2.08 (m, 6 H), 2.08 - 2.30 (m, 2 H), 3.33 - 3.43 (m, 2 H), 3.52 (s, 2 H), 4.75 (s, 1 H), 4.83 (s, 1 H), 5.06 (s, 2 H), 6.92 - 7.10 (m, J=7.63 Hz, 2 H), 7.20 - 7.33 (m, 1 H), 7.40 (d, J=7.63 Hz, 2 H), 7.46 (d, J=8.55 Hz, 1 H), 7.64 (d, J=7.63 Hz, 2 H), 7.75 (d, J=7.93 Hz, 2 H), 11.47 - 12.18 (m, 2 H). LC (Cond. 1): RT = 2.94 min; LRMS: Anal. Calcd. for $C_{37}H_{47}N_6O_3$ $(M+H)^+$ 655.36 found: 655.39.

Example OL-7g



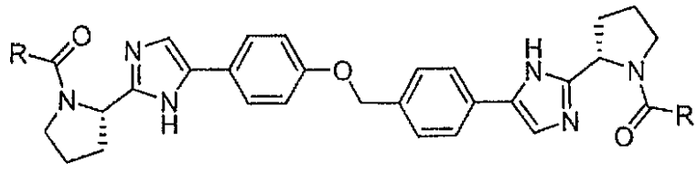
Example OL-7g was prepared from Example OL-7fe, according to the same procedure used for the preparation of Example OL-1e. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.93 - 2.07 (m, 2 H), 2.13 - 2.26 (m, 2 H), 2.40 - 2.48 (m, 3 H), 3.31 - 3.52 (m, 5 H), 4.91 - 5.09 (m, 2 H), 5.21 (s, 2 H), 7.17 (d, J=8.85 Hz, 2 H), 7.57 (d, J=8.24 Hz, 2 H), 7.87 (d, J=8.85 Hz, 2 H), 7.93 (d, J=8.24 Hz, 2 H), 8.03 (d, J=16.79 Hz, 2 H), 9.78 (s, 1 H), 9.95 (s, 1 H), 10.31 (s, 2 H). Note: the signal of the imidazole NH was too broad to assign a chemical shift. LC (Cond. 2): RT = 0.62 minutes; LCMS: Anal. Calcd. for $C_{27}H_{31}N_6O$ $(M+1)^+$ 455.26; found: 455.34.

Example OL-7

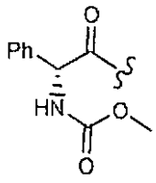
Example OL-7 was prepared from Example OL-7g according to the same procedure used for the preparation of Example OL-1. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.90 (d, J=2.44 Hz, 2 H), 2.04 (d, J=3.66 Hz, 4 H), 2.21 (s, 2 H), 2.36 (d, J=1.83 Hz, 2 H), 2.42 - 2.46 (m, 4 H), 2.83 (br. s, 4 H), 2.99 - 3.11 (m, 2 H), 3.98 (d, J=7.02 Hz,

2 H), 5.18 (s, 4 H), 5.42 (d, J=8.55 Hz, 2 H), 7.08 - 7.28 (m, 3 H), 7.50 - 7.67 (m, 11 H), 7.73 (d, J=7.32 Hz, 2 H), 7.80 (d, J=7.93 Hz, 2 H), 7.85 - 7.98 (m, J=10.38 Hz, 1 H). Note: the signal of the imidazole NH was too broad to assign a chemical shift. LC (Cond. 3): RT = 2.94 min; LRMS: Anal. Calcd. for $C_{47}H_{52}N_8O_3$ $(M+H)^+$ 777.42 found: 777.51; HRMS: Anal. Calcd. for $C_{47}H_{53}N_8O_3$ $(M+H)^+$ 777.4241 found: 777.4265.

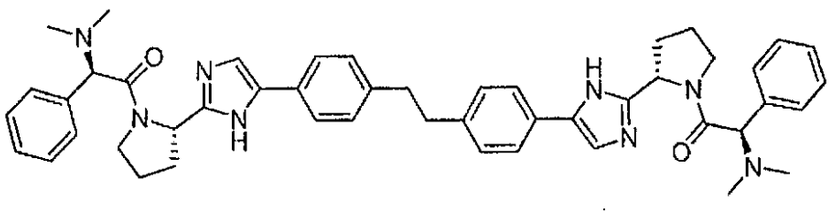
Example OL-8



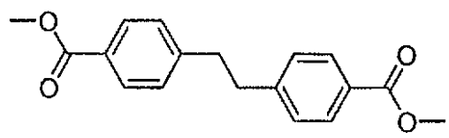
Example OL-8 was prepared as TFA salt by substituting the respective acid for Cap-1 according to the same method described for Example OL-7.

| Example |  Acid | RT (LC-Cond.); MS data |
|---|---|---|
| OL-8 |  Cap-4 | RT = 3.70 min. LC (Cond. 4); LCMS: Anal. Calcd. for $C_{47}H_{49}N_8O_7$ $(M+H)^+$ 837.37; Found: 837.54; HRMS: Anal. Calcd. for: $C_{47}H_{49}N_8O_7$ $(M+H)^+$ 837.3724; Found: 837.3715 |

Example OL-9

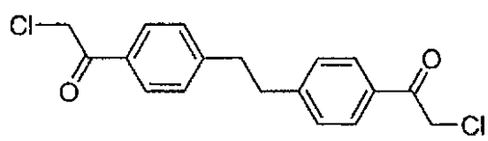


Example OL-9a



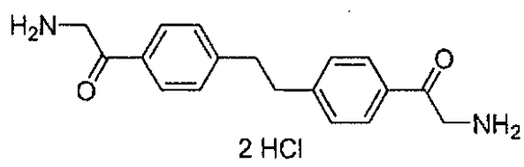
Palladium on carbon (10%, 300 mg) was added to a solution of dimethyl 4,4'-(ethene-1,2-diyl)dibenzoate (2g, 6.76 mmol) in methanol (100 mL). The suspension was purged with $N_2$, placed under 1 atm of $H_2$ (balloon) and stirred at ambient overnight. The mixture was then filtered through a plug of diatomaceous earth (CELITE®)and the solvent was concentrated under reduced pressure. A white solid was recovered (1.42 g) and used without further purification. $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 2.98 (s, 4 H), 3.90 (s, 6 H), 7.18 (d, J=7.32 Hz, 4 H), 7.93 (d, J=7.32 Hz, 4 H). LC (Cond. 1): RT = 2.65 min; LRMS: Anal. Calcd. for $C_{18}H_{19}O_4$ $(M+H)^+$ 299.13 found: 299.21.

Example OL-9b



Example OL-9b was prepared from Example OL-9a, according to the same procedure used for the preparation of Example OL-1a. $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 3.02 (s, 4 H), 4.67 (s, 4 H), 7.25 (d, J=8.24 Hz, 4 H), 7.86 (d, J=8.24 Hz, 4 H). LC (Cond. 2): RT = 0.62 min; LCMS: Anal. Calcd. for $C_{18}H_{17}Cl_2O_2$ $(M+1)^+$ 335.06; found: 335.12.

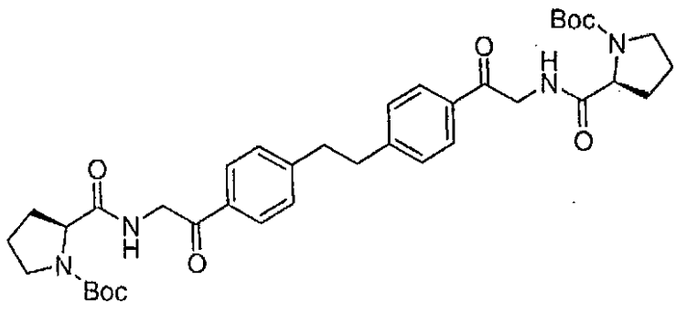
Example OL-9c



Example OL-9c was prepared from Example OL-9b, according to the same procedure used for the preparation of Example OL-1b. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm

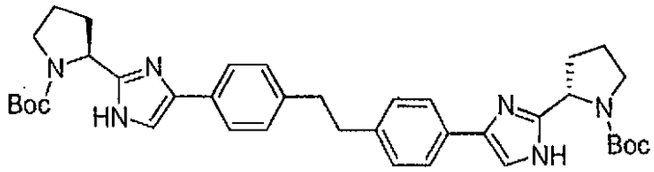
3.03 (s, 4 H), 4.51 (s, 4 H), 7.43 (d, J=8.55 Hz, 4 H), 7.92 (d, J=8.24 Hz, 4 H), 8.50 (s, 6 H). LC (Cond. 3): RT = 1.90 min; LRMS: Anal. Calcd. for $C_{18}H_{21}N_2O_2$ $(M+H)^+$ 297.16 found: 297.24.

Example OL-9d




Example OL-9d was prepared from Example OL-9c, according to the same procedure used for the preparation of Example OL-1c. $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 1.38 - 1.56 (m, 18 H), 1.83 - 2.00 (m, 4 H), 2.08 - 2.38 (m, 4 H), 3.01 (s, 4 H), 3.32 - 3.65 (m, 4 H), 4.28 (br. s, 1 H), 4.39 (br. s, 1 H), 4.63 - 4.71 (m, 2 H), 4.72 - 4.84 (m, J=4.58 Hz, 2 H), 7.01 (s, 1 H), 7.18 - 7.33 (m, 4 H), 7.47 (s, 1 H), 7.87 (d, J=7.93 Hz, 4 H). LC (Cond. 1): RT = 2.56 min; LRMS: Anal. Calcd. for $C_{38}H_{51}N_4O_8$ $(M+H)^+$ 691.37, found: 691.48.

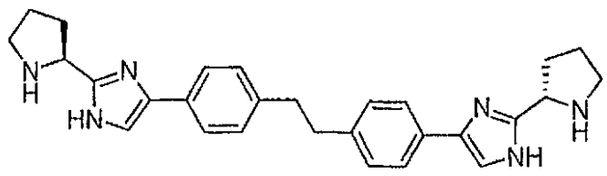
Example OL-9e




Example OL-9e was prepared from Example OL-9d, according to the same procedure used for the preparation of Example OL-1d. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.15/1.39(rotomers, s, 18 H), 1.75 - 1.92 (m, 3 H), 1.96 (s, 3 H), 2.09 - 2.27 (m, J=32.04 Hz, 2 H), 2.81 - 2.90 (m, 4 H), 3.31 - 3.40 (m, 2 H), 3.52 (s, 2 H), 4.66 - 4.88 (m, J=35.40 Hz, 2 H), 7.14 (d, J=7.02 Hz, 4 H), 7.21 (s, 1 H), 7.31 - 7.41 (m, 1 H), 7.51 (d, J=6.41 Hz, 1 H), 7.61 (d, J=7.93 Hz, 3 H), 11.62 - 12.08 (m, 2 H). LC

(Cond. 1): RT = 2.20 min; LRMS: Anal. Calcd. for $C_{38}H_{49}N_6O_4$ $(M+H)^+$ 653.38, found: 653.47.

Example OL-9f

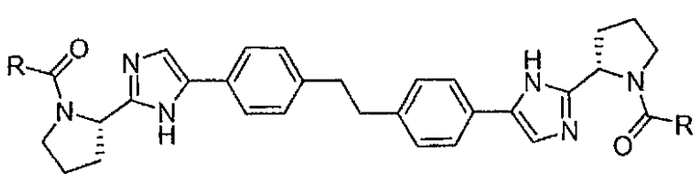


Example OL-9f was prepared from Example OL-9e, according to the same procedure used for the preparation of Example OL-1e. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.92 - 2.05 (m, 2 H), 2.11 - 2.25 (m, 2 H), 2.40 - 2.47 (m, 4 H), 2.89 - 3.03 (m, 4 H), 3.32 - 3.39 (m, 2 H), 3.40 - 3.49 (m, 2 H), 5.02 (t, J=7.78 Hz, 2 H), 7.32 (d, J=8.24 Hz, 4 H), 7.80 (d, J=8.24 Hz, 4 H), 9.91 (s, 2 H), 10.32 (s, 2 H). Note: the signal of the imidazole NH was too broad to assign a chemical shift. LC (Cond. 5): RT = 2.52 min; LRMS: Anal. Calcd. for $C_{28}H_{33}N_6$ $(M+H)^+$ 453.28, found: 453.31.

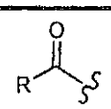
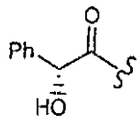
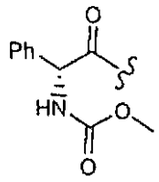
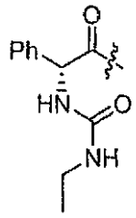
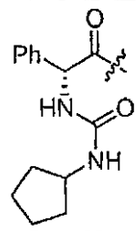
Example OL-9

Example OL-9 was prepared from Example OL-9f, according to the same procedure used for the preparation of Example OL-1. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.82 - 1.95 (m, 2 H), 1.97 - 2.10 (m, 4 H), 2.15 - 2.27 (m, J=4.58 Hz, 2 H), 2.28 - 2.45 (m, 4 H), 2.72 - 2.88 (m, 4 H), 2.94 (s, 5 H), 2.98 - 3.07 (m, 2 H), 3.97 (t, J=9.77 Hz, 2 H), 5.17 (d, J=6.10 Hz, 2 H), 5.41 (s, 2 H), 7.12 (s, 1 H), 7.38 (d, J=7.32 Hz, 4 H), 7.51 - 7.62 (m, 9 H), 7.69 (d, J=7.93 Hz, 4 H), 7.93 (s, 2 H). Note: the signal of the imidazole NH was too broad to assign a chemical shift. LC (Cond. 5): RT = 2.87 min; LRMS: Anal. Calcd. for $C_{48}H_{55}N_8O_2$ $(M+H)^+$ 775.44 found: 775.51; HRMS: Anal. Calcd. for $C_{48}H_{55}N_8O_2$ $(M+H)^+$ 775.4448 found: 775.4454.

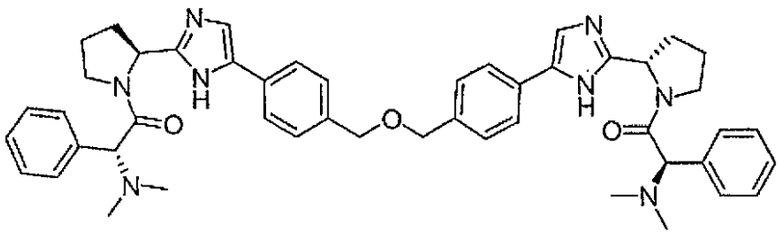
Examples OL-10 to OL-13



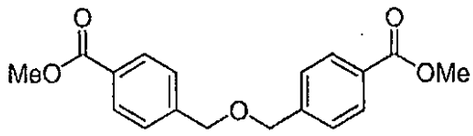
Examples OL-10 to OL-13 were prepared as TFA salts by substituting the respective acids for Cap-1 according to the same method described for Example OL-9.

| Example |  Acid | RT (LC-Cond.); MS data |
|---|---|---|
| OL-10 |  Mandelic acid | RT = 2.64 min. LC (Cond. 4); LCMS: Anal. Calcd. for: $C_{44}H_{45}N_6O_4$ $(M+H)^+$ 721.35; Found: 721.42; HRMS: Anal. Calcd. for $C_{44}H_{45}N_6O_4$ $(M+H)^+$ 721.3502; Found: 721.3518 |
| OL-11 |  Cap-4 | RT = 2.88 min. LC (Cond. 4); LCMS: Anal. Calcd. for: $C_{48}H_{51}N_8O_6$ $(M+H)^+$ 835.39; Found: 835.49; HRMS: Anal. Calcd. for: $C_{48}H_{50}N_8O_6$ $(M+H)^+$ 835.3932; Found: 835.3939 |
| OL-12 |  **Cap-46** | RT = 4.20 min. LC (Cond. 4); LCMS: Anal. Calcd. for: $C_{50}H_{57}N_{10}O_4$ $(M+H)^+$ 861.45; Found: 861.50; HRMS: Anal. Calcd. for: $C_{50}H_{57}N_{10}O_4$ $(M+H)^+$ 861.4564; Found: 861.4562 |
| OL-13 |  **Cap-48** | RT = 5.11 min. LC (Cond. 4); LCMS: Anal. Calcd. for: $C_{56}H_{64}N_{10}O_4$ $(M+H)^+$ 941.52; Found: 941.71; HRMS: Anal. Calcd. for: $C_{56}H_{65}N_{10}O_4$ $(M+H)^+$ 941.5190; Found: 941.5162 |

Example OL-14

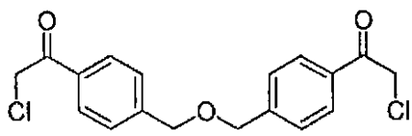


Example OL-14a



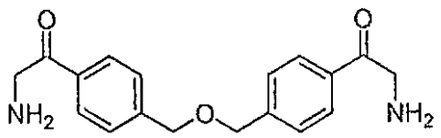
Triethyl silane (5.84 mL, 36.55 mmol) was added dropwise to a solution of methyl 4-formylbenzoate (5 g, 30.46 mmol) and bismuth tribromide (0.273 g, 0.61 mmol) in acetonitrile (75 mL) and the opaque solution was stirred at ambient for 15 min. Volatiles were removed under reduced pressure and the remaining residue was taken up in ethyl acetate. The organic layer was then washed with water and brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The recovered solid was then submitted to flash chromatography (silica gel; 10-20% ethyl acetate/hexanes) to provide OL-14a (3.05 g). $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 3.84 (s, 6 H), 4.65 (s, 4 H), 7.51 (d, J=8.24 Hz, 4 H), 7.95 (d, J=8.24 Hz, 4 H). LC (Cond. 2): RT = 1.68 min; LCMS: Anal. Calcd. for $C_{18}H_{19}O_5$ $(M+H)^+$ 315.12; found: 315.26.

Example OL-14b



Example OL-14b was prepared from Example OL-14a, according to the same procedure used for the preparation of Example OL-1a. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 4.67 (s, 4 H), 5.19 (s, 4 H), 7.55 (d, J=8.24 Hz, 4 H), 7.98 (d, J=8.24 Hz, 4 H). LC (Cond. 5): RT = 3.85 min; LRMS: Anal. Calcd. for $C_{18}H_{17}Cl_2O_3$ $(M+H)^+$ 351.05, found: 351.06.

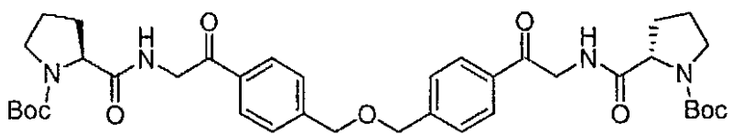
Example OL-14c



2 HCl

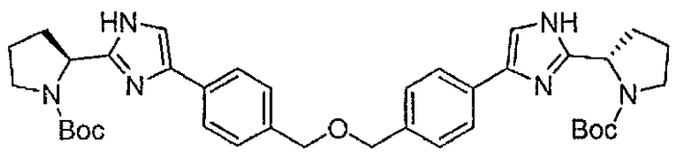
Example OL-14c was prepared from Example OL-14b, according to the same procedure used for the preparation of Example OL-1b. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 4.55 (s, 4 H), 4.69 (s, 4 H), 7.57 (d, J=8.24 Hz, 4 H), 8.02 (d, J=8.55 Hz, 4 H), 8.53 (s, 6 H). LC (Cond. 1): RT = 1.29 min; LRMS: Anal. Calcd. for $C_{18}H_{21}N_2O_3$ $(M+H)^+$ 313.15, found: 313.21.

Example OL-14d



Example OL-14d was prepared from Example OL-14c, according to the same procedure used for the preparation of Example OL-1c. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.34/1.40 (rotomers, s, 18 H), 1.70 - 1.92 (m, 6 H), 1.99 - 2.20 (m, 2 H), 3.24 - 3.33 (m, 2 H), 3.35 - 3.44 (m, 2 H), 4.11 - 4.25 (m, 2 H), 4.50 - 4.65 (m, 4 H), 4.66 (s, 4 H), 7.53 (d, J=8.24 Hz, 4 H), 7.99 (d, J=7.93 Hz, 4 H), 8.09 - 8.23 (m, 2 H). LC (Cond. 1): RT = 2.49 min; LRMS: Anal. Calcd. for $C_{38}H_{51}N_4O_9$ $(M+H)^+$ 707.36 found: 707.50.

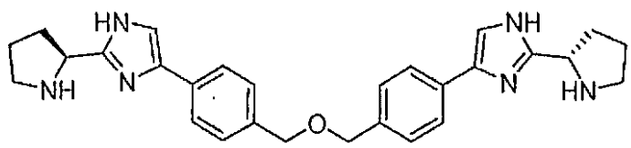
Example OL-14e



Example OL-14e was prepared from Example OL-14d, according to the same procedure used for the preparation of Example OL-1d. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.14/ 1.39 (rotomers, s, 18 H), 1.76 - 2.06 (m, 6 H), 2.08 - 2.30 (m, 2 H), 3.31 - 3.41 (m, 2 H), 3.52 (s, 2 H), 4.49 (s, 4 H), 4.70 - 4.78 (m, 1 H), 4.79 - 4.90 (m,

1 H), 7.29/7.35 (rotomers, d, J=7.93 Hz, 4 H), 7.40 - 7.54 (m, 2 H), 7.71/761 (rotomers, d, J=7.93 Hz, 4 H), 11.72 - 12.19 (m, 2 H). LC (Cond. 1): RT = 2.14 min; LRMS: Anal. Calcd. for $C_{38}H_{49}N_6O_5$ $(M+H)^+$669.38, found: 669.53.

Example OL-14f

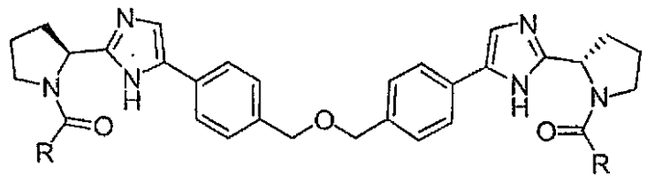



Example OL-14f was prepared from Example OL-14e, according to the same procedure used for the preparation of Example OL-1e. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.94 - 2.06 (m, 2 H), 2.11 - 2.25 (m, 2 H), 2.38 - 2.48 (m, 4 H), 3.32 - 3.50 (m, 4 H), 4.60 (s, 4 H), 4.92 - 5.06 (m, 2 H), 7.48 (d, J=7.93 Hz, 4 H), 7.89 (d, J=7.93 Hz, 4 H), 8.04 (s, 2 H), 9.78 (s, 2 H), 10.28 (s, 2 H). Note: the signal of the imidazole NH was too broad to assign a chemical shift. LC (Cond. 1): RT =1.69 min; LRMS: Anal. Calcd. for $C_{28}H_{33}N_6O$ $(M+H)^+$ 469.27 found: 469.34.

Example OL-14

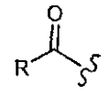
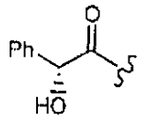
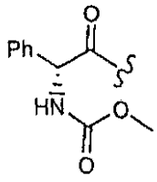
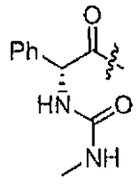
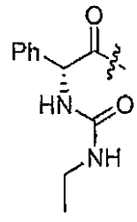
Example OL-14 was prepared from Example OL-14f, according to the same procedure used for the preparation of Example OL-1. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.82 - 2.11 (m, 6 H), 2.18 (d, J=6.10 Hz, 2 H), 2.31 - 2.47 (m, 4 H), 2.98 - 3.10 (m, 2 H), 3.92 - 4.07 (m, 2 H), 4.59 (s, 4 H), 5.10 - 5.22 (m, 2 H), 5.42 (s, 2 H), 7.07 - 7.13 (m, 2 H), 7.40 - 7.51 (m, 4 H), 7.54 - 7.67 (m, 10 H), 7.75 (d, J=7.32 Hz, 4 H). Note: the signal of the imidazole NH was too broad to assign a chemical shift. The signals for the Me groups of the cap fell underneath the solvent peak. LC (Cond. 4): RT = 1.83 min; LRMS: Anal. Calcd. for $C_{48}H_{55}N_8O_3$ $(M+H)^+$ 791.44; found: 791.60. HRMS: Anal. Calcd. for $C_{48}H_{55}N_8O_3$ $(M+H)^+$ 791.4397; found: 791.4406.

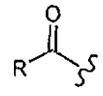
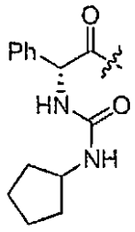
Examples OL-15 to OL-19



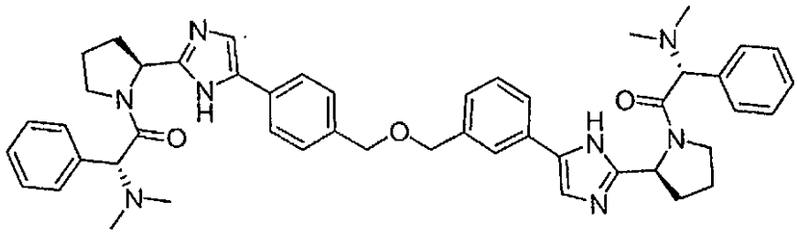
Examples OL-15 to OL-19 were prepared as TFA salts by substituting the respective acids for Cap-1 according to the same method described for Example OL-14.

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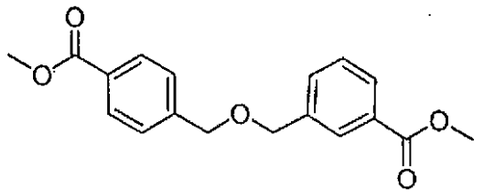
| Example |  Acid | RT (LC-Cond.); MS data |
|---|---|---|
| OL-15 |  Mandelic acid | RT = 2.86 min. LC (Cond. 4); LCMS: Anal. Calcd. for: $C_{44}H_{45}N_6O_5$ $(M+H)^+$ 737.34; Found: 737.38; HRMS: Anal. Calcd. for: $C_{44}H_{45}N_6O_5$ $(M+H)^+$ 737.3451; Found: 737.3452 |
| OL-16 |  Cap-4 | RT = 3.45 min. LC (Cond. 4); LCMS: Anal. Calcd. for: $C_{48}H_{51}N_8O_7$ $(M+H)^+$ 851.39; Found: 851.40; HRMS: Anal. Calcd. for: $C_{48}H_{51}N_8O_7$ $(M+H)^+$ 851.3881; Found: 851.3910 |
| OL-17 |  Cap-45a | RT = 1.16 min. LC (Cond. 2); LCMS: Anal. Calcd. for: $C_{48}H_{53}N_{10}O_5$ $(M+H)^+$ 849.42; Found: 849.61; HRMS: Anal. Calcd. for: $C_{48}H_{53}N_{10}O_5$ $(M+H)^+$ 849.4200; Found: 849.4182 |
| OL-18 |  Cap-46 | RT = 1.24 min. LC (Cond. 2); LCMS: Anal. Calcd. for: $C_{50}H_{56}N_{10}O_5$ $(M+H)^+$ 877.45; Found: 877.70; HRMS: Anal. Calcd. for: $C_{50}H_{57}N_{10}O_5$ $(M+H)^+$ 877.4513; Found: 877.4506 |

| Example |  Acid | RT (LC-Cond.); MS data |
|---|---|---|
| OL-19 |  Cap-48 | RT = 1.43 min. LC (Cond. 2); LCMS: Anal. Calcd. for: $C_{56}H_{65}N_{10}O_5$ $(M+H)^+$ 957.51; Found: 957.84; HRMS: Anal. Calcd. for: $C_{56}H_{65}N_{10}O_5$ $(M+H)^+$ 957.5139; Found: 957.5142 |

Example OL-20



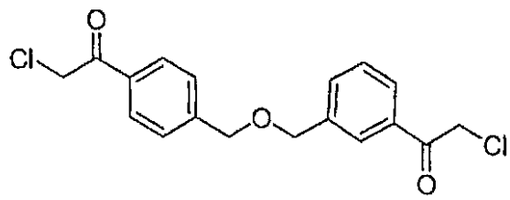
Example OL-20a



Sodium hydride (0.76 g, 18.95 mmol, 60% wt) was slowly added to a solution of methyl 4-(hydroxymethyl)benzoate (3 g, 18.05 mmol) in dimethylformamide (25 mL). The resulting dark blue solution was stirred at ambient for 15 min and methyl 3-(bromomethyl)benzoate (3.76g, 16.41 mmol) was added in one portion. The resulting yellow solution was stirred at ambient for 1 h and then the volatiles were removed under reduced pressure. The residue was taken up in ethyl acetate and washed with water and brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was submitted to flash chromatography (silica gel; 20 % ethyl

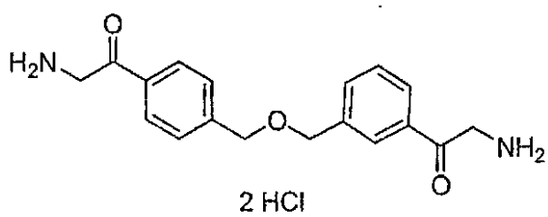
acetate/hexanes) to provide Example OL-20a as a clear oil that solidified upon standing (2.49 g). $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 3.91 (d, J=1.83 Hz, 6 H), 4.61 (d, J=2.56 Hz, 4 H), 7.39 - 7.49 (m, 3 H), 7.54 - 7.61 (m, 1 H), 7.93 - 8.00 (m, 1 H), 7.99 - 8.07 (m, 3 H). LC (Cond. 1): RT =2.56 min; LRMS: Anal. Calcd. for $C_{18}H_{19}O_5$ $(M+H)^+$ 315.12 found: 315.22.

Example OL-20b



Example OL-20b was prepared from Example OL-20a, according to the same procedure used for the preparation of Example OL-1a. $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 4.65 (d, J=4.58 Hz, 4 H), 4.69 (d, J=3.36 Hz, 4 H), 7.47 - 7.54 (m, J=7.63, 7.63 Hz, 3 H), 7.62 (d, J=7.63 Hz, 1 H), 7.89 (d, J=7.93 Hz, 1 H), 7.93 - 8.00 (m, 3 H). LC (Cond. 1): RT =2.34 min; LRMS: Anal. Calcd. for $C_{18}H_{17}Cl_2O_3$ $(M+H)^+$ 351.05 found: 351.12.

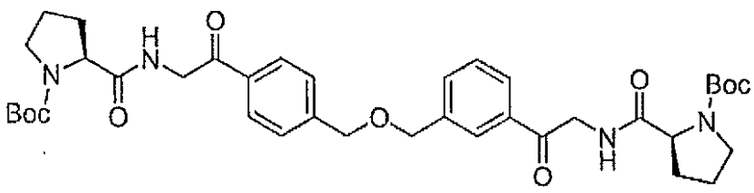
Example OL-20c



2 HCl

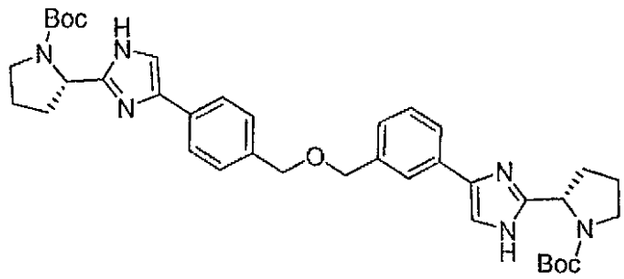
Example OL-20c was prepared from Example OL-20b, according to the same procedure used for the preparation of Example OL-1b. $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 4.57 (d, J=2.93 Hz, 4 H), 4.68 (d, J=5.85 Hz, 4 H), 7.52 - 7.67 (m, J=8.60, 8.60 Hz, 3 H), 7.73 (d, J=7.68 Hz, 1 H), 7.90 - 8.10 (m, 4 H), 8.53 (s, 6 H). LC (Cond. 1): RT =1.32 min; LRMS: Anal. Calcd. for $C_{18}H_{21}N_2O_3$ $(M+H)^+$ 313.15 found: 313.24.

Example OL-20d



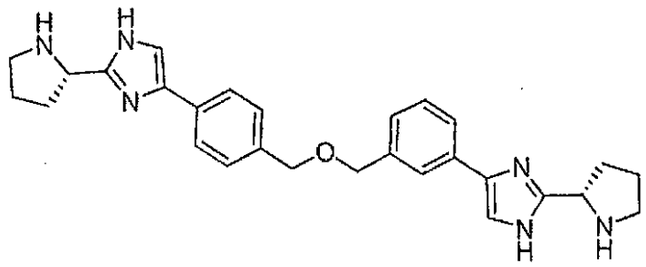
Example OL-20d was prepared from Example OL-20c, according to the same procedure used for the preparation of Example OL-1c. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.39/1.34 (rotomers, s, 18 H), 1.69 - 1.95 (m, 6 H), 2.00 - 2.18 (m, J=23.80 Hz, 2 H), 3.23 - 3.33 (m, 2 H), 3.34 - 3.43 (m, 2 H), 4.11 - 4.23 (m, 2 H), 4.50 - 4.63 (m, 4 H), 4.65 (d, J=6.71 Hz, 4 H), 7.48 - 7.56 (m, 3 H), 7.66 (d, J=7.63 Hz, 1 H), 7.89 - 8.02 (m, 4 H), 8.06 - 8.25 (m, 2 H). LC (Cond. 1): RT =2.53 min; LRMS: Anal. Calcd. for $C_{38}H_{51}N_4O_9$ $(M+H)^+$ 707.36 found: 707.44.

Example OL-20e



Example OL-20e was prepared from Example OL-20d, according to the same procedure used for the preparation of Example OL-1d. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.14/1.39 (rotomers, s, 18 H), 1.76 - 2.07 (m, 6 H), 2.08 - 2.29 (m, 2 H), 3.31 - 3.40 (m, 2 H), 3.52 (br. s, 2 H), 4.44 - 4.59 (m, J=8.55 Hz, 4 H), 4.75 (br. s, 1 H), 4.83 (br. s, 1 H), 7.08 - 7.23 (m, 2 H), 7.30 (d, J=7.63 Hz, 2 H), 7.34 - 7.50 (m, 2 H), 7.53 - 7.67 (m, 1 H), 7.68 - 7.79 (m, 3 H), 11.70 - 12.22 (m, 2 H). LC (Cond. 1): RT =2.19 min; LRMS: Anal. Calcd. for $C_{38}H_{48}N_6O_5$ $(M+H)^+$ 669.39, found: 669.40.

Example OL-20f

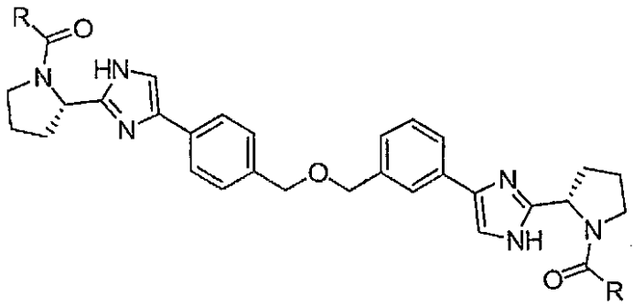


Example OL-20f was prepared from Example OL-20e, according to the same procedure used for the preparation of Example OL-1e. $^1$H NMR (500 MHz, DMSO-D6) δ ppm 1.94 - 2.08 (m, 2 H), 2.12 - 2.24 (m, 2 H), 2.39 - 2.48 (m, J=5.19 Hz, 4 H), 3.27 - 3.49 (m, 4 H), 4.61 (d, J=4.88 Hz, 4 H), 4.94 - 5.09 (m, J=7.93 Hz, 2 H), 7.38 (d, J=7.32 Hz, 1 H), 7.45 - 7.53 (m, 3 H), 7.83 (d, J=7.63 Hz, 1 H), 7.90 (d, J=7.02 Hz, 3 H), 8.07 (s, 2 H), 9.86 (br. s, 2 H), 10.33 (br. s, 2 H). Note: the signal of the imidazole NH was too broad to assign a chemical shift. LC (Cond. 1): RT = 1.75 min; LRMS: Anal. Calcd. for $C_{28}H_{32}N_6O$ $(M+H)^+$ 469.27, found: 469.23.

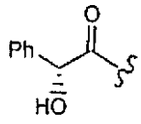
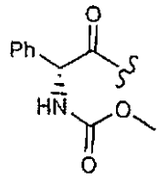
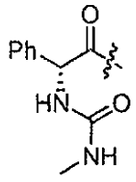
Example OL-20

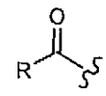
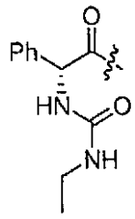
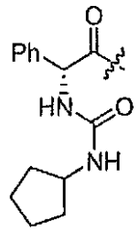
Example OL-20 was prepared from Example OL-20f, according to the same procedure used for the preparation of Example OL-1. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.84 - 1.95 (m, J=5.19 Hz, 2 H), 1.95 - 2.09 (m, J=8.24 Hz, 4 H), 2.15 - 2.28 (m, 2 H), 3.02 (q, J=7.73 Hz, 2 H), 3.93 - 4.05 (m, 2 H), 4.61 (br. s, 4 H), 5.12 - 5.22 (m, 2 H), 5.42 (br.s, 2 H), 7.12 (br. s, 1 H), 7.39 (s, 1 H), 7.45 - 7.51 (m, J=7.32 Hz, 3 H), 7.53 - 7.64 (m, 9 H), 7.66 - 7.82 (m, 4 H), 7.96 (s, 2 H). Note: the signal of the imidazole NH was too broad to assign a chemical shift. The signals for the Me groups of the cap fell underneath the solvent peak. LC (Cond. 4): RT = 1.93 min; LRMS: Anal. Calcd. for $C_{48}H_{55}N_8O_3$ $(M+H)^+$ 791.44; found: 791.57. HRMS: Anal. Calcd. for $C_{48}H_{55}N_8O_3$ $(M+H)^+$. 791.4397; found: 791.4373.

Examples OL-21 to OL-25

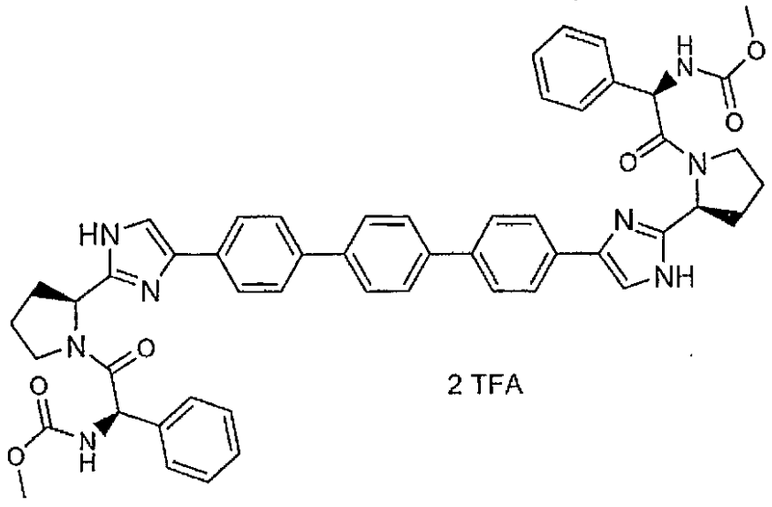


Examples OL-21 to OL-25 were prepared as TFA salts by substituting the respective acids for Cap-1 according to the same method described for Example OL-20.

| Example |  Acid | RT (LC-Cond.); MS data |
|---|---|---|
| OL-21 |  Mandelic acid | RT = 2.97 min. LC (Cond. 4); LCMS: Anal. Calcd. for: $C_{44}H_{45}N_6O_5$ $(M+H)^+$ 737.34; Found: 737.46; HRMS: Anal. Calcd. for: $C_{44}H_{45}N_6O_5$ $(M+H)^+$ 737.3451; Found: 737.3459 |
| OL-22 |  Cap-4 | RT = 3.59 min. LC (Cond. 4); LCMS: Anal. Calcd. for: $C_{48}H_{51}N_8O_7$ $(M+H)^+$ 851.38; Found: 851.50; HRMS: Anal. Calcd. for: $C_{48}H_{51}N_8O_7$ $(M+H)^+$ 851.3881; Found: 851.3893 |
| OL-23 |  Cap-45a | RT = 1.15 min. LC (Cond. 2); LCMS: Anal. Calcd. for: $C_{48}H_{52}N_{10}O_5$ $(M+H)^+$ 849.42; Found: 849.46; HRMS: Anal. Calcd. for: $C_{48}H_{53}N_{10}O_5$ $(M+H)^+$ 849.4200; Found: 849.4185 |

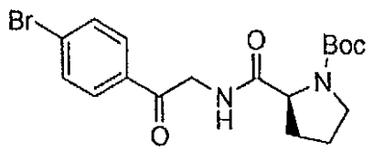
| Example |  Acid | RT (LC-Cond.); MS data |
|---|---|---|
| OL-34 |  Cap-46 | RT = 1.24 min. LC (Cond. 2); LCMS: Anal. Calcd. for: $C_{50}H_{56}N_{10}O_5$ $(M+H)^+$ 877.45 Found: 877.69; HRMS: Anal. Calcd. for: $C_{50}H_{57}N_{10}O_5$ $(M+H)^+$ 877.4513; Found: 877.4510 |
| OL-25 |  Cap-48 | RT = 4.89 min. LC (Cond. 4); LCMS: Anal. Calcd. for: $C_{56}H_{64}N_{10}O_5(M+H)^+$ 957.51; Found: 957.82; HRMS: Anal. Calcd. for: $C_{56}H_{65}N_{10}O_5$ $(M+H)^+$ 957.5139; Found: 957.5150 |

Example D-1



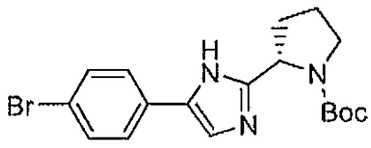
2 TFA

Example D-1, step a



*N,N*-Diisopropylethylamine (18 mL, 103.3 mmol) was added dropwise, over 15 minutes, to a heterogeneous mixture of *N*-Boc-L-proline (7.14 g, 33.17 mmol), HATU (13.32 g, 35.04 mmol), the HCl salt of 2-amino-1-(4-bromophenyl)ethanone (8.13 g, 32.44 mmol), and DMF (105 mL), and stirred at ambient condition for 55 minutes. Most of the volatile component was removed *in vacuo*, and the resulting residue was partitioned between ethyl acetate (300 mL) and water (200 mL). The organic layer was washed with water (200 mL) and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. A silica gel mesh was prepared from the residue and submitted to flash chromatography (silica gel; 50-60 % ethyl acetate/hexanes) to provide D-1a as a white solid (12.8 g). $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.40/1.34 (two app br s, 9 H), 1.90-1.70 (m, 3 H), 2.18-2.20 (m, 1 H), 3.30-3.23 (m, 1 H), 3.43-3.35 (m, 1 H), 4.22-4.12 (m, 1 H), 4.53 (dd, *J*=18.1, 5.6, 1 H), 4.61 (dd, *J*=18.3, 5.7, 1 H), 7.75 (br d, *J*=8.6, 2 H), 7.92 (br d, *J*=8.0, 2 H), 8.25-8.14 (m, 1H). LC (Cond. 7): RT = 1.70 min; LRMS: Anal. Calcd. for $(M+Na)^+$ $C_{18}H_{23}BrN_2NaO_4$: 433.07 found 433.09.

Example D-1, step b



A mixture of D-1a (12.8 g, 31.12 mmol) and $NH_4OAc$ (12.0 g, 155.7 mmol) in xylenes (155 mL) was heated in a sealed tube at 140 °C for 2 hours. The volatile component was removed *in vacuo*, and the residue was partitioned carefully between ethyl acetate and water, whereby enough saturated $NaHCO_3$ solution was added so as to make the pH of the aqueous phase slightly basic after the shaking of the biphasic system. The layers were separated, and the aqueous layer was extracted with additional ethyl acetate. The combined organic phase was washed with brine, dried

($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting material was recrystallized from ethyl acetate/hexanes to provide two crops of imidazole D-1b as a light-yellow, dense solid, weighing 5.85 g. The mother liquor was concentrated *in vacuo* and submitted to a flash chromatography (silica gel; 30% ethyl acetate/hexanes) to provide an additional 2.23 g of Example D-1b. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.40/1.15 (app br s, 9 H), 2.30-1.75 (m, 4 H), 3.36 (m, 1 H), 3.52 (app br s, 1 H), 4.86-4.70 (m, 1 H), 7.72-7.46/7.28 (m, 5 H), 12.17/11.92/11.86 (m, 1 H). LC (Cond. 7): RT = 1.71 min; LRMS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{23}BrN_3O_2$: 392.10; found 391.96; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{23}BrN_3O_2$: 392.0974; found 392.0959.

The optical purity of the two samples of Example D-1b was assessed according to the chiral HPLC conditions noted below (ee > 99% for the combined crops; ee = 96.7% for the sample from flash chromatography):

Column: Chiralpak AD, 10 um, 4.6 x 50 mm

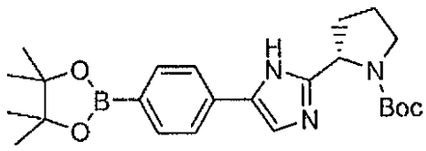
Solvent: 2% ethanol/heptane (isocratic)

Flow rate: 1 mL/min

Wavelength: either 220 or 254 nm

Relative retention time: 2.83 minutes (*R*), 5.34 minutes (*S*).

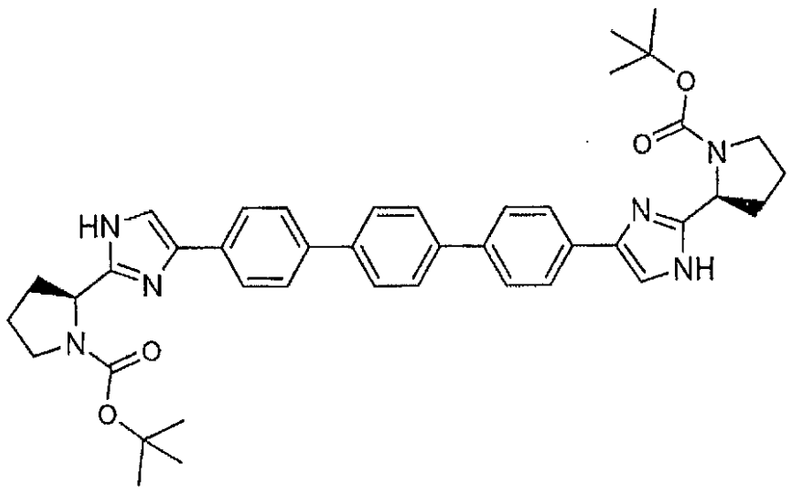
Example D-1, step c




$Pd(Ph_3P)_4$ (469 mg, 0.41 mmol) was added to a pressure tube containing a mixture of D-1b (4.01 g, 10.22 mmol), bis(pinacolato)diboron (5.42 g, 21.35 mmol), potassium acetate (2.57 g, 26.21 mmol) and 1,4-dioxane (80 mL). The pressure tube was purged with nitrogen, capped and heated in an oil bath at 80 °C for 16.5 hours. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The crude residue was partitioned carefully between $CH_2Cl_2$ (150 mL) and an aqueous medium (50 mL water and 10 mL saturated $NaHCO_3$ solution). The aqueous layer was extracted with $CH_2Cl_2$, and the combined organic phase was dried ($MgSO_4$), filtered, and

concentrated *in vacuo*. The resulting material was purified with flash chromatography (sample was loaded with eluting solvent; 20-35% ethyl acetate/$CH_2Cl_2$) to provide Example D-1c, contaminated with pinacol, as an off-white dense solid; the relative mole ratio of Example D-1c to pinacol was about 10:1 ($^1$H NMR). The sample weighed 3.925 g after ~2.5 days exposure to high vacuum. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.45-1.10 (m, 21H), 2.27-1.77 (m, 4H), 3.36 (m, 1H), 3.52 (app br s, 1H), 4.86-4.70 (m, 1H), 7.79-7.50/ 7.34-7.27 (m, 5H), 12.22/11.94/ 11.87 (m, 1H). LC (Cond. 7): RT = 1.64 min; LRMS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{35}BN_3O_4$: 440.27; found 440.23.

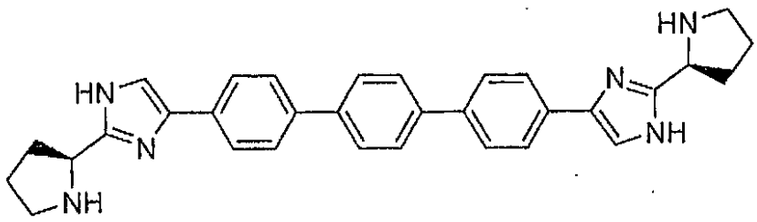
Example D-1, step d




Tetrakistriphenylphosphine palladium (17.5 mg, 0.015 mmol) was added in one portion to a stirred suspension of D-1c (320 mg, 0.85 mmol), 1,4- diiodobenzene (100 mg, 0.30 mmol) and sodium bicarbonate (180 mg, 2.18 mmol) in dimethoxyethane (2.4 mL) and water (7 mL) and heated to 90 °C for 2 h. The reaction was diluted with ethyl acetate and washed with saturated sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. The filtrate was taken up in methanol, filtered through a nylon syringe filter and then purified by preparative HPLC to provide D-1d as a white solid (101.1 mg, 20% yield). $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.17 (br s, 9 H), 1.41 (br s, 9 H), 1.80 - 2.06 (m, 4 H), 2.13 - 2.32 (m, 4 H), 3.35 - 3.43 (m, 2 H), 3.56 (br. s., 2 H), 4.80 (br s, 2 H), 7.54 (d, *J*=10.07 Hz,

2 H), 7.73 (d, *J*=7.63 Hz, 4 H), 7.79 (s, 4 H), 7.83 (d, *J*=8.24 Hz, 4 H). LC (Cond. 6): RT = 2.55 min; HRMS: Anal. Calcd. for $(M+H)^+$ $C_{42}H_{49}N_6O_4$ 701.3815; found: 701.3790.

Example D-1, step e

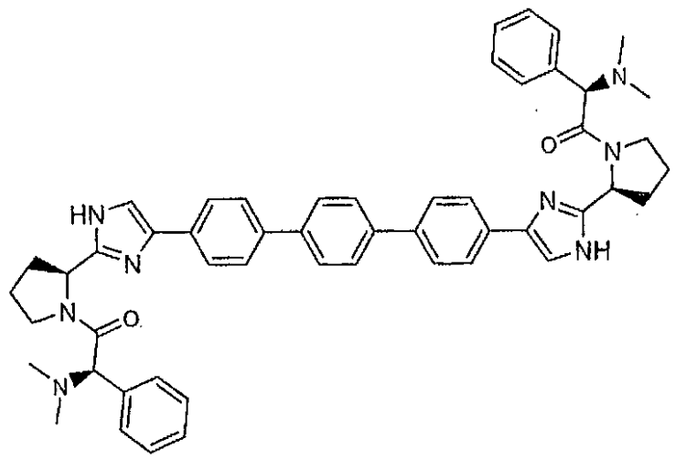


D-1e was prepared from D-1d, according to the same procedure used for the preparation of OL-1e except that methanol (1 mL) was used instead of dichloromethane. This gave D-1e as a tan solid and as a hydrochloride salt (101.5 mg, 96 % yield). $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.93 - 2.30 (m, 9 H), 2.32 - 2.44 (m, 3 H), 4.69 - 4.86 (m, 2 H), 7.68 - 7.87 (m, 12 H), 7.90 (d, *J* = 8.24 Hz, 2 H), 9.48 - 9.75 (m, 2 H). LC (*Cond. 6*): RT = 1.99 min; HRMS: Anal. Calcd. for $(M+H)^+$ $C_{32}H_{33}N_6$ 501.2767; found: 501.2753.

Example D-1

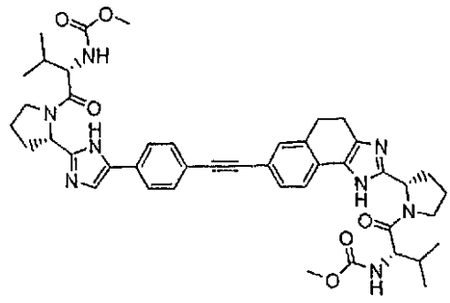
Example D-1 (TFA salt) was prepared from D-1e, according to the same procedure used for the preparation of Example OL-1. This gave Example D-1 as a tan solid (37.8 mg, 54 % yield). $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 2.05 (d, *J*=8.55 Hz, 8 H), 3.49 - 3.57 (m, 10 H), 3.94 (br s, 2 H), 5.52 (d, *J*=7.63 Hz, 2 H), 7.31 - 7.47 (m, 10 H), 7.72 (d, *J*=7.02 Hz, 2 H), 7.87 - 8.01 (m, 12 H). LC (*Cond. 6*): RT = 2.41 min; HRMS: Anal. Calcd. for $(M+H)^+$ $C_{52}H_{51}N_8O_6$ 883.3932; found: 883.3947.

Example D-2

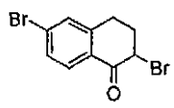


Example D-2 (TFA salt) was prepared from pyrrolidine D-1e, according to the same procedure used for the preparation of Example OL-1. This gave Example D-2 as a light yellow solid (15.4 mg, 38 % yield). $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 2.50-1.70 (m, 14 H), 2.98-2.62 (m, 6 H), 4.05-2.98 (m, 4 H), 5.79-5.12 (m, 4 H), 8.20-7.10 (m, 24 H), 10.25 (br s, 2 H). Note: The signal of the imidazole NH was too broad to assign a chemical shift. LC (*Cond. 6*): RT = 2.08 min; HRMS: Anal. Calcd. For $(M+H)^+$ $C_{52}H_{55}N_8O_2$ 823.4448; found: 823.4467.

Example D-3



Example D-3, step a

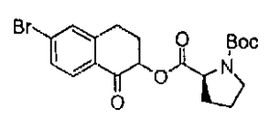
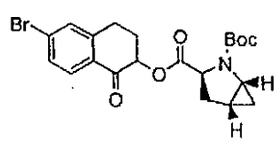


A solution of bromine (683 µL, 13.33 mmol) in acetic acid (7 mL) was added dropwise to a cold (10 °C) solution of 6-bromo-3,4-dihydronaphthalen-1(2*H*)-one

(purchased from *J* & W PharmLab, LLC) (3.00 g, 13.33 mmol) and 48% hydrogen bromide (20 μL, 13.33 mmol) in acetic acid (120 mL). The mixture was allowed to warm up to rt after the addition was complete and allowed to stir at rt for 1 h before it was diluted with dichloromethane and washed with water (3x), saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate and concentrated. There was isolated D-3a (4.19 g, 97% yield) as a colorless oil which solidified on standing under high vacuum to a white solid. This material was used without further purification. $^1$H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 7.85 (1 H, d, *J*=8.5 Hz), 7.71 (1 H, s), 7.62 (1 H, dd, *J*=8.5, 1.8 Hz), 5.06 (1 H, dd, *J*=6.1, 3.7 Hz), 2.93 - 3.15 (2 H, m), 2.55 - 2.64 (1 H, m), 2.32 - 2.42 (1 H, m). RT = 2.67 min (Cond. 6); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_9{}^{79}Br_2O$: 304.90; found: 304.91.

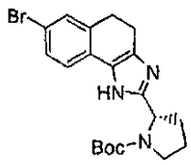
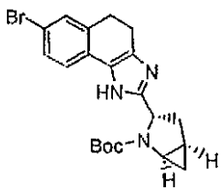
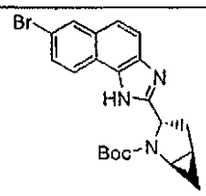
Examples D-3b1 and D-3b2 (step b)

D-3b1 and D-3b2 were prepared from D-3a and the appropriate Boc-protected prolines according to the same procedure used for the preparation of Example M3, step g.

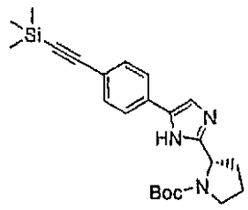
| | | |
|---|---|---|
| D-3b1 |  | RT = 3.00 and 3.19 min (Cond. 3); LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{20}H_{25}{}^{79}BrNO_5$: 460.08; found: 460.10. |
| D-3b2 |  | RT = 2.99 and 3.17 min (Cond. 3), LCMS: Calcd for $C_{21}H_{25}{}^{79}BrNO_5$ $[M+Na]^+$ 472.07; found: 472.10 |

Examples D-3c1 and D-3c2 (step c)

D-3c1 and D-3c2 were prepared from D-3b1 and D-3b2 respectively according to the same procedure used for the preparation of Example M3, step h.

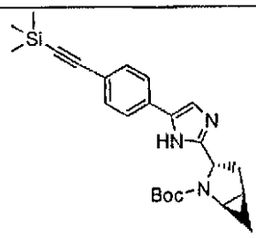
| | | |
|---|---|---|
| D-3c1 |  From D-3b1 | $^1$H NMR (500 MHz, *MeOD*, imidazole N-H missing) δ ppm 7.32 - 7.43 (3 H, m), 4.86 -4.97 (1 H, m), 3.63 - 3.74 (1 H, m), 3.47 - 3.57 (1 H, m), 2.98 - 3.07 (2 H, m), 2.83 (2 H, d, *J*=8.2 Hz), 2.25 - 2.45 (1 H, m), 2.00 - 2.11 (2 H, m), 1.93 - 1.99 (1 H, m), 1.25 - 1.48 (9 H, 2s). RT = 2.24 min (Cond. 3); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{20}H_{25}{}^{79}BrN_3O_2$: 418.13; found: 418.10. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{25}{}^{79}BrN_3O_2$: 430.1125; found 430.1124. |
| D-3c2 |  From D-3b2 | RT = 2.28 min (Cond. 3); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{25}{}^{79}BrN_3O_2$: 430.11; found:. 430.16. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{25}{}^{79}BrN_3O_2$: 430.1125; found 430.1123. |
| D-3c3 |  Prepared from D-3c2 according to the same procedure used for the preparation of D-3g1 | RT = 2.06 min (Cond. 3); LC/MS: Anal. Calcd for $C_{21}H_{23}{}^{81}BrN_3O_2$ $(M+H)^+$ 430.10; found: 429.98. |

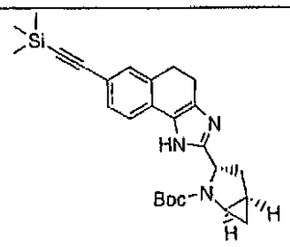
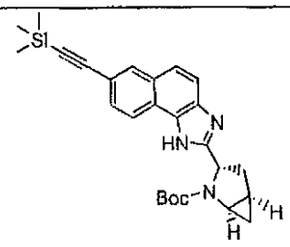
Example D-3d1 (step d)



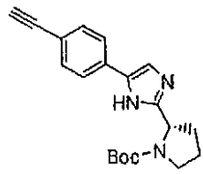
Ethynyltrimethylsilane (0.59 mL, 4.25 mmol) was added to a solution of D-1b (1.5 g, 3.82 mmol), triphenylphosphine (0.20 g, 0.77 mmol), diethylamine (4.25 mL, 40.70 mmol), copper (I) iodide (40 mg, 0.21 mmol) and *trans*-dichloro(bis-triphenylphosphine)palladium (II) (149 mg, 0.21 mmol) in dry DMF (1.4 mL) at rt in a microwave vessel. The vessel was capped and irradiated for 25 min at 120 °C. Two identical 1.5 g reactions were run in tandem. The reaction mixtures were diluted with ether and ethyl acetate, combined and shaken with 0.1*N* HCl. After standing for 20 min, the suspension was suction-filtered and the pad was washed with ether and ethyl acetate. The organic phase was then separated, washed with brine, dried over sodium sulfate, and concentrated. There was isolated the crude product (4.2 g) as a brownish-red foam which was taken up in dichloromethane and added directly to a Thompson 110 g silica gel column. Gradient elution of the residue with 20% ethyl acetate in dichloromethane to 100% ethyl acetate furnished D-3d1 (2.8 g, 40% yield) as a yellow solid after evaporation of the eluant which was taken forward directly. RT = 2.37 min (Cond. 3); LC/MS: Anal. Calcd for $C_{23}H_{32}N_3O_2Si$ $[M+H]^+$ 410.23; found: 410.12.

D-3d2 to D-3d4 were prepared according to the procedures described for D-3d1.

| | | |
|---|---|---|
| D-3d2 |  From M3, step h | RT = 2.34 min (Cond. 3); LC/MS: Anal. Calcd for $C_{24}H_{32}N_3O_2Si$ $[M+H]^+$ 422.22; found: 421.85. |

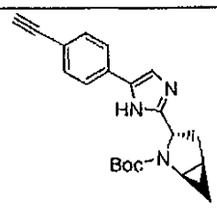
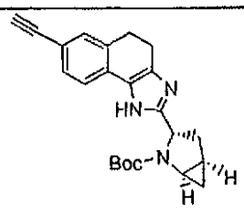
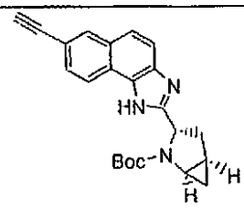
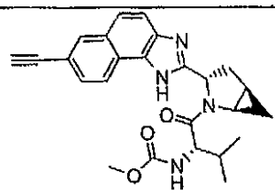
| | | |
|---|---|---|
| D-3d3 |  From D-3c2 | RT = 2.43 min (Cond. 3); LC/MS: Anal. Calcd for $C_{26}H_{34}N_3O_2Si$ $[M+H]^+$ 448.24; found: 448.82. |
| D-3d4 |  From D-3c3 | RT = 2.51 min (Cond. 3); LC/MS: Anal. Calcd for $C_{26}H_{32}N_3O_2Si$ $(M+H)^+$ 446.23; found: 446.05. |

Example D-3e1 (step e)

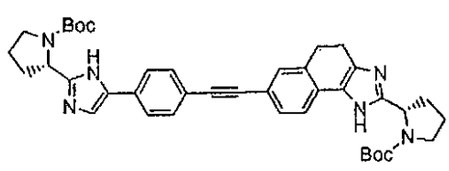


Potassium carbonate (91 mg, 0.66 mmol) was added in one portion to a stirred solution of D-3d1 (2.7 g, 6.6 mmol) in MeOH (60 mL) at rt. The mixture was stirred for 1 h before it was concentrated down *in vacuo*. The residue was taken up in dichloromethane and added directly to a 130 g Thompson silica gel column. Gradient elution of the residue with 15% ethyl acetate in hexanes to 100% ethyl acetate furnished D-3e1 (2.04 g, 87% yield) as a yellow foam after evaporation of the eluant. A small amount (approx. 20 mg) of the product was then subjected to preparative HPLC to afford a purer sample of D-3e1 as an off-white solid. $^1$H NMR (500 MHz, *MeOD*, imidazole N-H missing) δ ppm 7.68 (2 H, d, *J*=7.9 Hz), 7.46 (2 H, d, *J*=8.2 Hz), 7.34 - 7.40 (1 H, m), 4.89 (1 H, m), 3.64 - 3.73 (1 H, m), 3.49 (1 H, m), 3.49 (1 H, s), 3.31 - 3.34 (1 H, m), 2.25 - 2.44 (1 H, m), 1.99 - 2.11 (3 H, m), 1.25 and 1.47 (9 H, 2s). RT = 1.63 min (Cond. 3), LC/MS: Anal. Calcd for $C_{20}H_{24}N_3O_2$ $(M+H)^+$ 338.19; found: 338.12.

D-3e2 to D-3e5 were prepared according to the procedures described for alkyne D-3e1.

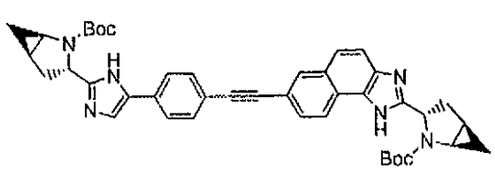
| | | |
|---|---|---|
| D-3e2 |  From D-3d2 | RT = 1.65 min (Cond. 3); LC/MS: Anal. Calcd for $C_{21}H_{24}N_3O_2$ $[M+H]^+$ 350.19; found: 350.10. |
| D-3e3 |  From D-3d3 | RT = 1.81 min (Cond. 3); LC/MS: Anal. Calcd for $C_{23}H_{26}N_3O_2$ $[M+H]^+$ 376.20; found: 376.20. |
| D-3e4 |  From D-3d4 | RT = 1.88 min (Cond. 3); LC/MS: Anal. Calcd for $C_{23}H_{24}N_3O_2$ $(M+H)^+$ 374.19; found: 374.04. |
| D-3e5 |  Prepared from D-3e4 and Cap-51 using the procedures outlined for D-3h1 and Example OL-1 | RT = 1.75 min (Cond. 3); LC/MS: Anal. Calcd for $C_{25}H_{27}N_4O_3$ $[M+H]^+$ 431.21; found: 431.09. |

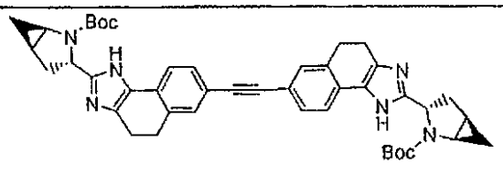
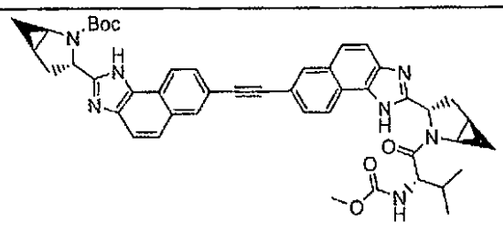
Example D-3f1 (step f)



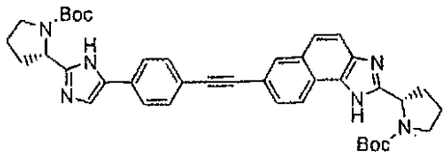
Tetrakis(triphenylphosphine)palladium (83 mg, 0.072 mmol) was added in one portion to a stirred, argon-degassed mixture of Example D-3c1 (300 mg, 0.717 mmol), D-3e1 (315 mg, 0.932 mmol), triethylamine (0.40 mL, 2.87 mmol) and copper(I) iodide (13.7 mg, 0.072 mmol) in anhydrous DMF (6 mL) at rt in a thick-walled, screw-top vial. The mixture was stirred at rt for 16 h and at 40 °C for 16 h before additional CuI (10 mg), TEA (0.4 mL) and $Pd(PPh_3)_4$ catalyst (40 mg) were added since the reaction was not complete after 32 h as judged by LCMS. The mixture was stirred further at 60 °C for 10 h before it was cooled to rt, diluted with ethyl acetate, THF and water and suction-filtered. The organic phase of the filtrate was separated, washed with saturated sodium bicarbonate solution and brine prior to drying over anhydrous sodium sulfate and evaporation. The residue was taken up in dichloromethane and added directly to a Thompson 80 g silica gel column. Gradient elution of the residue with 30% ethyl acetate in hexanes to 100% ethyl acetate followed by 0% methanol in ethyl acetate to 20% methanol in ethyl acetate furnished D-3f1 (366.7 mg, 68% yield) as a golden brown foam after evaporation of the eluant. A small amount (approx. 20 mg) of product was then subjected to preparative HPLC to afford a purer sample of Example D-3f1 as a tan solid. $^1$H NMR (500 MHz, *MeOD,* imidazole N-H's missing) δ ppm 7.73 (2 H, d, *J*=8.2 Hz), 7.47 - 7.57 (4 H, m), 7.41 (2 H, br s), 4.96 - 5.09 (1 H, m), 4.89 - 4.96 (1 H, m), 3.69 (2 H, br s), 3.54 (2 H, br s), 3.04 - 3.13 (2 H, m), 2.83 - 2.94 (2 H, m), 2.30 - 2.50 (2 H, m), 1.94 - 2.17 (6 H, m), 1.27 - 1.49 (18 H, 2s). RT = 2.06 min (Cond. 3); LC/MS: Anal. Calcd for $C_{40}H_{47}N_6O_4$ $(M+H)^+$ 675.37; found: 675.26.

D-3f2 to D-3f4 were prepared according to the procedure described for D-3f1.

| | | |
|---|---|---|
| D-3f2 |  D-3e2 and D-3c3 | RT = 2.12 min (Cond. 3); LC/MS: Anal. Calcd for $C_{42}H_{45}N_6O_4$ $[M+H]^+$ 697.35; found: 697.25. |
| D-3f3 | | RT = 2.14 min |

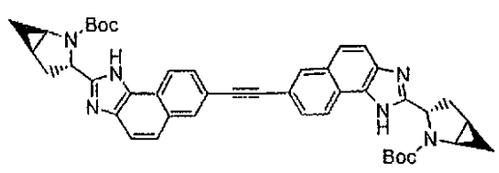
| | | |
|---|---|---|
| |  From D-3e3 and D-3c2 | (Cond. 3); LC/MS: Anal. Calcd for $C_{44}H_{49}N_6O_4$ $[M+H]^+$ 725.38; found: 725.25. |
| D-3f4 |  From D-3c3 and D-3e5 | LCMS: 2.18 min (Cond. 3); LC/MS: Anal. Calcd for $C_{45}H_{48}N_7O_5$ $(M+H)^+$ 778.37; found: 778.22. |

Example D-3g1 (step g)

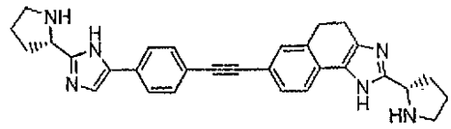


Activated manganese dioxide (2.0 g, 23.12 mmol) was added in one portion to a stirred solution of D-3f1 (260 mg, 0.39 mmol) in dry dichloromethane (5 mL). The suspension was stirred at rt for 6 h before additional activated manganese dioxide (1.0 g) was added. The suspension was stirred further for 14 h at rt before it suction-filtered through a pad of Celite with MeOH and the pad was washed with additional MeOH several times. The filtrate was then concentrated in vacuo to yield D-3g1 (225.1 mg, 82% yield) as a yellow solid. A small amount (approx. 20 mg) of the product was then subjected to preparative HPLC to afford a purer sample of D-3g1 as a light tan solid. $^1$H NMR (500 MHz, *MeOD*, imidazole N-H's missing) δ ppm 8.43 (1 H, d, *J*=8.5 Hz), 8.19 (1 H, br s), 7.68 - 7.78 (5 H, m), 7.62 (2 H, d, *J*=8.2 Hz), 7.54 (1 H, s), 4.90 - 5.27 (2 H, m), 3.76 - 3.85 (1 H, m), 3.66 - 3.74 (1 H, m), 3.51 - 3.66 (2 H, m), 2.35 - 2.60 (2 H, m), 1.94 - 2.21 (6 H, m), 1.49 (6 H, br s), 1.27 (6 H, br s), 1.14 (6 H, br s). RT = 2.12 min (Cond. 3); LC/MS: Anal. Calcd for $C_{40}H_{45}N_6O_4$ $(M+H)^+$ 673.35; found: 673.30.

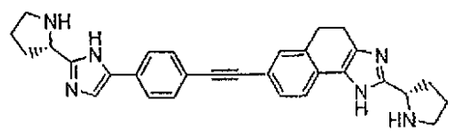
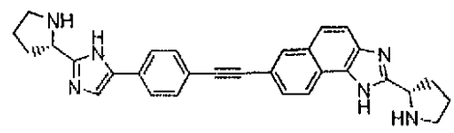
D-3g2 was prepared according to the procedure described for D-3g1.

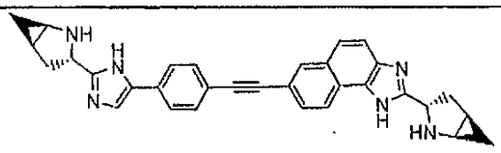
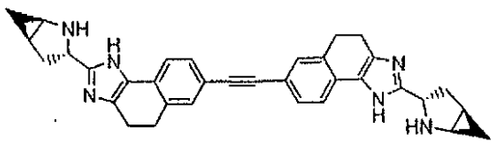
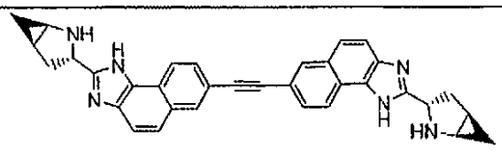
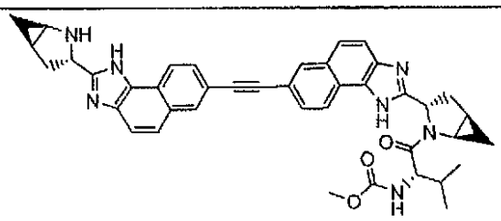
| | | |
|---|---|---|
| D-3g2 |  From D-3f3 | LCMS: 2.27 min (Cond. 3); LC/MS: Anal. Calcd for $C_{44}H_{45}N_6O_4$ $(M+H)^+$ 721.35; found: 721.25. |

Example D-3h1 (step h)



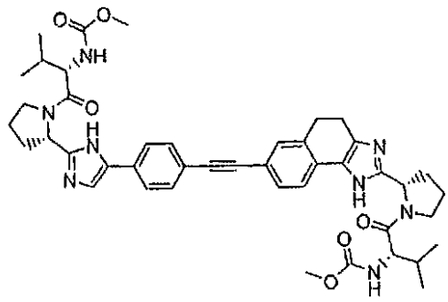
D-3h1 to D-3h6 were prepared from D-3f1, D-3g1, D-3f2, D-3f3, D-3g2 and D-3f4, respectively, according to the same procedure used for the preparation of OL-1e except that methanol (1 mL) was used instead of dichloromethane. This gave D-3h1 to D-3h6 as hydrochloride salts (or TFA salts when purified further with preparative HPLC) upon concentration of the solvent(s) in vacuo.

| | | |
|---|---|---|
| D-3h1 |  From D-3f1 | RT = 1.44 min (Cond. 3); LC/MS: Anal. Calcd for $C_{30}H_{31}N_6$ $[M+H]^+$ 475.26; found: 475.16. |
| D-3h2 |  From D-3g1 | $^1$H NMR (500 MHz, *MeOD*, imidazole N-H's missing) δ ppm 8.46 (1 H, d, *J*=8.5 Hz), 8.21 (1 H, s), 7.84 (2 H, d, *J*=8.2 Hz), 7.70 - 7.80 (4 H, m), 7.64 (2 H, d, *J*=8.5 Hz), 5.15 (1 H, s), 4.97 (1 H, s), 3.62 - 3.70 (1 H, m), |

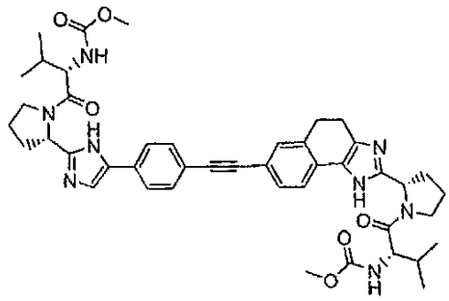
| | | |
|---|---|---|
| | | 3.56 (3 H, s), 2.65 - 2.75 (1 H, m), 2.55 - 2.64 (1 H, m), 2.17 - 2.53 (6 H, series of m). RT = 1.61 min (Cond. 3); LC/MS: Anal. Calcd for $C_{30}H_{29}N_6$ $(M+H)^+$ 473.25; found: 473.13. |
| D-3h3 |  From D-3f2 | RT = 1.62 min (Cond. 3); LC/MS: Anal. Calcd for $C_{32}H_{29}N_6$ $(M+H)^+$ 497.25; found: 497.13. |
| D-3h4 |  From D-3f3 | RT = 1.62 min (Cond. 3); LC/MS: Anal. Calcd for $C_{34}H_{33}N_6$ $[M+H]^+$ 525.28; found: 525.13. |
| D-3h5 |  From D-3g2 | LCMS: 1.78 min (Cond. 3); LC/MS: Anal. Calcd for $C_{34}H_{29}N_6$ $(M+H)^+$ 521.25; found: 521.13. |
| D-3h6 |  From D-3f4 | LCMS: 1.95 min (Cond. 3); LC/MS: Anal. Calcd for $C_{41}H_{40}N_7O_3$ $(M+H)^+$ 678.32; found: 678.45. |

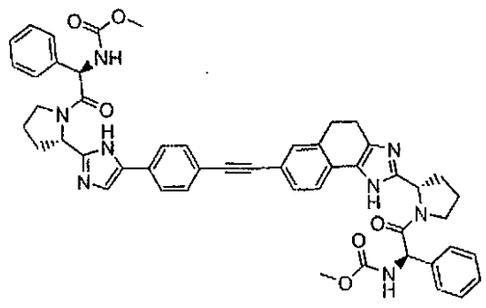
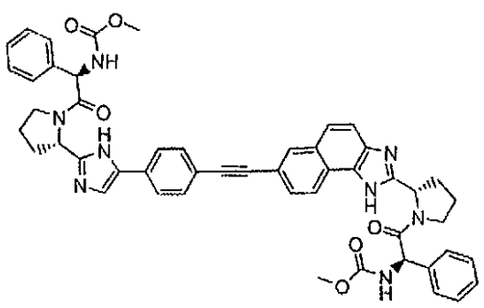
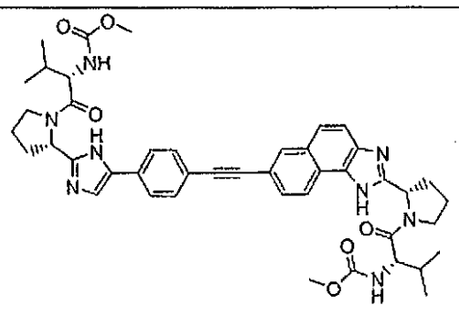
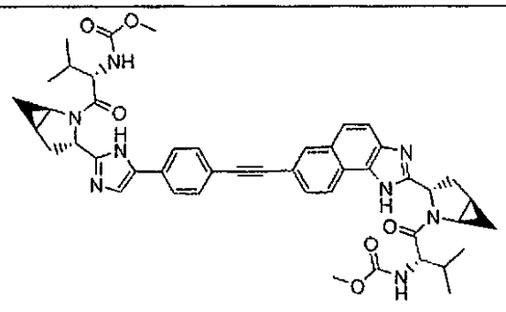
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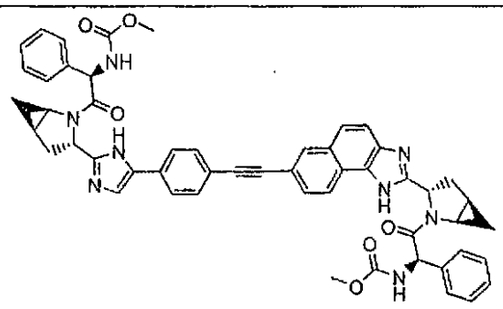
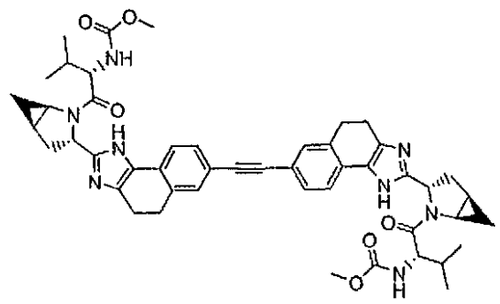
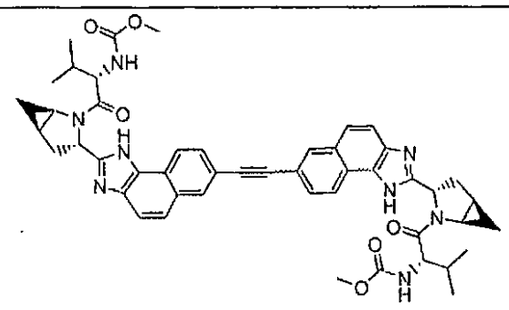
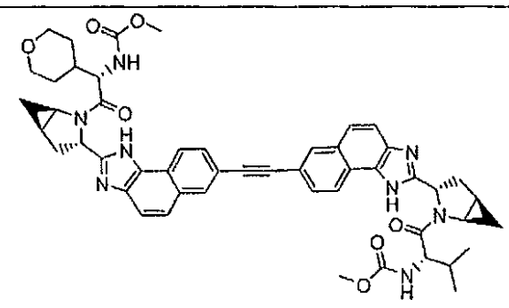
Example D-3 to D-11 (final step)



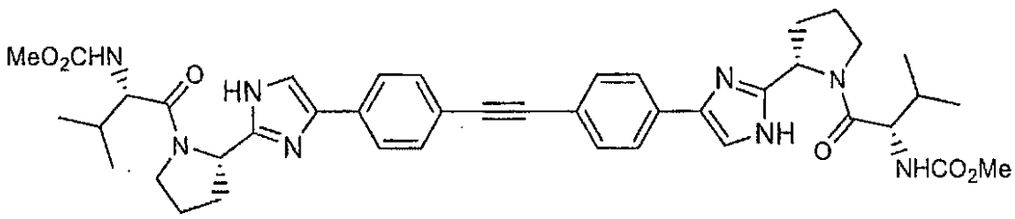
Examples D-3 to D-11 were prepared from D-3h1 to D-3h6 and the appropriate acids according to the same procedure used for the preparation of Example OL-1. This gave Examples D-3 to D-11 as TFA salts after HPLC purification.

| | | |
|---|---|---|
| D-3 |  From D-3h1 and Cap 51 | RT = 1.80 min (Cond. 3); LC/MS: Anal. Calcd for $C_{44}H_{53}N_8O_6$ $[M+H]^+$ 789.41; found: 789.27. $^1H$ NMR (500 MHz, *MeOD*, imidazole N-H's missing) δ ppm 7.86 - 7.91 (1 H, m), 7.73 - 7.80 (2 H, m), 7.64 - 7.71 (2 H, m), 7.50 - 7.59 (3 H, m), 5.59 - 5.65 and 5.16 - 5.31 (2 H, 2m), 4.21 - 4.29 (2 H, m), 4.06 - 4.16 (2 H, m), 3.81 - 3.93 (2 H, m), 3.67 (6 H, s), 3.15 - 3.24 (2 H, m), 2.95 - 3.07 (2 H, m), 2.51 - 2.65 (2 H, m), 2.25 - 2.37 (2 H, m), 2.14 - 2.23 (4 H, m), 1.99 - 2.11 (2 H, m), 0.09 – 0.95 |

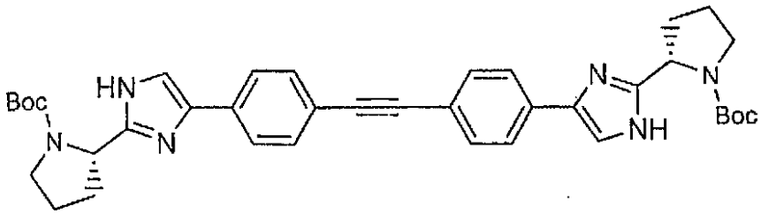
| | | |
|---|---|---|
| | | (12 H, m), 0.97 - 1.05 (2 H, m). |
| D-4 |  From D-3h1 and Cap 4 | RT = 1.88 min (Cond. 3); LC/MS: Anal. Calcd for $C_{50}H_{49}N_8O_6$ $[M+H]^+$ 857.38; found: 857.31. |
| D-5 |  From D-3h2 and Cap 4 | RT = 1.94 min (Cond. 3); LC/MS: Anal. Calcd for $C_{50}H_{47}N_8O_6$ $[M+H]^+$ 855.36; found: 855.28. |
| D-6 |  From D-3h2 and Cap 51 | RT = 1.88 min (Cond. 3); LC/MS: Anal. Calcd for $C_{44}H_{51}N_8O_6$ $[M+H]^+$ 787.40; found: 787.30. |
| D-7 |  | RT = 1.93 min (Cond. 3); LC/MS: Anal. Calcd for $C_{46}H_{51}N_8O_6$ $[M+H]^+$ 811.40; found: 811.26. |

| | | |
|---|---|---|
| | From D-3h3 and Cap 51 | |
| D-8 |  From D-3h3 and Cap 4 | RT = 2.01 min (Cond. 3); LC/MS: Anal. Calcd for $C_{52}H_{47}N_8O_6$ $[M+H]^+$ 879.36; found: 879.25. |
| D-9 |  From D-3h4 and Cap 51 | RT = 1.93 min (Cond. 3); LC/MS: Anal. Calcd for $C_{48}H_{55}N_8O_6$ $[M+H]^+$ 839.43; found: 839.26. |
| D-10 |  From D-3h5 and Cap 51 | RT = 2.07 min (Cond. 3); LC/MS: Anal. Calcd for $C_{48}H_{51}N_8O_6$ $[M+H]^+$ 835.40; found: 835.26. |
| D-11 |  From D-3h6 and Cap 170 | RT = 1.99 min (Cond. 3); LC/MS: Anal. Calcd for $C_{50}H_{53}N_8O_7$ $[M+H]^+$ 877.41; found: 877.63. |

Example M1

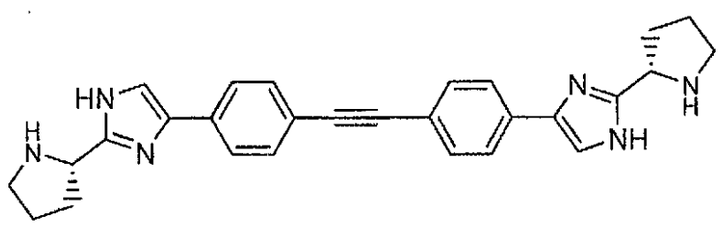



Example M1, Step a




$Pd(Ph_3P)_4$ (0.078 g, 0.067 mmol) was added to a DMF (5 mL) solution of (S)-tert-butyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate(D-1b) (0.675g, 1.721 mmol) and 1,2-bis(trimethylstannyl)ethyne (0.3134 g, 0.891 mmol) in a pressure tube, the mixture was flushed with nitrogen for 1 min and then heated at 90 °C for 15 h. The volatile component was removed in vacuo and the residue was directly submitted to a BIOTAGE® purification (110 g; EtOAc) to afford alkyne M1a as a yellowish orange foam containing unidentified impurity and residual solvent (430 mg). $^1$H NMR (DMSO, δ = 2.50 ppm, 400 MHz): 12.23/11.98/11.91 (three br s, 2H), 7.80-7.35 (m, 10H), 4.84-4.76 (m, 2H), 3.54 (m, 2H), 3.39-3.33 (m, 2H), 2.28-1.78 (m, 8H), 1.40 (br s, 7.54H), 1.16 (br s, 10.46H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{45}N_6O_4$: 649.35; found 649.27.

Example M1, Step b




HCl/dioxanes (4N; 8 mL, 32.0 mmol), $CH_2Cl_2$ (1 mL) and MeOH (1.0 mL) were added to bis-carbamate M1a (0.427 g, 0.658 mmol), and the heterogeneous mixture

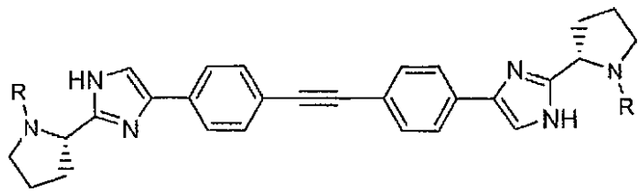
was stirred for 5 hr. The volatile component was removed in vacuo, and the residue was exposed to high vacuum to afford M1b (.4HCl) as an off-white solid (452 mg), which was submitted to the next step as such. $^1$H NMR analysis indicates that the sample may contain residual dioxane (~1 mol equiv). $^1$H NMR (DMSO, δ = 2.50 ppm, 400 MHz): 10.29 (br s, 2H), 9.73 (br s, 2H), 8.11 (s, 2H), 7.96 (d, J = 8.3, 4H), 7.67 (d, J = 8.6, 4H), 4.97 (br m, 2H), 3.47-3.31 (m, 4H), 2.50-2.36 ('m' partially overlapped with solvent signal, 4H), 2.23-2.14 (m, 2H), 2.07-1.95 (m, 2H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{28}H_{29}N_6$: 449.25; found 49.23.

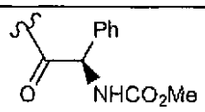
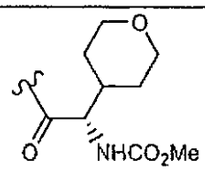
Example M1

HATU (0.069 g, 0.181 mmol) was added to the DMF solution of pyrrolodine M1b/4HCl (70.5 mg, 0.103 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (36.3 mg, 0.207 mmol) and DIEA (0.1 mL, 0.573 mmol) and stirred at room temperature for 70 min. The volatile component was removed in vacuo and the residue was dissolved in MeOH and submitted to a reverse phase HPLC purification (MeOH/water/TFA) to afford the TFA salt of Example M1 as an off-white foam (68.9 mg). LC (Cond. 9 and 10): >95% homogeneity index. LC/MS (Cond. 3): $R_t$ = 1.78 min. $^1$H NMR (DMSO, δ = 2.50 ppm, 400 MHz): 8.10 (br s, 2H), 7.88-7.83 (m, 4H), 7.71 (d, J = 8.3, 3.91H), 7.34 (d, J = 8.5, 2H; $NHCO_2$), 6.92 (app br s, 0.09H), 5.52 (br m, 0.17H), 5.12 (app t, 1.93H), 4.11 (app t, 2H), 3.89-3.77 (m, 4H), 3.54 (s, 5.52H), 3.33 (s, 0.48H), 2.41-2.33 (m, 2H), 2.21-1.93 (m, 8H), 0.89 (app t, 0.91H), 0.83/0.79 (two overlapping d, J = 6.8/6.8, 11.09 H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{51}N_8O_6$: 763.39; found 763.33.

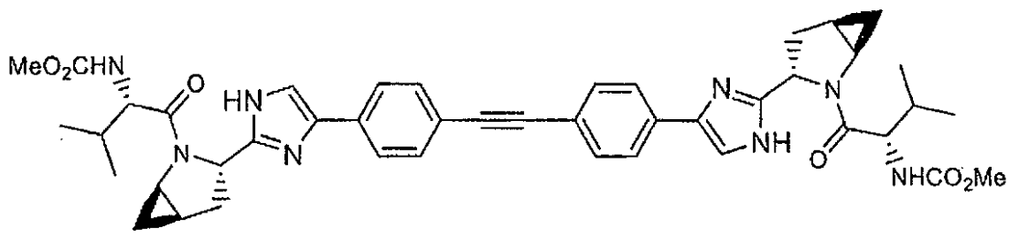
Example M2 to M2.1

Example M2 to M2.1 were prepared as TFA salts from pyrrolidine M1b and appropriate acids according to the procedure described for the preparation of Example M1 with a modified purification protocol noted in the table below.

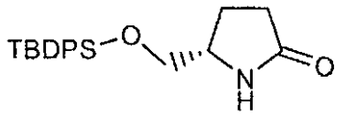


| Example | R | Analytical data |
|---|---|---|
| M2 |  | Purified using two different reverse phase HPLC conditions (Column: Phenomenex Luna, 30x100 mm, S10; MeOH/water/TFA) and (Waters Sunfire, 30x100 mm, S5; $CH_3CN$/water/TFA). LC (Cond. 9 and 10): >95% homogeneity index. LC/MS (Cond. 3): $R_t$ = 2.04 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{47}N_8O_6$: 831.36; found 841.41. |
| M2.1 |  | Purified using two different reverse phase HPLC conditions (Column: Xbridge, 19x100 mm, S5; MeOH/water/TFA) and (Waters Sunfire, 30x100 mm, S5; $CH_3CN$/water/TFA). LC (Cond. 9 and 10): 95% homogeneity index. LC/MS (Cond. 10d): $R_t$ = 2.82 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{55}N_8O_8$: 847.41; found 847.25. |

Example M3

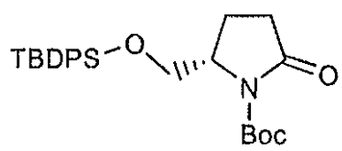


Example M3, Step a



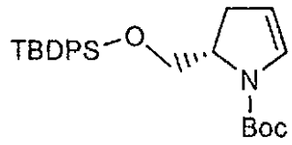

To a solution of (S)-5-(hydroxymethyl)pyrrolidin-2-one (10 g, 87 mmol) in $CH_2Cl_2$ (50 mL) was added tert-butylchlorodiphenylsilane (25.6 g, 93 mmol), $Et_3N$ (12.1 mL, 87 mmol) and DMAP (1.06 g, 8.7 mmol). The mixture was stirred at room temperature until the starting pyrrolidinone was completely consumed, and then it was diluted with $CH_2Cl_2$ (50 mL) and washed with water (50 mL). The organic layer was dried ($Na_2SO_4$), filtered, and evaporated in vacuo, and the crude material was submitted to flash chromatography (silica gel; 30 to 100% of EtOAc/hexanes) to afford ether M3a as a colorless oil (22.7 g, 74% yield). $^1$H-NMR (400 MHz, DMSO-$d_6$, $\delta$ = 2.5 ppm) 7.69 (br s, 1H), 7.64-7.61 (m, 4H), 7.50-7.42 (m, 6H), 3.67-3.62 (m, 1H), 3.58-3.51 (m, 2H), 2.24-2.04 (m, 3H), 1.87-1.81 (m, 1H), 1.00 (s, 9H). LC/MS $(M+H)^+$ = 354.58.

Example M3, Step b



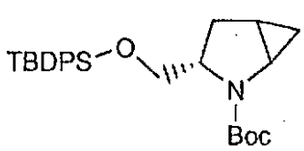

Di-tert-butyl dicarbonate (38.5 g, 177 mmol) was added in portions as a solid over 10 min to a $CH_2Cl_2$ (200 mL) solution of silyl ether M3a (31.2 g, 88.3 mmol), $Et_3N$ (8.93 g, 88 mmol), and DMAP (1.08 g, 8.83 mmol) and stirred for 18 h at 24 °C. Most of the volatile material was removed in vacuo and the crude material taken up in 20% EtOAc/Hex and applied to a 2 L funnel containing 1.3 L of silica gel and then eluted with 3 L of 20% EtOAc/hex and 2 L of 50% EtOAc). Upon concentration of the desired fractions in a rotary evaporator, a white slurry of solid formed which was filtered, washed with hexanes and dried in vacuo to afford carbamate M3b as a white solid (32.65 g, 82% yield). $^1$H-NMR (400 MHz, DMSO-$d_6$, $\delta$ = 2.5 ppm) 7.61-7.59 (m, 2H), 7.56-7.54 (m, 2H), 7.50-7.38 (m, 6H), 4.18 (m, 1H), 3.90 (dd, J = 10.4, 3.6, 1H), 3.68 (dd, J = 10.4, 2.1, 1H), 2.68-2.58 (m, 1H), 2.40-2.33 (m, 1H), 2.22-2.12 (m, 1H), 2.01-1.96 (m, 1H), 1.35 (s, 9H), 0.97 (s, 9H). LC/MS $(M-Boc+H)^+$ = 354.58.

Example M3, Step c




A three-necked flask equipped with a thermometer and a nitrogen inlet was charged with carbamate M3b (10.05 g, 22.16 mmol) and toluene (36 mL), and lowered into -55 °C cooling bath. When the internal temperature of the mixture reached -50 °C, lithium triethylborohydride (23 mL of 1.0 M/THF, 23.00 mmol) was added dropwise over 30 min and the mixture stirred for 35 min while maintaining the internal temperature between -50 °C and -45 °C. Hunig's base (16.5 mL, 94 mmol) was added dropwise over 10 min. Then, DMAP (34 mg, 0.278 mmol) was added in one batch, followed by the addition of trifluoroacetic anhydride (3.6 mL, 25.5 mmol) over 15 min, while maintaining the internal temperature between -50 °C and -45 °C. The bath was removed 10 min later, and the reaction mixture was stirred for 14 h while allowing it to rise to ambient temperature. It was diluted with toluene (15 mL), cooled with an ice-water bath, and treated slowly with water (55 mL) over 5 min. The phases were separated and the organic layer washed with water (50 mL, 2x) and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel; 5% EtOAc/hexanes) to afford dihydropyrrole M3c as a colorless viscous oil (7.947 g, 82% yield). LC/MS (Cond. 7): $R_t$ = 2.41 min. $^1$H-NMR (400 MHz, DMSO-$d_6$, $\delta$ = 2.5 ppm) 7.62-7.58 (m, 4H), 7.49-7.40 (m, 6H), 6.47 (br s, 1H), 5.07/5.01 (overlapping br d, 1H), 4.18 (br s, 1H), 3.89 (br s, 0.49H), 3.69 (br s, 1.51H), 2.90-2.58 (br m, 2H), 1.40/1.26 (overlapping br s, 9H), 0.98 (s, 9H). LC/MS: $[M+Na]^+$ = 460.19.

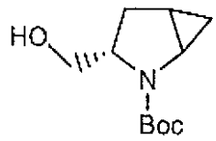
Example M3, Step d




**M3d-1**: *trans*-isomer
**M3d-2**: *cis*-isomer

Diethylzinc (19 mL of ~1.1 M in toluene, 20.9 mmol) was added dropwise over 15 min to a cooled (-30 °C) toluene (27 mL) solution of dihydropyrrole M3c (3.94 g, 9.0 mmol). Chloroiodomethane (stabilized over copper; 3.0 mL, 41.2 mmol) was added dropwise over 10 min, and stirred while maintaining the bath temperature at -25 °C for 1 h and between -25 °C and -21 °C for 18.5 h. The reaction mixture was opened to the air and quenched by the slow addition of 50% saturated $NaHCO_3$ solution (40 mL), and then removed from the cooling bath and stirred at ambient temperature for 20 min. It was filtered through a filter paper and the white cake was washed with 50 mL of toluene. The organic phase of the filtrate was separated and washed with water (40 mL, 2x), dried ($MgSO_4$) and concentrated in vacuo. The crude material was purified using a BIOTAGE® system (350 g silica gel; sample was loaded with 7% EtOAc/hexanes; eluted with 7-20% EtOAc/hexanes) to afford a mixture of methanopyrrolidines M3d-1 and M3d-2 as a colorless viscous oil (3.69 g, 90.7%). [Note: the exact cis/trans-isomer ratio was not determined at this stage]. LC/MS (Cond. 7): $R_t$ = 2.39 min $^1$H-NMR (400 MHz, DMSO-$d_6$, $\delta$ = 2.5 ppm) 7.62-7.60 (m, 4H), 7.49-7.40 (m, 6H), 3.77/3.67 (overlapping br s, 3H), 3.11-3.07 (m, 1H), 2.23 (app br s, 1H), 2.05-2.00 (m, 1H), 1.56-1.50 (m, 1H), 1.33 (very broad s, 9H), 1.00 (s, 9H), 0.80 (m, 1H), 0.30 (m, 1H). LC/MS: $[M+Na]^+$ = 474.14.

Example M3, Step e

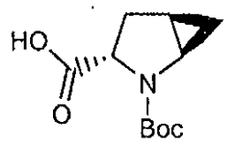



**M3e-1**: *trans*-isomer
**M3e-2**: *cis*-isomer

TBAF (7.27 mL of 1.0 M in THF, 7.27 mmol) was added dropwise over 5 min to a THF (30 mL) solution of silyl ether M3d-1/-2 (3.13 g, 6.93 mmol) and the mixture stirred at ambient temperature for 4.75 h. After the addition of saturated $NH_4Cl$ solution (5 mL), most of the volatile material was removed in vacuo and the residue partitioned between $CH_2Cl_2$ (70 mL) and 50% saturated $NH_4Cl$ solution (30 mL). The aqueous phase was extracted with $CH_2Cl_2$ (30 mL), and the combined organic

phase was dried ($MgSO_4$), filtered, concentrated in vacuo and then exposed to high vacuum overnight. The crude material was purified using a BIOTAGE® (silica gel; 40-50% EtOAc/hexanes) to afford a mixture of alcohols M3e-1 and M3e-2, contaminated with traces of a lower $R_f$ spot, as a colorless oil (1.39 g, ~94% yield). [Note: the exact cis/trans isomer ratio was not determined at this stage.] $^1$H-NMR (400 MHz, DMSO-$d_6$, $\delta$ = 2.5 ppm) 4.70 (t, J = 5.7, 1H), 3.62-3.56 (m, 1H), 3.49-3.44 (m, 1H), 3.33-3.27 (m, 1H), 3.08-3.04 (m, 1H), 2.07 (br m, 1H), 1.93-1.87 (m, 1H), 1.51-1.44 (m, 1H), 1.40 (s, 9H), 0.76-0.71 (m, 1H), 0.26 (m, 1H). LC/MS $(M+Na)^+$ = 236.20.

Example M3, Step f

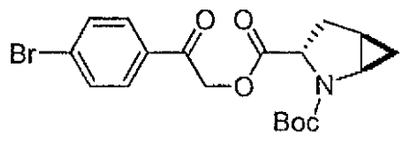



**M3f-1**: trans isomer
**M3f-2**: cis isomer

A semi-solution of $NaIO_4$ (6.46 g, 30.2 mmol) in $H_2O$ (31 mL) was added to a solution of alcohol M3e-1/-2 (2.15 g, 10.08 mmol) in $CH_3CN$ (20 mL) and $CCl_4$ (20 mL). $RuCl_3$ (0.044 g, 0.212 mmol) was added immediately and the heterogeneous reaction mixture was stirred vigorously for 75 min. The reaction mixture was diluted with $H_2O$ (60 mL) and extracted with $CH_2Cl_2$ (50 mL, 3x). The combined organic phase was treated with 1 mL MeOH, allowed to stand for about 5 min, and then filtered through a pad of diatomaceous earth (CELITE®). The CELITE® was washed with $CH_2Cl_2$ (50 mL), and the filtrate was concentrated in vacuo to afford a light charcoal-colored solid. $^1$H-NMR analysis of this crude material indicated a 1.00:0.04:0.18 mole ratio of trans acid M3f-1:cis acid M3f-2:presumed side product, tert-butyl 3-oxo-2-azabicyclo[3.1.0]hexane-2-carboxylate. The crude material was dissolved in EtOAc (~10 mL) with heating and allowed to stand at ambient temperature with seeding. About 15 min into the cooling phase, a rapid crystal formation was observed. About 1 h later, hexanes (~6 mL) was added and the mixture refrigerated overnight (it did not appear that additional material precipitated

out). The mixture was filtered and washed with ice/water-cooled hexanes/EtOAc (2:1 ratio; 20 mL) and dried under high vacuum to afford the first crop of acid M3f-1 (off-white crystals, 1.222 g). The mother liquor was concentrated in vacuo, and the residue dissolved in ~3 mL of EtOAc with heating, allowed to stand at ambient temperature for 1 h, and then 3 mL hexanes was added and stored in a refrigerator for ~15 h. A second crop of acid M3f-1 was retrieved similarly (grey crystals, 0.133 g), for a combined yield of 59%. Acid M3f-1: Rt = 1.48 min under the following HPLC conditions: Solvent gradient from 100% A : 0% B to 0% A : 100% B (A = 0.1% TFA in 1:9 MeOH/$H_2O$; B = 0.1% TFA in 9:1 MeOH/$H_2O$) over 3 min; detection @ 220 nm; PHENOMENEX®-Luna 3.0X50 mm S10 column. MP (dec.) for the first crop = 147.5-149.5 °C. $^1$H-NMR (400 MHz, DMSO-$d_6$, δ = 2.5 ppm) 12.46 (s, 1H), 3.88 (app br s, 1H), 3.27 (app br s, 1H; overlapped with water signal), 2.28 (br m, 1H), 2.07 (app br s, 1H), 1.56 (app s, 1H), 1.40/1.34 (two overlapped s, 9H), 0.71 (m, 1H), 0.45 (m, 1H). $^{13}$C-NMR (100.6 MHz, DMSO-$d_6$, δ = 39.21 ppm) 172.96, 172.60, 154.45, 153.68, 78.74, 59.88, 59.58, 36.91, 31.97, 31.17, 27.77, 27.52, 14.86, 14.53, 13.69. LC/MS $[M+Na]^+$ = 250.22. Anal. Calcd. for $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54; N, 6.16. Found (for first crop): C, 58.24; H, 7.84; N, 6.07. Optical rotation (10 mg/mL in $CHCl_3$): $[\alpha]_D$ = -216 and -212 for the first and second crop, respectively.

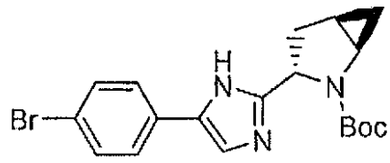
Example M3, Step g




DIEA (1.3 mL, 7.44 mmol) was added dropwise over 2 min to a semi-heterogeneous mixture of acid M3f-1 (1.697 g, 7.47 mmol) and 2-bromo-1-(4-bromophenyl)ethanone (2.01 g, 7.23 mmol) in $CH_3CN$ (30 mL) and stirred at room temperature for 8 hr. The volatile component was removed in vacuo and the residue was taken up in $CH_2Cl_2$ (100 mL), washed with water (30 mL), dried ($MgSO_4$) and concentrated in vacuo to afford ketoester M3g as an off-white viscous semi-foamy oil (3.076 g). $^1$H-NMR (400 MHz, DMSO-$d_6$, δ = 2.5 ppm): 7.92 (d, J = 8.3, 2H), 7.78 (d, J = 8.5, 2H), 5.61-5.42 (m, 2H), 4.16 (m, 1H), 3.34 ('m' partially overlapped with

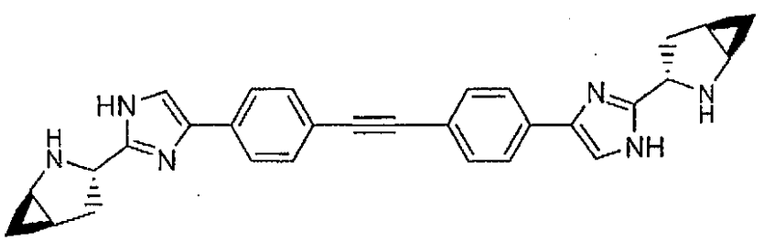
water signal, 1H), 2.40 (m, 2H), 1.63 (m, 1H), 1.41/1.35 (two overlapped 's', 9H), 0.74 (m, 1H), 0.53 (m, 1H). LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{19}H_{22}{}^{79}BrNNaO_5$: 446.06; found 446.06.

Example M3, Step h



A 350 ml pressure tube was charged with keto-ester M3g (3.07g, 7.24 mmol), ammonium acetate (5.48 g, 71.1 mmol) and Xylene (70 mL), capped and heated with an oil bath (140 °C) for 4.5 hr. The reaction mixture was allowed to cool to room temperature and the volatile component was removed in vacuo. $CH_2Cl_2$ (100 mL) and 50% saturated $NaHCO_3$ solution (30 mL) were added to the residue, vigorously stirred until gas evolution ceased, and the phases were separated. The organic layer was dried ($MgSO_4$), concentrated in vacuo, and purified with a BIOTAGE® (240 g silica gel; sample was loaded with $CH_2Cl_2$; 40-80% EtOAc/hexanes) to afford imidazole M3h as a dark yellow foam (2.40 g). $^1$H-NMR (400 MHz, DMSO-$d_6$, δ = 2.5 ppm): 12.21 (s, 0.11H), 1.93 (s, 0.89H), 7.69 (d, J = 8.8, 1.8H), 7.62-7.55 (m, 0.4H), 7.53 (br d, J = 2, 0.87H), 7.49 (d, J = 8.5, 1.8H), 7.29 (br d, J = 1.6, 0.13H), 4.59 (m, 1H), 3.41 (m, 1H), 2.37-2.17 (br m, 2H), 1.62 (m, 1H), 1.21 (very broad 's', 9H), 0.75 (m, 1H), 0.54 (m, 1H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{19}H_{23}{}^{81}BrN_3O_2$: 406.10; found, 406.14.

Example M3, Step i

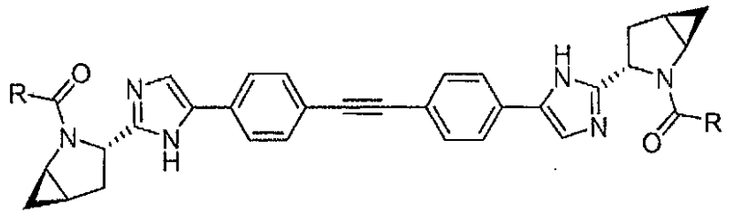


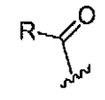
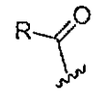
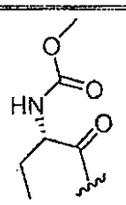
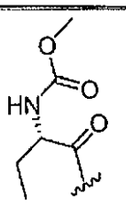
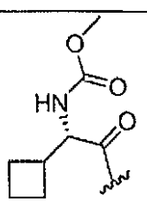
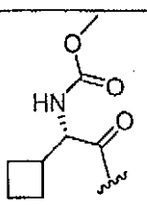
Pyrrolidine M3i (4HCl) was prepared from bromide M3h according to the procedure described for the synthesis of pyrrolidine M1b (.4HCl) from bromide D-1b. $^1$H-NMR

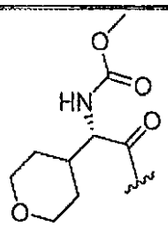
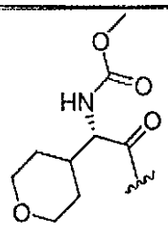
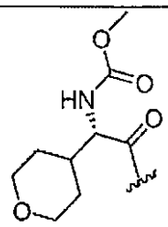
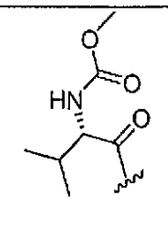
(400 MHz, DMSO-$d_6$, δ = 2.5 ppm): 10.51 (app br s, 4H), 8.08 (s, 2H), 7.92 (d, J= 7.8, 4H), 7.66 (d, J = 8.5, 4H), 4.78 (m, 2H), 3.42 (m, 2H), 2.65 (m, 2H), ~2.53 ('m' partially overlapped with solvent signal, 2H), 1.94 (m, 2H), 1.10 (m, 2H), 0.86 (m, 2H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{30}H_{29}N_6$: 473.25; found 473.21.

Example M3 (and Examples M4-M7)

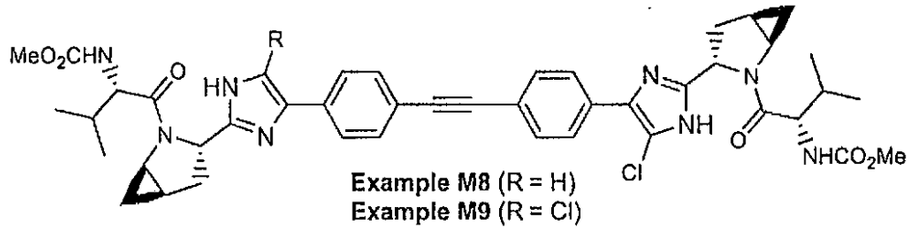
Example M3, along with its analogs Examples M4-M7 highlighted in the table below, were prepared as TFA salts from pyrrolidine M3i (.4HCl) by employing the procedure described for the synthesis of Example M1 and appropriate acids. In the case of Example M7 an equimolar mixture of (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid was employed for the coupling step and the resultant statistical mixture of products was separated by the HPLC technique described for Example M1. Example M3: LC (Cond. 9 and 10): >95% homogeneity index. LC/MS (Cond. 3): $R_t$ = 1.89 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{51}N_8O_6$: 787.39; found 787.40.



| Example |  |  | $R_t$ (Cond. 3); % homogeneity index (Cond. 9 and 10); LC/MS data |
|---|---|---|---|
| M4 |  |  | 1.74 min; >95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_6$: 759.36; found 759.35 |
| M5 |  |  | 1.98 min; >95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{51}N_8O_6$: 811.39; found 811.37 |

| Example |  |  | $R_t$ (Cond. 3); % homogeneity index (Cond. 9 and 10); LC/MS data |
|---|---|---|---|
| M6 |  |  | 1.67 min; >95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{55}N_8O_8$: 871.41; found 871.20. |
| M7 |  |  | 1.78 min; >95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{53}N_8O_7$: 829.40; found 829.53 |

Examples M8-M9



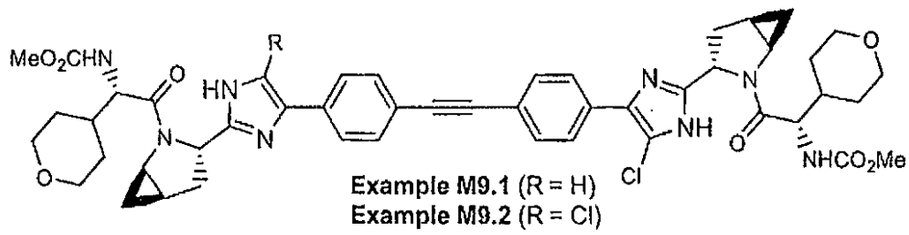
**Example M8** (R = H)
**Example M9** (R = Cl)

NCS (0.0195 g, 0.143 mmol) was added to a DMF (2 mL) solution of the free base form of Example M3 (obtained from the TFA salt via a standard MCX free-basing protocol; 0.109 g, 0.139 mmol), and stirred at room temperature for 16 hr and at 50°C for 25 hr. Most of the solvent was removed in vacuo, and the residue was dissolved in MeOH and submitted to a reverse phase HPLC purification (MeOH/water/TFA) to afford the TFA salt of Example M8 (50 mg) and Example M9 (17.5 mg).

| Example | $R_t$ (Cond. 3); % homogeneity index (Cond. 9a and 10a); LC/MS data |
|---|---|
| M8 | 2.42 min; >95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{50}ClN_8O_6$: 821.35; found 821.31 |

| Example | $R_t$ (Cond. 3); % homogeneity index (Cond. 9a and 10a); LC/MS data |
|---|---|
| M9 | 2.95 min; >95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{49}Cl_2N_8O_6$: 855.32; found 855.24 |

Example M9.1-M9.2

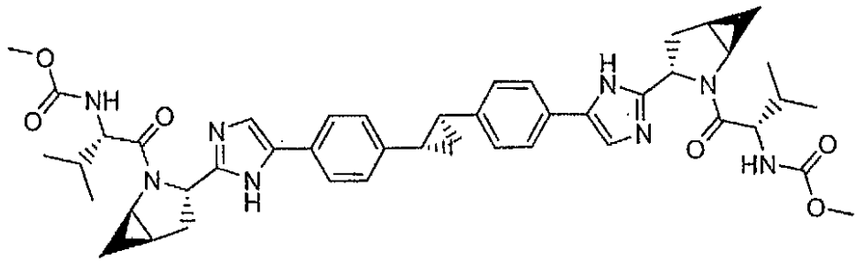



**Example M9.1** (R = H)
**Example M9.2** (R = Cl)

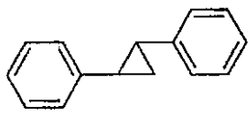
NCS (0.021 g, 0.158 mmol) was added to a DMF (1.5 mL) solution of the free base form of Example M6 (obtained from the TFA salt *via* a standard MCX free-basing protocol; 0.1059 g, 0.122 mmol), and stirred at 50°C for 24 hr. The reaction mixture was diluted with MeOH (2.5 mL) and submitted to a reverse phase HPLC purification condition (XTERRA, 30X100 mm, S5; MeOH/water/TFA). The resultant sample was repurified with a different reverse phase HPLC condition (Waters-Sunfire, 30X100 mm, S5; acetonitrile/water/TFA) to afford Example M9.1 (38.8 mg) and Example M9.2 (32.6 mg) as TFA salts.

| Example | $R_t$ (Cond. 3); % homogeneity index (Cond. 9a and 10a); LC/MS data |
|---|---|
| M9.1 | 2.26 min; >95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{54}ClN_8O_8$: 905.38; found 905.44 |
| M9.2 | 2.78 min; >95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}Cl_2N_8O_8$: 939.34; found 939.40 |

Example M9.3

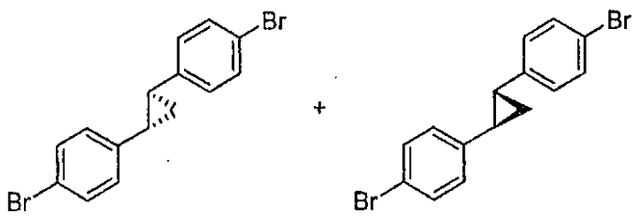


Example M9.3, step a



To a cooled (0°C) $CH_2Cl_2$ (22 mL) was added diethylzinc (1M in hexanes, 60.5 mL, 60.5 mmol) under nitrogen followed by the dropwise addition of trifluoroacetic acid (5.1 mL, 66.2 mmol) in 10 mL $CH_2Cl_2$ over 15 min. The reaction was stirred for 15 min, and then diiodomethane (5.4 mL, 66.9 mmol) in 10 mL $CH_2Cl_2$ was added dropwise to the reaction. The reaction was continued to stir at 0 °C for 1 hr, and then (E)-1,2-diphenylethene (2 g, 11.10 mmol) in 10 mL $CH_2Cl_2$ was added. The mixture was removed from the cold bath and stirred at ~25 °C under nitrogen for 20 h. The reaction was quenched with 0.1N HCl (50 mL), the layers were separated, and the aqueous layer was extracted with hexanes (2 x 100 mL). The combined organic phase was washed with saturated $NaHCO_3$ (aq) (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was submitted to a silica gel flash chromatography (hexanes) to afford biphenyl M9.3a as a colorless oil (1.6 g). $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.34-7.31 (m, 4H), 7.24-7.17 (m, 6H), 2.22-2.18 (m, 2H), 1.51-1.47 (m, 2H).

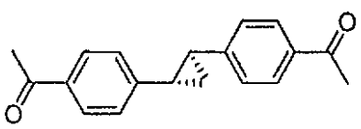
Example M9.3, step b




M9.3b1 M9.3b2

To a solution of biphenyl M9.3a (3.3 g, 16.99 mmol) in 1,2-dimethoxyethane (197 mL) and water (82 mL) was added NBS (12.09 g, 67.9 mmol). The reaction flask was covered with aluminum foil and stirred at room temperature for 51 hr. The reaction was partitioned between diethyl ether and water, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was submitted to a flash chromatography (sample was loaded with chloroform; eluted with hexanes) to afford a stereoisomeric mixture of dibrominated product as a white solid (3.1 g). The stereoisomeric mixture was separated by chiral SFC (Chiral pak AD-H column, 30X250 mm, 5 μm; 80% $CO_2$-20% EtOH; 35 °C; 150 bar; 70 mL/min for 20 min; 220 nm) to isolate two enantiomers: M9.3b1 (white solid, 1.1 g); $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.43 (d, J = 8.6 Hz, 4H), 7.02 (d, J = 8.6 Hz, 4H), 2.12-2.09 (m, 2H), 1.47-1.43 (m, 2H); OR: +361.79, 3.15 mg in 1 mL $CHCl_3$, λ = 589 nm, 50 mm cell. M9.3b2 (white solid, 1.2 g); $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.43 (d, J = 8.6 Hz, 4H), 7.02 (d, J = 8.6 Hz, 4H), 2.12-2.09 (m, 2H), 1.47-1.43 (m, 2H); OR: -376.70, 3.03 mg in 1 mL $CHCl_3$, λ = 589 nm, 50 mm cell.

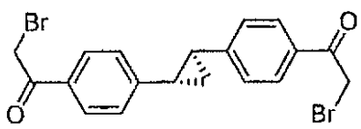
Example M9.3, Step c




To a solution of dibromide M9.3b1 (0.8806 g, 2.501 mmol) and tributyl(1-ethoxyvinyl)stannane (2.71 g, 7.50 mmol) in 1,4-dioxane (17 mL) was added dichlorobis(triphenylphosphine)-palladium(II) (0.105 g, 0.150 mmol). The reaction

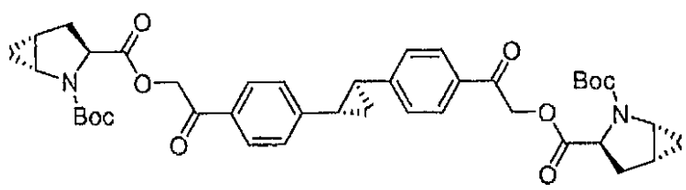
was thoroughly flushed with nitrogen, sealed, and heated at 80 °C for 16 h. The reaction was removed from the heat, 1N HCl (aq) (17 mL) was added, and the mixture was stirred for 4 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified with a flash chromatography (35% ethyl acetate/hexanes), and the retrieved sample was triturated with hexanes (3 x 50 mL) to afford ketone M9.3c as an off-white solid (412.5 mg). $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 7.92 (d, J = 8.5 Hz, 4H), 7.23 (d, J = 8.6 Hz, 4H), 2.61 (s, 6H), 2.32-2.28 (m, 2H), 1.67-1.63 (m, 2H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{19}H_{19}O_2$: 279.14; found 279.13.

Example M9.3, Step d




To a solution of ketone M9.3c (0.4072 g, 1.463 mmol) in THF (7 mL) was added phenyltrimethylammonium tribromide (1.10 g, 2.93 mmol), and the reaction mixture was stirred at ~25 °C for 15 h. The volatile component was removed *in vacuo*, and the residue was partitioned between water (25 mL) and $CH_2Cl_2$ (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford dibromide M9.3d, which was used without further purification. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{19}H_{17}{}^{79}Br_2O_2$: 434.96; found 434.98.

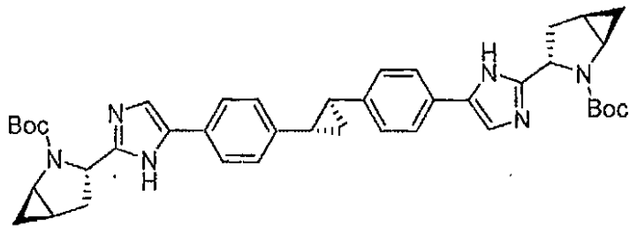
Example M9.3, Step e




To a solution of dibromide M9.3d (~1.463 mmol) and acid M3f1 (0.698 g, 3.07 mmol) in acetonitrile (10 mL) was added N,N-diisopropylethylamine (0.537 mL, 3.07 mmol), and the reaction was stirred at ~25 °C for 5h. The volatile component was removed *in vacuo*, and the residue was taken up in chloroform (4 mL) and loaded

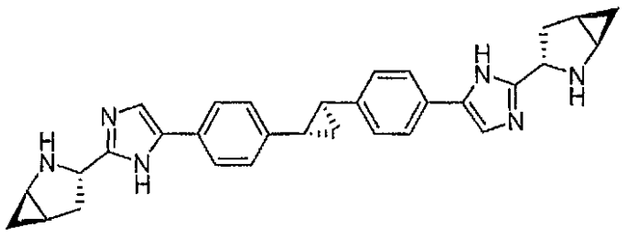
onto a silica gel column and eluted with 8% ethyl acetate/methylene chloride over 1296 mL solvents to afford diketoester M9.3e as a light yellow foam containing unidentified impurities (0.723 g). $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 7.90 (d, J = 8.0 Hz, 4H), 7.37 (d, J = 8.3 Hz, 4H), 5.59-5.40 (m, 3H), 4.24-4.09 (m, 2H), 3.37-3.25 (m, 2H), 2.47-2.36 (m, 5H), 1.87-1.80 (m, 2H), 1.72-1.68 (m, 2H), 1.57-1.49 (m, 2H), 1.41 (s, 7H), 1.35 (s, 11H), 0.80-0.67 (m, 2H), 0.58-0.48 (m, 2H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{48}N_2NaO_{10}$: 751.32; found 751.55.

Example M9.3, Step f




A mixture of diketoester M9.3e (0.723 g, 0.992 mmol) and ammonium acetate (1.529 g, 19.84 mmol) in xylene (10 mL) in a sealed reaction vessel was heated at 140 °C for 2.5 h. After the reaction was allowed to cool to ambient condition, the volatile component was removed *in vacuo*. The residue was taken up in 20% MeOH/$CHCl_3$ (50 mL) and treated with saturated $NaHCO_3$ (aq) (20 mL), stirred and the layers were separated. The aqueous layer was extracted further with 20% MeOH/$CHCl_3$ (2 x 50 mL), and the combined organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was taken up in $CHCl_3$ (4 mL), loaded onto a silica gel column and eluted with 45% ehtyl acetate/methylene chloride over 1296 mL to afford imidazole M9.3f as an orange solid (261.7 mg). $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 12.08 (s, 0.5H), 11.81 (s, 1.5H), 7.64 (d, J = 8.3 Hz, 3H), 7.55 (d, J = 8.3 Hz, 1H), 7.41 (d, J = 1.7 Hz, 1.7H), 7.19-1.17 (m, 1.3H), 7.11 (d, J = 8.3 Hz, 3H), 4.59 (app br s, 2H), 3.41 (app br s, 2H), 2.37-2.14 (m, 6H), 1.68-1.57 (m, 2H), 1.48-1.40 (m, 2H), 1.40-0.95 (br s, 18H), 0.79-0.69 (m, 2H), 0.59-0.48 (m, 2H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{49}N_6O_4$: 689.38; found 689.43.

Example M9.3, Step g

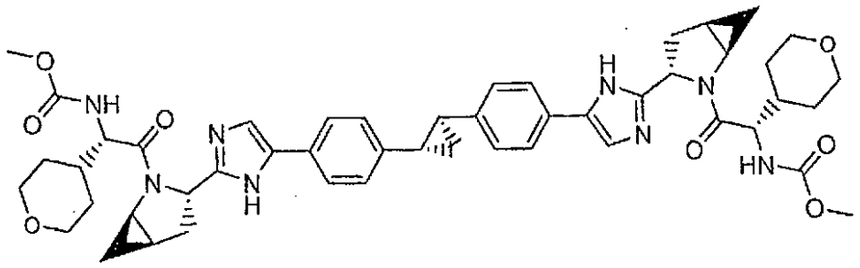


A solution of carbamate M9.3f (0.2391 g, 0.347 mmol) in 25% TFA/$CH_2Cl_2$ (1.7 mL) was stirred at ~25 °C for 1h. The volatile component was removed *in vacuo* to afford the TFA salt of pyrrolidine M9.3g as a tan foam (328 mg). $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 10.01 (br s, 2H), 7.70-7.68 (m, 6H), 7.20 (d, J = 8.6 Hz, 4H), 4.63-4.58 (m, 2H), 3.37-3.33 (m, 2H), 2.51-2.42 (m, 6H), 2.24-2.20 (m, 2H), 1.93-1.86 (m, 2H), 1.51-1.47 (m, 2H), 1.16-1.09 (m, 2H), 0.084-0.78 (m, 2H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{31}H_{33}N_6$: 489.28; found 489.26.

Example M9.3

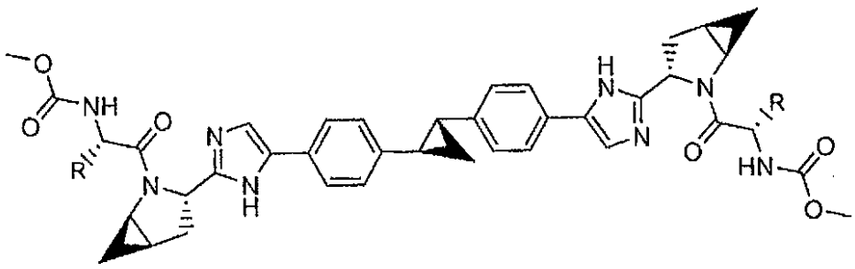
To a solution of pyrrolidine M9.3g/TFA salt (0.0834 g, 0.088 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.034 g, 0.194 mmol), and N,N-diisopropylethylamine (0.123 mL, 0.706 mmol) in DMF (1.5 mL) was added HATU (0.070 g, 0.185 mmol), and the mixture was stirred at 25 °C for 4h. The reaction mixture was diluted with MeOH (2.5 mL) and submitted to a reverse phase HPLC purification (XTERRA, 30X100 mm, S5; MeOH/$H_2O$/TFA) to afford Example M9.3 as an off-white foam (58 mg). $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 14.90-14.20 (bs, 3H), 8.00 (br s, 2H), 7.68 (d, J = 8.3 Hz, 4H), 7.34 (d, J = 8.6 Hz, 4H), 7.25 (d, J = 8.6 Hz, 2H), 5.00-4.96 (m, 2H), 4.42-4.39 (m, 2H), 3.79-3.69 (m, 2H), 3.54 (s, 6H), 2.38-2.31 (m, 5H), 2.16-2.07 (m, 2H), 1.95-1.88 (m, 2H), 1.61-1.58 (m, 2H), 0.97-0.90 (m, 8H), 0.80 (d, J = 6.5 Hz, 8H). $R_t$ = 1.96 min (Cond. 3); >95% homogeneity index (Cond. 9 and 10); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{55}N_8O_6$: 803.42; found 803.43.

Example M9.4



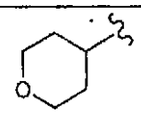
Example M9.4 was prepared from pyrrolidine M9.3g/TFA salt and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid according to the same procedure used for the preparation of Example M9.3. $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 15-14 (bs, 6H), 7.98 (br s, 2H), 7.66 (d, J = 8.3 Hz, 4H), 7.34-7.32 (m, 5H), 4.98-4.94 (m, 2H), 4.50-4.46 (m, 2H), 3.84-3.78 (m, 6H), 3.54 (s, 6H), 3.32-3.18 (m, 4H), 2.39-2.29 (m, 4H), 2.11-1.97 (m, 2H), 1.97-1.88 (m, 2H), 1.60-1.57 (m, 2H), 1.51-1.26 (m, 8H), 0.99-0.87 (m, 2H), 0.84-0.72 (m, 2H). $R_t$ = 1.77 min (Cond. 3); >95% homogeneity index (Cond. 9 and 10); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{49}H_{59}N_8O_8$: 887.45; found 887.50.

Examples M9.5 and M9.6

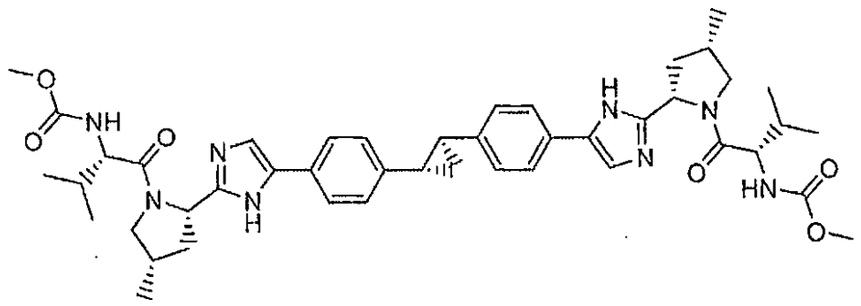


Examples M9.5 and M9.6 were prepared as TFA salts starting from dibromide M9.3b2 according to the procedures described for the preparation of Examples M9.3 and M9.4 from the corresponding stereoisomer dibromide M9.3b1.

| Example | R | $R_t$ (Cond. 3); homogeneity index (Cond. 9 and 10); LC/MS data |
|---|---|---|
| M9.5 |  | 1.98 min; >95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{55}N_8O_6$: 803.42; found 803.43 |

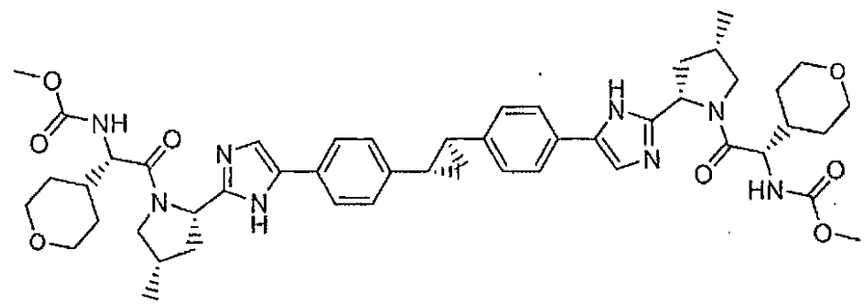
| | | |
|---|---|---|
| M9.6 |  | 1.77 min; >95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{49}H_{59}N_8O_8$: 887.45; found 887.60 |

Example M9.7



Example M9.7 (TFA salt) was prepared from dibromide M9.3d and acid M12.2c according to the procedures described for the preparation of Examples M9.3. $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 14.90-14.42 (br s, 4H), 8.02 (br s, 2H), 7.70 (d, J = 8.5 Hz, 4H), 7.36 (d, J = 8.6 Hz, 4H), 7.25 (d, J = 8.3 Hz, 2H), 5.07 (dd, J = 10.7 Hz/7.1 Hz, 2H), 4.18-4.13 (app t, 2H), 4.12-4.08 (app t, 2H), 3.55 (s, 6H), 3.42-3.37 (app t, 2H), 2.49-2.39 (m, 2H), 2.37-2.31 (app t, 2H), 2.02-1.93 (m, 2H), 1.87-1.78 (app q, 2H), 1.62-1.59 (app t, 2H), 1.14 (d, J = 6.3 Hz, 6H), 0.82 (d, J = 6.5 Hz, 6H), 0.77 (d, J = 6.8 Hz, 6H). $R_t$ = 3.12 min (Cond. 10d); >95% homogeneity index (Cond. 9 and 10); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{59}N_8O_6$: 807.46; found 807.45.

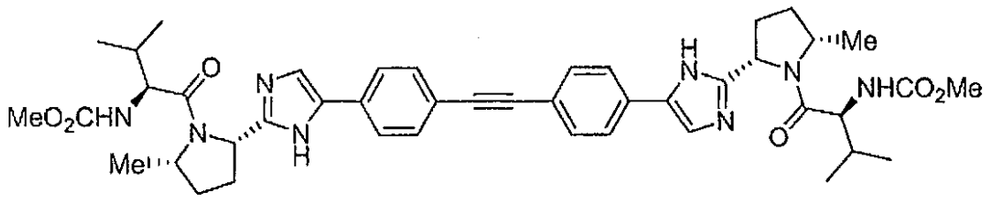
Example M9.8



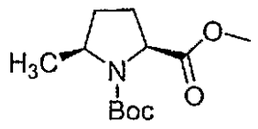
Example M9.7 (TFA salt) was prepared from dibromide M9.3d and acid M12.2c according to the procedures described for the preparation of Examples M9.4.

$R_t$ = 3.01 min (Cond. 10d); >95% homogeneity index (Cond. 9 and 10); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{49}H_{63}N_8O_8$: 891.48; found 891.52.

Example M10

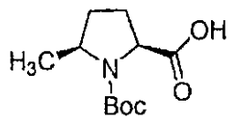


Example M10, Step a



The title compound, containing a diastereomeric impurity, was prepared in 5 steps from (S)-methyl 5 –oxopyrrolidine-2-carboxylate by employing the procedure described J. Med. Chem., 49:3520-3535 (2006) for the synthesis of its ethyl ester analog. $^1$H NMR ($CDCl_3$, 400 MHz): 4.35 (m, 0.5H), 4.25 (m, 0.5H), 4.05 (m, 0.5H), 3.90 (m, 0.5H), 3.73 (s, 3H), 2.20 (m, 1H), 2.00 (m, 2H), 1.65 (m, 1H), 1.50/1.40 (two overlapping br s, 9H), 1.31 (d, J = 6.0, 3H).

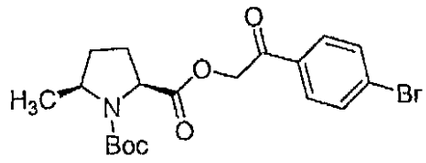
Example M10, Step b



A solution of lithium hydroxide (0.23g, 9.62 mmol) in water (5 mL) was added dropwise to a solution of ester M10a (1.8g, 7.4 mmol) in ethanol (10 mL), and stirred at room temperature for 17 hr. Most of the solvent was evaporated, and the residue was diluted with water, 1 N HCl was added dropwise to bring it to pH 3. It was extracted with ethyl acetate (20 mL, 4x), dried ($Na_2SO_4$) and evaporated in vacuo to afford a colorless oil, which yielded crystals when dissolved in EtOAc/hexanes solvent system and allowed to stand at room temperature. The white solid was

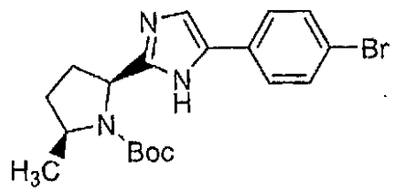
filtrated and dried in vacuo (1.42g). $^1$H NMR ($CDCl_3$, 400 MHz, d = 7.24 ppm): 4.35 (m, 1H), 3.95 (m, 1H), 2.35 (m, 1H), 2.05 (m, 2H), 1.70 (m, 1H), 1.50 (br s, 9H), 1.25 (d, J = 7.1, 3H).

Example M10, Step c




To a solution of acid M10b (2.16 g, 9.42 mmol) and 2-bromo-1-(4-bromophenyl)ethanone (2.62 g, 9.42 mmol) in acetonitrile (50 mL) was added slowly diisopropylethylamine (1.645 mL, 9.42 mmol), and the reaction mixture was stirred at room temperature for 5 hr. Solvent was removed in vacuo, and the residue was partitioned between ethyl acetate and water (1:1, 100 mL). The organic layer was washed with sat. $NaHCO_3$, dried ($Na_2SO_4$) and concentrated in vacuo to afford ketoester M10c as white solid (3.9g), which was used in the next step without further purification. $^1$H NMR (400 MHz , DMSO-$d_6$, δ = 2.5 ppm): 7.92 (d, J = 8.3, 2H), 7.78 (d, J = 8.5, 2H), 5.6-5.4 (m, 2H), 4.35 (m, 1H), 3.85 (m, 1H), 2.25 (m, 1H), 2.05 (m, 2H), 1.60 (m, 1H), 1.5/1.4 (two overlapping br s, 9H), 1.18 (d, J = 6.6, 3H). LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{19}H_{24}{}^{81}BrNaNO_5$: 450.07; found: 450.00.

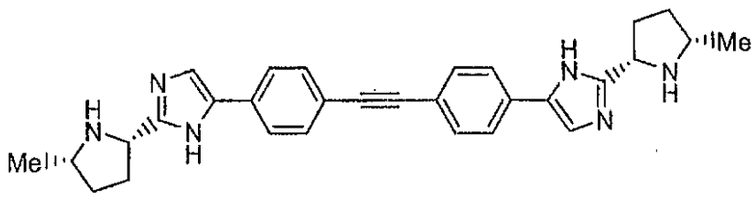
Example M10, Step d




To a solution of ketoester M10c (3.9 g, 9.15 mmol) in xylene (60 mL) in a 500 mL pressure tube, ammonium acetate (7.05 g, 91 mmol) was added. The reaction vessel was sealed and heated at 140 °C for 5 hr. The solvent was removed in vacuo, and the residue was partitioned between $CH_2Cl_2$ (100 mL) and water (100 mL). The organic layer was washed (Sat. $NaHCO_3$), dried ($Na_2SO_4$), and evaporated in vacuo. The resulting crude material was purified with flash chromatograph (30-100%

EtOAc/Hexane) to afford bromide M10d as a brown foam (3.0 g, yield 81%). $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 400 MHz): 11.77 (s, 1H), 7.70 (d, J = 8.5, 2H), 7.52 (br s, 1H), 7.50 (d, J = 8.5, 2H), 4.80 (m, 1H), 3.85 (m, 1H), 2.10 (m, 3H), 2.70 (m, 1H), 1.5/1.3 (overlapping br s, 9H), 1.20 (m, 3H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{19}H_{25}{}^{79}BrN_3O_2$: 406.11; found: 406.18.

Example M10, Step e



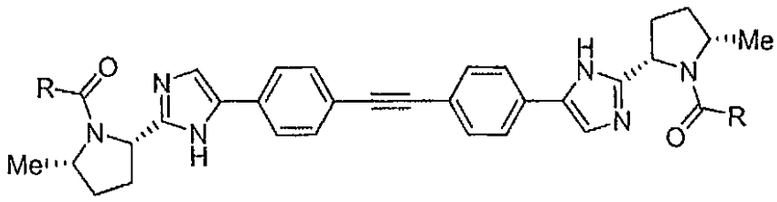

Pyrrolidine M10e (HCl salt) was prepared bromide M10d according to the procedure described for the synthesis of pyrrolidine M1b (HCl salt) from bromide D1b.

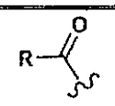
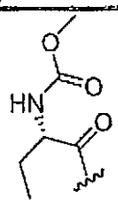
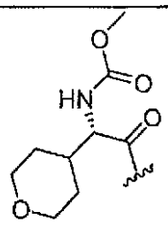
Example M10

Example M10 (TFA salt) was prepared from bromide pyrrolidine M10e (HCl salt) according to the procedure described for the synthesis of Example M1 from pyrroldine M3i (HCl salt). $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 400 MHz): 8.05 (s, 2H), 7.85 (d, J = 8.1, 4H), 7.69 (d, J = 7.6, 4H), 7.56 (d, J = 8.0, 2H), 5.5 (m, 0.4H), 5.0 (m, 1.6H), 4.75 (1.6H), 4.10 (m, 0.4H), 3.95 (m, 2H), 3.50 (s, 6H), 2.50-2.30 (m, 4H), 2.10 (m, 2H), 1.85 (m, 4H), 1.46 (d, J = 6.6, 5H), 1.20 (d, J = 6.8, 1H), 0.9-0.9 (m, 7.2H), 0.74 (d, J = 6.8, 4.8H). LC (Cond. 9 and 10): >95% homogeneity index. LC/MS (Cond. 3): $R_t$ = 2.03 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{55}N_8O_6$: 791.42; found: 791.39.

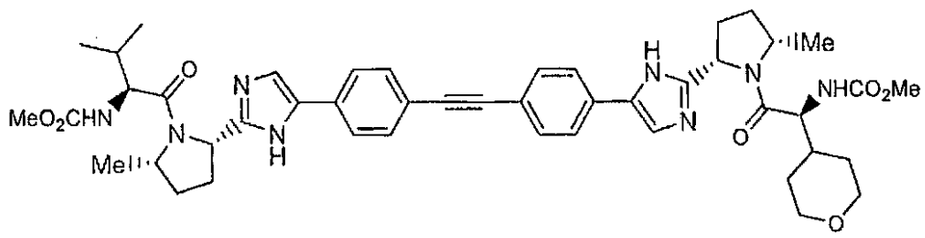
Examples M11-M12

The TFA salts Examples M11-M12 were prepared according to the procedure described for Example M10 and by employing appropriate acids.



| Example |  | $R_t$ (Cond. 3); % homogeneity index (Cond. 9 and 10); LC/MS data |
|---|---|---|
| M11 |  | 1.89 min.; >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{51}N_8O_6$: 763.39; found 763.40. |
| M12 |  | 1.82 min.; >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{59}N_8O_8$: 875.45; found 875.42. |

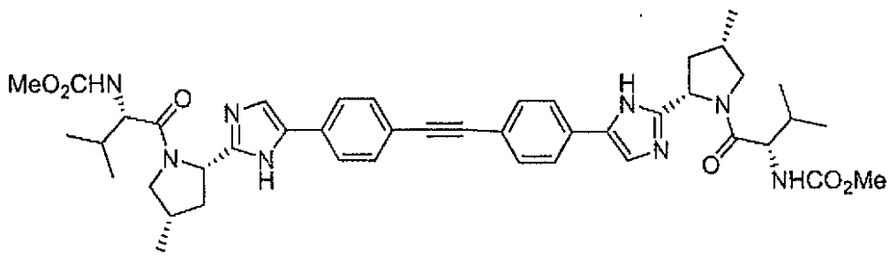
Example M12.1



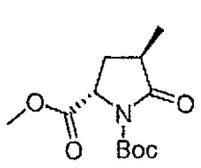
To a solution of pyrrolidine M10e/HCl salt (119 mg, 0.191 mmol), (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (49.0 mg, 0.226 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (40.9 mg, 0.233 mmol) in DMF (5 mL) was added DIEA (0.200 mL, 1.147 mmol) and HATU (148 mg, 0.390 mmol), and the mixture was stirred at room temperature for 1 hr. Solvent was removed in vacuo and the residue was dissolved in methanol and purified with a reverse phase HPLC (MeOH/TFA/Water) to separate the statistical mixture of products, one of which was Example M12.1 (TFA salt; light yellow foam; 55 mg). $^1$H NMR (DMSO-$d_6$, $\delta$ = 2.5 ppm, 400 MHz): 8.09-7.82 (m, 6H), 7.68-7.55 (m, 6H),

5.00 (m, 2H), 4.64 (app t, 2H), 4.21-3.75 (m, 6H), 3.53 (m, 6H), 3.17 (m, 2H), 2.33-2.21 (m, 6H), 1.85 (m, 3H), 1.62-1.17 (overlay of 'd' and 'm', J for 'd' = 6.6 Hz, 9H), 0.88 (m, 3.6H), 0.74 (d, J = 6.8 Hz, 2.4H). LC (Cond. 9 and 10): >95% homogeneity index. LC/MS (Cond. 10h): $R_t$ = 1.92 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{57}N_8O_7$: 833.44; found: 833.40.

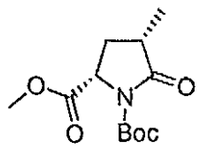
Example M12.2



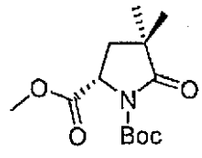

Example M12.2, Step a




M12.2a-1



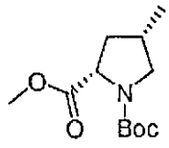

M12.2a-2




M12.2a-3

The above three esters were prepared from (S)-1-tert-butyl 2-methyl 5-oxopyrrolidine-1,2-dicarboxylate according to the procedure described in Tetrahedon Letters, 2003, 3203-3205.

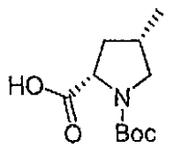
Example M12.2, Step b




Borane-methyl sulfide complex (5.44 mL, 10.88 mmol) was added to a solution of ester M12.2a-2 (1.4 g, 5.44 mmol) in THF (25 mL), and the reaction mixture was heated at 40 °C for 7 hr. The volatile component was removed in vacuo and the residue was partitioned between EtOAc and water (50 mL each). The

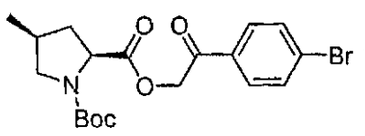
aqueous layer was extracted with EtOAc (30 mL), and the combined organic phase was dried with $Na_2SO_4$, and concentrated in vacuo. The resultant colorless oil was purified with a flash chromatography (0-50% EtOAc/Hexane) to afford ester M12.2b as a colorless oil (0.77 g). $^1$H NMR ($CDCl_3$, $\delta$ = 7.24 ppm, 400 MHz): 4.29-4.18 (m, 1H), 3.78-3.66 (m, 4H), 2.99 (app t, J = 10.1, 1H), 2.43-2.97 (m, 1H), 2.43-2.37 (m, 1H), 2.30-2.18 (m, 1H), 1.60-1.52 (m, 1H), 1.47/1.42 (two 's', 9H), 1.08-1.05 (m, 3H).

Example M12.2, Step c




To a solution of ester M12.2b (1.69 g, 6.95 mmol) in ethanol (10 mL) was added solution of LiOH (0.250 g, 10.42 mmol) in water (5.00 mL), and the reaction mixture was stirred at room temperature for 5 hr. The organic solvent was evaporated in vacuo and the residue was diluted with water (10 mL) and washed with ether (10 mL). It was chilled in ice-water bath, and acidified to a pH range of ~2 with 1N HCl. It was then extracted with EtOAc (20 mL, 3x). The organic layer was dried with $Na_2SO_4$ and concentrated in vacuo to afford acid M12.2c as a colorless oil, which became a white solid upon extended exposure to high vacuum (1.38g). $^1$H NMR ($CDCl_3$, $\delta$ = 7.24 ppm, 400 MHz): 4.39-4.22 (m, 1H), 3.80-3.69 (m, 0.91H), 3.59-3.35 (m, 0.18H), 3.03-2.89 (m, 0.91H), 2.51-2.22 (m, 2H), 1.98-1.91 (m, 0.71H), 1.68-1.60 (0.29H), 1.50/1.44 (two 's', 9H), 1.09 (app m, 3H).

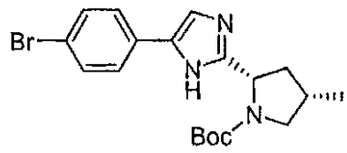
Example M12.2, step d




To a solution of M12.2c (1.38 g, 6.02 mmol) and 2-bromo-1-(4-bromophenyl)ethanone (1.673 g, 6.02 mmol) in acetonitrile (35 mL) was added DIEA

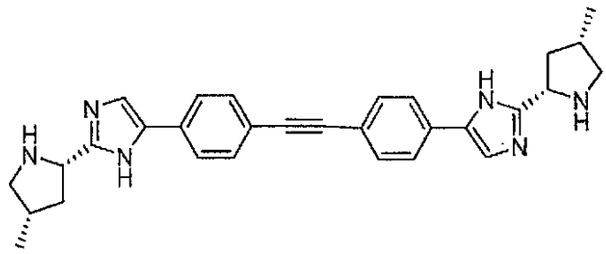
(1.051 mL, 6.02 mmol). It was stirred at room temperature for 5 hrs. The solvent was evaporated in vacuo and water (50 mL) and EtOAc (70 mL) were added, organic layer was separated and washed by sat. $NaHCO_3$ (30 mL), dried with $Na_2SO_4$, evaporated in vacuo to give crude M12.2d as a red oil (2.71 g), which was used in the next step without further purification. $^1H$ NMR (DMSO-$d_6$, $\delta$ = 2.5 ppm, 400 MHz): 7.91 (m, 2H), 7.78 (d, J = 8.5 Hz, 2H), 5.60-4.90 (m, 2H), 4.29 (app t, 1H), 3.61 (m, 1H), 2.85 (m, 1H), 2.35-1.80 (m, 2H), 1.65 (m, 1H), 1.40-1.32 (two s, 9H), 1.02 (d, J = 6.5 Hz, 3H). LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{19}H_{24}{}^{81}BrNNaO_5$: 450.07; found: 450.11.

Example M12.2, step e




To a pressure tube containing a solution of ketoester M12.2d (2.57 g, 6.03 mmol) in xylene (50 mL was added ammonium acetate (4.65 g, 60.3 mmol). The vessel was capped and heated at 140 $^0C$ for 5 hrs. The volatile component was removed in vacuo and the residue was partitioned between DCM (50 mL) and water (40 mL). The organic layer was dried with $Na_2SO_4$, and concentrated in vacuo. The resulting crude mixture was purified with flash chromatograph (30-100% EtOAc/Hexane) to afford imidazole M12.2.e as a brown solid (1.24g). $^1H$ NMR (DMSO-$d_6$, $\delta$ = 2.5 ppm, 400 MHz): 7.69 (d, J = 8.5 Hz, 2H), 7.58-7.48 (m, 3H), 4.70 (m, 1H), 3.65 (m, 1H), 3.02(m, 1H), 2.37 (m, 1H), 2.22 (m, 1H), 1.74-1.54 (m, 1H), 1.37-1.08 (two s, 9H), 1.03 (d, J = 6.3 Hz, 3H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{19}H_{25}{}^{79}BrN_3O_2$: 406.11; found: 406.18.

Example M12.2, step f

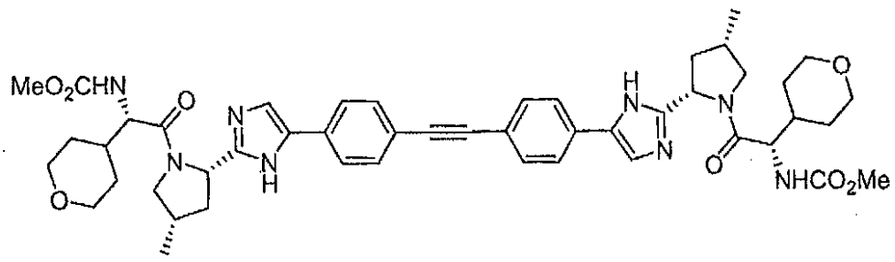


Pyrrolidine M12.2f (HCl salt) was prepared bromide M12.2e according to the procedure described for the synthesis of pyrrolidine M1b (HCl salt) from bromide D1b.

Example M12.2

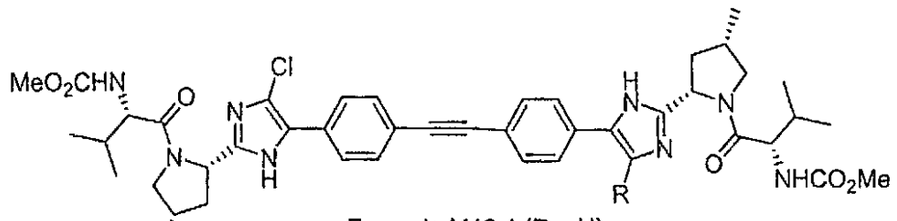
To a mixture of pyrrolidine M12.2f /HCl salt (200 mg, 0.321 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (124 mg, 0.707 mmol) in DMF (5 mL) were added DIEA (0.337 mL, 1.928 mmol) and HATU (250 mg, 0.659 mmol), and the mixture was stirred at room temperature for 2 hrs. The volatile component was removed in vacuo and the residue was purified with a reverse phase HPLC (Phenomenex-Luna 30X100mm, S10 Axia, MeOH/TFA/Water). The resultant sample was repurified with a different reverse phase HPLC (Water-Sunfire 30X100mm S5, ACN/TFA/Water) to afford the TFA salt of Example M12.2 as a light yellow foam (77.1 mg). $^1$H NMR (Methanol-$d_4$, $\delta$ = 3.29 ppm, 400 MHz): 7.90 (s, 2H), 7.74 (d, J = 8.6 Hz, 4H), 7.67 (d, J = 8.5 Hz, 4H), 5.18 (m, 2H), 4.30 (app t, 2H), 4.18 (d, J= 7.3 Hz, 2H), 3.63 (s, 6H), 3.38 (m, 2H), 2.63 (m, 2H), 2.51 (m, 2H), 1.98 (m, 2H), 1.81 (m, 2H), 1.21 (d, J = 6.3 Hz, 6H), 0.83-0.90 (m, 12H). LC (Cond. 9 and 10): >95% homogeneity index. LC/MS (Cond. 10h): $R_t$ = 2.01 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{55}N_8O_6$: 791.42; found: 791.46.

Example M12.3



Example M12.3 (TFA salt) was prepared from pyrrolidine M12.2f /HCl and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid according to the procedure described for the preparation of Example M12.2. RT: LC (Cond. 9 and 10): >95% homogeneity index. LC/MS (Cond. 10h): $R_t$ = 1.89 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{59}N_8O_8$: 875.45; found 875.42.

Example M12.4-M12.5

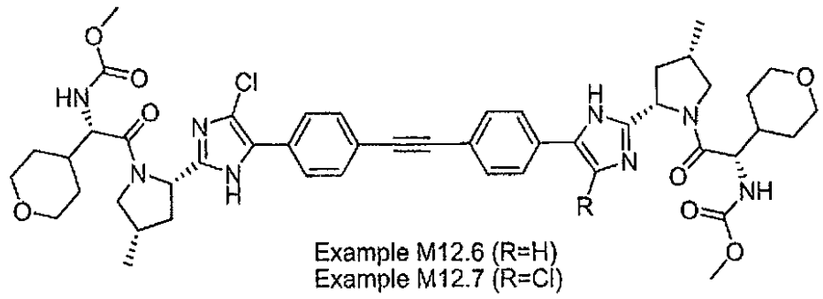


Example M12.4 (R = H)
Example M12.5 (R = Cl)

To a solution of Example M12.2 (free-based using MCX column and 2N $NH_3$/MeOH) (80 mg, 0.101 mmol) in DMF (5 mL) was added NCS (17.56 mg, 0.131 mmol), and heated at 50 °C for 3 hrs. Additional NCS (5 mg, 0.037 mmol) was added to the mixture and heating was continued for 5 more hours. The volatile component was removed in vacuo and the residue was dissoled in MeOH and submitted to a reverse phase HPLC condition (MeOH/TFA/Water) to afford Example M12.4/TFA salt (light yellow foam, 24 mg) and Example M12.5/TFA salt (light yellow foam, 28 mg). Example M12.4/TFA salt: $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 400 MHz): 8.17(s, 1H), 7.83-7.73 (m, 6H), 7.66 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 8.3 Hz, 1H), 7.22 (d, J = 8.3 Hz, 1H), 5.05 (m, 1H), 4.85 (m, 1H), 4.16-4.02 (m, 4H), 3.52 (s, 6H), 3.37 (m, 1H), 3.23 (m, 1H), 2.54-2.24 (m, 4H), 1.87-1.63 (m, 4H), 1.13-1.08 (m, 6H), 0.85-0.74 (m, 12H). LC (Cond. 9a.1 and 10a.1): >95% homogeneity index. LC/MS (Cond. 11): $R_t$ = 4.26 min. LC/MS: Anal. Calcd. for $[M+H]^+$

$C_{44}H_{54}ClN_8O_8$: 825.39; found: 825.50. Example M12.5/TFA salt: (DMSO-$d_6$, δ = 2.5 ppm, 400 MHz): 7.79 (d, J = 8.4 Hz, 4H), 7.66 (d, J = 8.4 Hz, 4H), 7.22 (d, J = 8.3 Hz, 2H), 4.85 (m, 2H), 4.13 (app t, 2H), 4.04 (app t, 2H), 3.53 (s, 6H), 3.24 (app t, 2H), 2.39 (m, 2H), 2.26 (m, 2H), 1.90 (m, 2H), 1.66 (m, 2H), 1.09 (d, J = 6.5 Hz, 6H), 0.85 (d, J = 6.8 Hz, 6H), 0.80 (d, J = 6.5 Hz, 6H). LC (Cond. 9a and 10a.1): >95% homogeneity index. LC/MS (Cond. 11): $R_t$ = 4.44 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}Cl_2N_8O_6$: 859.35; found: 859.30.

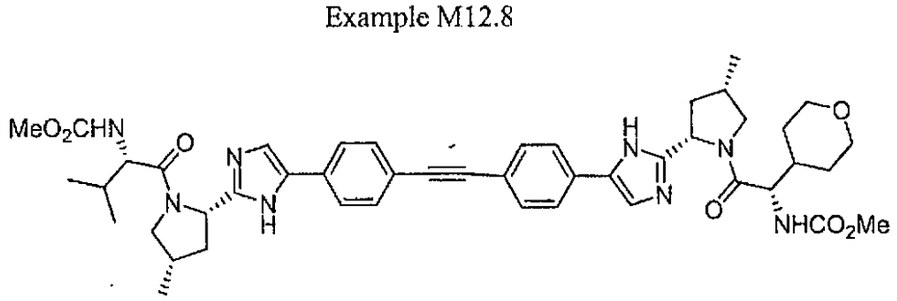
Example M12.6-M12.7



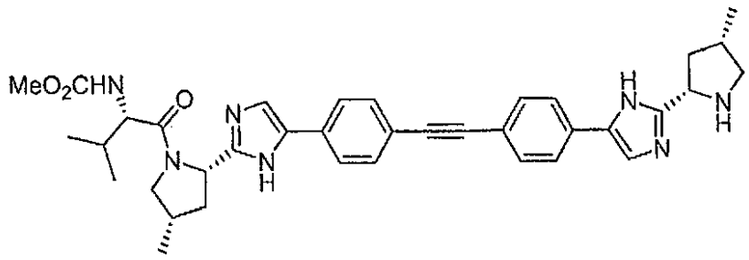

Example 12.6 - 12.7 were prepared as TFA salts from Example M12.3 according to the procedure described for the preparation of Example 12.4 - 12.5.

| Example | RT (Cond. 12); % homogeneity index (Cond. 12); MS data |
|---|---|
| **M12.6** | 13.68 min.; >95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{58}ClN_8O_8$: 909.41; found 909.8 |
| **M12.7** | 17.12 min; >95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{57}Cl_2N_8O_8$: 943.37; found 943.7 |

Example M12.8



Example M12.8, step a



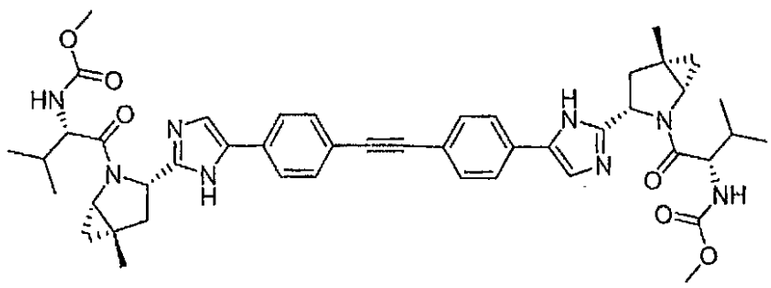
To a mixture of pyrrolidine M12.2f/HCl salt (120 mg, 0.193 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (35.1 mg, 0.200 mmol) in DMF (2 mL), were added DIEA (0.168 mL, 0.964 mmol) followed by HATU (70.4 mg, 0.185 mmol), and the mixture was stirred at room temperature for 1 hr. The volatile component was removed in vacuo and the residue was dissoled in MeOH and submitted to a reverse phase HPLC condition (MeOH/TFA/Water) to isolate the TFA salt of pyrrolidine M12.8a as yellow solid (36mg). The sample was free based (MCX column; MeOH wash; 2 N $NH_3$ /MeOH elution) to afford a yellow solid (22.3 mg). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{44}N_7O_3$: 634.35; found: 634.35.

Example M12.8

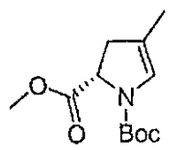
To a solution of pyrrolidine M12.8a (22.3 mg, 0.035 mmol) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (12.99 mg, 0.060 mmol) in DMF (2 mL) were added DIEA (0.018 mL, 0.106 mmol) and HATU (13.65 mg, 0.036 mmol), and the mixture was stirred at room temperature for 2 hrs. The volatile component was removed in vacuo and the residue was dissoled in MeOH and submitted to a reverse phase HPLC condition (Column: Phenomenex-Luna 30X100mm, S10 Axia; MeOH/TFA/Water). The resulting sample was repurified with a second reverse phase HPLC (Column: Water-Sunfire 30X100mm S5; ACN/TFA/Water) to afford the TFA salt of Example M12.8 as a light yellow foam (16 mg). $^1$H NMR (Methanol-$d_4$, $\delta$ = 3.29 ppm, 400 MHz): 7.92 (d, J = 5.0 Hz, 2H), 7.77 (d, J = 8.5 Hz, 4H), 7.72-7.69 (m, 4H), 5.21 (m, 2H), 4.39-4.22 (m, 4H), 3.92 (m, 2H), 3.67 (s, 6H), 3.47-3.28 (m, 4H), 2.68 (m, 2H), 2.54 (m, 2H), 2.06-1.85 (m, 4H), 1.25 (d, J = 6.5 Hz, 6H), 0.93 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 7.3 Hz, 6H). LC

(Cond. 9 and 10): >95% homogeneity index. LC/MS (Cond. 10d): $R_t$ = 3.10 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{57}N_8O_7$: 833.44; found: 833.47.

Example M12.9

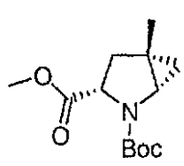


Example M12.9, Step a

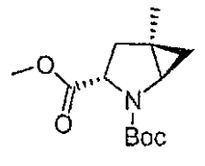


To a solution of mixture of M12.2a-1 and M12.2a-2 (4.75g, 18.46 mmol) was added Superhydride (19.20 mL, 19.20 mmol) dropwise at -50 °C in a dryice/acetone bath for 10 min. Hunig's base (13.58 mL, 78 mmol) was added, and stirred for 10 min and DMAP (0.122 g, 0.997 mmol) was added as a solid, stirred for 15 min, and trifluoroacetic anhydride (2.98 mL, 21.08 mmol) was added dropwise over 15 mins Then the dryice/acetone bath was removed, and the reaction mixture was stirred for 4 hr while allowing it to thaw to room temperature. The reaction mixture was washed with water (50 mL), sat. NaCl (30 mL), and concentrated *in vacuo*. The resulting crude material was purified with flash chromatography (8-60% EtOAc/Hexane) to afford ester M12.9a as a yellow oil (2.85 g). $^1$H NMR ($CDCl_3$, 400 MHz): 6.36 (s, 0.5H), 6.25 (s, 0.5H), 4.70-4.57 (m, 1H), 3.78 (s, 3H), 2.96 (m, 1H), 2.54 (m, 1H), 1.70 (s, 3H), 1.50 (s, 4.5H), 1.44 (s, 4.5H).

Example M12.9, Step b



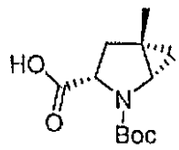

M12.9b-1




M12.9b-2

Diethylzinc (1.1 M in toluene, 59.1 mL, 65.0 mmol) was added dropwise over 20 min to a cooled (-23 °C) toluene (60 mL) solution of ester M12.9a (5.23 g, 21.68 mmol), and stirred for 10 min. Chloroiodomethane (9.44 mL, 130 mmol) was added dropwise over 10 min, and the reaction mixture was stirred at -21 °C for 16 hr. Sat. $NaHCO_3$ (60 mL) was added to the reaction mixture, the cooling bath was removed, and the mixture was stirred for 10 min. It was then filtered, and the filter cake was washed with toluene (50 mL). The filterate was partitioned, and the organic layer was dried with $Na_2SO_4$, and concentrated *in vacuo*. The resulting crude material was purified with flash chromatography (2-10% EtOAc/Hexane) to afford ester ester M12.9b-1 (first elute; colorless oil; 2.88 g) and ester M12.9b-2 (second elute; colorless oil; 1.01g). Relative stereochemical assignment was made based on NOE studies. Ester M12.9b-1: $^1$H NMR ($CDCl_3$, 400 MHz): 4.65-4.52 (m, 1H), 3.72 (s, 3H), 3.28-3.17 (m, 1H), 2.44-2.32 (m, 1H), 2.16-2.10 (m, 1H), 1.51-1.42 (two s, 9H), 1.24 (s, 3H), 1.07 (m, 1H), 0.69-0.60 (m, 1H).

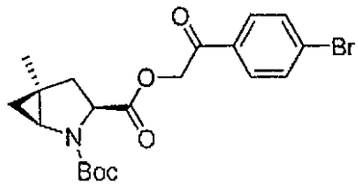
Example M12.9, Step c




To a solution of M12.9b-1 (2.88 g, 11.28 mmol) in Ethanol (20 mL) was added a solution of LiOH (0.324 g, 13.54 mmol) in water (10.00 mL), and the mixture was stirred at room temperature for 6 hr. Most of the volatile component was removed *in vacuo*, and the residue was partitioned between water (20 mL) and ether (20 mL). The aqueous layer was chilled in an ice-water bath, acidified with a 1N HCl to a pH region of 2, and extracted with EtOAc (30 mL, 4x). The combined

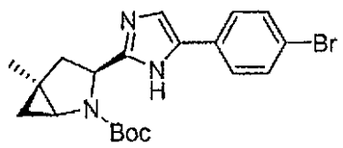
organic phase was dried with $Na_2SO_4$, evaporated *in vacuo* to give acid M12.9c as a sticky solid (2.55g). $^1$H NMR ($CDCl_3$, 400 MHz): 4.64 (m, 1H), 3.25 (appt s, 1H), 2.70-2.40 (m, 1H), 2.14 (m, 1H), 1.54-1.44 (m, 9H), 1.27 (s, 3H), 1.10-0.80 (m, 1H), 0.67 (m, 1H).

Example M12.9, Step d




To a solution of acid M12.9c (2.05 g, 8.50 mmol) in Acetonitrile (50 mL) was added 2-bromo-1-(4-bromophenyl)ethanone (2.361 g, 8.50 mmol) followed by DIEA (1.484 mL, 8.50 mmol), and the reaction mixture was stirred at room temperature for 16 hr. Most of the volatile component was removed *in vacuo*, and the residue was partitioned between EtOAc (50 mL) and water (50 mL). The organic layer was washed with sat. $NaHCO_3$ (30 mL) and sat. NaCl (20 mL), dried with $Na_2SO_4$, and evaporated *in vacuo* to afford ketoester M12.9d as white foam (3.5g). LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{20}H_{24}{}^{81}BrNNaO_5$: 462.07; found: 461.91.

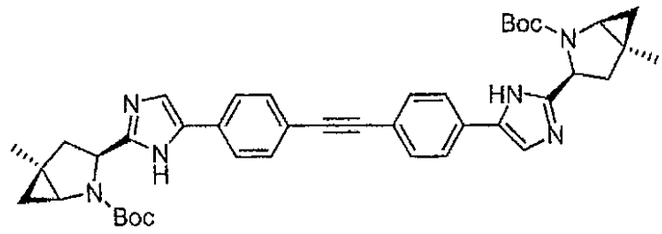
Example M12.9, Step e




To a mixture of ketoester M12.9e (3.5 g, 7.99 mmol) and xylene (80 mL) in a pressure tube was added ammonium acetate (6.16 g, 80 mmol), and the reaction mixture was capped and heated at 140 °C for 4.5 hr. The volatile component was removed *in vacuo* and the residue was partitioned between DCM (70 mL) and water (70 mL). The organic layer was washed with sat. $NaHCO_3$ (30 mL), and concentrated *in vacuo*. The resulting crude material was purified with flash chromatograph (40-100% EtOAc/Hexane) to afford imidazole M12.9e as a brown solid (2.8 g). $^1$H NMR (DMSO-$d_6$, $\delta$ = 2.5 ppm, 400 MHz): 7.68 (m, 2H), 7.57-7.49 (m, 3H), 5.08 (m, 1H),

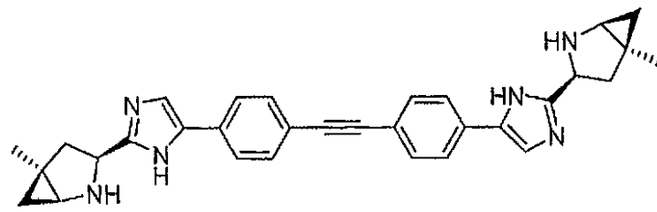
3.20 (m, 1H), 2.45-2.09 (M, 2H), 1.69-1.52 (m, 1H), 1.42-1.16 (m, 12H), 0.62 (m, 1H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{20}H_{25}{}^{81}BrN_3O_2$: 420.11; found: 420.02.

Example M12.9, Step f




To a pressure tube containing a solution of bromide M12.9e (0.354 g, 1.007 mmol) and 1,2-bis(trimethylstannyl)ethyne (0.354 g, 1.007 mmol) in DMF (15 mL) was added Pd $(Ph_3P)_4$ (0.070 g, 0.060 mmol), and the reaction mixture was degassed for 10 min and the reaction vessel was capped and heated at 90 °C for 14 hr. Most of the volatile component was removed *in vacuo*, and the residue was partitioned between DCM (60 mL) and water (40 mL). The organic layer was dried with $Na_2SO_4$, and evaporated *in vacuo*. The resulting crude material was purified with flash chromatograph (40-100% EtOAc/hexanes) to afford alkyne M12.9f as a red solid (0.3 g). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{49}N_6O_4$: 701.38; found: 701.43.

Example M12.9, Step g

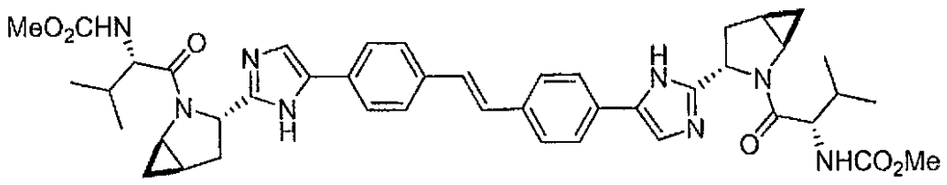



4N HCl in dioxane (3.90 mL, 128 mmol) was added to carbamate M12.9f (0.3 g, 0.428 mmol), and the mixture was stirred at room temperature for 5 hr. The volatile component was removed *in vacuo* and the residue was dried under high vacuum overnight to afford the HCl salt of pyrrolidine M12.9g as a yellow solid (0.27 g). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{32}H_{33}N_6$: 501.28; found: 501.22.

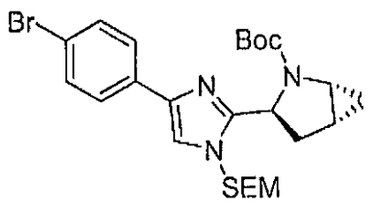
Example M12.9

To a mixture of M12.9g/HCl salt (60 mg, 0.093 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (35.8 mg, 0.204 mmol) in DMF (2 mL) were added DIEA (0.097 mL, 0.557 mmol) and HATU (72.7 mg, 0.191 mmol), and the reaction mixture was stirred at room temperature for 2 hr. The volatile component was removed in vacuo and the residue was dissoled in MeOH and submitted to a reverse phase HPLC purification (Phenomenex-Luna 30X100mm, S10 Axia, MeOH/TFA/Water). The resulting sample was repurified with a second reverse phase HPLC (Water-Sunfire 30X150mm OBD, ACN/TFA/Water) to afford the TFA salt of Example M12.9 as light yellow foam (37 mg). LC/MS (Cond. 10d): $R_t$ = 3.08 min. LC (Cond. 9 and 10): >95% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{55}N_8O_6$: 815.42; found: 815.46.

Example M13




Example M13, Step a

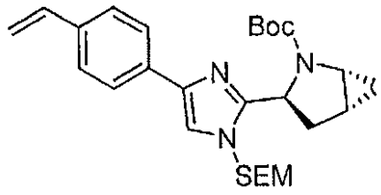



(SEM regiochemistry was not determined)

To a solution of bromide M3h (1.0 g, 2.47 mmol) in DMF (25 mL) was added sodium hydride (60%; 0.109 g, 2.72 mmol), and the reaction mixture was stirred at room temperature for 20 min. Then (2-(chloromethoxy)ethyl)trimethylsilane (0.482 mL, 2.72 mmol) was added dropwise, and the reaction was stirred for 21h. The volatile component was removed in vacuo, and the residue was partitioned between ethyl acetate (25 mL) and water (25 mL). The aqueous layer was extracted with ethyl

acetate (2 x 25 mL), and the combined organic phase was washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was taken up in $CHCl_3$ (2 mL) and loaded on a Thomson's silica gel cartridge eluting with 25% ethyl acetate/hexanes to afford bromide M13a of unknown regio-chemical make up as light yellow foam (1.171 g). $^1$H NMR (DMSO-$d_6$, $\delta$ = 2.5 ppm, 400 MHz): 7.71 (s, 1H), 7.69 (d, J = 8.6, 2H), 7.52 (d, J = 8.6, 2H), 5.62–5.31 (br s, 1H), 5.26 (d, J = 10.8, 1H), 4.84–4.66 (app br s, 1H), 3.57–3.36 (app br s, 1H), 3.50 (t, J = 8.1, 2H), 2.44–2.20 (app br s, 2H), 1.77–1.60 (app br s, 1H), 1.52–1.23 (br s, 4H), 1.23–0.96 (br s, 5H), 0.92–0.79 (m, 2H), 0.78–0.69 (m, 1H), 0.64– 0.55 (app br s, 1H), 0.00 (s, 9H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{37}{}^{79}BrN_3O_3Si$: 534.18; found: 533.99.

Example M13, Step b

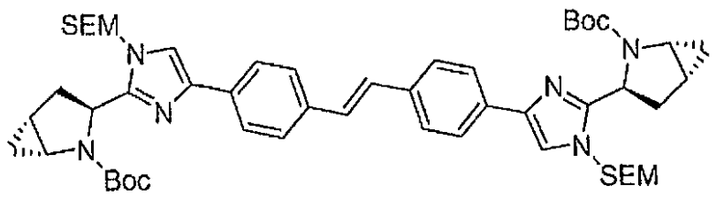



(SEM regiochemistry was not determined)

To a solution of bromide M13a (0.5542 g, 1.037 mmol) and triethylamine (0.434 mL, 3.11 mmol) in 2-propanol (2.000 mL) and water (1 mL) in a sealed reaction vessel was added potassium vinyltrifluoroborate (0.181 g, 1.348 mmol) followed by 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.085 g, 0.104 mmol). The reaction mixture was flushed with nitrogen, capped and heated at 100 °C for 17h. The volatile component was removed in vacuo, and the residue was partitioned between ethyl acetate (25 mL) and water (25 mL), and the aqueous phase was extracted with ethyl acetate (2 x 25 mL). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was taken up in $CHCl_3$ (4 mL) and loaded onto a Thomson's silica gel cartridge eluting with 25% ethyl acetate/hexanes to afford alkene M13b as a light yellow viscous oil (345.4 mg). $^1$H NMR (DMSO-$d_6$, $\delta$ = 2.5 ppm, 400 MHz): 7.71 (d, J = 8.3, 2H), 7.67 (s, 1H), 7.45 (d, J = 8.3, 2H), 6.72 (dd, J = 17.6,11.1, 1H), 5.8 (dd, J = 0.8, 17.6, 1H), 5.60–5.29 (app br s, 1H), 5.26 (d, J = 10.8, 1H), 5.22 (d, J = 11.8, 1H), 4.83–4.67

(app br s, 1H), 3.59 – 3.35 (app br s, 1H), 3.51 (t, J = 8.1, 2H), 2.41–2.23 (app br s, 2H), 1.76–1.59 (app br s, 1H), 1.51–1.22 (app br s, 4H), 1.22–0.97 (app br s, 5H), 0.93-0.80 (m, 2H), 0.80–0.71 (m, 1H), 0.65–0.56 (app br s, 1H), 0.00 (s, 9H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{40}N_3O_3Si$: 482.28; found: 482.24.

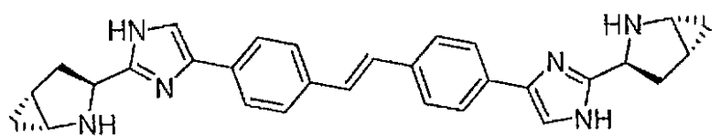
Example M13, Step c




(SEM regiochemistry was not determined)

To a solution of alkene M13b (0.748 g, 1.552 mmol) in $CH_2Cl_2$ (2 mL) was added Grubbs 2nd Generation Catalyst (0.132 g, 0.155 mmol), and stirred at room temperature under nitrogen for 18 hr. The reaction was loaded onto a Thomson's silica gel cartridge eluting with 30% ethyl acetate/hexanes to afford M13c as a tan foam (0.50 g). $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 400 MHz): 7.74 (d, J = 8.4, 4H), 7.68 (s, 2H), 7.58 (d, J = 8.3, 4H), 7.22 (s, 2H), 5.72-5.34 (bs, 3H), 5.34-5.21 (m, 2H), 4.94-4.63 (app br s, 3H), 3.52 (t, J = 7.8, 4H), 2.45-2.20 (app br s, 4H), 1.88-1.57 (app br s, 2H), 1.57-1.26 (br s, 8H), 1.26-0.98 (br s, 10H), 0.93-0.80 (m, 4H), 0.80-0.69 (m, 2H), 0.69 -0.51 (app bs, 2H), 0.00 (s, 18H).

Example M13, Step d




4N HCl/Dioxane (13 mL) was carefully added to a flask containing M13c (0.4799 g, 0.513 mmol) that was cooled with an ice/water bath. A mixture of water (4 mL) and 12N HCl (2 mL) was added to the above mixture and the cooling bath was removed and stirring of the reaction mixture continued for 24h. MeOH (2 mL) was added to the reaction, and stirring was continued for 17h. All solvents were removed in vacuo to afford pyrrolidine M13d (.4HCl) as a yellow/tan solid (317 mg). $^1$H NMR (DMSO-

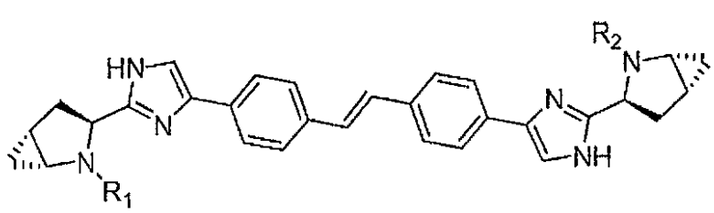
$d_6$, δ = 2.5 ppm, 400 MHz): 10.78-9.87 (very br s, ~3H), 8.01 (s, 2H), 7.87 (d, J = 8.4, 4H), 7.71 (d, J = 8.6, 4H), 7.35 (s, 2H), 4.76 (app t, J = 8.8, 2H), 3.43 (app t, J = 5.1, 2H), 2.64 (m, 2H), 2.55-2.52 (m, 2H), 1.95 (m, 2H), 1.16-1.05 (m, 2H), 0.86 (m, 2H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{30}H_{31}N_6$: 475.26; found: 475.26.

Example M13

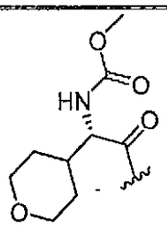
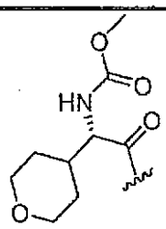
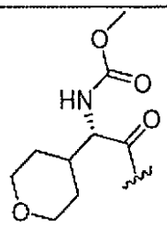
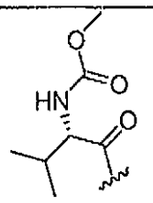
The TFA salt of Example M13 was prepared from pyrrolidine M13d (.4HCl) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid according to the procedure described for the preparation of Example M1. $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 400 MHz): 8.14-7.95 (br s, 2H), 7.80-7.74 (m, 8H), 7.40 (s, 2H), 7.25 (d, J = 8.3, 2H), 5.0 (app t, J = 7.3, 2H), 4.41 (app t, J = 7.6, 2H), 3.81-3.67 (m, 2H), 3.54 (s, 6H), 2.57-2.46 (overlapped with DMSO-$_{d6}$) (m, 2H), 2.44-2.31 (m, 2H), 2.19-2.05 (m, 2H), 1.98-1.87 (m, 2H), 1.02-0.89 (m, 7.5H), 0.89-0.70 (m, 8.5H). LC (Cond. 3): $R_t$ = 1.92 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_6$: 789.41; found: 789.46.

Examples M14-M15

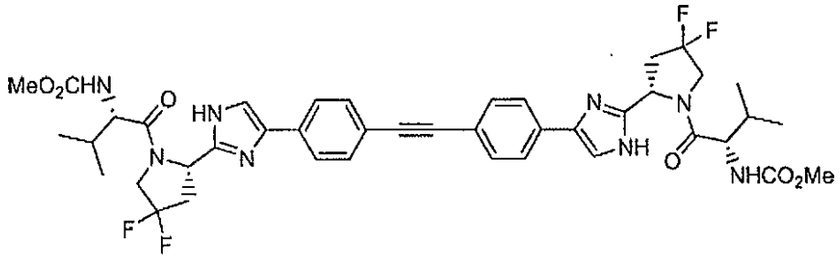
Example M14 (TFA salt) was prepared from pyrrolidine M13d and appropriate acid by employing the procedure described for the synthesis of Example M1. In the case of Example M15 an equimolar mixture of (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid was employed for the coupling step and the resultant statistical mixture of products was separated by the HPLC technique described for Example M1.



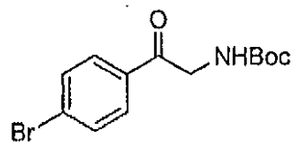

| Example | $R_1$ | $R_2$ | $R_t$ (Cond. 3); % homogeneity index (Cond. 9 and 10); LC/MS data |
|---|---|---|---|

| Example | $R_1$ | $R_2$ | $R_t$ (Cond. 3); % homogeneity index (Cond. 9 and 10); LC/MS data |
|---|---|---|---|
| M14 |  |  | 1.72 min.; >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{57}N_8O_8$: 873.43; found 873.48 |
| M15 |  |  | 1.82 min.; >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{55}N_8O_7$: 831.42; found 831.47 |

Example N1



Example N1, Step a



To a suspension of 2-amino-1-(4-bromophenyl)ethanone, HCl (4.0 g, 15.97 mmol) in DCM (50.0 mL) was added sodium bicarbonate (4.02 g, 47.9 mmol). Then Boc-anhydride (3.89 mL, 16.77 mmol) was added to the solution and the reaction mixture was warmed to rt and stirred for 18 hrs. Then DIEA (3 mL, 17.18 mmol) was added and the reaction mixture was stirred at rt for 2 hrs, LCMS showed that the reaction was complete. The reaction mixture was diluted with EtOAc and water, the organic phase was washed with 5% citric acid, water and sat. NaCl, dried over anhydrous $Na_2SO_4$, filtered and concentrated to yield bromide N1A (5.0 g) as a

yellow solid, which was used in the next step without further purification. $^1$H NMR (400 MHz, MeOD) ppm 7.89 (2 H, m), 7.68 (2 H, m, *J*=8.53 Hz), 4.52 (2 H, s), 1.38 - 1.51 (9 H, m). LC/MS (Cond. 10d): $R_t$ = 3.56 min. LC/MS: Anal. Calcd. For $[M+Na]^+$ $C_{13}H_{16}BrNaNO_3$: 336.03; found: 335.97.

Example N1, Step b



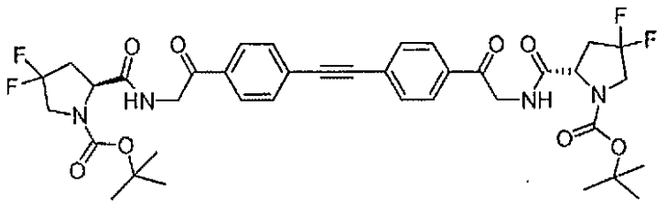

To a solution of carbamate N1a (2.0 g, 6.37 mmol) in DMF (5 mL) was added 1,2-bis(trimethylstannyl)ethyne (1.119 g, 3.18 mmol). The reaction mixture was degassed, tetrakis(triphenylphosphine)palladium(0) (0.184 g, 0.159 mmol) was added, and the mixture was heated at 90 °C for 4 hrs. The crude reaction mixture was charged to a 90 g silica gel cartridge which was eluted with a 20 min gradient of 0-60% EtOAc in hexane. Alkyne N1b (0.83 g) was collected as a yellow solid. LC/MS (Cond. 10d): $R_t$ = 4.1 min. LC/MS: Anal. Calcd. For $[M+Na]^+$ $C_{28}H_{32}NaN_2O_6$: 515.23; found: 515.10.

Example N1, Step c



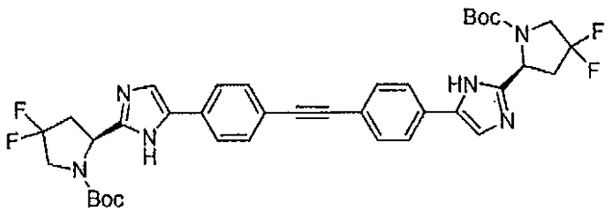

To a solution of alkyne N1b (1.13 g, 2.294 mmol) in 1,4-dioxane (5 mL) was added 4 M HCl in dioxane (4 mL, 16.00 mmol). The reaction mixture was stirred at rt for 2 hrs. The reaction mixture was concentrated to dryness to yield a yellow solid. The solid was washed with hexane and EtOAc, then dried to yield aminoketone N1c, 2 HCl (0.508 g). $^1$H NMR (400 MHz, MeOD) ppm 8.10 (4 H, d, *J*=8.53 Hz), 7.78 (4 H, d, *J*=8.53 Hz), 4.64 (4 H, s). LC/MS (Cond. 10d): $R_t$ = 1.94 min. LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{18}H_{17}N_2O_2$: 293.12; found: 293.07.

Example N1, Step d



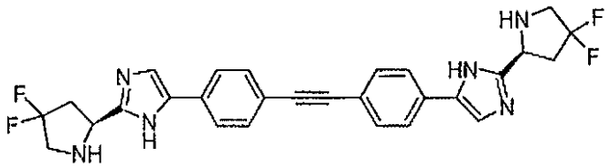
To a mixture of (S)-1-(tert-butoxycarbonyl)-4,4-difluoropyrrolidine-2-carboxylic acid (0.25 g, 0.995 mmol), aminoketone N1c, 2 HCl (0.182 g, 0.498 mmol), HATU (0.189 g, 0.498 mmol) in DMF (2 mL) was added DIEA (0.521 mL, 2.99 mmol). The reaction mixture was stirred at rt for 3 hrs. The crude mixture was charged to an 80 g silica gel cartridge which was eluted with a 20 min gradient of 0-100% EtOAc in hexane. ketoamide N1d (0.12 g) was collected as a yellow solid. LC/MS (Cond. 10d): $R_t$ = 4.08 min. LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{38}H_{43}F_4N_4O_8$ : 759.29; found: 759.03.

Example N1, Step e



In a sealed tube, a mixture of ketoamide N1d (0.12 g, 0.158 mmol) and ammonium acetate (0.122 g, 1.582 mmol) in xylene (2 mL) was heated at 140 °C for 4 hrs. The reaction mixture was partitioned between EtOAc and water, the organic layer was washed with sat. $NaHCO_3$ and sat. NaCl, dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was dissolved in a small amount of methylene chloride and charged to a 40 g silica gel cartridge which was eluted with a 20 min gradient of 0-100% EtOAc in hexane. Imidazole N1e (0.054 g) was collected as a yellow solid. LC/MS (Cond. 10d): $R_t$ = 3.3 min. LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{38}H_{41}F_4N_6O_4$: 721.3; found: 721.10.

Example N1, Step f

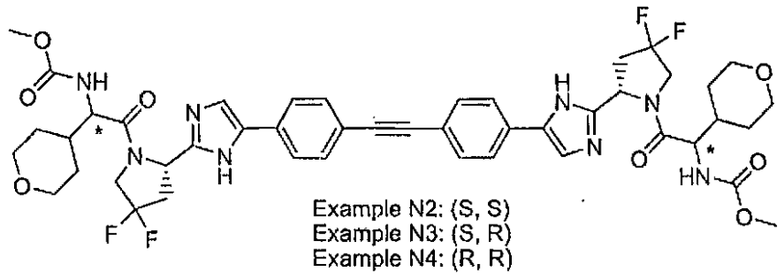


To a solution of imidazole N1e (0.054 g, 0.075 mmol) in 1,4-Dioxane was added 4 M HCl in dioxane (0.5 mL, 2.0 mmol) plus a few drops of MeOH. The reaction mixture was stirred at rt for 4 hrs, and concentrated to yield pyrrolidine N1f, 4 HCl (0.055 g) as a pale yellow solid. LC/MS (Cond. 10d): $R_t$ = 2.94 min. LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{28}H_{25}F_4N_6$: 520.2; found: 521.10.

Example N1

To a mixture of (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.014 g, 0.079 mmol), pyrrolidine N1f, 4 HCl (0.025 g, 0.038 mmol), HATU (0.030 g, 0.079 mmol) in DMF (2 mL) was added DIEA (0.039 mL, 0.225 mmol). The reaction mixture was stirred at rt for 18 hrs, diluted with MeOH, filtered and purified by reverse phase HPLC to yield TFA salt of Example N1 (0.026 g) as a white solid. LC (Cond. 10b and 10c): >95% homogeneity index. LC/MS (Cond. 10d): $R_t$ = 3.11 min. LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{42}H_{47}F_4N_8O_6$: 835.35; found: 835.16.

Example N2



Example N2: (S, S)
Example N3: (S, R)
Example N4: (R, R)

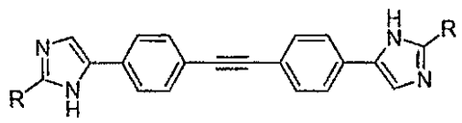
Pyrrolidine N1f was coupled with 2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid by employing the procedure described for the synthesis of Example N1. The resultant three diastereomers (TFA salts) were separated by employing the following condition: Column = Waters-Sunfire 30 X 100 mm S5; Start %B = 0; Final %B = 32; Gradient time = 25 min; Stop time = 25 min; Flow Rate = 40

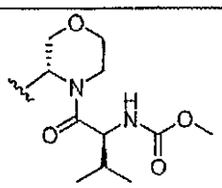
mL/min; Wavelength = 220 nm; Solvent A = 0.1 % TFA in 10% MeCN/90% water; Solvent B = 0.1 % TFA in 90% MeCN/10% water.

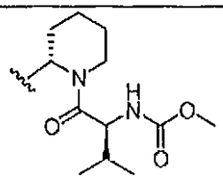
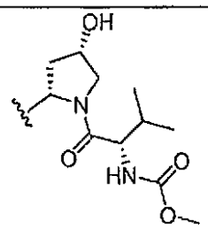
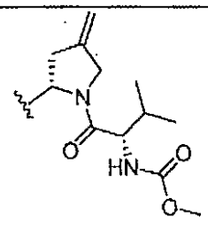
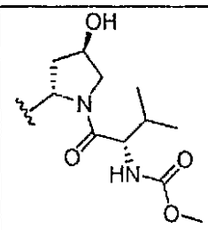
| Example | Analytical conditions |
|---|---|
| N2 | LC (Cond. 10b and 10c): >95% homogeneity index. LC/MS (Cond. 10d): $R_t$ = 2.90 min. LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{46}H_{51}F_4N_8O_8$: 919.37; found: 919.41. |
| N3 | LC (Cond. 10b and 10c): >95% homogeneity index. LC/MS (Cond. 10d): $R_t$ = 2.96 min. LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{46}H_{51}F_4N_8O_8$: 919.37; found: 919.41. |
| N4 | LC (Cond. 10b and 10c): >95% homogeneity index. LC/MS (Cond. 10d): $R_t$ = 3.00 min. LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{46}H_{51}F_4N_8O_8$: 919.37; found: 919.41. |

Example N5-N7

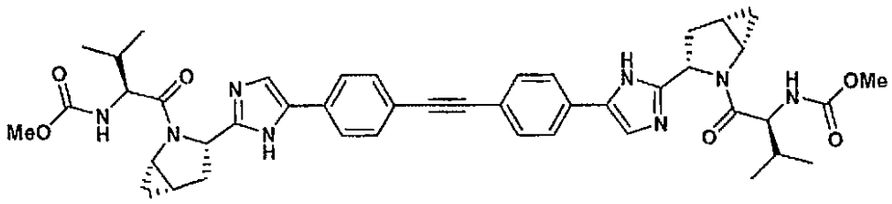
Example N5-N7 (TFA salt) were prepared starting from aminoketone N1c and appropriate starting materials, obtained from commercial sources, by employing the procedures described for the synthesis of Example N1.



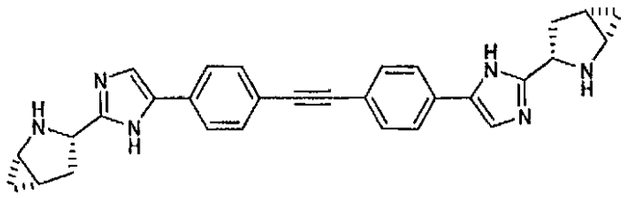
| Example | R | Analytical conditions |
|---|---|---|
| N5 |  | LC (Cond. 10b and 10c): >95% homogeneity index. LC/MS (Cond. 10d): $R_t$ = 3.05 min. LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{42}H_{51}N_8O_8$: 795.38; found: 795.23. |

| | | |
|---|---|---|
| N6 |  | LC (Cond. 10b and 10c): >95% homogeneity index. LC/MS (Cond. 10d): $R_t$ = 3.23 min. LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{44}H_{55}N_8O_6$: 791.42; found: 791.54. |
| N7 |  | LC (Cond. 10b and 10c): 93% homogeneity index. LC/MS (Cond. 10d): $R_t$ = 3.06 min. LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{42}H_{51}N_8O_8$: 795.38; found: 795.4. |
| N7.1 |  | LC (Cond. 10b and 10c): 97% homogeneity index. LC/MS (Cond. 10d): $R_t$ = 3.056 min. LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{44}H_{51}N_8O_6$: 787.39; found: 787.4. |
| N7.2 |  | LC (Cond. 10b and 10c): 98% homogeneity index. LC/MS (Cond. 10d): $R_t$ = 2.878 min. LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{42}H_{51}N_8O_8$: 795.38; found: 795.41. |

Example N8



Example N8, step a

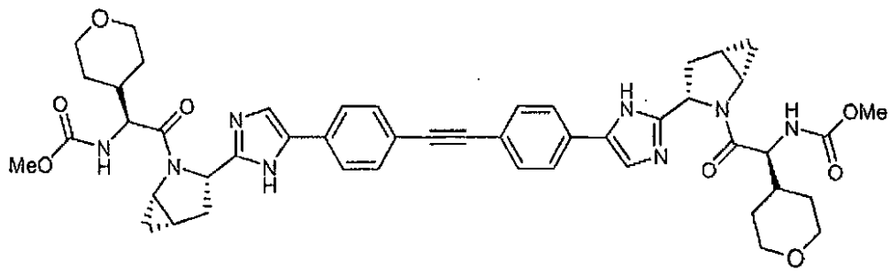


Pyrrolidine N8a (HCl salt) was prepared staring from aminoketone N1c and (1S,3S,5S)-2-(tert-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (for its preparative method, see WO2004/052850) according to the procedures described for the preparation of pyrrolidine N1f. $^1$H NMR (MeOD, δ = 3.33 ppm, 400 MHz): 7.98 (s, 2H ), 7.87 (d, J = 8.4, 4H), 7.69 (d, J = 8.4, 4H), 5.59 (dd, J = 10.2, 5.4, 2H), 3.61-3.56 (m, 2H), 3.05-2.98 (m, 2H), 2.67 (dd, J = 14.2, 5.4, 2H), 2.20-2.14 (m, 2H), 1.28-1.22 (m, 2H), 1.19-1.13 (m, 2H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{30}H_{29}N_6$: 473.24; found 473.2.

Example N8

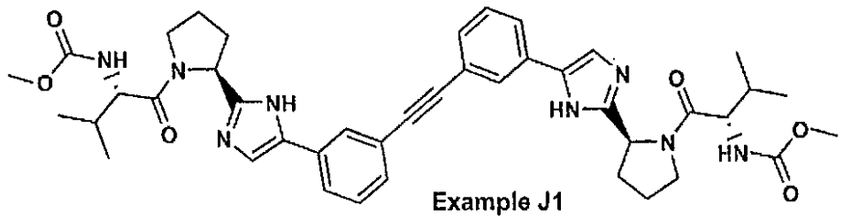
Example N8 was prepared from pyrrolidine N8a according to the procedure described for the preparation of Example N1 with the exception that the purification was conducted under a modified reverse phase HPLC condition (ACN/water/$NH_4OAc$). Example N8 was retrieved as a pale-yellow solid. LC (Cond. 10e): >99% homogeneity index. LC/MS (Cond. 10f): $R_t$ = 2.21 min. $^1$H NMR (DMSO, δ = 2.50 ppm, 400 MHz): 12.33 (s, 0.28H), 11.86 (s, 1.72H), 7.74 (d, J = 8.4, 3.42H), 7.65 (d, J = 8.4, 0.58H), 7.55 (d, J = 8.4, 0.58H), 7.51 (s, 2H), 7.49 (d, J = 8.4, 3..42H), 7.31 (d, J = 8.8, 2H), 5.39 (app d, 0.15H), 3.34 (dd, J = 10.8, 2.4, 3.85H), 4.29 (app t, 2H), 3.90 (br m, 2H), 3.55 (s, 6H), 2.64-2.56 (m, 2H), 2.17 (app d, 2H), 2.08-1.98 (m, 2H), 1.79-1.74 (m, 4H), 0.92-0.83 (m, 14H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{51}N_8O_6$: 787.39; found 787.8.

Example N9

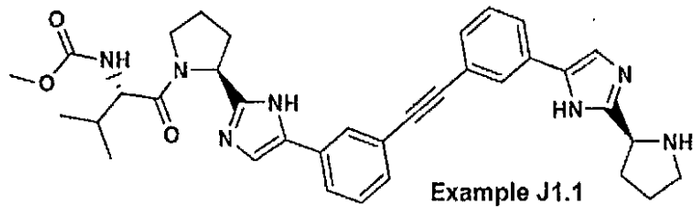


Compound N9 (TFA salt) was prepared from pyrrolidine N8a and (*S*)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid according to the procedure described for the preparation of Example N1 with the exception that ACN/water/TFA solvent system was employed in its purification. LC (Cond. 10e): >97% homogeneity index. LC/MS (Cond. 10g): $R_t$ = 1.82 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{55}N_8O_8$: 871.41; found 871.6.

Example J1 to J1.1

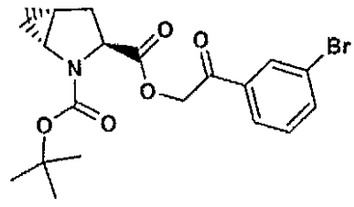


Example J1



Example J1.1

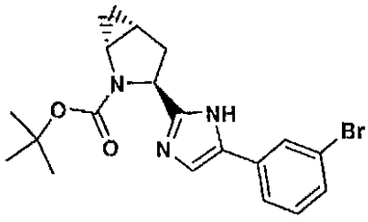
Example J1, step a



DIPEA (2.8 mL, 16 mmol) was added to a slurry of acid M3f (2.00 g, 8.80 mmol) and 2-bromo-1-(3-bromophenyl)ethanone (2.22 g, 8.00 mmol) in acetonitrile

(25 mL) and the reaction mixture was stirred overnight at rt. The reaction mixture was concentrated and purified with a Biotage Horizon (80g $SiO_2$, 10-25% EtOAc/hexanes) to yield ketoester J1a (3.37 g) as a viscous light yellow oil. LC-MS retention time 1.853 min; m/z 423 and 425.98 (1:1) (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Waters Xterra MS 7u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min , a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 2 min, a hold time of 1 min, and an analysis time of 3 min where solvent A was 5% MeOH / 95% $H_2O$ / 10 mM ammonium acetate and solvent B was 5% $H_2O$ / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode. $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 8.04 (t, *J*=1.8 Hz, 1H), 7.83 (d, *J*=7.8 Hz, 1H), 7.75 (d, *J*=8.0 Hz, 1H), 7.38 (t, *J*=7.9 Hz, 1H), 5.33 - 5.59 (m, 1H), 5.13 - 5.32 (m, 1H), 4.22 (br s, 1H), 3.40 - 3.63 (m, 1H), 2.52 - 2.63 (m, 1H), 2.46 (dd, *J*=13.1, 9.3 Hz, 1H), 1.63 - 1.73 (m, 1H), 1.47 (br s, 9H), 0.86 (br s, 1H), 0.51 (br s, 1H).

Example J1, step b

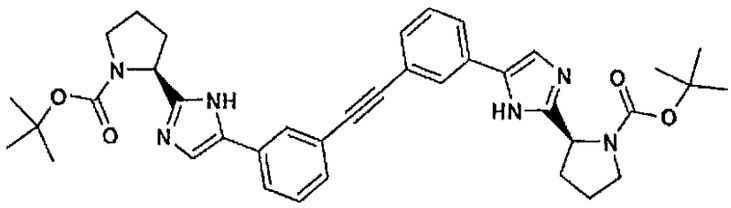



A solution of ketoester J1a (3.33 g, 7.85 mmol) in xylene (75 mL) was added to ammonium acetate (5.94 g, 77 mmol) in a pressure vessel and the reaction mixture was stirred under nitrogen for 5 min. The reaction vessel was sealed and then placed into an oil bath which had been preheated to 140 °C and the reaction was held at that temperature for 6h. The reaction was cooled to rt, stirred overnight and reheated at 140 °C for 5 hr. Additional ammonium acetate (3.0g) was added and the reaction was stirred at 145 C for 8 hrs, cooled to rt and concentrated under high vacuum to a brown oil. The oil was partitioned between DCM (~ 200 mL) and 1/2 sat. sodium bicarbonate (~200 mL). The organic layer was dried ($MgSO_4$), filtered and

concentrated. The crude orange solidified foam was purified on a Biotage Horizon (20-50% EtOAc/hexanes, 160 g $SiO_2$) to yield imidazole J1b (2.03 g) as a yellow solidified foam.

LC-MS retention time 2.450 min; m/z 404 and 406.06 (1:1) (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min , a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where solvent A was 5% MeOH / 95% $H_2O$ / 10 mM ammonium acetate and solvent B was 5% $H_2O$ / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode. $^1$H NMR (400 MHz, MeOD) δ ppm 7.89 (br s, 1H), 7.65 (d, *J*=6.5 Hz, 1H), 7.32 - 7.44 (m, 2H), 7.26 (t, *J*=7.8 Hz, 1H), 4.66 (br s, 1H), 3.52 - 3.63 (m, 1H), 2.51 (dd, *J*=13.1, 8.8 Hz, 1H), 2.25 - 2.37 (m, 1H), 1.66 - 1.75 (m, 1H), 1.29 (br s, 9H), 0.84 (ddd, *J*=8.2, 6.0, 5.8 Hz, 1H), 0.56 - 0.63 (m, 1H).

Example J1, step c

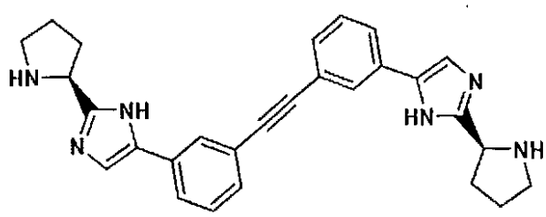



Nitrogen was bubbled through a stirred solution of bromide J1b (854 mg, 2.18 mmol) and 1,2-bis(trimethylstannyl)ethyne (403 mg, 1.15 mmol) in DMF (10 mL) for 10 minutes. Then $Pd(PPh_3)_4$ (79 mg, 0.069 mmol) was added, nitrogen was bubbled through the reaction for 1 min and then the reaction was heated at 90 °C under nitrogen for 17h. The reaction mixture was cooled to rt, concentrated to a viscous oil and purified on a Biotage Horizon (40 g $SiO_2$, 70-100% EtOAc/hexanes, loaded with DCM)) to yield alkyne J1c (500 mg) as a yellow solidified foam.

LC-MS retention time 2.876 min; m/z 649.51 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u

C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min , a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where solvent A was 5% MeOH / 95% $H_2O$ / 10 mM ammonium acetate and solvent B was 5% $H_2O$ / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode. $^1$H NMR (400 MHz, MeOD) δ ppm 7.89 (s, 2H), 7.67 - 7.74 (m, 2H), 7.35 - 7.44 (m, 6H), 4.85 - 5.04 (m, 2H), 3.64 - 3.74 (m, 2H), 3.47 - 3.56 (m, 2H), 2.29 - 2.45 (m, 2H), 1.90 - 2.13 (m, 6H), 1.48 (br s, 6H), 1.26 (br s, 12H).

Example J1, step d




TFA (3 mL, 38.9 mmol) was added to a stirred solution of carbamate J1c (238 mg, 0.367 mmol) in DCE (7 mL) and the reaction was stirred at rt for 1h. The reaction mixture was concentrated under vacuum to yield a TFA salt of pyrrolidine J1d (260 mg) as a yellow solid.

LC-MS retention time 2.505 min; m/z 449.22 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min , a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where solvent A was 5% MeOH / 95% $H_2O$ / 10 mM ammonium acetate and solvent B was 5% $H_2O$ / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode. $^1$H NMR (400 MHz, MeOD) δ ppm 7.96 - 8.00 (m, 2H), 7.79 (dt, *J*=6.6, 2.1 Hz, 2H), 7.65 (s, 2H), 7.41 - 7.48 (m,

4H), 4.91 (t, *J*=7.8 Hz, 2H), 3.44 - 3.61 (m, 4H), 2.51 - 2.62 (m, 2H), 2.27 - 2.45 (m, 4H), 2.16 - 2.24 (m, 2H).

Example J1 to J1.1

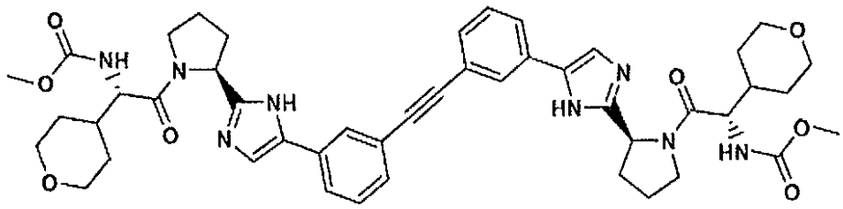
HATU (61.8 mg, 0.162 mmol) was added to a stirred solution of a TFA salt of pyrrolidine J1d (110 mg, 0.12 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (28.5 mg, 0.162 mmol) in DMF (0.7 mL) and Hunig'sBase (0.10 mL, 0.54 mmol). The reaction mixture was stirred at rt for 3 hours and then concentrated under a stream of nitrogen. The reaction was purified in two injections by preparative HPLC (MeOH/water /10 mM ammonium acetate) to yield Example J1 (31.5 mg) as a light yellow solid and Example J1.1 (41.1 mg) as a a light yellow solid.

Example J1: LC-MS retention time 2.605 min; m/z 763.36 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where solvent A was 5% MeOH / 95% $H_2O$ / 10 mM ammonium acetate and solvent B was 5% $H_2O$ / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode. The $^1$H NMR presents as a 4 :1 mixture of rotamers. The major rotamer is: $^1$H NMR (400 MHz, MeOD) δ ppm 7.86 (s, 2H), 7.64 - 7.70 (m, 2H), 7.36 - 7.43 (m, 4H), 7.34 (s, 2H), 5.17 (dd, *J*=7.8, 5.3 Hz, 2H), 4.24 (d, *J*=7.3 Hz, 2H), 3.95 - 4.04 (m, 2H), 3.84 - 3.92 (m, 2H), 3.66 (s, 6H), 2.17 - 2.42 (m, 6H), 2.00 - 2.13 (m, 4H), 0.96 (d, *J*=6.8 Hz, 6H), 0.91 (d, *J*=6.8 Hz, 6H).

Example J1.1: LC-MS retention time 2.620 min; m/z 606.23 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min , a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100%

solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where solvent A was 5% MeOH / 95% $H_2O$ / 10 mM ammonium acetate and solvent B was 5% $H_2O$ / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode. The $^1H$ NMR presents as a 3 :1 mixture of rotamers. $^1H$ NMR (400 MHz, MeOD) δ ppm 7.94 (s, 1H), 7.87 (s, 1H), 7.74 (ddd, *J*=5.6, 3.4, 1.8 Hz, 1H), 7.65 - 7.70 (m, 1H), 7.51 (s, 1H), 7.36 - 7.44 (m, 6H), 7.35 (s, 1H), 5.18 (dd, *J*=7.7, 5.4 Hz, 1H), 4.68 (t, *J*=7.8 Hz, 1H), 4.24 (d, *J*=7.5 Hz, 1H), 3.95 - 4.06 (m, 1H), 3.85 - 3.92 (m, 1H), 3.66 (s, 3H), 3.35 - 3.52 (m, 2H), 2.01 - 2.50 (m, 9H), 0.96 (d, *J*=6.8 Hz, 3H), 0.91 (d, *J*=6.8 Hz, 3H).

Example J2

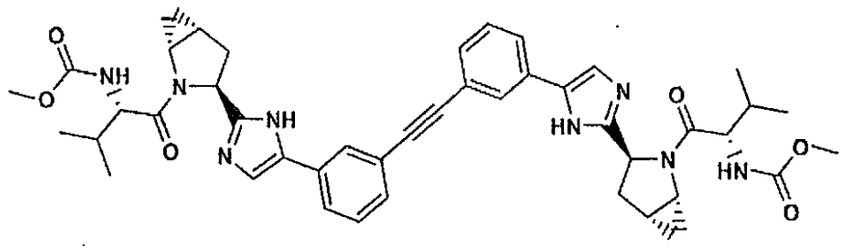


HATU (118 mg, 0.310 mmol) was added to a stirred solution of a TFA salt of pyrrolidine J1d (93.4 mg, 0.103 mmol) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (67.3 mg, 0.310 mmol) in DIPEA (0.18 mL, 1.0 mmol) and DMF (1 mL) and the reaction was stirred at rt for 2h. The reaction was concentrated under a stream of nitrogen, dissolved into MeOH and purified by preparative HPLC (MeOH/water 10 mM ammonium acetate) to yield Example J2 (18.1 mg) as a light pink solid

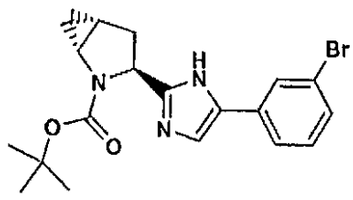
LC-MS retention time 2.428 min; m/z 847.39 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min , a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where solvent A was 5% MeOH / 95% $H_2O$ / 10 mM ammonium acetate and solvent B was 5% $H_2O$ / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a

Micromass Platform for LC in electrospray mode. The $^1$H NMR exhibits as a 4:1 mixture of rotamers. The major rotamer is : 1H NMR (400 MHz, MeOD) δ ppm 7.83 (s, 2H), 7.62 - 7.67 (m, 2H), 7.33 - 7.42 (m, 6H), 5.15 (dd, *J*=7.5, 5.5 Hz, 2H), 4.32 (d, *J*=8.3 Hz, 2H), 3.89 - 4.08 (m, 6H), 3.66 (s, 6H), 3.33 - 3.50 (m, 6H), 2.23 - 2.40 (m, 4H), 2.13 - 2.22 (m, 2H), 1.92 - 2.10 (m, 4H), 1.61 - 1.71 (m, 4H), 1.32 - 1.56 (m, 4H).

Example J3

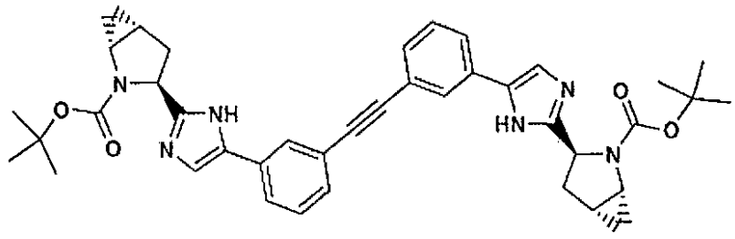


Example J3, step a



Bromide J3a was prepared from acid M3f according to the procedure described for bromide J1b.

Example J3, step b

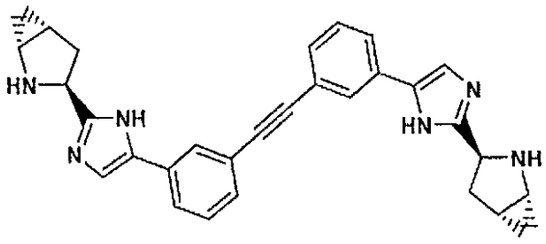


Nitrogen was bubbled through a stirred solution of bromidie J3a (825 mg, 2.041 mmol) and 1,2-bis(trimethylstannyl)ethyne (378 mg, 1.074 mmol) in DMF (10 mL) for 10 minutes. Then, $Pd(PPh_3)_4$ (74.5 mg, 0.064 mmol) was added to the

reaction mixture, nitrogen was bubbled through the reaction for 1 min and then the reaction was heated at 90 °C under nitrogen for 17h. The reaction mixture was cooled to rt, concentrated to a thick black oil, diluted with DCM and purified on a Biotage Horizon (40 g $SiO_2$, 60-100% EtOAc/hexanes) to yield alkyne J3b (312 mg) as a yellow solid.

LC-MS retention time 2.800 min; m/z 671.53 (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min , a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where solvent A was 5% MeOH / 95% $H_2O$ / 10 mM ammonium acetate and solvent B was 5% $H_2O$ / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode. $^1$H NMR (400 MHz, MeOD) δ ppm 7.89 (s, 2H), 7.70 (ddd, *J*=5.6, 3.3, 1.9 Hz, 2H), 7.38 - 7.43 (m, 6H), 4.69 (br s, 2H), 3.59 (br s, 2H), 2.53 (dd, *J*=13.2, 8.9 Hz, 2H), 2.28 - 2.39 (m, 2H), 1.68 - 1.77 (m, 2H), 1.29 - 1.31 (m, 18H), 0.85 (dt, *J*=8.5, 5.8 Hz, 2H), 0.58 - 0.64 (m, 2H).

Example J3, step c




TFA (3 mL, 38.9 mmol) was added to a stirred solution of carbamate J3b (316 mg, 0.470 mmol) in DCE (7 mL) and the reaction was stirred at rt for 1h. The reaction mixture was concentrated under vacuum to yield a TFA salt of pyrrolidine J3c (360 mg) as a yellow solid.

LC-MS retention time 2.711min; m/z 473.24 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave

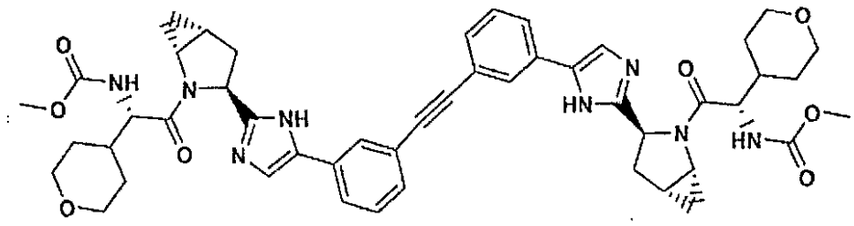
length of 220 nM. The elution conditions employed a flow rate of 4 mL/min , a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where solvent A was 5% MeOH / 95% $H_2O$ / 10 mM ammonium acetate and solvent B was 5% $H_2O$ / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode.

Example J3

HATU (69.6 mg, 0.183 mmol) was added to a stirred solution of a TFA salt of pyrrolidine J3c (56.7 mg, 0.061 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (32.1 mg, 0.183 mmol) in DMF (0.7 mL) and Hunig'sBase (0.11 mL, 0.61 mmol) and the reaction mixture was stirred at rt for 3 h. The reaction was concentrated under a stream of nitrogen, dissolved into MeOH and purified in two injections by preparative HPLC (MeOH/water 10 mM ammonium acetate) to yield Example J3 (31.8 mg) as a light yellow solid.

LC-MS retention time 2.605 min; m/z 787.36 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min , a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where solvent A was 5% MeOH / 95% $H_2O$ / 10 mM ammonium acetate and solvent B was 5% $H_2O$ / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode. $^1$H NMR (400 MHz, MeOD) δ ppm 7.87 (s, 2H), 7.65 - 7.71 (m, 2H), 7.37 - 7.43 (m, 4H), 7.36 (s, 2H), 5.16 (dd, *J*=8.8, 4.8 Hz, 2H), 4.59 (d, *J*=6.5 Hz, 2H), 3.67 (s, 6H), 3.63 - 3.68 (m, 2H), 2.49 - 2.58 (m, 2H), 2.37 - 2.45 (m, 2H), 2.10 - 2.21 (m, 2H), 1.98 - 2.07 (m, 2H), 1.12 (ddd, *J*=8.7, 5.6, 5.5 Hz, 2H), 1.01 (d, *J*=6.8 Hz, 6H), 0.93 (d, *J*=6.8 Hz, 6H), 0.78 (br s, 2H).

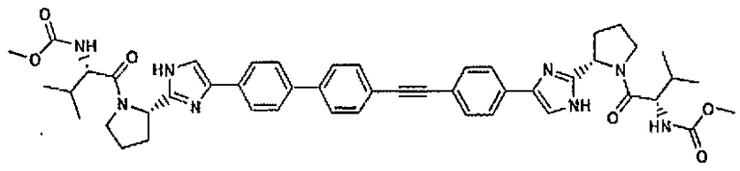
Example J4



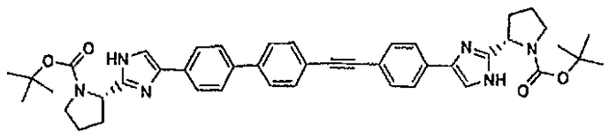
HATU (120 mg, 0.317 mmol) was added to a stirred solution of a TFA salt of pyrrolidine J3c (98 mg, 0.106 mmol) and (S)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (68.8 mg, 0.317 mmol) in DIPEA (0.18 mL, 1.1 mmol) and DMF (1 mL) and the reaction was stirred at rt for 3h. The reaction was concentrated under a stream of nitrogen, dissolved into MeOH and purified in by preparative HPLC (MeOH/water 10 mM ammonium acetate) and then repurified by prep HPLC (MeOH/water 0.1% TFA) to yield a TFA salt of Example J4 (18 mg) as a white solid.

LC-MS retention time 2.463 min; m/z 869.40 (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220 nM. The elution conditions employed a flow rate of 4 mL/min, a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where solvent A was 5% MeOH / 95% $H_2O$ / 10 mM ammonium acetate and solvent B was 5% $H_2O$ / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode. $^1$H NMR (400 MHz, MeOD) δ ppm 7.89 - 7.92 (m, 2H), 7.87 (s, 2H), 7.74 (dt, *J*=7.8, 1.5 Hz, 2H), 7.61 - 7.66 (m, 2H), 7.54 - 7.60 (m, 2H), 5.11 (dd, *J*=9.0, 7.0 Hz, 2H), 4.59 (d, *J*=7.5 Hz, 2H), 3.91 - 3.99 (m, 4H), 3.83 (t, *J*=4.8 Hz, 2H), 3.67 (s, 6H), 3.33 - 3.45 (m, 4H), 2.67 (dd, *J*=13.7, 9.4 Hz, 2H), 2.43 - 2.52 (m, 2H), 2.02 - 2.14 (m, 4H), 1.39 - 1.63 (m, 8H), 1.03 - 1.11 (m, 2H), 0.83 - 0.90 (m, 2H).

Example J5



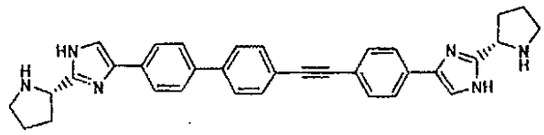
Example J5, Step a



Nitrogen was bubbled through a stirred solution of (S)-tert-butyl 2-(4-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (bromide D-1b) (400 mg, 1.02 mmol), 4-ethynylphenylboronic acid (149 mg, 1.02 mmol) and sodium bicarbonate (214 mg, 2.55 mmol) in DME (8 mL) and water (2 mL) for 15 min. Then $Pd(PPh_3)_4$ (58.9 mg, 0.051 mmol) was added and the nitrogen bubbling was continued for 5 min. before the reaction vessel was sealed and heated at 90 °C overnight. The reaction was cooled, diluted with THF, washed with brine and concentrated to dryness. The residue was purified by Biotage Horizon (60-90% EtOAc/hexanes) to yield carbamate J5a (85 mg) as a yellow solid.

LC-MS retention time 2.911 min; m/z 723.64 (MH-). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min , a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 3 min, a hold time of 1 min, and an analysis time of 4 min where solvent A was 5% MeOH / 95% $H_2O$ / 10 mM ammonium acetate and solvent B was 5% $H_2O$ / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode. $^1H$ NMR (400 MHz, MeOD) δ ppm 7.78 (d, *J*=8.0 Hz, 2H), 7.72 (d, *J*=8.0 Hz, 2H), 7.64 - 7.69 (m, 4H), 7.58 (d, *J*=8.3 Hz, 2H), 7.52 (d, *J*=8.3 Hz, 2H), 7.31 - 7.41 (m, 2H), 4.86 - 5.03 (m, 2H), 3.68 (br s, 2H), 3.46 - 3.57 (m, 2H), 2.37 (br s, 2H), 1.89 - 2.13 (m, 6H), 1.47 (br s, 6H), 1.25 (br s, 12H).

Example J5, Step b



TFA (250 μL, 3.24 mmol) was added to a solution of carbamate J5a in DCE (1 mL) and the reaction was stirred at rt for 1.5 hr. The reaction was concentrated under a stream of nitrogen to provide a TFA salt of pyrrolidine J5b (45 mg). LC-MS retention time 2.928 min; m/z 525.32 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min , a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where solvent A was 5% MeOH / 95% $H_2O$ / 10 mM ammonium acetate and solvent B was 5% $H_2O$ / 95% MeOH / 10 mM ammonium acetate. MS data was determined using a Micromass Platform for LC in electrospray mode.

Example J5

HATU (53 mg, 0.14 mmol) was added to a solution of a TFA salt of J5b (45 mg, 0.046 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (24.2 mg, 0.138 mmol) in DMF (0.7 mL) and TEA (0.038 mL, 0.28 mmol) and the reaction was stirred for 30 min. The reaction was diluted with MeOH, filtered and purified by prep HPLC (MeOH/water with 10 mM ammonium acetate) to yield Example J5 (14.7 mg) as a light yellow solid. LC-MS retention time 2.728 min; m/z 839.57 (MH+). LC data was recorded on a Shimadzu LC-10AS liquid chromatograph equipped with a Phenomenex-Luna 10u C18 3.0x50mm column using a SPD-10AV UV-Vis detector at a detector wave length of 220nM. The elution conditions employed a flow rate of 4 mL/min , a gradient of 100% solvent A / 0% solvent B to 0% solvent A / 100% solvent B, a gradient time of 4 min, a hold time of 1 min, and an analysis time of 5 min where solvent A was 5% MeOH / 95% $H_2O$ / 10 mM ammonium acetate and solvent B was 5% $H_2O$ / 95% MeOH / 10 mM ammonium acetate. MS data was

determined using a Micromass Platform for LC in electrospray mode. $^1$H NMR (400 MHz, MeOD) δ ppm 7.73 - 7.78 (m, 2H), 7.65 - 7.71 (m, 6H), 7.57 - 7.62 (m, 2H), 7.52 (d, *J*=8.5 Hz, 2H), 7.33 - 7.36 (m, 2H), 5.18 (dt, *J*=7.6, 5.2 Hz, 2H), 4.21 - 4.27 (m, 2H), 3.96 - 4.05 (m, 2H), 3.84 - 3.92 (m, 2H), 3.66 (s, 6H), 2.17 - 2.42 (m, 6H), 2.00 - 2.13 (m, 4H), 0.95 (dd, *J*=6.8, 1.3 Hz, 6H), 0.91 (dd, *J*=6.8, 1.0 Hz, 6H).

*Synthesis of common caps*

*Compound analysis conditions:* Purity assessment and low resolution mass analysis were conducted on a Shimadzu LC system coupled with Waters Micromass ZQ MS system. It should be noted that retention times may vary slightly between machines. Additional LC conditions applicable to the current section, unless noted otherwise.

*Cond.-MS-W1*

| | |
|---|---|
| Column | = XTERRA 3.0 X 50 mm S7 |
| Start %B | = 0 |
| Final %B | = 100 |
| Gradient time | = 2 min |
| Stop time | = 3 min |
| Flow Rate | = 5 mL/min |
| Wavelength | = 220 nm |
| Solvent A | = 0.1% TFA in 10% methanol/90%$H_2O$ |
| Solvent B | = 0.1% TFA in 90% methanol/10% $H_2O$ |

*Cond.-MS-W2*

| | |
|---|---|
| Column | = XTERRA 3.0 X 50 mm S7 |
| Start %B | = 0 |
| Final %B | = 100 |
| Gradient time | = 3 min |
| Stop time | = 4 min |

| | |
|---|---|
| Flow Rate | = 4 mL/min |
| Wavelength | = 220 nm |
| Solvent A | = 0.1% TFA in 10% methanol/90%$H_2O$ |
| Solvent B | = 0.1% TFA in 90% methanol/10% $H_2O$ |

*Cond.-MS-W5*

| | |
|---|---|
| Column | = XTERRA 3.0 X 50 mm S7 |
| Start %B | = 0 |
| Final %B | = 30 |
| Gradient time | = 2 min |
| Stop time | = 3 min |
| Flow Rate | = 5 mL/min |
| Wavelength | = 220 nm |
| Solvent A | = 0.1% TFA in 10% methanol/90%$H_2O$ |
| Solvent B | = 0.1% TFA in 90% methanol/10% $H_2O$ |

*Cond.-D1*

| | |
|---|---|
| Column | = XTERRA C18 3.0 X 50 mm S7 |
| Start %B | = 0 |
| Final %B | = 100 |
| Gradient time | = 3 min |
| Stop time | = 4 min |
| Flow Rate | = 4 mL/min |
| Wavelength | = 220 nm |
| Solvent A | = 0.1% TFA in 10% methanol/90%$H_2O$ |
| Solvent B | = 0.1% TFA in 90% methanol/10% $H_2O$ |

*Cond.-D2*

| | |
|---|---|
| Column | = Phenomenex-Luna 4.6 X 50 mm S10 |
| Start %B | = 0 |
| Final %B | = 100 |

| | | |
|---|---|---|
| | Gradient time | = 3 min |
| | Stop time | = 4 min |
| | Flow Rate | = 4 mL/min |
| | Wavelength | = 220 nm |
| 5 | Solvent A | = 0.1% TFA in 10% methanol/90%$H_2O$ |
| | Solvent B | = 0.1% TFA in 90% methanol/10% $H_2O$ |

*Cond.-MD1*

| | | |
|---|---|---|
| | Column | = XTERRA 4.6 X 50 mm S5 |
| 10 | Start %B | = 0 |
| | Final %B | = 100 |
| | Gradient time | = 3 min |
| | Stop time | = 4 min |
| | Flow Rate | = 4 mL/min |
| 15 | Wavelength | = 220 nm |
| | Solvent A | = 0.1% TFA in 10% methanol/90%$H_2O$ |
| | Solvent B | = 0.1% TFA in 90% methanol/10% $H_2O$ |

*Cond.-M3*

| | | |
|---|---|---|
| 20 | Column | = XTERRA C18 3.0 X 50 mm S7 |
| | Start %B | = 0 |
| | Final %B | = 40 |
| | Gradient time | = 2 min |
| | Stop time | = 3 min |
| 25 | Flow Rate | = 5 mL/min |
| | Wavelength | = 220 nm |
| | Solvent A | = 0.1% TFA in 10% methanol/90%$H_2O$ |
| | Solvent B | = 0.1% TFA in 90% methanol/10% $H_2O$ |

30 *Condition OL1*

Column = Phenomenex-Luna 3.0 X 50 mm S10

Start %B = 0
Final %B = 100
Gradient time = 4 min
Stop time = 5 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%$H_2O$
Solvent B = 0.1% TFA in 90% methanol/10% $H_2O$

*Condition OL2*

Column = Phenomenex-Luna 50X 2 mm 3 u
Start %B = 0
Final %B = 100
Gradient time = 4 min
Stop time = 5 min
Flow Rate = 0.8 mL/min
Oven Temp = 40 °C
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% Acetonitrile/90%$H_2O$
Solvent B = 0.1% TFA in 90% Acetonitrile/10% $H_2O$

Condition I

Column = Phenomenex-Luna 3.0 X 50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 2 min
Stop time = 3 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%$H_2O$
Solvent B = 0.1% TFA in 90% methanol/10% $H_2O$

Condition II

Column = Phenomenex-Luna 4.6 X 50 mm S10

Start %B = 0

Final %B = 100

Gradient time = 2 min

Stop time = 3 min

Flow Rate = 5 mL/min

Wavelength = 220 nm

Solvent A = 0.1% TFA in 10% methanol/90%$H_2O$

Solvent B = 0.1% TFA in 90% methanol/10% $H_2O$

Condition III

Column = XTERRA C18 3.0 x 50mm S7

Start %B = 0

Final %B = 100

Gradient time = 3 min

Stop time = 4 min

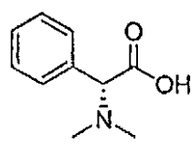
Flow Rate = 4 mL/min

Wavelength = 220 nm

Solvent A = 0.1% TFA in 10% methanol/90%$H_2O$

Solvent B = 0.1% TFA in 90% methanol/10% $H_2O$

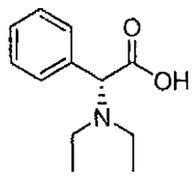
*Cap-1*




A suspension of 10% Pd/C (2.0g) in methanol (10 mL) was added to a mixture of (R)-2-phenylglycine (10g, 66.2 mmol), formaldehyde (33 mL of 37% wt. in water), 1N HCl (30 mL) and methanol (30 mL), and exposed to $H_2$ (60 psi) for 3 hours. The reaction mixture was filtered through diatomaceous earth (Celite®), and the filtrate was concentrated *in vacuo*. The resulting crude material was recrystallized

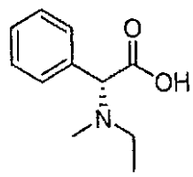
from isopropanol to provide the HCl salt of Cap-1 as a white needle (4.0 g). Optical rotation: -117.1° [c=9.95 mg/mL in $H_2O$; λ=589 nm]. $^1$H NMR (DMSO-$d_6$, δ=2.5 ppm, 500 MHz): δ 7.43-7.34 (m, 5H), 4.14 (s, 1H), 2.43 (s, 6H); LC (Cond. I): RT=0.25; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{14}NO_2$ 180.10; found 180.17; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{14}NO_2$ 180.1025; found 180.1017.

*Cap-2*




$NaBH_3CN$ (6.22g, 94 mmol) was added in portions over a few minutes to a cooled (ice/water) mixture of (R)-2-Phenylglycine (6.02 g, 39.8 mmol) and methanol (100 mL), and stirred for 5 minutes. Acetaldehyde (10 mL) was added dropwise over 10 minutes and stirring was continued at the same cooled temperature for 45 minutes and at ambient temperature for ~6.5 hours. The reaction mixture was cooled back with ice-water bath, treated with water (3 mL) and then quenched with a dropwise addition of concentrated HCl over ~ 45 minutes until the pH of the mixture was ~ 1.5 – 2.0. The cooling bath was removed and the stirring was continued while adding concentrated HCl in order to maintain the pH of the mixture around 1.5-2.0. The reaction mixture was stirred overnight, filtered to remove the white suspension, and the filtrate was concentrated *in vacuo*. The crude material was recrystallized from ethanol to afford the HCl salt of Cap-2 as a shining white solid in two crops (crop-1: 4.16 g; crop-2: 2.19 g). $^1$H NMR (DMSO-$d_6$, $\delta$=2.5 ppm, 400 MHz): 10.44 (1.00, br s, 1H), 7.66 (m, 2H), 7.51 (m, 3H), 5.30 (s, 1H), 3.15 (br m, 2H), 2.98 (br m, 2H), 1.20 (app br s, 6H). Crop-1: $[\alpha]^{25}$ -102.21° (c=0.357, $H_2O$); crop-2: $[\alpha]^{25}$ -99.7° (c=0.357, $H_2O$). LC (Cond. I): RT=0.43 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{18}NO_2$: 208.13; found 208.26.

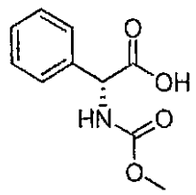
*Cap-3*



Acetaldehyde (5.0 mL, 89.1 mmol) and a suspension of 10% Pd/C (720 mg) in methanol/$H_2O$ (4mL/1 mL) was sequentially added to a cooled (~ 15 °C) mixture of (R)-2-phenylglycine (3.096g, 20.48 mmol), 1N HCl (30 mL) and methanol (40 mL). The cooling bath was removed and the reaction mixture was stirred under a balloon of $H_2$ for 17 hours. An additional acetaldehyde (10 mL, 178.2 mmol) was added and stirring continued under $H_2$ atmosphere for 24 hours [Note: the supply of $H_2$ was replenished as needed throughout the reaction]. The reaction mixture was filtered through diatomaceous earth (Celite®), and the filtrate was concentrated *in vacuo*. The resulting crude material was recrystallized from isopropanol to provide the HCl salt of (R)-2-(ethylamino)-2-phenylacetic acid as a shining white solid (2.846g). $^1$H NMR (DMSO-$d_6$, δ=2.5 ppm, 400 MHz): δ 14.15 (br s, 1H), 9.55 (br s, 2H), 7.55-7.48 (m, 5H), 2.88 (br m, 1H), 2.73 (br m, 1H), 1.20 (app t, *J*=7.2, 3H). LC (Cond. I): RT=0.39 min; >95 % homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{14}NO_2$: 180.10; found 180.18.

A suspension of 10% Pd/C (536 mg) in methanol/$H_2O$ (3 mL/1 mL) was added to a mixture of (R)-2-(ethylamino)-2-phenylacetic acid/HCl (1.492g, 6.918 mmol), formaldehyde (20 mL of 37% wt. in water), 1N HCl (20 mL) and methanol (23 mL). The reaction mixture was stirred under a balloon of $H_2$ for ~72 hours, where the $H_2$ supply was replenished as needed. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated *in vacuo*. The resulting crude material was recrystallized from isopropanol (50 mL) to provide the HCl salt of Cap-3 as a white solid (985 mg). $^1$H NMR (DMSO-$d_6$, δ=2.5 ppm, 400 MHz): δ 10.48 (br s, 1H), 7.59-7.51 (m, 5H), 5.26 (s, 1H), 3.08 (app br s, 2H), 2.65 (br s, 3H), 1.24 (br m, 3H). LC (Cond. I): RT=0.39 min; >95 % homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.12; found 194.18; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.1180; found 194.1181.

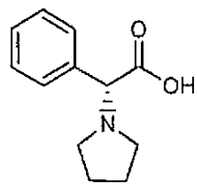
*Cap-4*



$ClCO_2Me$ (3.2 mL, 41.4 mmol) was added dropwise to a cooled (ice/water) THF (410 mL) semi-solution of (R)-*tert*-butyl 2-amino-2-phenylacetate/HCl (9.877 g, 40.52 mmol) and diisopropylethylamine (14.2 mL, 81.52 mmol) over 6 min, and stirred at similar temperature for 5.5 hours. The volatile component was removed *in vacuo*, and the residue was partitioned between water (100 mL) and ethyl acetate (200 mL). The organic layer was washed with 1N HCl (25 mL) and saturated $NaHCO_3$ solution (30 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resultant colorless oil was triturated from hexanes, filtered and washed with hexanes (100 mL) to provide (R)-tert-butyl 2-(methoxycarbonylamino)-2-phenylacetate as a white solid (7.7 g). $^1H$ NMR (DMSO-$d_6$, δ=2.5 ppm, 400 MHz): 7.98 (d, *J*=8.0, 1H), 7.37-7.29 (m, 5H), 5.09 (d, *J*=8, 1H), 3.56 (s, 3H), 1.33 (s, 9H). LC (Cond. I): RT=1.53 min; ~90 % homogeneity index; LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{14}H_{19}NNaO_4$: 288.12; found 288.15.

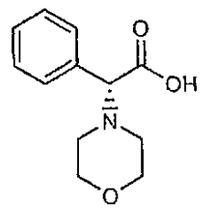
TFA (16 mL) was added dropwise to a cooled (ice/water) $CH_2Cl_2$ (160 mL) solution of the above product over 7 minutes, and the cooling bath was removed and the reaction mixture was stirred for 20 hours. Since the deprotection was still not complete, an additional TFA (1.0 mL) was added and stirring continued for an additional 2 hours. The volatile component was removed *in vacuo*, and the resulting oil residue was treated with diethyl ether (15 mL) and hexanes (12 mL) to provide a precipitate. The precipitate was filtered and washed with diethyl ether/hexanes (~1:3 ratio; 30 mL) and dried *in vacuo* to provide Cap-4 as a fluffy white solid (5.57 g). Optical rotation: -176.9° [c=3.7 mg/mL in $H_2O$; λ=589 nm]. $^1H$ NMR (DMSO-$d_6$, δ=2.5 ppm, 400 MHz): δ 12.84 (br s, 1H), 7.96 (d, *J*=8.3, 1H), 7.41-7.29 (m, 5H), 5.14 (d, *J*=8.3, 1H), 3.55 (s, 3H). LC (Cond. I): RT=1.01 min; >95 % homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{12}NO_4$ 210.08; found 210.17; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{12}NO_4$ 210.0766; found 210.0756.

*Cap-5*



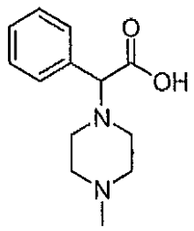
A mixture of (R)- 2-phenylglycine (1.0 g, 6.62 mmol), 1,4-dibromobutane (1.57 g, 7.27 mmol) and $Na_2CO_3$ (2.10 g, 19.8 mmol) in ethanol (40 mL) was heated at 100 °C for 21 hours. The reaction mixture was cooled to ambient temperature and filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in ethanol and acidified with 1N HCl to pH 3-4, and the volatile component was removed *in vacuo*. The resulting crude material was purified by a reverse phase HPLC (water/methanol/TFA) to provide the TFA salt of Cap-5 as a semi-viscous white foam (1.0 g). $^1$H NMR (DMSO-$d_6$, δ=2.5, 500 MHz) δ 10.68 (br s, 1H), 7.51 (m, 5H), 5.23 (s, 1H), 3.34 (app br s, 2H), 3.05 (app br s, 2H), 1.95 (app br s, 4H); RT=0.30 minutes (Cond. I); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_2$: 206.12; found 206.25.

*Cap-6*



The TFA salt of Cap-6 was synthesized from (R)-2-phenylglycine and 1-bromo-2-(2-bromoethoxy)ethane by using the method of preparation of Cap-5. $^1$H NMR (DMSO-$d_6$, δ=2.5, 500 MHz) δ 12.20 (br s, 1H), 7.50 (m, 5H), 4.92 (s, 1H), 3.78 (app br s, 4H), 3.08 (app br s, 2H), 2.81 (app br s, 2H); RT=0.32 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_3$: 222.11; found 222.20; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_3$: 222.1130; found 222.1121.

*Cap-7*



Cap-7a: enantiomer-1
Cap-7b: enantiomer-2

A $CH_2Cl_2$ (200 mL) solution of p-toluenesulfonyl chloride (8.65 g, 45.4 mmol) was added dropwise to a cooled (-5 °C) $CH_2Cl_2$ (200 mL) solution of (S)-benzyl 2-hydroxy-2-phenylacetate (10.0 g, 41.3 mmol), triethylamine (5.75 mL, 41.3 mmol) and 4-dimethylaminopyridine (0.504 g, 4.13 mmol), while maintaining the temperature between -5 °C and 0 °C. The reaction was stirred at 0 °C for 9 hours, and then stored in a freezer (-25 °C) for 14 hours. It was allowed to thaw to ambient temperature and washed with water (200 mL), 1N HCl (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide benzyl 2-phenyl-2-(tosyloxy)acetate as a viscous oil which solidified upon standing (16.5 g). The chiral integrity of the product was not checked and that product was used for the next step without further purification. $^1$H NMR (DMSO-$d_6$, δ=2.5, 500 MHz) δ 7.78 (d, *J*= 8.6, 2H), 7.43-7.29 (m, 10H), 7.20 (m, 2H), 6.12 (s, 1H), 5.16 (d, *J*=12.5, 1H), 5.10 (d, *J*=12.5, 1H), 2.39 (s, 3H). RT=3.00 (Cond. III); >90% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{22}H_{20}NaO_5S$: 419.09; found 419.04.

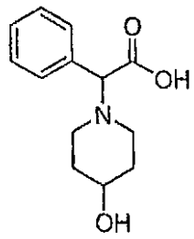
A THF (75 mL) solution of benzyl 2-phenyl-2-(tosyloxy)acetate (6.0 g, 15.1 mmol), 1-methylpiperazine (3.36 mL, 30.3 mmol) and N,N-diisopropylethylamine (13.2 mL, 75.8 mmol) was heated at 65 °C for 7 hours. The reaction was allowed to cool to ambient temperature and the volatile component was removed *in vacuo*. The residue was partitioned between ethylacetate and water, and the organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified by flash chromatography (silica gel, ethyl acetate) to provide benzyl 2-(4-methylpiperazin-1-yl)-2-phenylacetate as an orangish-brown viscous oil (4.56 g). Chiral HPLC analysis (Chiralcel OD-H) indicated that the sample is a mixture of enantiomers in a 38.2 to 58.7 ratio. The separation of the enantiomers were effected as follow: the product was dissolved in 120 mL of

ethanol/heptane (1:1) and injected (5 mL/injection) on chiral HPLC column (Chiracel OJ, 5 cm ID x 50 cm L, 20 μm) eluting with 85:15 Heptane/ethanol at 75 mL/min, and monitored at 220 nm. Enantiomer-1 (1.474 g ) and enantiomer-2 (2.2149 g) were retrieved as viscous oil. $^1$H NMR ($CDCl_3$, δ=7.26, 500 MHz) 7.44-7.40 (m, 2H), 7.33-7.24 (m, 6H), 7.21-7.16 (m, 2H), 5.13 (d, *J*=12.5, 1H), 5.08 (d, *J*=12.5, 1H), 4.02 (s, 1H), 2.65-2.38 (app br s, 8H), 2.25 (s, 3H). RT=2.10 (Cond. III); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{20}H_{25}N_2O_2$: 325.19; found 325.20.

A methanol (10 mL) solution of either enantiomer of benzyl 2-(4-methylpiperazin-1-yl)-2-phenylacetate (1.0 g, 3.1 mmol) was added to a suspension of 10% Pd/C (120 mg) in methanol (5.0 mL). The reaction mixture was exposed to a balloon of hydrogen, under a careful monitoring, for <50 minutes. Immediately after the completion of the reaction, the catalyst was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated *in vacuo* to provide Cap-7, contaminated with phenylacetic acid as a tan foam (867.6 mg; mass is above the theoretical yield). The product was used for the next step without further purification. $^1$H NMR (DMSO-$d_6$, δ=2.5, 500 MHz) δ 7.44-7.37 (m, 2H), 7.37-7.24 (m, 3H), 3.92 (s, 1H), 2.63-2.48 (app. br s, 2H), 2.48-2.32 (m, 6H), 2.19 (s, 3H); RT=0.31 (Cond. II); >90% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235.14; found 235.15; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235.1447; found 235.1440.

The synthesis of Cap-8 and Cap-9 was conducted according to the synthesis of Cap-7 by using appropriate amines for the $SN_2$ displacement step (i.e., 4-hydroxypiperidine for Cap-8 and (S)-3-fluoropyrrolidine for Cap-9) and modified conditions for the separation of the respective stereoisomeric intermedites, as described below.

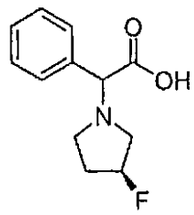
*Cap-8*



8a: enantiomer-1
8b: enantiomer-2

The enantiomeric separation of the intermediate benzyl 2-(4-hydroxypiperidin-1-yl)-2-phenyl acetate was effected by employing the following conditions: the compound (500 mg) was dissolved in ethanol/heptane (5 mL/45 mL). The resulting solution was injected (5 mL/injection) on a chiral HPLC column (Chiracel OJ, 2 cm ID x 25 cm L, 10 μm) eluting with 80:20 heptane/ethanol at 10 mL/min, monitored at 220 nm, to provide 186.3 mg of enantiomer-1 and 209.1 mg of enantiomer-2 as light-yellow viscous oils. These benzyl ester was hydrogenolysed according to the preparation of Cap-7 to provide Cap-8: $^1$H NMR (DMSO-$d_6$, δ=2.5, 500 MHz) 7.40 (d, *J*=7, 2H), 7.28-7.20 (m, 3H), 3.78 (s 1H), 3.46 (m, 1H), 2.93 (m, 1H), 2.62 (m, 1H), 2.20 (m, 2H), 1.70 (m, 2H), 1.42 (m, 2H). RT=0.28 (Cond. II); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{18}NO_3$: 236.13; found 236.07; HRMS: Calcd. for $[M+H]^+$ $C_{13}H_{18}NO_3$: 236.1287; found 236.1283.

*Cap-9*

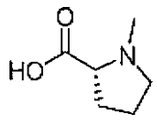


9a: diastereomer-1
9b: diastereomer-2

The diastereomeric separation of the intermediate benzyl 2-((S)-3-fluoropyrrolidin-1-yl)-2-phenylacetate was effected by employing the following conditions: the ester (220 mg) was separated on a chiral HPLC column (Chiracel OJ-H, 0.46 cm ID x 25 cm L, 5 μm) eluting with 95% $CO_2$ / 5% methanol with 0.1% TFA, at 10 bar pressure, 70 mL/min flow rate, and a temperature of 35 °C. The HPLC elute for the respective stereoisomers was concentrated, and the residue was dissolved in $CH_2Cl_2$ (20 mL) and washed with an aqueous medium (10 mL water + 1

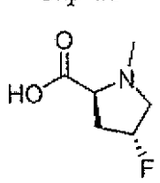
mL saturated $NaHCO_3$ solution). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide 92.5 mg of fraction-1 and 59.6 mg of fraction-2. These benzyl esters were hydrogenolysed according to the preparation of Cap-7 to prepare Caps 9a and 9b. Cap-9a (diastereomer-1; the sample is a TFA salt as a result of purification on a reverse phase HPLC using $H_2O$/methanol/TFA solvent): $^1H$ NMR (DMSO-$d_6$, δ=2.5, 400 MHz) 7.55-7.48 (m, 5H), 5.38 (d of m, *J*=53.7, 1H), 5.09 (br s, 1H), 3.84-2.82 (br m, 4H), 2.31-2.09 (m, 2H). RT=0.42 (Cond. I); >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; found 224.14; Cap-9b (diastereomer-2): $^1H$ NMR (DMSO-$d_6$, δ=2.5, 400 MHz) 7.43-7.21 (m, 5H), 5.19 (d of m, *J*=55.9, 1H), 3.97 (s, 1H), 2.95-2.43 (m, 4H), 2.19-1.78 (m, 2H). RT=0.44 (Cond. I); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; found 224.14.

*Cap-10*



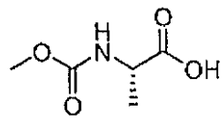
To a solution of D-proline (2.0 g, 17 mmol) and formaldehyde (2.0 mL of 37% wt. in $H_2O$) in methanol (15 mL) was added a suspension of 10% Pd/C (500 mg) in methanol (5 mL). The mixture was stirred under a balloon of hydrogen for 23 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and concentrated *in vacuo* to provide Cap-10 as an off-white solid (2.15 g). $^1H$ NMR (DMSO-$d_6$, δ=2.5, 500 MHz) 3.42 (m, 1H), 3.37 (dd, *J*=9.4, 6.1, 1H), 2.85-2.78 (m, 1H), 2.66 (s, 3H), 2.21-2.13 (m, 1H), 1.93-1.84 (m, 2H), 1.75-1.66 (m, 1H). RT=0.28 (Cond. II); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{12}NO_2$: 130.09; found 129.96.

*Cap-11*



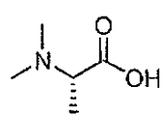
A mixture of (2S,4R)-4-fluoropyrrolidine-2-carboxylic acid (0.50 g, 3.8 mmol), formaldehyde (0.5 mL of 37% wt. in $H_2O$), 12 N HCl (0.25 mL) and 10% Pd/C (50 mg) in methanol (20 mL) was stirred under a balloon of hydrogen for 19 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated *in vacuo*. The residue was recrystallized from isopropanol to provide the HCl salt of Cap-11 as a white solid (337.7 mg). $^1$H NMR (DMSO-$d_6$, δ=2.5, 500 MHz) 5.39 (d m, *J*=53.7, 1H), 4.30 (m, 1H), 3.90 (ddd, *J*=31.5, 13.5, 4.5, 1H), 3.33 (dd, *J*=25.6, 13.4, 1H), 2.85 (s, 3H), 2.60-2.51 (m, 1H), 2.39-2.26 (m, 1H). RT=0.28 (Cond. II); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{11}FNO_2$: 148.08; found 148.06.

*Cap-12 (same as cap 52)*



L-Alanine (2.0 g, 22.5 mmol) was dissolved in 10% aqueous sodium carbonate solution (50 mL), and a THF (50 mL) solution of methyl chloroformate (4.0 mL) was added to it. The reaction mixture was stirred under ambient conditions for 4.5 hours and concentrated *in vacuo*. The resulting white solid was dissolved in water and acidified with 1N HCl to a pH ~ 2-3. The resulting solutions was extracted with ethyl acetate (3 x 100 mL), and the combined organic phase was dried ($Na_2SO_4$), filtered, and concentrated *in vacuo* to provide a colorless oil (2.58 g). 500 mg of this material was purified by a reverse phase HPLC ($H_2O$/methanol/TFA) to provide 150 mg of Cap-12 as a colorless oil . $^1$H NMR (DMSO-$d_6$, δ=2.5, 500 MHz) 7.44 (d, *J*=7.3, 0.8H), 7.10 (br s, 0.2H), 3.97 (m, 1H), 3.53 (s, 3H), 1.25 (d, *J*=7.3, 3H).

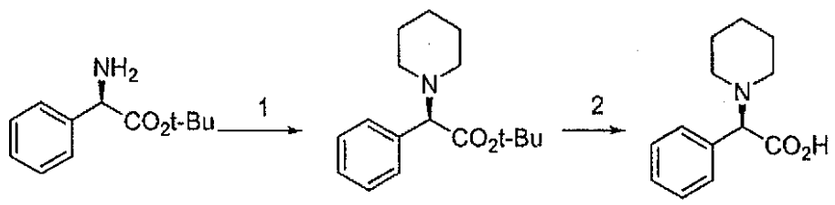
*Cap-13*



A mixture of L-alanine (2.5 g, 28 mmol), formaldehyde (8.4 g, 37 wt. %), 1N HCl (30 mL) and 10% Pd/C (500 mg) in methanol (30 mL) was stirred under a

hydrogen atmosphere (50 psi) for 5 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated *in vacuo* to provide the HCl salt of Cap-13 as an oil which solidified upon standing under vacuum (4.4 g; the mass is above theoretical yield). The product was used without further purification. $^1$H NMR (DMSO-$d_6$, δ=2.5, 500 MHz) δ 12.1 (br s, 1H), 4.06 (q, *J*=7.4, 1H), 2.76 (s, 6H), 1.46 (d, *J*=7.3, 3H).

*Cap-14*



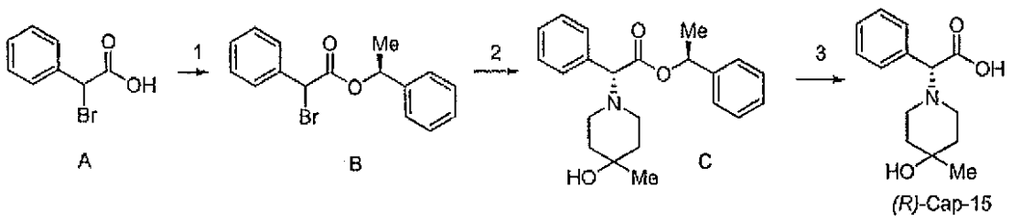

Cap-14

*Step 1:* A mixture of (R)-(-)-D-phenylglycine tert-butyl ester (3.00 g, 12.3 mmol), $NaBH_3CN$ (0.773 g, 12.3 mmol), KOH (0.690 g, 12.3 mmol) and acetic acid (0.352 mL, 6.15 mmol) were stirred in methanol at 0 °C. To this mixture was added glutaric dialdehyde (2.23 mL, 12.3 mmol) dropwise over 5 minutes. The reaction mixture was stirred as it was allowed to warm to ambient temperature and stirring was continued at the same temperature for 16 hours. The solvent was subsequently removed and the residue was partitioned with 10% aqueous NaOH and ethyl acetate. The organic phase was separated, dried ($MgSO_4$), filtered and concentrated to dryness to provide a clear oil. This material was purified by reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; $CH_3CN$-$H_2O$-0.1% TFA) to give the intermediate ester (2.70 g, 56%) as a clear oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.53-7.44 (m, 3H), 7.40-7.37 (m, 2H), 3.87 (d, *J*=10.9 Hz, 1H), 3.59 (d, *J*=10.9 Hz, 1H), 2.99 (t, *J*=11.2 Hz, 1H), 2.59 (t, *J*=11.4 Hz, 1H), 2.07-2.02 (m, 2H), 1.82 (d, *J*=1.82 Hz, 3H), 1.40 (s, 9H). LC/MS: Anal. Calcd. for $C_{17}H_{25}NO_2$: 275; found: 276 $(M+H)^+$.

*Step 2:* To a stirred solution of the intermediate ester (1.12g, 2.88mmol) in dichloromethane (10 mL) was added TFA (3 mL). The reaction mixture was stirred at ambient temperature for 4 hours and then it was concentrated to dryness to give a light yellow oil. The oil was purified using reverse-phase preparative HPLC

(Primesphere C-18, 30 x 100mm; $CH_3CN$-$H_2O$-0.1% TFA). The appropriate fractions were combined and concentrated to dryness *in vacuo*. The residue was then dissolved in a minimum amount of methanol and applied to applied to MCX LP extraction cartridges (2 x 6 g). The cartridges were rinsed with methanol (40 mL) and then the desired compound was eluted using 2M ammonia in methanol (50 mL). Product-containing fractions were combined and concentrated and the residue was taken up in water. Lyophilization of this solution provided the title compound (0.492 g, 78%) as a light yellow solid. $^1$H NMR (DMSO-$d_6$) δ 7.50 (s, 5H), 5.13 (s, 1H), 3.09 (br s, 2H), 2.92-2.89 (m, 2H), 1.74 (m, 4H), 1.48 (br s, 2H). LC/MS: Anal. Calcd. for $C_{13}H_{17}NO_2$: 219; found: 220 $(M+H)^+$.

*Cap-15*



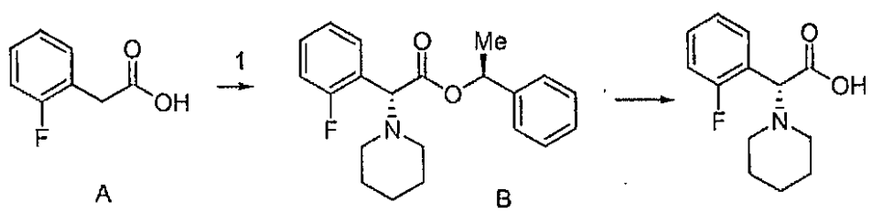

*Step 1*: (S)-1-Phenylethyl 2-bromo-2-phenylacetate: To a mixture of α-bromophenylacetic acid (10.75 g, 0.050 mol), (S)-(-)-1-phenylethanol (7.94 g, 0.065 mol) and DMAP (0.61 g, 5.0 mmol) in dry dichloromethane (100 mL) was added solid EDCI (12.46 g, 0.065 mol) all at once. The resulting solution was stirred at room temperature under Ar for 18 hours and then it was diluted with ethyl acetate, washed ($H_2O$ x 2, brine), dried ($Na_2SO_4$), filtered, and concentrated to give a pale yellow oil. Flash chromatography ($SiO_2$/ hexane-ethyl acetate, 4:1) of this oil provided the title compound (11.64 g, 73%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.53-7.17 (m, 10H), 5.95 (q, *J*=6.6 Hz, 0.5H), 5.94 (q, *J*=6.6 Hz, 0.5H), 5.41 (s, 0.5H), 5.39 (s, 0.5H), 1.58 (d, *J*=6.6 Hz, 1.5H), 1.51 (d, *J*=6.6 Hz, 1.5H).

*Step 2*: (S)-1-Phenylethyl (R)-2-(4-hydroxy-4-methylpiperidin-1-yl)- 2-phenylacetate: To a solution of (S)-1-phenylethyl 2-bromo-2-phenylacetate (0.464 g, 1.45 mmol) in THF (8 mL) was added triethylamine (0.61 mL, 4.35 mmol), followed by tetrabutylammonium iodide (0.215 g, 0.58 mmol). The reaction mixture was stirred at room temperature for 5 minutes and then a solution of 4-methyl-4-

hydroxypiperidine (0.251 g, 2.18 mmol) in THF (2 mL) was added. The mixture was stirred for 1 hour at room temperature and then it was heated at 55-60 °C (oil bath temperature) for 4 hours. The cooled reaction mixture was then diluted with ethyl acetate (30 mL), washed ($H_2O$ x2, brine), dried ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel chromatography (0-60% ethyl acetate-hexane) to provide first the (S,R)-isomer of the title compound (0.306 g, 60%) as a white solid and then the corresponding (S,S)-isomer (0.120 g, 23%), also as a white solid. (S,R)-isomer: $^1$H NMR ($CD_3OD$) δ 7.51-7.45 (m, 2H), 7.41-7.25 (m, 8H), 5.85 (q, *J*=6.6 Hz, 1H), 4.05 (s, 1H), 2.56-2.45 (m, 2H), 2.41-2.29 (m, 2H), 1.71-1.49 (m, 4H), 1.38 (d, *J*=6.6 Hz, 3H), 1.18 (s, 3H). LCMS: Anal. Calcd. for $C_{22}H_{27}NO_3$: 353; found: 354 $(M+H)^+$. (S,S)-isomer: $^1$H NMR ($CD_3OD$) δ 7.41-7.30 (m, 5H), 7.20-7.14 (m, 3H), 7.06-7.00 (m, 2H), 5.85 (q, *J*=6.6 Hz, 1H), 4.06 (s, 1H), 2.70-2.60 (m, 1H), 2.51 (dt, *J*=6.6, 3.3 Hz, 1H), 2.44-2.31 (m, 2H), 1.75-1.65 (m, 1H), 1.65-1.54 (m, 3H), 1.50 (d, *J*=6.8 Hz, 3H), 1.20 (s, 3H). LCMS: Anal. Calcd. for $C_{22}H_{27}NO_3$: 353; found: 354 $(M+H)^+$.

*Step 3*: (R)-2-(4-Hydroxy-4-methylpiperidin-1-yl)-2-phenylacetic acid: To a solution of (S)-1-phenylethyl (R)-2-(4-hydroxy-4-methylpiperidin-1-yl)-2-phenylacetate (0.185 g, 0.52 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (1 mL) and the mixture was stirred at room temperature for 2 hours. The volatiles were subsequently removed *in vacuo* and the residue was purified by reverse-phase preparative HPLC (Primesphere C-18, 20 x 100mm; $CH_3CN$-$H_2O$-0.1% TFA) to give the title compound (as TFA salt) as a pale bluish solid (0,128 g, 98%). LCMS: Anal. Calcd. for $C_{14}H_{19}NO_3$: 249; found: 250 $(M+H)^+$.

*Cap-16*




*(R)*-Cap-16

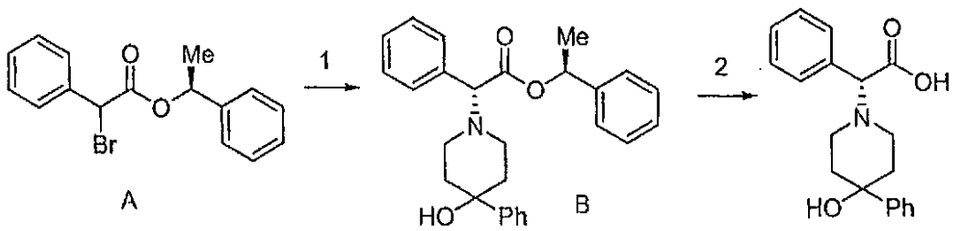
*Step 1:* (S)-1-Phenylethyl 2-(2-fluorophenyl)acetate: A mixture of 2-fluorophenylacetic acid (5.45 g, 35.4 mmol), (S)-1-phenylethanol (5.62 g, 46.0 mmol), EDCI (8.82 g, 46.0 mmol) and DMAP (0.561 g, 4.60 mmol) in $CH_2Cl_2$ (100 mL) was stirred at room temperature for 12 hours. The solvent was then concentrated and the residue partitioned with $H_2O$-ethyl acetate. The phases were separated and the aqueous layer back-extracted with ethyl acetate (2x). The combined organic phases were washed ($H_2O$, brine), dried ($Na_2SO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Biotage/ 0-20% ethyl acetate-hexane) to provide the title compound as a colorless oil (8.38 g, 92%). $^1$H NMR (400 MHz, $CD_3OD$) δ 7.32-7.23 (m, 7H), 7.10-7.04 (m, 2), 5.85 (q, *J*=6.5 Hz, 1H), 3.71 (s, 2H), 1.48 (d, *J*=6.5 Hz, 3H).

*Step 2*: (R)-((S)-1-Phenylethyl) 2-(2-fluorophenyl)-2-(piperidin-1-yl)acetate: To a solution of (S)-1-phenylethyl 2-(2-fluorophenyl)acetate (5.00 g, 19.4 mmol) in THF (1200 mL) at 0 °C was added DBU (6.19 g, 40.7 mmol) and the solution was allowed to warm to room temperature while stirring for 30 minutes. The solution was then cooled to -78 °C and a solution of $CBr_4$ (13.5 g, 40.7 mmol) in THF (100 mL) was added and the mixture was allowed to warm to -10 °C and stirred at this temperature for 2 hours. The reaction mixture was quenched with saturated aq. $NH_4Cl$ and the layers were separated. The aqueous layer was back-extracted with ethyl acetate (2x) and the combined organic phases were washed ($H_2O$, brine), dried ($Na_2SO_4$), filtered, and concentrated *in vacuo*. To the residue was added piperidine (5.73 mL, 58.1 mmol) and the solution was stirred at room temperature for 24 hours. The volatiles were then concentrated *in vacuo* and the residue was purified by silica gel chromatography (Biotage/ 0-30% diethyl ether-hexane) to provide a pure mixture of diastereomers (2:1 ratio by $^1$H NMR) as a yellow oil (2.07 g, 31%), along with unreacted starting material (2.53 g, 51%). Further chromatography of the diastereomeric mixture (Biotage/ 0-10% diethyl ether-toluene) provided the title compound as a colorless oil (0.737 g, 11%). $^1$H NMR (400 MHz, $CD_3OD$) δ 7.52 (ddd, *J*=9.4, 7.6, 1.8 Hz, 1H), 7.33 – 7.40 (m, 1), 7.23 – 7.23 (m, 4H), 7.02 – 7.23 (m, 4H), 5.86 (q, *J*=6.6 Hz, 1H), 4.45 (s, 1H), 2.39 – 2.45 (m, 4H), 1.52 – 1.58 (m, 4H),

1.40 – 1.42 (m, 1H), 1.38 (d, *J*=6.6 Hz, 3H). LCMS: Anal. Calcd. for $C_{21}H_{24}FNO_2$: 341; found: 342 $(M+H)^+$.

*Step 3:* (R)-2-(2-fluorophenyl)-2-(piperidin-1-yl)acetic acid: A mixture of (R)-((S)-1-phenylethyl) 2-(2-fluorophenyl)-2-(piperidin-1-yl)acetate (0.737 g, 2.16 mmol) and 20% $Pd(OH)_2/C$ (0.070 g) in ethanol (30 mL) was hydrogenated at room temperature and atmospheric pressure ($H_2$ balloon) for 2 hours. The solution was then purged with Ar, filtered through diatomaceous earth (Celite®), and concentrated *in vacuo*. This provided the title compound as a colorless solid (0.503 g, 98%). $^1H$ NMR (400 MHz, $CD_3OD$) δ 7.65 (ddd, *J*=9.1, 7.6, 1.5 Hz, 1H), 7.47-7.53 (m, 1H), 7.21-7.30 (m, 2H), 3.07-3.13 (m, 4H), 1.84 (br s, 4H), 1.62 (br s, 2H). LCMS: Anal. Calcd. for $C_{13}H_{16}FNO_2$: 237; found: 238 $(M+H)^+$.

*Cap-17*

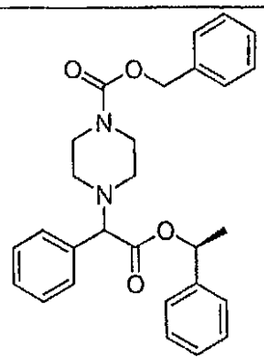


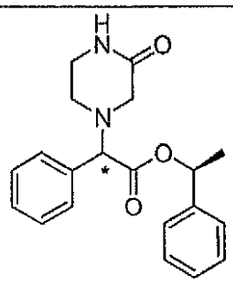
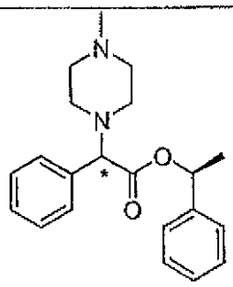

A B *(R)*-Cap-17

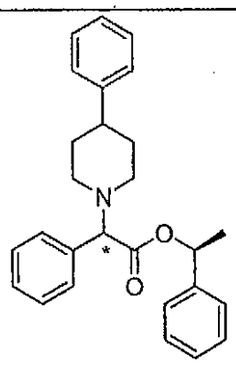
*Step 1*: (S)-1-Phenylethyl (R)-2-(4-hydroxy-4-phenylpiperidin-1-yl)- 2-phenylacetate: To a solution of (S)-1-phenylethyl 2-bromo-2-phenylacetate (1.50 g, 4.70 mmol) in THF (25 mL) was added triethylamine (1.31 mL, 9.42 mmol), followed by tetrabutylammonium iodide (0.347 g, 0.94 mmol). The reaction mixture was stirred at room temperature for 5 minutes and then a solution of 4-phenyl-4-hydroxypiperidine (1.00 g, 5.64 mmol) in THF (5 mL) was added. The mixture was stirred for 16 hours and then it was diluted with ethyl acetate (100 mL), washed ($H_2O$ x2, brine), dried ($MgSO_4$), filtered and concentrated. The residue was purified on a silica gel column (0-60% ethyl acetate-hexane) to provide an approximately 2:1 mixture of diastereomers, as judged by $^1H$ NMR. Separation of these isomers was performed using supercritical fluid chromatography (Chiralcel OJ-H, 30 x 250mm; 20% ethanol in $CO_2$ at 35 °C), to give first the (R)-isomer of the title compound (0.534 g, 27%) as a yellow oil and then the corresponding (S)-isomer (0.271 g, 14%),

also as a yellow oil. (S,R)-isomer: $^1$H NMR (400 MHz, $CD_3OD$) δ 7.55-7.47 (m, 4H), 7.44-7.25 (m, 10H), 7.25-7.17 (m, 1H), 5.88 (q, *J*=6.6 Hz, 1H), 4.12 (s, 1H), 2.82-2.72 (m, 1H), 2.64 (dt, *J*=11.1, 2.5 Hz, 1H), 2.58-2.52 (m, 1H), 2.40 (dt, *J*=11.1, 2.5 Hz, 1H), 2.20 (dt, *J*=12.1, 4.6 Hz, 1H), 2.10 (dt, *J*=12.1, 4.6 Hz, 1H), 1.72-1.57 (m, 2H), 1.53 (d, *J*=6.5 Hz, 3H). LCMS: Anal. Calcd. for $C_{27}H_{29}NO_3$: 415; found: 416 $(M+H)^+$; (S,S)-isomer: $H^1$NMR (400 MHz, $CD_3OD$) δ 7.55-7.48 (m, 2H), 7.45-7.39 (m, 2H), 7.38-7.30 (m, 5H), 7.25-7.13 (m, 4H), 7.08-7.00 (m, 2H), 5.88 (q, *J*=6.6 Hz, 1H), 4.12 (s, 1H), 2.95-2.85 (m, 1H), 2.68 (dt, *J*=11.1, 2.5 Hz, 1H), 2.57-2.52 (m, 1H), 2.42 (dt, *J*=11.1, 2.5 Hz, 1H), 2.25 (dt, *J*=12.1, 4.6 Hz, 1H), 2.12 (dt, *J*=12.1, 4.6 Hz, 1H), 1.73 (dd, *J*=13.6, 3.0 Hz, 1H), 1.64 (dd, *J*=13.6, 3.0 Hz, 1H), 1.40 (d, *J*=6.6 Hz, 3H). LCMS: Anal. Calcd. for $C_{27}H_{29}NO_3$: 415; found: 416 $(M+H)^+$.

The following esters were prepared in similar fashion:

| | | |
|---|---|---|
| *Intermediate-17a* |  | Diastereomer 1: $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.36 (d, *J*=6.41 Hz, 3H) 2.23-2.51 (m, 4H) 3.35 (s, 4H) 4.25 (s, 1H) 5.05 (s, 2H) 5.82 (d, *J*=6.71 Hz, 1H) 7.15-7.52 (m, 15H). LCMS: Anal. Calcd. for: $C_{28}H_{30}N_2O_4$ 458.22; Found: 459.44 $(M+H)^+$.<br><br>Diastereomer 2: $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.45 (d, *J*=6.71 Hz, 3H) 2.27-2.44 (m, 4H) 3.39 (s, 4H) 4.23 (s, 1H) |

| | | |
|---|---|---|
| | | 5.06 (s, 2H) 5.83 (d, *J*=6.71 Hz, 1H) 7.12 (dd, *J*=6.41, 3.05 Hz, 2H) 7.19-7.27 (m, 3H) 7.27-7.44 (m, 10H). LCMS: Anal. Calcd. for: $C_{28}H_{30}N_2O_4$ 458.22; Found: 459.44 $(M+H)^+$. |
| *Intermediate -17b* |  | Diasteromer 1: RT=11.76 minutes (Cond'n II); LCMS: Anal. Calcd. for: $C_{20}H_{22}N_2O_3$ 338.16 Found: 339.39 $(M+H)^+$; Diastereomer 2: RT=10.05 minutes (Cond'n II); LCMS: Anal. Calcd. for: $C_{20}H_{22}N_2O_3$ 338.16; Found: 339.39 $(M+H)^+$. |
| *Intermediate -17c* |  | Diastereomer 1: $T_R$=4.55 minutes (Cond'n I); LCMS: Anal. Calcd. for: $C_{21}H_{26}N_2O_2$ 338.20 Found: 339.45 $(M+H)^+$; Diastereomer 2: $T_R$=6.00 minutes (Cond'n I); LCMS: Anal. Calcd. for: $C_{21}H_{26}N_2O_2$ 338.20 Found: 339.45 $(M+H)^+$. |

| | | |
|---|---|---|
| *Intermediate -17d* |  | Diastereomer 1: RT=7.19 minutes (Cond'n I); LCMS: Anal. Calcd. for: $C_{27}H_{29}NO_2$ 399.22 Found: 400.48 $(M+H)^+$; Diastereomer 2: RT=9.76 minutes (Cond'n I); LCMS: Anal. Calcd. for: $C_{27}H_{29}NO_2$ 399.22 Found: 400.48 $(M+H)^+$. |

Chiral SFC Conditions for determining retention time

Condition I

Column: Chiralpak AD-H Column, 4.62x50 mm, 5μm

Solvents: 90% CO2-10% methanol with 0.1%DEA

Temp: 35 °C

Pressure: 150 bar

Flow rate: 2.0 mL/min.

UV monitored @ 220 nm

Injection: 1.0 mg/3mL methanol

Condition II

Column: Chiralcel OD-H Column, 4.62x50 mm, 5μm

Solvents: 90% CO2-10% methanol with 0.1%DEA

Temp: 35 °C

Pressure: 150 bar

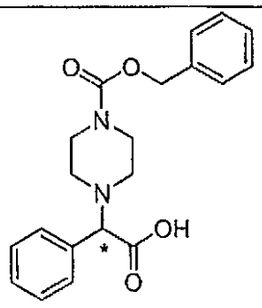
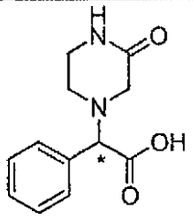
Flow rate: 2.0 mL/min.

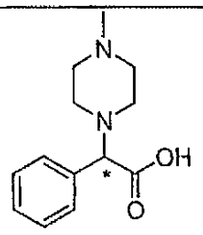
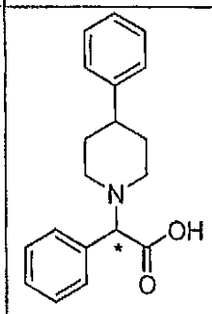
UV monitored @ 220 nm

Injection: 1.0 mg/mL methanol

Cap 17, Step 2; (R)-2-(4-Hydroxy-4-phenylpiperidin-1-yl)-2-phenylacetic acid: To a solution of (S)-1-phenylethyl (R)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-2-phenylacetate (0.350 g, 0.84 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1 mL) and the mixture was stirred at room temperature for 2 hours. The volatiles were subsequently removed *in vacuo* and the residue was purified by reverse-phase preparative HPLC (Primesphere C-18, 20 x 100mm; $CH_3CN$-$H_2O$-0.1% TFA) to give the title compound (as TFA salt) as a white solid (0.230 g, 88%). LCMS: Anal. Calcd. for $C_{19}H_{21}NO_3$: 311.15; found: 312 $(M+H)^+$.

The following carboxylic acids were prepared in optically pure form in a similar fashion:

| | | |
|---|---|---|
| *Cap-17a* |  | RT=2.21 (Cond'n II); $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 2.20-2.35 (m, 2H) 2.34-2.47 (m, 2H) 3.37 (s, 4H) 3.71 (s, 1H) 5.06 (s, 2H) 7.06-7.53 (m, 10H). LCMS: Anal. Calcd. for: $C_{20}H_{22}N_2O_4$ 354.16; Found: 355.38 $(M+H)^+$. |
| *Cap-17b* |  | RT=0.27 (Cond'n III); LCMS: Anal. Calcd. for: $C_{12}H_{14}N_2O_3$ 234.10; Found: 235.22 $(M+H)^+$. |

| | | |
|---|---|---|
| *Cap-17c* |  | RT=0.48 (Cond'n II); LCMS: Anal. Calcd. for: $C_{13}H_{18}N_2O_2$ 234.14; Found: 235.31 $(M+H)^+$. |
| *Cap-17d* |  | RT=2.21 (Cond'n I); LCMS: Anal. Calcd. for: $C_{19}H_{21}NO_2$ 295.16; Found: 296.33 $(M+H)^+$. |

LCMS Conditions for determining retention time

Condition I

Column: Phenomenex-Luna 4.6 X 50 mm S10

Start % B=0

Fianl % B=100

Gradient Time=4 min

Flow Rate=4 mL/min

Wavelength=220

Solvent A=10% methanol – 90% $H_2O$ – 0.1% TFA

Solvent B=90% methanol – 10% $H_2O$ – 0.1% TFA

Condition II

Column: Waters-Sunfire 4.6 X 50 mm S5

Start % B=0

Fianl % B=100

Gradient Time=2 min

Flow Rate=4 mL/min

Wavelength=220

Solvent A=10% methanol – 90% $H_2O$ – 0.1% TFA

Solvent B=90% methanol – 10% $H_2O$ – 0.1% TFA

Condition III

Column: Phenomenex 10µ 3.0 X 50 mm

Start % B=0

Fianl % B=100

Gradient Time=2 min

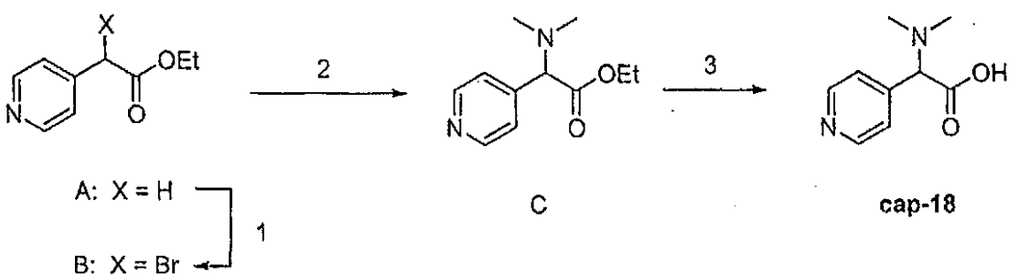
Flow Rate=4 mL/min

Wavelength=220

Solvent A=10% methanol – 90% $H_2O$ – 0.1% TFA

Solvent B=90% methanol – 10% $H_2O$ – 0.1% TFA

*Cap-18*



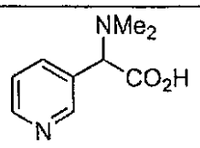
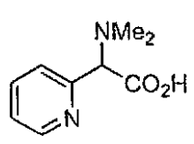

*Step 1;* (R,S)-Ethyl 2-(4-pyridyl)-2-bromoacetate: To a solution of ethyl 4-pyridylacetate (1.00 g, 6.05 mmol) in dry THF (150 mL) at 0 °C under argon was added DBU (0.99 mL, 6.66 mmol). The reaction mixture was allowed to warm to room temperature over 30 minutes and then it was cooled to -78 °C. To this mixture was added $CBr_4$ (2.21 g, 6.66 mmol) and stirring was continued at -78 °C for 2 hours. The reaction mixture was then quenched with sat. aq. $NH_4Cl$ and the phases were separated. The organic phase was washed (brine), dried ($Na_2SO_4$), filtered, and concentrated *in vacuo*. The resulting yellow oil was immediately purified by flash chromatography ($SiO_2$/ hexane-ethyl acetate, 1:1) to provide the title compound (1.40 g, 95%) as a somewhat unstable yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.62 (dd, *J*=4.6, 1.8 Hz, 2H), 7.45 (dd, *J*=4.6, 1.8 Hz, 2H), 5.24 (s, 1H), 4.21-4.29 (m, 2H),

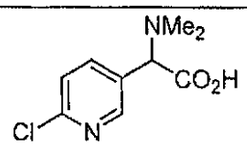
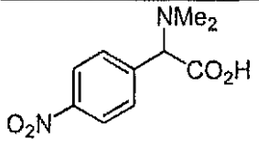
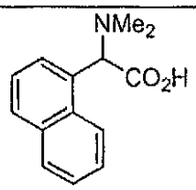
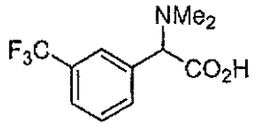
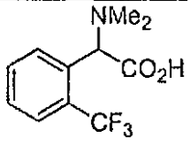
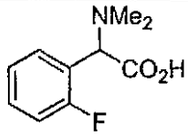
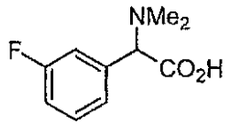
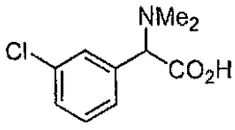
1.28 (t, $J$=7.1 Hz, 3H). LCMS: Anal. Calcd. for $C_9H_{10}BrNO_2$: 242, 244; found: 243, 245 $(M+H)^+$.

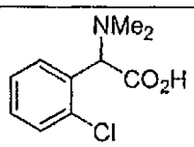
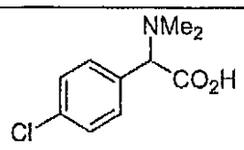
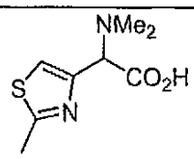
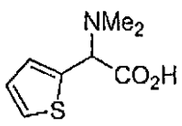
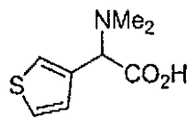
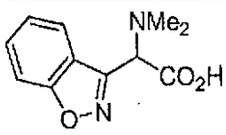
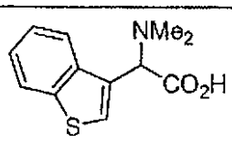
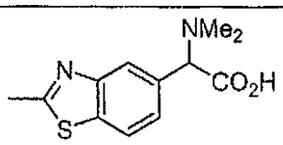
*Step 2*; (R,S)-Ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate: To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-bromoacetate (1.40 g, 8.48 mmol) in DMF (10 mL) at room temperature was added dimethylamine (2M in THF, 8.5 mL, 17.0 mmol). After completion of the reaction (as judged by thin layer chromatography) the volatiles were removed *in vacuo* and the residue was purified by flash chromatography (Biotage, 40+M $SiO_2$ column; 50%-100% ethyl acetate-hexane) to provide the title compound (0.539 g, 31%) as a light yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, $J$=6.0 Hz, 2H), 7.36 (d, $J$=6.0 Hz, 2H), 4.17 (m, 2H), 3.92 (s, 1H), 2.27 (s, 6H), 1.22 (t, $J$=7.0 Hz). LCMS: Anal. Calcd. for $C_{11}H_{16}N_2O_2$: 208; found: 209 $(M+H)^+$.

*Step 3;* (R,S)-2-(4-Pyridyl)-2-(N,N-dimethylamino)acetic acid: To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate (0.200 g, 0.960 mmol) in a mixture of THF-methanol-$H_2O$ (1:1:1, 6 mL) was added powdered LiOH (0.120 g, 4.99 mmol) at room temperature. The solution was stirred for 3 hours and then it was acidified to pH 6 using 1N HCl. The aqueous phase was washed with ethyl acetate and then it was lyophilized to give the dihydrochloride of the title compound as a yellow solid (containing LiCl). The product was used as such in subsequent steps. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.49 (d, $J$=5.7 Hz, 2H), 7.34 (d, $J$=5.7 Hz, 2H), 3.56 (s, 1H), 2.21 (s, 6H).

The following examples were prepared in similar fashion using the method described above;

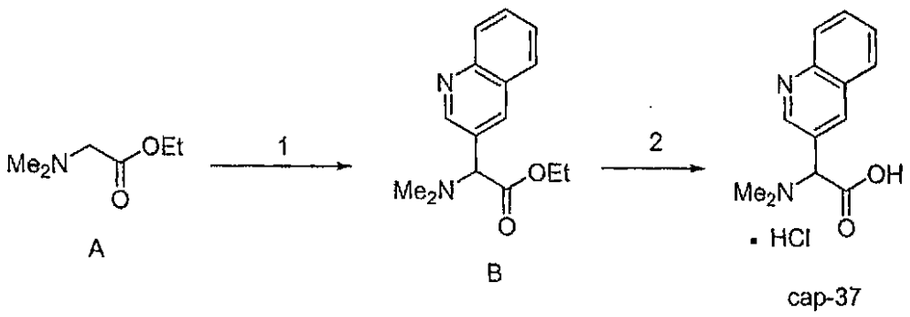
| | | |
|---|---|---|
| *Cap-19* |  | LCMS: Anal. Calcd. for $C_9H_{12}N_2O_2$: 180; found: 181 $(M+H)^+$. |
| *Cap-20* |  | LCMS: no ionization. $^1$H NMR (400 MHz, $CD_3OD$) δ 8.55 (d, $J$=4.3 Hz, 1H), 7.84 (app t, $J$=5.3 Hz, 1H), 7.61 (d, $J$=7.8 Hz, 1H), 7.37 (app t, $J$=5.3 Hz, |

| | | |
|---|---|---|
| | | 1H), 4.35 (s, 1H), 2.60 (s, 6H). |
| *Cap-21* |  | LCMS: Anal. Calcd. for $C_9H_{11}ClN_2O_2$: 214, 216; found: 215, 217 $(M+H)^+$. |
| *Cap-22* |  | LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$. |
| *Cap-23* |  | LCMS: Anal. Calcd. for $C_{14}H_{15}NO_2$: 229; found: 230 $(M+H)^+$. |
| *Cap-24* |  | LCMS: Anal. Calcd. for $C_{11}H_{12}F_3NO_2$: 247; found: 248 $(M+H)^+$. |
| *Cap-25* |  | LCMS: Anal. Calcd. for $C_{11}H_{12}F_3NO_2$: 247; found: 248 $(M+H)^+$. |
| *Cap-26* |  | LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 197; found: 198 $(M+H)^+$. |
| *Cap-27* |  | LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 247; found: 248 $(M+H)^+$. |
| *Cap-28* |  | LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213; found: 214 $(M+H)^+$. |

| | | |
|---|---|---|
| *Cap-29* |  | LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213; found: 214 $(M+H)^+$. |
| *Cap-30* |  | LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213; found: 214 $(M+H)^+$. |
| *Cap-31* |  | LCMS: Anal. Calcd. for $C_8H_{12}N_2O_2S$: 200; found: 201 $(M+H)^+$. |
| *Cap-32* |  | LCMS: Anal. Calcd. for $C_8H_{11}NO_2S$: 185; found: 186 $(M+H)^+$. |
| *Cap-33* |  | LCMS: Anal. Calcd. for $C_8H_{11}NO_2S$: 185; found: 186 $(M+H)^+$. |
| *Cap-34* |  | LCMS: Anal. Calcd. for $C_{11}H_{12}N_2O_3$: 220; found: 221 $(M+H)^+$. |
| *Cap-35* |  | LCMS: Anal. Calcd. for $C_{12}H_{13}NO_2S$: 235; found: 236 $(M+H)^+$. |
| *Cap-36* |  | LCMS: Anal. Calcd. for $C_{12}H_{14}N_2O_2S$: 250; found: 251 $(M+H)^+$. |

5

*Cap-37*

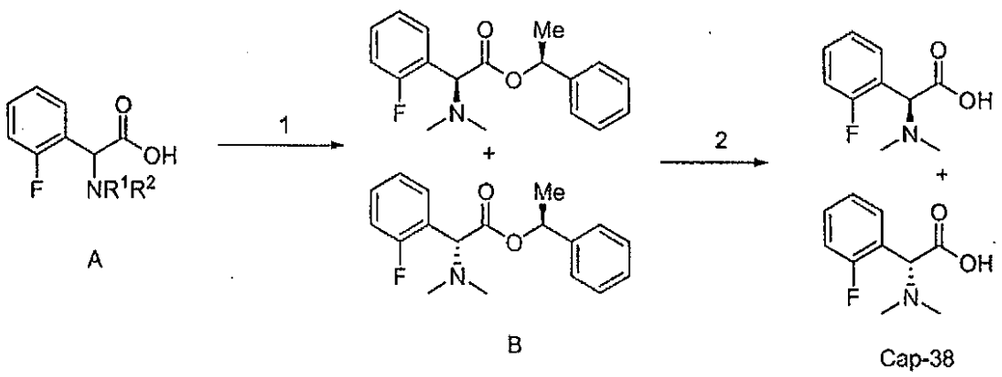



A B cap-37

*Step 1*; (R,S)-Ethyl 2-(quinolin-3-yl)-2-(N,N-dimethylamino)-acetate: A mixture of ethyl N,N-dimethylaminoacetate (0.462 g, 3.54 mmol), $K_3PO_4$ (1.90 g, 8.95 mmol), $Pd(t\text{-}Bu_3P)_2$ (0.090 g, 0.176 mmol) and toluene (10 mL) was degassed with a stream of Ar bubbles for 15 minutes. The reaction mixture was then heated at 100 °C for 12 hours, after which it was cooled to room temperature and poured into $H_2O$. The mixture was extracted with ethyl acetate (2x) and the combined organic phases were washed ($H_2O$, brine), dried ($Na_2SO_4$), filtered, and concentrated *in vacuo*. The residue was purified first by reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; $CH_3CN$-$H_2O$-5 mM $NH_4OAc$) and then by flash chromatography ($SiO_2$/ hexane-ethyl acetate, 1:1) to provide the title compound (0.128 g, 17%) as an orange oil. $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.90 (d, *J*=2.0 Hz, 1H), 8.32 (d, *J*=2.0 Hz, 1H), 8.03-8.01 (m, 2H), 7.77 (ddd, *J*=8.3, 6.8, 1.5 Hz, 1H), 7.62 (ddd, *J*=8.3, 6.8, 1.5 Hz, 1H), 4.35 (s, 1H), 4.13 (m, 2H), 2.22 (s, 6H), 1.15 (t, *J*=7.0 Hz, 3H). LCMS: Anal. Calcd. for $C_{15}H_{18}N_2O_2$: 258; found: 259 $(M+H)^+$.

*Step 2*; (R,S) 2-(Quinolin-3-yl)-2-(N,N-dimethylamino)acetic acid: A mixture of (R,S)-ethyl 2-(quinolin-3-yl)-2-(N,N-dimethylamino)acetate (0.122 g, 0.472 mmol) and 6M HCl (3 mL) was heated at 100 °C for 12 hours. The solvent was removed *in vacuo* to provide the dihydrochloride of the title compound (0.169 g, >100%) as a light yellow foam. The unpurified material was used in subsequent steps without further purification. LCMS: Anal. Calcd. for $C_{13}H_{14}N_2O_2$: 230; found: 231 $(M+H)^+$.

*Cap-38*

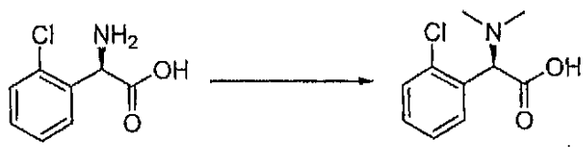



*Step 1*; (R)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate and (S)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate: To a mixture of (RS)-2-(dimethylamino)-2-(2-fluorophenyl)acetic acid (2.60 g, 13.19 mmol), DMAP (0.209 g, 1.71 mmol) and (S)-1-phenylethanol (2.09 g, 17.15 mmol) in $CH_2Cl_2$ (40 mL) was added EDCI (3.29 g, 17.15 mmol) and the mixture was allowed to stir at room temperature for 12 hours. The solvent was then removed *in vacuo* and the residue partitioned with ethyl acetate-$H_2O$. The layers were separated, the aqueous layer was back-extracted with ethyl acetate (2x) and the combined organic phases were washed ($H_2O$, brine), dried ($Na_2SO_4$), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Biotage/ 0-50% diethyl ether-hexane). The resulting pure diastereomeric mixture was then separated by reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; $CH_3CN$-$H_2O$-0.1% TFA) to give first (S)-1-phenethyl (R)-2-(dimethylamino)-2-(2-fluorophenyl)acetate (0.501 g, 13%) and then (S)-1-phenethyl (S)-2-(dimethylamino)-2-(2-fluorophenyl)-acetate (0.727 g. 18%), both as their TFA salts. (S,R)-isomer: $^1$H NMR (400 MHz, $CD_3OD$) δ 7.65-7.70 (m, 1H), 7.55-7.60 (ddd, *J*=9.4, 8.1, 1.5 Hz, 1H), 7.36-7.41 (m, 2H), 7.28-7.34 (m, 5H), 6.04 (q, *J*=6.5 Hz, 1H), 5.60 (s, 1H), 2.84 (s, 6H), 1.43 (d, *J*=6.5 Hz, 3H). LCMS: Anal. Calcd. for $C_{18}H_{20}FNO_2$: 301; found: 302 $(M+H)^+$; (S,S)-isomer: $^1$H NMR (400 MHz, $CD_3OD$) δ 7.58-7.63 (m, 1H), 7.18-7.31 (m, 6H), 7.00 (dd, *J*=8.5, 1.5 Hz, 2H), 6.02 (q, *J*=6.5 Hz, 1H), 5.60 (s, 1H), 2.88 (s, 6H), 1.54 (d, *J*=6.5 Hz, 3H). LCMS: Anal. Calcd. for $C_{18}H_{20}FNO_2$: 301; found: 302 $(M+H)^+$.

*Step 2*; (R)-2-(dimethylamino)-2-(2-fluorophenyl)acetic acid: A mixture of (R)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate TFA salt (1.25 g, 3.01 mmol) and 20% $Pd(OH)_2/C$ (0.125 g) in ethanol (30 mL) was hydrogenated at room temperature and atmospheric pressure ($H_2$ balloon) for 4 hours. The solution was then purged with Ar, filtered through diatomaceous earth (Celite®), and concentrated *in vacuo*. This gave the title compound as a colorless solid (0.503 g, 98%). $^1H$ NMR (400 MHz, $CD_3OD$) δ 7.53-7.63 (m, 2H), 7.33-7.38 (m, 2H), 5.36 (s, 1H), 2.86 (s, 6H). LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 197; found: 198 $(M+H)^+$.

The S-isomer could be obtained from (S)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate TFA salt in similar fashion.

*Cap-39*




**cap-39**

A mixture of (R)-(2-chlorophenyl)glycine (0.300 g, 1.62 mmol), formaldehyde (35% aqueous solution, 0.80 mL, 3.23 mmol) and 20% $Pd(OH)_2/C$ (0.050 g) was hydrogenated at room temperature and atmospheric pressure ($H_2$ balloon) for 4 hours. The solution was then purged with Ar, filtered through diatomaceous earth (Celite®) and concentrated *in vacuo*. The residue was purified by reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; $CH_3CN$-$H_2O$-0.1% TFA) to give theTFA salt of the title compound (R)-2-(dimethylamino)-2-(2-chlorophenyl)acetic acid as a colorless oil (0.290 g, 55%). $^1H$ NMR (400 MHz, $CD_3OD$) δ 7.59-7.65 (m, 2H), 7.45-7.53 (m, 2H), 5.40 (s, 1H), 2.87 (s, 6H). LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213; found: 214 $(M+H)^+$.

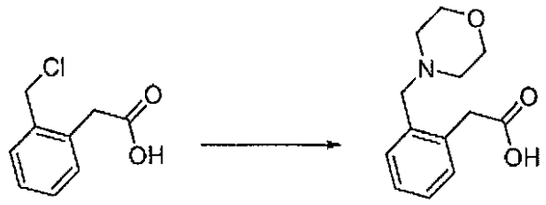
*Cap-40*



cap-40

To an ice-cold solution of (R)-(2-chlorophenyl)glycine (1.00 g, 5.38 mmol) and NaOH (0.862 g, 21.6 mmol) in $H_2O$ (5.5 mL) was added methyl chloroformate (1.00 mL, 13.5 mmol) dropwise. The mixture was allowed to stir at 0 °C for 1 hour and then it was acidified by the addition of conc. HCl (2.5 mL). The mixture was extracted with ethyl acetate (2x) and the combined organic phase was washed ($H_2O$, brine), dried ($Na_2SO_4$), filtered, and concentrated *in vacuo* to give the title compound (R)-2-(methoxycarbonylamino)-2-(2-chlorophenyl)acetic acid as a yellow-orange foam (1.31 g, 96%). $^1$H NMR (400 MHz, $CD_3OD$) δ 7.39 – 7.43 (m, 2H), 7.29 – 7.31 (m, 2H), 5.69 (s, 1H), 3.65 (s, 3H). LCMS: Anal. Calcd. for $C_{10}H_{10}ClNO_4$: 243; found: 244 $(M+H)^+$.

*Cap-41*

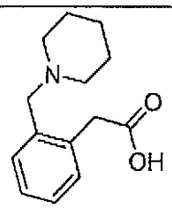
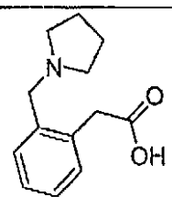
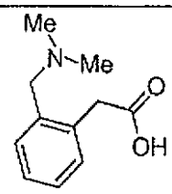
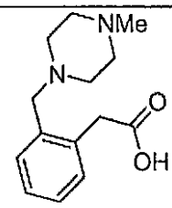


cap-41

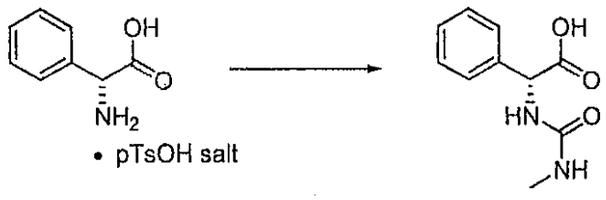
To a suspension of 2-(2-(chloromethyl)phenyl)acetic acid (2.00 g, 10.8 mmol) in THF (20 mL) was added morpholine (1.89 g, 21.7 mmol) and the solution was stirred at room temperature for 3 hours. The reaction mixture was then diluted with ethyl acetate and extracted with $H_2O$ (2x). The aqueous phase was lyophilized and the residue was purified by silica gel chromatography (Biotage/ 0-10% methanol-$CH_2Cl_2$) to give the title compound 2-(2-(Morpholinomethyl)phenyl)acetic acid as a colorless solid (2.22 g, 87%). $^1$H NMR (400 MHz, $CD_3OD$) δ 7.37-7.44 (m, 3H),

7.29-7.33 (m, 1H), 4.24 (s, 2H), 3.83 (br s, 4H), 3.68 (s, 2H), 3.14 (br s, 4H). LCMS: Anal. Calcd. for $C_{13}H_{17}NO_3$: 235; found: 236 $(M+H)^+$.

The following examples were similarly prepared using the method described for Cap-41:

| | | |
|---|---|---|
| *Cap-42* |  | LCMS: Anal. Calcd. for $C_{14}H_{19}NO_2$: 233; found: 234 $(M+H)^+$. |
| *Cap-43* |  | LCMS: Anal. Calcd. for $C_{13}H_{17}NO_2$: 219; found: 220 $(M+H)^+$. |
| *Cap-44* |  | LCMS: Anal. Calcd. for $C_{11}H_{15}NO_2$: 193; found: 194 $(M+H)^+$. |
| *Cap-45* |  | LCMS: Anal. Calcd. for $C_{14}H_{20}N_2O_2$: 248; found: 249 $(M+H)^+$. |

*Cap-45a*



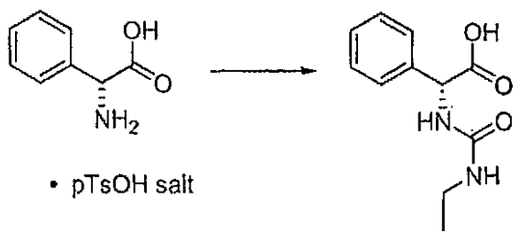
• pTsOH salt

Cap-45a

HMDS (1.85 mL, 8.77 mmol) was added to a suspension of (R)-2-amino-2-phenylacetic acid p-toluenesulfonate (2.83 g, 8.77 mmol) in $CH_2Cl_2$ (10 mL) and the mixture was stirred at room temperature for 30 minutes. Methyl isocyanate (0.5 g,

8.77 mmol) was added in one portion stirring continued for 30 minutes. The reaction was quenched by addition of $H_2O$ (5 mL) and the resulting precipitate was filtered, washed with $H_2O$ and n-hexanes, and dried under vacuum. (R)-2-(3-methylureido)-2-phenylacetic acid (1.5 g; 82 %).was recovered as a white solid and it was used without further purification. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 2.54 (d, *J*=4.88 Hz, 3H) 5.17 (d, *J*=7.93 Hz, 1H) 5.95 (q, *J*=4.48 Hz, 1H) 6.66 (d, *J*=7.93 Hz, 1H) 7.26-7.38 (m, 5H) 12.67 (s, 1H). LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_3$ 208.08 found 209.121 $(M+H)^+$; HPLC Phenomenex C-18 3.0 × 46 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=1.38 min, 90% homogeneity index.

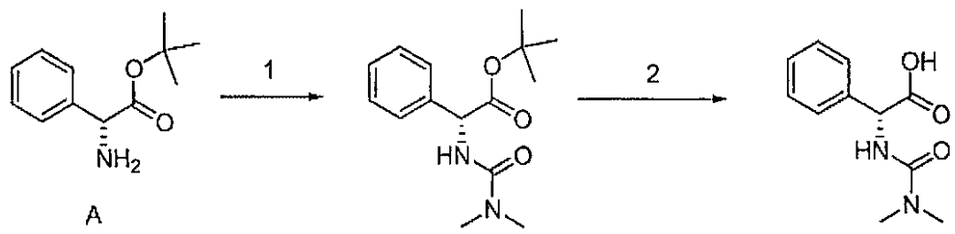
*Cap-46*




cap-46

The desired product was prepared according to the method described for Cap-45a. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 0.96 (t, *J*=7.17 Hz, 3H) 2.94-3.05 (m, 2H) 5.17 (d, *J*=7.93 Hz, 1H) 6.05 (t, *J*=5.19 Hz, 1H) 6.60 (d, *J*=7.63 Hz, 1H) 7.26-7.38 (m, 5H) 12.68 (s, 1H). LCMS: Anal. Calcd. for $C_{11}H_{14}N_2O_3$ 222.10 found 223.15 $(M+H)^+$. HPLC XTERRA C-18 3.0 × 506 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.2% $H_3PO_4$, B=10% water, 90% methanol, 0.2% $H_3PO_4$, RT=0.87 min, 90% homogeneity index.

*Cap-47*

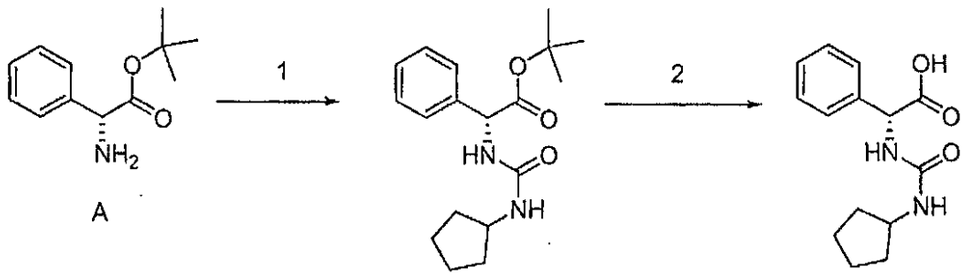



*Step 1*; (R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate: To a stirred solution of (R)-tert–butyl-2-amino-2-phenylacetate (1.0 g, 4.10 mmol) and Hunig's base (1.79 mL, 10.25 mmol) in DMF (40 mL) was added dimethylcarbamoyl chloride (0.38 mL, 4.18 mmol) dropwise over 10 minutes. After stirring at room temperature for 3 hours, the reaction was concentrated under reduced pressure and the resulting residue was dissolved in ethyl acetate. The organic layer was washed with $H_2O$, 1N aq. HCl and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. (R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate was obtained as a white solid ( 0.86 g; 75%) and used without further purification. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.33 (s, 9H) 2.82 (s, 6H) 5.17 (d, *J*=7.63 Hz, 1H) 6.55 (d, *J*=7.32 Hz, 1H) 7.24-7.41 (m, 5H). LCMS: Anal. Calcd. for $C_{15}H_{22}N_2O_3$ 278.16 found 279.23 $(M+H)^+$; HPLC Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=2.26 min, 97% homogeneity index.

*Step 2*; (R)-2-(3,3-dimethylureido)-2-phenylacetic acid: To a stirred solution of ((R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate ( 0.86 g, 3.10 mmol) in $CH_2Cl_2$ (250 mL) was added TFA (15 mL) dropwise and the resulting solution was stirred at rt for 3 hours. The desired compound was then precipitated out of solution with a mixture of EtOAC:Hexanes (5:20), filtered off and dried under reduced pressure. (R)-2-(3,3-dimethylureido)-2-phenylacetic acid was isolated as a white solid (0.59g, 86%) and used without further purification. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 2.82 (s, 6H) 5.22 (d, *J*=7.32 Hz, 1H) 6.58 (d, *J*=7.32 Hz, 1H) 7.28 (t, *J*=7.17 Hz, 1H) 7.33 (t, *J*=7.32 Hz, 2H) 7.38-7.43 (m, 2H) 12.65 (s, 1H). LCMS: Anal. Calcd. for $C_{11}H_{14}N_2O_3$: 222.24; found: 223.21 $(M+H)^+$. HPLC XTERRA C-

18 3.0 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.2% $H_3PO_4$, B=10% water, 90% methanol, 0.2% $H_3PO_4$, RT=0.75 min, 93% homogeneity index.

*Cap-48*




*Step 1*; (R)-tert-butyl 2-(3-cyclopentylureido)-2-phenylacetate: To a stirred solution of (R)-2-amino-2-phenylacetic acid hydrochloride (1.0 g, 4.10 mmol) and Hunig's base (1.0 mL, 6.15 mmol) in DMF (15 mL) was added cyclopentyl isocyanate (0.46 mL, 4.10 mmol) dropwise and over 10 minutes. After stirring at room temperature for 3 hours, the reaction was concentrated under reduced pressure and the resulting residue was traken up in ethyl acetate. The organic layer was washed with $H_2O$ and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. (R)-tert-butyl 2-(3-cyclopentylureido)-2-phenylacetate was obtained as an opaque oil (1.32 g; 100 %) and used without further purification. $^1H$ NMR (500 MHz, $CD_3Cl$-D) δ ppm 1.50-1.57 (m, 2H) 1.58-1.66 (m, 2H) 1.87-1.97 (m, 2H) 3.89-3.98 (m, 1H) 5.37 (s, 1H) 7.26-7.38 (m, 5H). LCMS: Anal. Calcd. for $C_{18}H_{26}N_2O_3$ 318.19 found 319.21 $(M+H)^+$; HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.1% TFA, B=10% water, 90% methanol, 0.1% TFA, RT=2.82 min, 96% homogeneity index.

*Step 2*; (R)-2-(3-cyclopentylureido)-2-phenylacetic acid: To a stirred solution of (R)-tert-butyl 2-(3-cyclopentylureido)-2-phenylacetate (1.31 g, 4.10 mmol) in $CH_2Cl_2$ (25 mL) was added TFA (4 mL) and triethylsilane (1.64 mL; 10.3 mmol) dropwise, and the resulting solution was stirred at room temperature for 6 hours. The volatile components were removed under reduced pressure and the crude product was recrystallized in ethyl acetate/pentanes to yield (R)-2-(3-cyclopentylureido)-2-

phenylacetic acid as a white solid (0.69 g, 64%). $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.17-1.35 (m, 2H) 1.42-1.52 (m, 2H) 1.53-1.64 (m, 2H) 1.67-1.80 (m, 2H) 3.75-3.89 (m, 1H) 5.17 (d, *J*=7.93 Hz, 1H) 6.12 (d, *J*=7.32 Hz, 1H) 6.48 (d, *J*=7.93 Hz, 1H) 7.24-7.40 (m, 5H) 12.73 (s, 1H). LCMS: Anal. Calcd. for $C_{14}H_{18}N_2O_3$: 262.31; found: 263.15 $(M+H)^+$. HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A=90% water, 10% methanol, 0.2% $H_3PO_4$, B=10% water, 90% methanol, 0.2% $H_3PO_4$, RT=1.24 min, 100% homogeneity index.

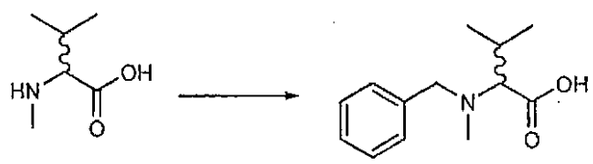
*Cap-49*



cap-49

To a stirred solution of 2-(benzylamino)acetic acid (2.0 g, 12.1 mmol) in formic acid (91 mL) was added formaldehyde (6.94 mL, 93.2 mmol). After five hours at 70 °C, the reaction mixture was concentrated under reduced pressure to 20 mL and a white solid precipitated. Following filtration, the mother liquors were collected and further concentrated under reduced pressure providing the crude product. Purification by reverse-phase preparative HPLC (Xterra 30 X 100 mm, detection at 220 nm, flow rate 35 mL/min, 0 to 35% B over 8 min; A= 90% water, 10 % methanol, 0.1% TFA, B=10% water, 90 % methanol, 0.1% TFA) provided the title compound 2-(benzyl(methyl)-amino)acetic acid as its TFA salt (723 mg, 33%) as a colorless wax. $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 2.75 (s, 3H) 4.04 (s, 2H) 4.34 (s, 2H) 7.29-7.68 (m, 5H). LCMS: Anal. Calcd. for: $C_{10}H_{13}NO_2$ 179.09; Found: 180.20 $(M+H)^+$.

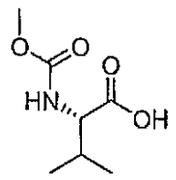
*Cap-50*



Cap-50

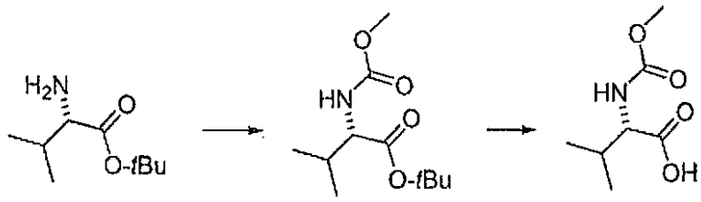
To a stirred solution of 3-methyl-2-(methylamino)butanoic acid (0.50 g, 3.81 mmol) in water ( 30 mL) was added $K_2CO_3$ (2.63 g, 19.1 mmol) and benzyl chloride (1.32 g, 11.4 mmol). The reaction mixture was stirred at ambient temperature for 18 hours. The reaction mixture was extracted with ethyl acetate (30 mL x 2) and the aqueous layer was concentrated under reduced pressure providing the crude product which was purified by reverse-phase preparative HPLC (Xterra 30 x 100mm, detection at 220 nm, flow rate 40 mL/min, 20 to 80% B over 6 min; A= 90% water, 10 % methanol, 0.1% TFA, B=10% water, 90 % methanol, 0.1% TFA) to provide 2-(benzyl(methyl)amino)-3-methylbutanoic acid, TFA salt (126 mg, 19%) as a colorless wax. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 0.98 (d, 3H) 1.07 (d, 3H) 2.33-2.48 (m, 1H) 2.54-2.78 (m, 3H) 3.69 (s, 1H) 4.24 (s, 2H) 7.29-7.65 (m, 5H). LCMS: Anal. Calcd. for: $C_{13}H_{19}NO_2$ 221.14; Found: 222.28 $(M+H)^+$.

*Cap-51*



$Na_2CO_3$ (1.83g, 17.2 mmol) was added to NaOH (33 mL of 1M/$H_2O$, 33 mmol) solution of L-valine (3.9 g, 33.29 mmol) and the resulting solution was cooled with ice-water bath. Methyl chloroformate (2.8 mL, 36.1 mmol) was added dropwise over 15 min, the cooling bath was removed and the reaction mixture was stirred at ambient temperature for 3.25 hr. The reaction mixture was washed with ether (50 mL, 3x), and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 1-2, and extracted with $CH_2Cl_2$ (50 mL, 3x). The organic phase was dried ($MgSO_4$) and evaporated *in vacuo* to afford Cap-51 as a white solid (6 g). $^1$H NMR for the dominant rotamer (DMSO-$d_6$, $\delta$=2.5 ppm, 500 MHz): 12.54 (s, 1H), 7.33 (d, *J*=8.6, 1H), 3.84 (dd, *J*=8.4, 6.0, 1H), 3.54 (s, 3H), 2.03 (m, 1H), 0.87 (m, 6H). HRMS: Anal. Calcd. for $[M+H]^+$ $C_7H_{14}NO_4$: 176.0923; found 176.0922.

*Cap 51 (alternate route)*



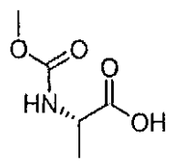

DIEA (137.5 mL, 0.766 mol) was added to a suspension of (*S*)-*tert*-butyl 2-amino-3-methylbutanoate hydrochloride (75.0 g, 0.357 mol) in THF (900 mL), and the mixture was cooled to 0 °C (ice/water bath). Methyl chloroformate (29.0 mL, 0.375 mol) was added dropwise over 45 min, the cooling bath was removed and the heterogeneous mixture was stirred at ambient temperature for 3 h. The solvent was removed under diminished pressure and the residue partitioned between EtOAc and water (1 L each). The organic layer was washed with $H_2O$ (1 L) and brine (1 L), dried ($MgSO_4$), filtered and concentrated under diminished pressure. The crude material was passed through a plug of silica gel (1 kg), eluting with hexanes (4 L) and 15:85 EtOAc/hexanes (4 L) to afford (S)-tert-butyl 2-(methoxycarbonylamino)-3-methylbutanoate as a clear oil (82.0 g, 99% yield). $^1$H-NMR (500 MHz, DMSO-$d_6$, δ = 2.5 ppm) 7.34 (d, $J$ = 8.6, 1 H), 3.77 (dd, $J$ = 8.6, 6.1, 1 H), 3.53 (s, 3 H), 1.94 - 2.05 (m, 1 H), 1.39 (s, 9 H), 0.83 - 0.92 (m, 6 H). $^{13}$C-NMR (126 MHz, DMSO-$d_6$, δ = 39.2 ppm) 170.92, 156.84, 80.38, 60.00, 51.34, 29.76, 27.62, 18.92, 17.95. LC/MS: $[M+Na]^+$ 254.17.

Trifluoroacetic acid (343 mL, 4.62 mol) and $Et_3SiH$ (142 mL, 0.887 mol) were added sequentially to a solution of (S)-tert-butyl 2-(methoxycarbonylamino)-3-methylbutanoate (82.0 g, 0.355 mol) in $CH_2Cl_2$ (675 mL), and the mixture was stirred at ambient temperature for 4 h. The volatile component was removed under diminished pressure and the resultant oil triturated with petroleum ether (600 mL) to afford a white solid, which was filtered and washed with hexanes (500 mL) and petroleum ether (500 mL). Recrystallization from EtOAc/petroleum ether afforded *Cap-51* as white flaky crystals (54.8 g, 88 % yield). MP = 108.5-109.5 °C. $^1$H NMR (500 MHz, DMSO-$d_6$, δ = 2.5 ppm) 12.52 (s, 1 H), 7.31 (d, $J$ = 8.6, 1 H), 3.83 (dd, $J$ = 8.6, 6.1, 1 H), 3.53 (s, 3 H), 1.94 - 2.07 (m, 1 H), 0.86 (dd, $J$ = 8.9, 7.0, 6 H). $^{13}$C NMR (126 MHz, DMSO-$d_6$, δ = 39.2 ppm) 173.30, 156.94, 59.48, 51.37, 29.52, 19.15, 17.98. LC/MS: $[M+H]^+$ =

176.11. Anal. Calcd. for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 7.99. Found: C, 48.17; H, 7.55; N, 7.99. Optical Rotation: $[\alpha]_D$ = -4.16 (12.02 mg/mL; MeOH). Optical purity: >99.5 % ee. Note: the optical purity assessment was made on the methyl ester derivative of *Cap-51*, which was prepared under a standard $TMSCHN_2$ (benzene/MeOH) esterification protocol. HPLC analytical conditions: column, ChiralPak AD-H (4.6 x 250mm, 5μm); solvent, 95% heptane / 5% IPA (isocratic); flow rate, 1 mL/min; temperature, 35 °C; UV monitored at 205 nm.

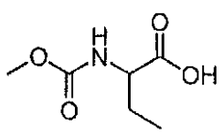
[Note: Cap 51 could also be purchased from Flamm.]

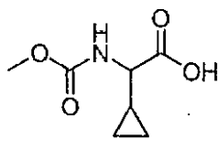
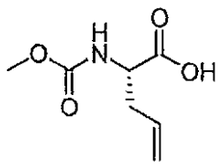
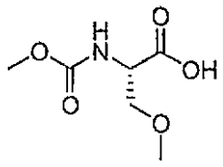
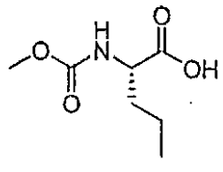
*Cap-52 (Same as Cap-12)*

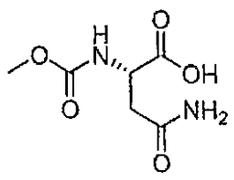
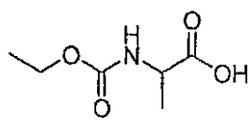
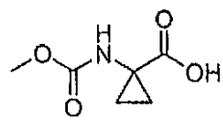
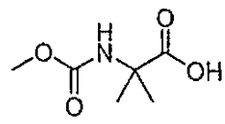


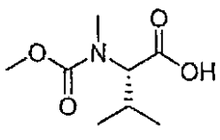
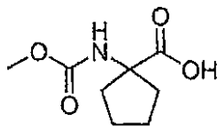
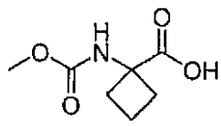
Cap-52 was synthesized from L-alanine according to the procedure described for the synthesis of Cap-51. For characterization purposes, a portion of the crude material was purified by a reverse phase HPLC ($H_2O$/methanol/TFA) to afford Cap-52 as a colorless viscous oil. $^1H$ NMR (DMSO-$d_6$, $\delta$=2.5 ppm, 500 MHz): 12.49 (br s, 1H), 7.43 (d, $J$=7.3, 0.88H), 7.09 (app br s, 0.12H), 3.97 (m, 1H), 3.53 (s, 3H), 1.25 (d, $J$=7.3, 3H).

*Cap*-53 to -*64* were prepared from appropriate starting materials according to the procedure described for the synthesis of *Cap*-51, with noted modifications if any.

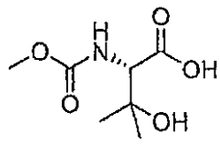
| Cap | Structure | Data |
|---|---|---|
| *Cap-53a*: (R) *Cap-53b*: (S) |  | $^1H$ NMR (DMSO-$d_6$, $\delta$ = 2.5 ppm, 500 MHz): $\delta$ 12.51 (br s, 1H), 7.4 (d, $J$ = 7.9, 0.9H), 7.06 (app s, 0.1H), 3.86-3.82 (m, 1H), 3.53 (s, 3H), 1.75-1.67 (m, 1H), 1.62-1.54 (m, 1H), 0.88 (d, $J$ = 7.3, 3H). RT = 0.77 minutes (Cond. 2); LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_6H_{11}NNaO_4$ : 184.06; |

| | | |
|---|---|---|
| | | found 184.07. HRMS Calcd. for $[M+Na]^+$ $C_6H_{11}NNaO_4$: 184.0586; found 184.0592. |
| *Cap-54a*: (R) *Cap-54b*: (S) |  | $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 500 MHz): δ 12.48 (s, 1H), 7.58 (d, *J* = 7.6, 0.9H), 7.25 (app s, 0.1H), 3.52 (s, 3H), 3.36-3.33 (m, 1H), 1.10-1.01 (m, 1H), 0.54-0.49 (m, 1H), 0.46-0.40 (m, 1H), 0.39-0.35 (m, 1H), 0.31-0.21 (m, 1H). HRMS Calcd. for $[M+H]^+$ $C_7H_{12}NO_4$: 174.0766; found 174.0771 |
| *Cap-55* |  | $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 500 MHz): δ 12.62 (s, 1H), 7.42 (d, *J* = 8.2, 0.9H), 7.07 (app s, 0.1H), 5.80-5.72 (m, 1H), 5.10 (d, *J* = 17.1, 1H), 5.04 (d, *J* = 10.4, 1H), 4.01-3.96 (m, 1H), 3.53 (s, 3H), 2.47-2.42 (m, 1H), 2.35-2.29 (m, 1H). |
| *Cap-56* |  | $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 500 MHz): δ 12.75 (s, 1H), 7.38 (d, *J* = 8.3, 0.9H), 6.96 (app s, 0.1H), 4.20-4.16 (m, 1H), 3.60-3.55 (m, 2H), 3.54 (s, 3H), 3.24 (s, 3H). |
| *Cap-57* |  | $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 500 MHz): δ 12.50 (s, 1H), 8.02 (d, *J* = 7.7, 0.08H), 7.40 (d, *J* = 7.9, 0.76H), 7.19 (d, *J* = 8.2, 0.07H), 7.07 (d, *J* = 6.7, 0.09H), 4.21-4.12 (m, 0.08H), 4.06-3.97 (m, 0.07H), 3.96-3.80 (m, 0.85H), 3.53 (s, 3H), 1.69-1.51 (m, 2H), 1.39-1.26 (m, 2H), 0.85 (t, *J* = 7.4, 3H). LC (Cond. 2): RT = 1.39 LC/MS: Anal. Calcd. for $[M+H]^+$ |

| | | |
|---|---|---|
| | | $C_7H_{14}NO_4$: 176.09; found 176.06. |
| *Cap-58* |  | $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 500 MHz): δ 12.63 (br s, 1H), 7.35 (s,1H), 7.31 ( d, *J* = 8.2, 1H), 6.92 (s, 1H), 4.33-4.29 (m, 1H), 3.54 (s, 3H), 2.54(dd, *J* = 15.5, 5.4, 1H), 2.43 (dd, *J* = 15.6, 8.0, 1H). RT = 0.16 min (Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{11}N_2O_5$: 191.07; found 191.14. |
| *Cap-59a*: (R) *Cap-59b*: (S) |  | $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 400 MHz): δ 12.49 (br s, 1H), 7.40 (d, *J* = 7.3, 0.89H), 7.04 (br s, 0.11H), 4.00-3.95 (m, 3H), 1.24 (d, *J* = 7.3, 3H), 1.15 (t, *J* = 7.2, 3H). HRMS: Anal. Calcd. for $[M+H]^+$ $C_6H_{12}NO_4$: 162.0766; found 162.0771. |
| *Cap-60* |  | The crude material was purified with a reverse phase HPLC ($H_2O$/MeOH/TFA) to afford a colorless viscous oil that crystallized to a white solid upon exposure to high vacuum. $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 400 MHz): δ 12.38 (br s, 1H), 7.74 (s, 0.82H), 7.48 (s, 0.18H), 3.54/3.51 (two s, 3H), 1.30 (m, 2H), 0.98 (m, 2H). HRMS: Anal. Calcd. for $[M+H]^+$ $C_6H_{10}NO_4$: 160.0610; found 160.0604. |
| *Cap-61* |  | $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 400 MHz): δ 12.27 (br s, 1H), 7.40 (br s, 1H), 3.50 (s, 3H), 1.32 (s, 6H). HRMS: Anal. Calcd. for $[M+H]^+$ $C_6H_{12}NO_4$: 162.0766; found 162.0765. |

| | | |
|---|---|---|
| *Cap-62* |  | $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 400 MHz): δ 12.74 (br s, 1H), 4.21 (d, *J* = 10.3, 0.6H), 4.05 (d, *J* = 10.0, 0.4H), 3.62/3.60 (two singlets, 3H), 3.0 (s, 3H), 2.14-2.05 (m, 1H), 0.95 (d, *J* = 6.3, 3H), 0.81 (d, *J* = 6.6, 3H). LC/MS: Anal. Calcd. for [M-H]$^-$ $C_8H_{14}NO_4$: 188.09; found 188.05. |
| *Cap-63* |  | [Note: the reaction was allowed to run for longer than what was noted for the general procedure.] $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 400 MHz): 12.21 (br s, 1H), 7.42 (br s, 1H), 3.50 (s, 3H), 2.02-1.85 (m, 4H), 1.66-1.58 (m, 4H). LC/MS: Anal. Calcd. for [M+H]$^+$ $C_8H_{14}NO_4$: 188.09; found 188.19. |
| *Cap-64* |  | [Note: the reaction was allowed to run for longer than what was noted for the general procedure.] $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 400 MHz): 12.35 (br s, 1H), 7.77 (s, 0.82H), 7.56/7.52 (overlapping br s, 0.18H), 3.50 (s, 3H), 2.47-2.40 (m, 2H), 2.14-2.07 (m, 2H), 1.93-1.82 (m, 2H). |

*Cap-65*

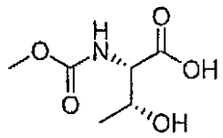


Methyl chloroformate (0.65 mL, 8.39 mmol) was added dropwise over 5 min to a cooled (ice-water) mixture of $Na_2CO_3$ (0.449 g, 4.23 mmol), NaOH (8.2 mL of 1M/$H_2O$, 8.2 mmol) and (*S*)-2-amino-3-hydroxy-3-methylbutanoic acid (1.04 g, 7.81 mmol). The reaction mixture was stirred for 45 min, and then the cooling bath was

removed and stirring was continued for an additional 3.75 hr. The reaction mixture was washed with $CH_2Cl_2$, and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 1-2. The volatile component was removed *in vacuo* and the residue was taken up in a 2:1 mixture of MeOH/$CH_2Cl_2$ (15 mL) and filtered, and the filterate was rotervaped to afford *Cap*-65 as a white semi-viscous foam (1.236 g). $^1$H NMR (DMSO-$d_6$, $\delta$ = 2.5 ppm, 400 MHz): $\delta$ 6.94 (d, $J$ = 8.5, 0.9 H), 6.53 (br s, 0.1H), 3.89 (d, $J$ = 8.8, 1H), 2.94 (s, 3H), 1.15 (s, 3H), 1.13 (s, 3H).

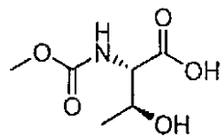
*Cap*-66 and -67 were prepared from appropriate commercially available starting materials by employing the procedure described for the synthesis of *Cap*-65.

*Cap-66*



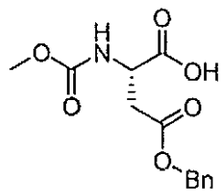
$^1$H NMR (DMSO-$d_6$, $\delta$ = 2.5 ppm, 400 MHz): $\delta$ 12.58 (br s, 1H), 7.07 (d, $J$ = 8.3, 0.13H), 6.81 (d, $J$ = 8.8, 0.67H), 4.10-4.02 (m, 1.15H), 3.91 (dd, $J$ = 9.1, 3.5, 0.85H), 3.56 (s, 3H), 1.09 (d, $J$ = 6.2, 3H). [Note: only the dominant signals of NH were noted].

*Cap-67*



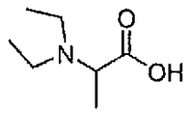
$^1$H NMR (DMSO-$d_6$, $\delta$ = 2.5 ppm, 400 MHz): 12.51 (br s, 1H), 7.25 (d, $J$ = 8.4, 0.75H), 7.12 (br d, $J$ = 0.4, 0.05H), 6.86 (br s, 0.08H), 3.95-3.85 (m, 2H), 3.54 (s, 3H), 1.08 (d, $J$ = 6.3, 3H). [Note: only the dominant signals of NH were noted].

*Cap-68*



Methyl chloroformate (0.38 ml, 4.9 mmol) was added drop-wise to a mixture of 1N NaOH (aq) (9.0 ml, 9.0 mmol), 1M $NaHCO_3$ (aq) (9.0 ml, 9.0 mol), L-aspartic acid β-benzyl ester (1.0 g, 4.5 mmol) and Dioxane (9 ml). The reaction mixture was stirred at ambient conditions for 3 hr, and then washed with Ethyl acetate (50 ml, 3x). The aqueous layer was acidified with 12N HCl to a pH ~ 1-2, and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with brine, dried ($Na_2SO_4$), filtered, and concentrated *in vacuo* to afford *Cap*-68 as a light yellow oil (1.37g; mass is above theoretical yield, and the product was used without further purification). $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 500 MHz): δ 12.88 (br s, 1H), 7.55 (d, *J* = 8.5, 1H), 7.40-7.32 (m, 5H), 5.13 (d, *J* = 12.8, 1H), 5.10 (d, *J* = 12.9, 1H), 4.42-4.38 (m, 1H), 3.55 (s, 3H), 2.87 (dd, *J* = 16.2, 5.5, 1H), 2.71 (dd, *J* =16.2, 8.3, 1H). LC (Cond. 2): RT = 1.90 min; LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{13}H_{16}NO_6$: 282.10; found 282.12.

*Cap-69a and -69b*

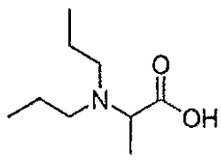
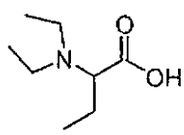
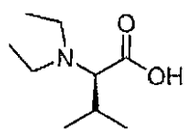
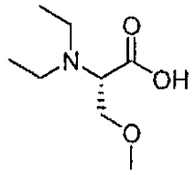


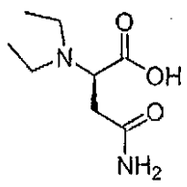
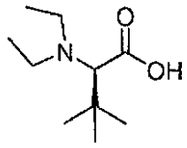
*Cap-69a: (R)-enantiomer*
*Cap-69b: (S)-enantiomer*

$NaCNBH_3$ (2.416 g, 36.5 mmol) was added in batches to a chilled (~15 °C) water (17 mL)/MeOH (10 mL) solution of alanine (1.338 g, 15.0 mmol). A few minutes later acetaldehyde (4.0 mL, 71.3 mmol) was added drop-wise over 4 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition for 6 hr. An additional acetaldehyde (4.0 mL) was added and the reaction was stirred for 2 hr. Concentrated HCl was added slowly to the reaction mixture until the pH reached ~ 1.5, and the resulting mixture was heated for 1 hr at 40 °C. Most of the volatile component was removed *in vacuo* and the residue was purified with a Dowex® 50WX8-100 ion-exchange resin (column was washed with water, and the

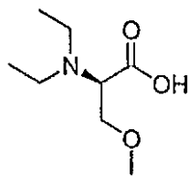
compound was eluted with dilute $NH_4OH$, prepared by mixing 18 ml of $NH_4OH$ and 282 ml of water) to afford *Cap*-69 (2.0 g) as an off-white soft hygroscopic solid. $^1H$ NMR (DMSO-$d_6$, δ = 2.5 ppm, 400 MHz): δ 3.44 (q, *J* = 7.1, 1H), 2.99-2.90 (m, 2H), 2.89-2.80 (m, 2H), 1.23 (d, *J* = 7.1, 3H), 1.13 (t, *J* = 7.3, 6H).

*Cap-70* to *-74x* were prepared according to the procedure described for the synthesis of *Cap*-69 by employing appropriate starting materials.

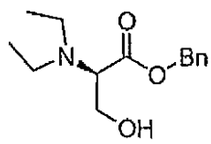
| | | |
|---|---|---|
| *Cap-70a*: (R) *Cap-70b*: (S) |  | $^1H$ NMR (DMSO-$d_6$, δ = 2.5 ppm, 400 MHz): δ 3.42 (q, *J* = 7.1, 1H), 2.68-2.60 (m, 4H), 1.53-1.44 (m, 4H), 1.19 (d, *J* = 7.3, 3H), 0.85 (t, *J* = 7.5, 6H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{20}NO_2$: 174.15; found 174.13. |
| *Cap-71a*: (R) *Cap-71b*: (S) |  | $^1H$ NMR (DMSO-$d_6$, δ = 2.5 ppm, 500 MHz): δ 3.18-3.14 (m, 1H), 2.84-2.77 (m, 2H), 2.76-2.68 (m, 2H), 1.69-1.54 (m, 2H), 1.05 (t, *J* = 7.2, 6H), 0.91 (t, *J* = 7.3, 3H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{18}NO_2$: 160.13; found 160.06. |
| *Cap-72* |  | $^1H$ NMR (DMSO-$d_6$, δ = 2.5 ppm, 400 MHz): δ 2.77-2.66 (m, 3H), 2.39-2.31 (m, 2H), 1.94-1.85 (m, 1H), 0.98 (t, *J* = 7.1, 6H), 0.91 (d, *J* = 6.5, 3H), 0.85 (d, *J* = 6.5, 3H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{20}NO_2$: 174.15; found 174.15. |
| *Cap-73* |  | $^1H$ NMR (DMSO-$d_6$, δ = 2.5 ppm, 500 MHz): δ 9.5 (br s, 1H), 3.77 (dd, *J* = 10.8, 4.1,1H), 3.69-3.61 ( m, 2H), 3.26 (s, 3H), 2.99-2.88 (m, 4H), 1.13 (t, *J* = |

| | | |
|---|---|---|
| | | 7.2, 6H). |
| *Cap-74* |  | $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 500 MHz): δ 7.54 (s, 1H), 6.89 (s, 1H), 3.81 (t, *J* = 6.6, k,1H), 2.82-2.71 (m, 4H), 2.63 (dd, *J* = 15.6, 7.0, 1H), 2.36 (dd, *J* = 15.4, 6.3, 1H), 1.09 (t, *J* = 7.2, 6H). RT = 0.125 minutes (Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{17}N_2O_3$: 189.12; found 189.13. |
| *Cap-74x* |  | LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{22}NO_2$: 188.17; found 188.21 |

*Cap-75*



*Cap-75, step a*



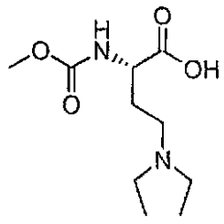
$NaBH_3CN$ (1.6 g, 25.5 mmol) was added to a cooled (ice/water bath) water (25 ml)/methanol (15 ml) solution of H-D-Ser-OBzl HCl (2.0 g, 8.6 mmol). Acetaldehyde (1.5 ml, 12.5 mmol) was added drop-wise over 5 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition for 2 hr. The reaction was carefully quenched with 12N HCl and concentrated *in vacuo*. The residue was dissolved in water and purified with a reverse phase HPLC ($MeOH/H_2O$/TFA) to afford the TFA salt of (R)-benzyl 2-(diethylamino)-3-hydroxypropanoate as a colorless viscous oil (1.9g). $^1$H NMR (DMSO-$d_6$, δ = 2.5

ppm, 500 MHz): δ 9.73 (br s, 1H), 7.52-7.36 (m, 5H), 5.32 (d, $J$ = 12.2, 1H), 5.27 (d, $J$ = 12.5, 1H), 4.54-4.32 (m, 1H), 4.05-3.97 (m, 2H), 3.43-3.21 (m, 4H), 1.23 (t, $J$ = 7.2, 6H). LC/MS (Cond. 2): RT = 1.38 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{22}NO_3$: 252.16; found 252.19.

*Cap-75*

NaH (0.0727 g, 1.82 mmol, 60%) was added to a cooled (ice-water) THF (3.0 mL) solution of the TFA salt (R)-benzyl 2-(diethylamino)-3-hydroxypropanoate (0.3019 g, 0.8264 mmol) prepared above, and the mixture was stirred for 15 min. Methyl iodide (56 µL, 0.90 mmol) was added and stirring was continued for 18 hr while allowing the bath to thaw to ambient condition. The reaction was quenched with water and loaded onto a MeOH pre-conditioned MCX (6 g) cartridge, and washed with methanol followed by compound elution with 2N $NH_3$/Methanol. Removal of the volatile component *in vacuo* afforded *Cap*-75, contaminated with (R)-2-(diethylamino)-3-hydroxypropanoic acid, as a yellow semi-solid (100 mg). The product was used as is without further purification.

*Cap-76*

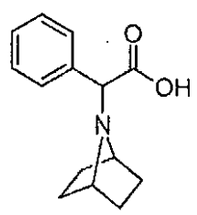


$NaCNBH_3$ (1.60 g, 24.2 mmol) was added in batches to a chilled (~15 °C) water/MeOH (12 mL each) solution of (*S*)-4-amino-2-(tert-butoxycarbonylamino) butanoic acid (2.17 g, 9.94 mmol). A few minutes later acetaldehyde (2.7 mL, 48.1 mmol) was added drop-wise over 2 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition for 3.5 hr. An additional acetaldehyde (2.7 mL, 48.1 mmol) was added and the reaction was stirred for 20.5 hr. Most of the MeOH component was removed *in vacuo*, and the remaining mixture was treated with concentrated HCl until its pH reached ~ 1.0 and then heated for 2 hr

at 40 °C. The volatile component was removed *in vacuo*, and the residue was treated with 4 M HCl/dioxane (20 mL) and stirred at ambient condition for 7.5 hr. The volatile component was removed *in vacuo* and the residue was purified with Dowex ® 50WX8-100 ion-exchange resin (column was washed with water and the compound was eluted with dilute $NH_4OH$, prepared from 18 ml of $NH_4OH$ and 282 ml of water) to afford intermediate (S)-2-amino-4-(diethylamino)butanoic acid as an off-white solid (1.73 g).

Methyl chloroformate (0.36 mL, 4.65 mmol) was added drop-wise over 11 min to a cooled (ice-water) mixture of $Na_2CO_3$ (0.243 g, 2.29 mmol), NaOH (4.6 mL of 1M/$H_2O$, 4.6 mmol) and the above product (802.4 mg). The reaction mixture was stirred for 55 min, and then the cooling bath was removed and stirring was continued for an additional 5.25 hr. The reaction mixture was diluted with equal volume of water and washed with $CH_2Cl_2$ (30 mL, 2x), and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 2. The volatile component was then removed *in vacuo* and the crude material was free-based with MCX resin (6.0g; column was washed with water, and sample was eluted with 2.0 M $NH_3$/MeOH) to afford impure *Cap*-76 as an off-white solid (704 mg). $^1$H NMR (MeOH-$d_4$, $\delta$ = 3.29 ppm, 400 MHz): $\delta$ 3.99 (dd, $J$ = 7.5, 4.7, 1H), 3.62 (s, 3H), 3.25-3.06 (m, 6H), 2.18-2.09 (m, 1H), 2.04-1.96 (m, 1H), 1.28 (t, $J$ = 7.3, 6H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{21}N_2O_4$: 233.15; found 233.24.

*Cap-77a and -77b*

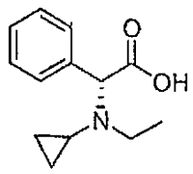



*Cap-77a: enantiomer-1*
*Cap-77b: enantiomer-2*

The synthesis of *Cap*-77 was conducted according to the procedure described for *Cap*-7 by using 7-azabicyclo[2.2.1]heptane for the $SN_2$ displacement step, and by effecting the enantiomeric separation of the intermediate benzyl 2-(7-azabicyclo[2.2.1]heptan-7-yl)-2-phenylacetate using the following condition: the intermediate (303.7 mg) was dissolved in ethanol, and the resulting solution was

injected on a chiral HPLC column (Chiracel AD-H column, 30 x 250 mm, 5 um) eluting with 90% $CO_2$-10% EtOH at 70 mL/min, and a temperature of 35 °C to provide 124.5 mg of enantiomer-1 and 133.8 mg of enantiomer-2. These benzyl esters were hydrogenolysed according to the preparation of *Cap*-7 to provide *Cap*-77: $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 400 MHz): δ 7.55 (m, 2H), 7.38-7.30 (m, 3H), 4.16 (s, 1H), 3.54 (app br s, 2H), 2.08-1.88 (m, 4 H), 1.57-1.46 (m, 4H). LC (Cond. 1): RT = 0.67 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{18}NO_2$: 232.13; found 232.18. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{18}NO_2$: 232.1338; found 232.1340.

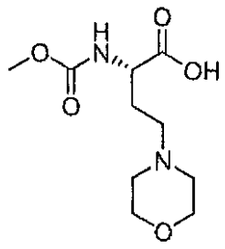
*Cap-78*




$NaCNBH_3$ (0.5828 g, 9.27 mmol) was added to a mixture of the HCl salt of (*R*)-2-(ethylamino)-2-phenylacetic acid (an intermediate in the synthesis of *Cap*-3; 0.9923 mg, 4.60 mmol) and (1-ethoxycyclopropoxy)trimethylsilane (1.640 g, 9.40 mmol) in MeOH (10 mL), and the semi-heterogeneous mixture was heated at 50 °C with an oil bath for 20 hr. More (1-ethoxycyclopropoxy)trimethylsilane (150 mg, 0.86 mmol) and $NaCNBH_3$ (52 mg, 0.827 mmol) were added and the reaction mixture was heated for an additional 3.5 hr. It was then allowed to cool to ambient temperature and acidified to a ~ pH region of 2 with concentrated HCl, and the mixture was filtered and the filtrate was rotervaped. The resulting crude material was taken up in *i*-PrOH (6 mL) and heated to effect dissolution, and the non-dissolved part was filtered off and the filtrate concentrated *in vacuo*. About 1/3 of the resultant crude material was purified with a reverse phase HPLC ($H_2O$/MeOH/TFA) to afford the TFA salt of *Cap*-78 as a colorless viscous oil (353 mg). $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 400 MHz; after $D_2O$ exchange): δ 7.56-7.49 (m, 5H), 5.35 (S, 1H), 3.35 (m, 1H), 3.06 (app br s, 1H), 2.66 (m, 1H), 1.26 (t, *J* = 7.3, 3H), 0.92 (m, 1H), 0.83-0.44 (m, 3H). LC (Cond. 1): RT = 0.64 min; LC/MS: Anal. Calcd. for $[M+H]^+$

$C_{13}H_{18}NO_2$: 220.13; found 220.21. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{18}NO_2$: 220.1338; found 220.1343.

*Cap-79*

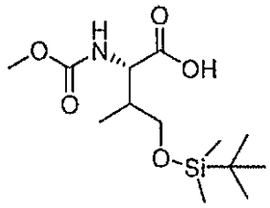


Ozone was bubbled through a cooled (-78 °C) $CH_2Cl_2$ (5.0 mL) solution *Cap*-55 (369 mg, 2.13 mmol) for about 50 min until the reaction mixture attained a tint of blue color. $Me_2S$ (10 pipet drops) was added, and the reaction mixture was stirred for 35 min. The -78 °C bath was replaced with a -10 °C bath and stirring continued for an additional 30 min, and then the volatile component was removed *in vacuo* to afford a colorless viscous oil.

$NaBH_3CN$ (149 mg, 2.25 mmol) was added to a MeOH (5.0 mL) solution of the above crude material and morpholine (500 μL, 5.72 mmol) and the mixture was stirred at ambient condition for 4 hr. It was cooled to ice-water temperature and treated with concentrated HCl to bring its pH to ~2.0, and then stirred for 2.5 hr. The volatile component was removed *in vacuo*, and the residue was purified with a combination of MCX resin (MeOH wash; 2.0 N $NH_3$/MeOH elution) and a reverse phase HPLC ($H_2O$/MeOH/TFA) to afford *Cap*-79 containing unknown amount of morpholine.

In order to consume the morpholine contaminant, the above material was dissolved in $CH_2Cl_2$ (1.5 mL) and treated with $Et_3N$ (0.27 mL, 1.94 mmol) followed by acetic anhydride (0.10 mL, 1.06 mmol) and stirred at ambient condition for 18 hr. THF (1.0 mL) and $H_2O$ (0.5 mL) were added and stirring continued for 1.5 hr. The volatile component was removed *in vacuo*, and the resultant residue was passed through MCX resin (MeOH wash; 2.0 N $NH_3$/MeOH elution) to afford impure *Cap*-79 as a brown viscous oil, which was used for the next step without further purification.

*Cap-80a and -80b*



*Cap-80a: S/S-diastereomer*
*Cap-80b: S/R-diastereomer*

$SOCl_2$ (6.60 mL, 90.5 mmol) was added drop-wise over 15 min to a cooled (ice-water) mixture of (S)-3-amino-4-(benzyloxy)-4-oxobutanoic acid (10.04g, 44.98 mmol) and MeOH (300 mL), the cooling bath was removed and the reaction mixture was stirred at ambient condition for 29 hr. Most of the volatile component was removed *in vacuo* and the residue was carefully partitioned between EtOAc (150 mL) and saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc (150 mL, 2x), and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford (S)-1-benzyl 4-methyl 2-aminosuccinate as a colorless oil (9.706g). $^1H$ NMR (DMSO-$d_6$, $\delta$ = 2.5 ppm, 400 MHz): $\delta$ 7.40-7.32 (m, 5H), 5.11 (s, 2H), 3.72 (app t, $J$ = 6.6, 1H), 3.55 (s, 3H), 2.68 (dd, $J$ = 15.9, 6.3, 1H), 2.58 (dd, $J$ = 15.9, 6.8, 1H), 1.96 (s, 2H). LC (Cond. 1): RT = 0.90 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_4$: 238.11; found 238.22.

$Pb(NO_3)_2$ (6.06 g, 18.3 mmol) was added over 1 min to a $CH_2Cl_2$ (80 mL) solution of (S)-1-benzyl 4-methyl 2-aminosuccinate (4.50 g, 19.0 mmol), 9-bromo-9-phenyl-9*H*-fluorene (6.44 g, 20.0 mmol) and $Et_3N$ (3.0 mL, 21.5 mmol), and the heterogeneous mixture was stirred at ambient condition for 48 hr. The mixture was filtered and the filtrate was treated with $MgSO_4$ and filtered again, and the final filtrate was concentrated. The resulting crude material was submitted to a Biotage purification (350 g silica gel, $CH_2Cl_2$ elution) to afford (S)-1-benzyl 4-methyl 2-(9-phenyl-9H-fluoren-9-ylamino)succinate as highly viscous colorless oil (7.93 g). $^1H$ NMR (DMSO-$d_6$, $\delta$ = 2.5 ppm, 400 MHz): $\delta$ 7.82 (m, 2H), 7.39-7.13 (m, 16H), 4.71 (d, $J$ = 12.4, 1H), 4.51 (d, $J$ = 12.6, 1H), 3.78 (d, $J$ = 9.1, NH), 3.50 (s, 3H), 2.99 (m, 1H), 2.50-2.41 (m, 2H, partially overlapped with solvent). LC (Cond. 1): RT = 2.16 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{31}H_{28}NO_4$: 478.20; found 478.19.

LiHMDS (9.2 mL of 1.0 M/THF, 9.2 mmol) was added drop-wise over 10 min to a cooled (-78 °C) THF (50 mL) solution of (S)-1-benzyl 4-methyl 2-(9-phenyl-

9H-fluoren-9-ylamino)succinate (3.907 g, 8.18 mmol) and stirred for ~1 hr. MeI (0.57 mL, 9.2 mmol) was added drop-wise over 8 min to the mixture, and stirring was continued for 16.5 hr while allowing the cooling bath to thaw to room temperature. After quenching with saturated $NH_4Cl$ solution (5 mL), most of the organic component was removed *in vacuo* and the residue was partitioned between $CH_2Cl_2$ (100 mL) and water (40 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*, and the resulting crude material was purified with a Biotage (350 g silica gel; 25% EtOAc/hexanes) to afford 3.65 g of a 2S/3S and 2S/3R diastereomeric mixtures of 1-benzyl 4-methyl 3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)succinate in ~1.0:0.65 ratio ($^1$H NMR). The stereochemistry of the dominant isomer was not determined at this juncture, and the mixture was submitted to the next step without separation. Partial $^1$H NMR data (DMSO-$d_6$, $\delta$ = 2.5 ppm, 400 MHz): major diastereomer, $\delta$ 4.39 (d, $J$ = 12.3, 1H of $CH_2$), 3.33 (s, 3H, overlapped with $H_2O$ signal), 3.50 (d, $J$ = 10.9, NH), 1.13 (d, $J$ = 7.1, 3H); minor diastereomer, $\delta$ 4.27 (d, $J$ =12.3, 1H of $CH_2$), 3.76 (d, $J$ = 10.9, NH), 3.64 (s, 3H), 0.77 (d, $J$ = 7.0, 3H). LC (Cond. 1): RT = 2.19 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{32}H_{30}NO_4$: 492.22; found 492.15.

Diisobutylaluminum hydride (20.57 ml of 1.0 M in hexanes, 20.57 mmol) was added drop-wise over 10 min to a cooled (-78 °C) THF (120 mL) solution of (2S)-1-benzyl 4-methyl 3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)succinate (3.37 g, 6.86 mmol) prepared above, and stirred at -78 °C for 20 hr. The reaction mixture was removed from the cooling bath and rapidly poured into ~1M $H_3PO_4/H_2O$ (250 mL) with stirring, and the mixture was extracted with ether (100 mL, 2x). The combined organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to chromatography (25% EtOAc/hexanes; gravity elution) to afford 1.1g of (2S,3S)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate, contaminated with benzyl alcohol, as a colorless viscous oil and (2S,3R)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate containing the (2S,3R) stereoisomer as an impurity. The later sample was resubmitted to the same column chromatography purification conditions to afford 750 mg of purified material

as a white foam. [Note: the (2S, 3S) isomer elutes before the (2S,3R) isomer under the above condition]. (2S, 3S) isomer: $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 400 MHz): 7.81 (m, 2H), 7.39-7.08 (m, 16H), 4.67 (d, *J* = 12.3, 1H), 4.43 (d, *J* = 12.4, 1H), 4.21 (app t, *J* = 5.2, OH), 3.22 (d, *J* = 10.1, NH), 3.17 (m, 1H), 3.08 (m, 1H), ~2.5 (m, 1H, overlapped with the solvent signal), 1.58 (m, 1H), 0.88 (d, *J* = 6.8, 3H). LC (Cond. 1): RT = 2.00 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{31}H_{30}NO_3$: 464.45; found 464.22. (2S, 3R) isomer: $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 400 MHz): 7.81 (d, *J* = 7.5, 2H), 7.39-7.10 (m, 16H), 4.63 (d, *J*= 12.1, 1H), 4.50 (app t, *J* = 4.9, 1H), 4.32 (d, *J* = 12.1, 1H), 3.59-3.53 (m, 2H), 3.23 (m, 1H), 2.44 (dd, *J* = 9.0, 8.3, 1H), 1.70 (m, 1H), 0.57 (d, *J* = 6.8, 3H). LC (Cond. 1): RT = 1.92 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{31}H_{30}NO_3$: 464.45; found 464.52.

The relative stereochemical assignments of the DIBAL-reduction products were made based on NOE studies conducted on lactone derivatives prepared from each isomer by employing the following protocol: LiHMDS (50 µL of 1.0 M/THF, 0.05 mmol) was added to a cooled (ice-water) THF (2.0 mL) solution of (2S,3S)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate (62.7 mg, 0.135 mmol), and the reaction mixture was stirred at similar temperature for ~2 hr. The volatile component was removed *in vacuo* and the residue was partitioned between $CH_2Cl_2$ (30 mL), water (20 mL) and saturated aqueous $NH_4Cl$ solution (1 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*, and the resulting crude material was submitted to a Biotage purification (40 g silica gel; 10-15% EtOAc/hexanes) to afford (3S,4S)-4-methyl-3-(9-phenyl-9*H*-fluoren-9-ylamino)dihydrofuran-2(3*H*)-one as a colorless film of solid (28.1 mg). (2S,3R)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate was elaborated similarly to (3S,4R)-4-methyl-3-(9-phenyl-9*H*-fluoren-9-ylamino)dihydrofuran-2(3*H*)-one. (3S,4S)-lactone isomer: $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 400 MHz), 7.83 (d, *J* = 7.5, 2H), 7.46-7.17 (m, 11H), 4.14 (app t, *J* = 8.3, 1H), 3.60 (d, *J* = 5.8, NH), 3.45 (app t, *J* = 9.2, 1H), ~2.47 (m, 1H, partially overlapped with solvent signal), 2.16 (m, 1H), 0.27 (d, *J* = 6.6, 3H). LC (Cond. 1): RT = 1.98 min; LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378.15; found 378.42. (3S,4R)-lactone isomer: $^1$H NMR (DMSO-$d_6$, δ = 2.5 ppm, 400 MHz), 7.89

(d, $J$ = 7.6, 1H), 7.85 (d, $J$ = 7.3, 1H), 7.46-7.20 (m, 11H), 3.95 (dd, $J$ = 9.1, 4.8, 1H), 3.76 (d, $J$ = 8.8, 1H), 2.96 (d, $J$ = 3.0, NH), 2.92 (dd, $J$ = 6.8, 3, NCH), 1.55 (m, 1H), 0.97 (d, $J$ = 7.0, 3H). LC (Cond. 1): RT = 2.03 min; LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378.15; found 378.49.

TBDMS-Cl (48 mg, 0.312 mmol) followed by imidazole (28.8 mg, 0.423 mmol) were added to a $CH_2Cl_2$ (3 ml) solution of (2S,3S)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate (119.5 mg, 0.258 mmol), and the mixture was stirred at ambient condition for 14.25 hr. The reaction mixture was then diluted with $CH_2Cl_2$ (30 mL) and washed with water (15 mL), and the organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resultant crude material was purified with a Biotage (40 g silica gel; 5% EtOAc/hexanes) to afford (2S,3S)-benzyl 4-(tert-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate, contaminated with TBDMS based impurities, as a colorless viscous oil (124.4 mg). (2S,3R)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate was elaborated similarly to (2S,3R)-benzyl 4-(tert-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate. (2S,3S)-silyl ether isomer: $^1$H NMR (DMSO-$d_6$, $\delta$ = 2.5 ppm, 400 MHz), 7.82 (d, $J$ = 4.1, 1H), 7.80 (d, $J$ = 4.0, 1H), 7.38-7.07 (m, 16 H), 4.70 (d, $J$ = 12.4, 1H), 4.42 (d, $J$ = 12.3, 1H), 3.28-3.19 (m, 3H), 2.56 (dd, $J$ = 10.1, 5.5, 1H), 1.61 (m, 1H), 0.90 (d, $J$ = 6.8, 3H), 0.70 (s, 9H), -0.13 (s, 3H), -0.16 (s, 3H). LC (Cond. 1, where the run time was extended to 4 min): RT = 3.26 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{44}NO_3Si$: 578.31; found 578.40. (2S,3R)-silyl ether isomer: $^1$H NMR (DMSO-$d_6$, $\delta$ = 2.5 ppm, 400 MHz), 7.82 (d, $J$ = 3.0, 1H), 7.80 (d, $J$ = 3.1, 1H), 7.39-7.10 (m, 16H), 4.66 (d, $J$ = 12.4, 1H), 4.39 (d, $J$ = 12.4, 1H), 3.61 (dd, $J$ = 9.9, 5.6, 1H), 3.45 (d, $J$ = 9.5, 1H), 3.41 (dd, $J$ = 10, 6.2, 1H), 2.55 (dd, $J$ = 9.5, 7.3, 1H), 1.74 (m, 1H), 0.77 (s, 9H), 0.61 (d, $J$ = 7.1, 3H), -0.06 (s, 3H), -0.08 (s, 3H).

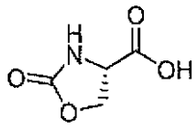
A balloon of hydrogen was attached to a mixture of (2S,3S)-benzyl 4-(tert-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate (836 mg, 1.447 mmol) and 10% Pd/C (213 mg) in EtOAc (16 mL) and the mixture was stirred at room temperature for ~ 21 hr, where the balloon was recharged with $H_2$ as necessary. The reaction mixture was diluted with $CH_2Cl_2$ and filtered through a pad

of diatomaceous earth (Celite-545®), and the pad was washed with EtOAc (200 mL), EtOAc/MeOH (1:1 mixture, 200 mL) and MeOH (750 mL). The combined organic phase was concentrated, and a silica gel mesh was prepared from the resulting crude material and submitted to a flash chromatography (8:2:1 mixture of EtOAc/i-PrOH/$H_2O$) to afford (2S,3S)-2-amino-4-(tert-butyldimethylsilyloxy)-3-methylbutanoic acid as a white fluffy solid (325 mg). (2S,3R)-benzyl 4-(tert-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate was similarly elaborated to (2S,3R)-2-amino-4-(tert-butyldimethylsilyloxy)-3-methylbutanoic acid. (2S,3S)-amino acid isomer: $^1$H NMR (Methanol-$d_4$, $\delta$ = 3.29 ppm, 400 MHz); 3.76 (dd, $J$ = 10.5, 5.2, 1H), 3.73 (d, $J$ = 3.0, 1H), 3.67 (dd, $J$ = 10.5, 7.0, 1H), 2.37 (m, 1H), 0.97 (d, $J$ = 7.0, 3H), 0.92 (s, 9H), 0.10 (s, 6H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{26}NO_3Si$: 248.17; found 248.44. (2S,3R)-amino acid isomer: $^1$H NMR (Methanol-$d_4$, $\delta$ = 3.29 ppm, 400 MHz), 3.76-3.75 (m, 2H), 3.60 (d, $J$ = 4.1, 1H), 2.16 (m, 1H), 1.06 (d, $J$ = 7.3, 3H), 0.91 (s, 9H), 0.09 (s, 6H). Anal. Calcd. for $[M+H]^+$ $C_{11}H_{26}NO_3Si$: 248.17; found 248.44.

Water (1 mL) and NaOH (0.18 mL of 1.0 M/$H_2O$, 0.18 mmol) were added to a mixture of (2S,3S)-2-amino-4-(tert-butyldimethylsilyloxy)-3-methylbutanoic acid (41.9 mg, 0.169 mmol) and $Na_2CO_3$ (11.9 mg, 0.112 mmol), and sonicated for about 1 min to effect dissolution of reactants. The mixture was then cooled with an ice-water bath, methyl chloroformate (0.02 mL, 0.259 mmol) was added over 30 s, and vigorous stirring was continued at similar temperature for 40 min and then at ambient temperature for 2.7 hr. The reaction mixture was diluted with water (5 mL), cooled with ice-water bath and treated drop-wise with 1.0 N HCl aqueous solution (~0.23 mL). The mixture was further diluted with water (10 mL) and extracted with $CH_2Cl_2$ (15 mL, 2x). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford *Cap*-80a as an off-white solid. (2S,3R)-2-amino-4-(tert-butyldimethylsilyloxy)-3-methylbutanoic acid was similarly elaborated to *Cap*-80b. *Cap*-80a: $^1$H NMR (DMSO-$d_6$, $\delta$ = 2.5 ppm, 400 MHz), 12.57 (br s, 1H), 7.64 (d, $J$ = 8.3, 0.3H), 7.19 (d, $J$ = 8.8, 0.7H), 4.44 (dd, $J$ = 8.1, 4.6, 0.3H), 4.23 (dd, $J$ = 8.7, 4.4, 0.7H), 3.56/3.53 (two singlets, 3H), 3.48-3.40 (m, 2H), 2.22-2.10 (m, 1H), 0.85 (s, 9H), ~0.84 (d, 0.9H, overlapped with t-Bu signal), 0.79 (d, $J$ = 7, 2.1H),

0.02/0.01/0.00 (three overlapping singlets, 6H). LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328.16; found 328.46. *Cap*-80b: $^1H$ NMR ($CDCl_3$, $\delta = 7.24$ ppm, 400 MHz), 6.00 (br d, $J = 6.8$, 1H), 4.36 (dd, $J = 7.1$, 3.1, 1H), 3.87 (dd, $J = 10.5$, 3.0, 1H), 3.67 (s, 3H), 3.58 (dd, $J = 10.6$, 4.8, 1H), 2.35 (m, 1H), 1.03 (d, $J = 7.1$, 3H), 0.90 (s, 9H), 0.08 (s, 6H). LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328.16; found 328.53. The crude products were utilized without further purification.

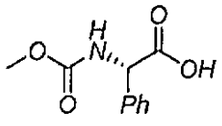
*Cap-81*



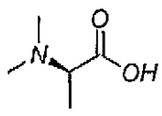
Prepared according to the protocol described by Falb et al. *Synthetic Communications* 1993, *23*, 2839.

*Cap-82 to Cap-85*

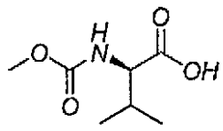
*Cap*-82 to *Cap*-85 were synthesized from appropriate starting materials according to the procedure described for *Cap*-51 or *Cap*-13. The samples exhibited similar spectral profiles as that of their enantiomers (i.e., *Cap*-4, *Cap*-13, *Cap*-51 and *Cap*-52, respectively).



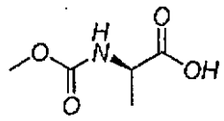
*Cap-82*



*Cap-83*

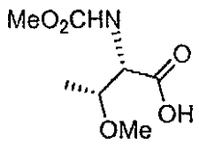


*Cap-84*



*Cap-85*

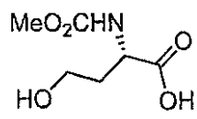
*Cap-86*



To a mixture of O-methyl-L-threonine (3.0 g, 22.55 mmol), NaOH (0.902 g, 22.55 mmol) in $H_2O$ (15 mL) was added $ClCO_2Me$ (1.74 mL, 22.55 mmol) dropwise at 0°C. The mixture was allowed to stir for 12 h and acidified to pH 1 using 1N HCl.

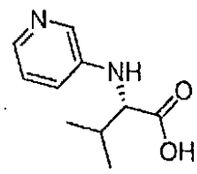
The aqueous phase was extracted with EtOAc and (2x250 mL) and 10% MeOH in $CH_2Cl_2$ (250 mL) and the combined organic phases were concentrated under *in vacuo* to afford a colorless oil (4.18 g, 97%) which was of sufficient purity for use in subsequent steps. $^1$HNMR (400 MHz, $CDCl_3$) δ 4.19 (s, 1H), 3.92-3.97 (m, 1H), 3.66 (s, 3H), 1.17 (d, $J$ = 7.7 Hz, 3H). LCMS: Anal. Calcd. for $C_7H_{13}NO_5$: 191; found: 190 $(M-H)^-$.

*Cap-87*




To a mixture of L-homoserine (2.0 g, 9.79 mmol), $Na_2CO_3$ (2.08 g, 19.59 mmol) in $H_2O$ (15 mL) was added $ClCO_2Me$ (0.76 mL, 9.79 mmol) dropwise at 0°C. The mixture was allowed to stir for 48 h and acidified to pH 1 using 1N HCl. The aqueous phase was extracted with EtOAc and (2X250 mL) and the combined organic phases were concentrated *in vacuo* to afford a colorless solid (0.719 g, 28%) which was of sufficient purity for use in subsequent steps. $^1$HNMR (400 MHz, $CDCl_3$) δ 4.23 (dd, $J$ = 4.5, 9.1 Hz, 1H), 3.66 (s, 3H), 3.43-3.49 (m, 2H), 2.08 – 2.14 (m, 1H), 1.82 – 1.89 (m, 1H). LCMS: Anal. Calcd. for $C_7H_{13}NO_5$: 191; found: 192 $(M+H)^+$.

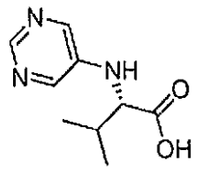
*Cap-88*




A mixture of L-valine (1.0 g, 8.54 mmol), 3-bromopyridine (1.8 mL, 18.7 mmol), $K_2CO_3$ (2.45 g, 17.7 mmol) and CuI (169 mg, 0.887 mmol) in DMSO (10 mL) was heated at 100°C for 12h. The reaction mixture was cooled to rt, poured into $H_2O$ (ca. 150 mL) and washed with EtOAc (x2). The organic layers were extracted with a small amount of $H_2O$ and the combined aq phases were acidified to ca. pH 2 with 6N HCl. The volume was reduced to about one-third and 20g of cation exchange resin (Strata) was added. The slurry was allowed to stand for 20 min and

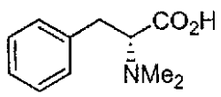
loaded onto a pad of cation exchange resin (Strata) (ca. 25g). The pad was washed with $H_2O$ (200 mL), MeOH (200 mL), and then $NH_3$ (3M in MeOH, 2X200 mL). The appropriate fractions was concentrated *in vacuo* and the residue (ca. 1.1 g) was dissolved in $H_2O$, frozen and lyophyllized. The title compound was obtained as a foam (1.02 g, 62%). $^1$HNMR (400 MHz, DMSO-$d_6$) δ 8.00 (s, br, 1H), 7.68 – 7.71 (m, 1H), 7.01 (s, br, 1H), 6.88 (d, $J$ = 7.5 Hz, 1H), 5.75 (s, br, 1H), 3.54 (s, 1H), 2.04 – 2.06 (m, 1H), 0.95 (d, $J$ = 6.0 Hz, 3H), 0.91 (d, $J$ = 6.6 Hz, 3H). LCMS: Anal. Calcd. for $C_{10}H_{14}N_2O_2$: 194; found: 195 $(M+H)^+$.

*Cap-89*



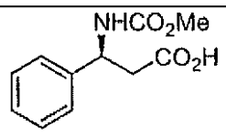
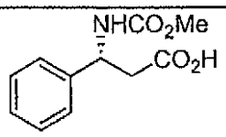
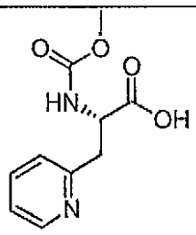
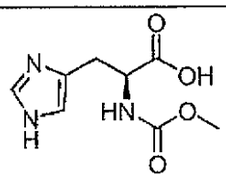
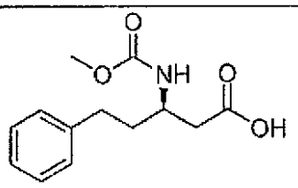

A mixture of L-valine (1.0 g, 8.54 mmol), 5-bromopyrimidine (4.03 g, 17.0 mmol), $K_2CO_3$ (2.40 g, 17.4 mmol) and CuI (179 mg, 0.94 mmol) in DMSO (10 mL) was heated at 100°C for 12h. The reaction mixture was cooled to RT, poured into $H_2O$ (ca. 150 mL) and washed with EtOAc (x2). The organic layers were extracted with a small amount of $H_2O$ and the combined aq phases were acidified to ca. pH 2 with 6N HCl. The volume was reduced to about one-third and 20g of cation exchange resin (Strata) was added. The slurry was allowed to stand for 20 min and loaded onto a pad of cation exchange resin (Strata) (ca. 25g). The pad was washed with $H_2O$ (200 mL), MeOH (200 mL), and then $NH_3$ (3M in MeOH, 2x200 mL). The appropriate fractions was concentrated *in vacuo* and the residue (ca. 1.1 g) was dissolved in $H_2O$, frozen and lyophyllized. The title compound was obtained as a foam (1.02 g, 62%). $^1$HNMR (400 MHz, $CD_3OD$) showed the mixture to contain valine and the purity could not be estimated. The material was used as is in subsequent reactions. LCMS: Anal. Calcd. for $C_9H_{13}N_3O_2$: 195; found: 196 $(M+H)^+$.

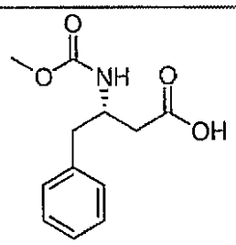
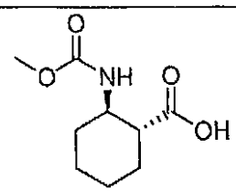
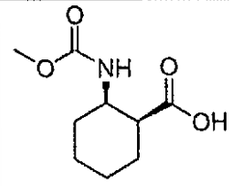
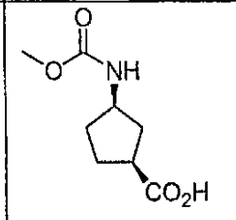
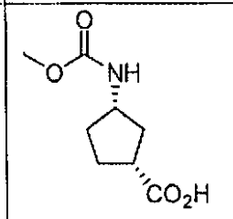
*Cap–90*

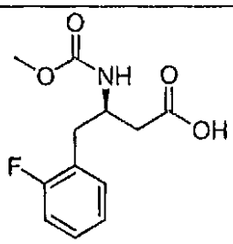
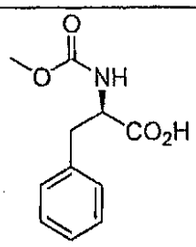
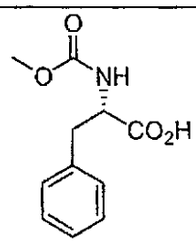
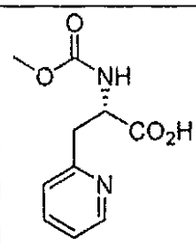
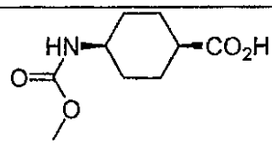
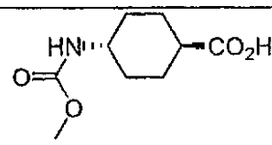


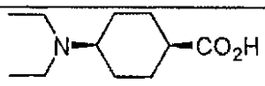
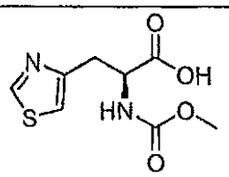
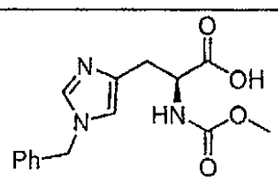
*Cap*-90 was prepared according to the method described for the preparation of *Cap*-1. The crude material was used as is in subsequent steps. LCMS: Anal. Calcd. for $C_{11}H_{15}NO_2$: 193; found: 192 $(M-H)^-$.

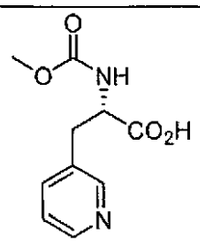
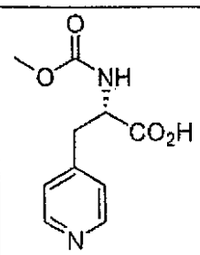
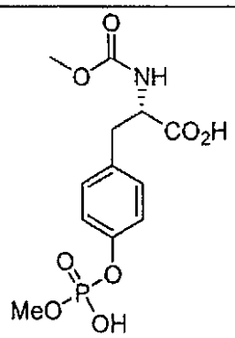
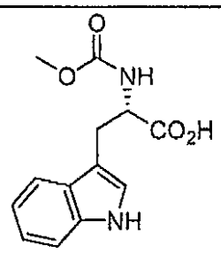
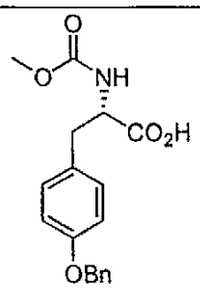
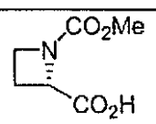
The following caps were prepared according to the method used for preparation of cap 51 unless noted otherwise:

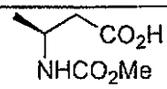
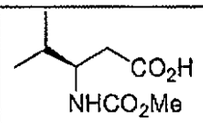
| Cap | Structure | LCMS |
|---|---|---|
| *Cap-91* |  | LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$. |
| *Cap-92* |  | LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$. |
| *Cap-93* |  | LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$. |
| *Cap-94* |  | LCMS: Anal. Calcd. for $C_8H_{11}N_3O_4$: 213; found: 214 $(M+H)^+$. |
| *Cap-95* |  | LCMS: Anal. Calcd. for $C_{13}H_{17}NO_4$: 251; found: 250 $(M-H)^-$. |

| | | |
|---|---|---|
| *Cap-96* |  | LCMS: Anal. Calcd. for $C_{12}H_{15}NO_4$: 237; found: 236 $(M-H)^-$. |
| *Cap-97* |  | LCMS: Anal. Calcd. for $C_9H_{15}NO_4$: 201; found: 200 $(M-H)^-$. |
| *Cap-98* |  | LCMS: Anal. Calcd. for $C_9H_{15}NO_4$: 201; found: 202 $(M+H)^+$. |
| *Cap-99* |  | $^1$HNMR (400 MHz, $CD_3OD$) δ 3.88 – 3.94 (m, 1H), 3.60, 3.61 (s, 3H), 2.80 (m, 1H), 2.20 (m 1H), 1.82 – 1.94 (m, 3H), 1.45 – 1.71 (m, 2H). |
| *Cap-99a* |  | $^1$HNMR (400 MHz, $CD_3OD$) δ 3.88 – 3.94 (m, 1H), 3.60, 3.61 (s, 3H), 2.80 (m, 1H), 2.20 (m 1H), 1.82 – 1.94 (m, 3H), 1.45 – 1.71 (m, 2H). |

| | | |
|---|---|---|
| *Cap-100* |  | LCMS: Anal. Calcd. for $C_{12}H_{14}NO_4F$: 255; found: 256 $(M+H)^+$. |
| *Cap-101* |  | LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$. |
| *Cap-102* |  | LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$ |
| *Cap-103* |  | LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$. |
| *Cap-104* |  | $^1$HNMR (400 MHz, $CD_3OD$) δ 3.60 (s, 3H), 3.50 – 3.53 (m, 1H), 2.66 – 2.69 and 2.44 – 2.49 (m, 1H), 1.91 – 2.01 (m, 2H), 1.62 – 1.74 (m, 4H), 1.51 – 1.62 (m, 2H). |
| *Cap-105* |  | $^1$HNMR (400 MHz, $CD_3OD$) δ 3.60 (s, 3H), 3.33 – 3.35 (m, 1H, partially obscured by |

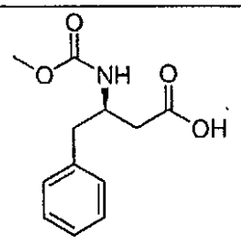
| | | |
|---|---|---|
| | | solvent), 2.37 – 2.41 and 2.16 – 2.23 (m, 1H), 1.94 – 2.01 (m, 4H), 1.43 – 1.53 (m, 2H), 1.17 – 1.29 (m, 2H). |
| *Cap-106* |  Prepared from cis-4-aminocyclohexane carboxylic acid and acetaldehyde by employing a similar procedure described for the synthesis of Cap-2. The crude HCl salt was passed through MCX ($MeOH/H_2O/CH_2Cl_2$ wash; 2 N $NH_3$/MeOH elution) to afford an oil, which was dissolved in $CH_3CN/H_2O$ and lyophilized to afford a tan solid. | $^1$HNMR (400 MHz, $CD_3OD$) δ 3.16 (q, $J$ = 7.3 Hz, 4H), 2.38 - 2.41 (m, 1H), 2.28 – 2.31 (m, 2H), 1.79 – 1.89 (m, 2H), 1.74 (app, ddd $J$ = 3.5, 12.5, 15.9 Hz, 2H), 1.46 (app dt $J$ = 4.0, 12.9 Hz, 2H), 1.26 (t, $J$ = 7.3 Hz, 6H) |
| *Cap-107* |  | LCMS: Anal. Calcd. for $C_8H_{10}N_2O_4S$: 230; found: 231 $(M+H)^+$. |
| *Cap-108* |  | LCMS: Anal. Calcd. for $C_{15}H_{17}N_3O_4$: 303; found: 304 $(M+H)^+$. |

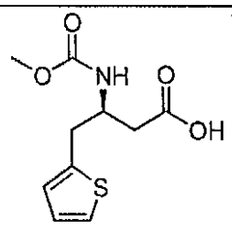
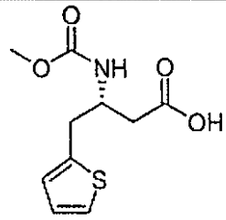
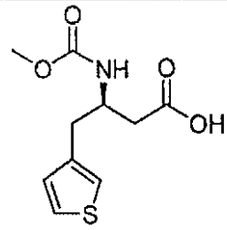
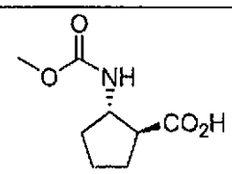
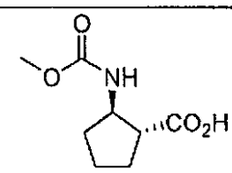
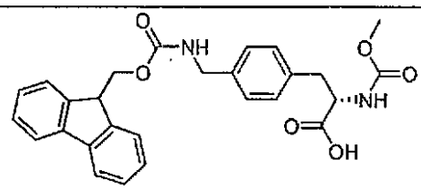
| | | |
|---|---|---|
| *Cap-109* |  | LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$. |
| *Cap-110* |  | LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$. |
| *Cap-111* |  | LCMS: Anal. Calcd. for $C_{12}H_{16}NO_8P$: 333; found: 334 $(M+H)^+$. |
| *Cap-112* |  | LCMS: Anal. Calcd. for $C_{13}H_{14}N_2O_4$: 262; found: 263 $(M+H)^+$. |
| *Cap-113* |  | LCMS: Anal. Calcd. for $C_{18}H_{19}NO_5$: 329; found: 330 $(M+H)^+$. |
| *Cap-114* |  | $^1$HNMR (400 MHz, $CDCl_3$) δ 4.82 – 4.84 (m, 1H), 4.00 – 4.05 (m, 2H), 3.77 (s, 3H), 2.56 (s, br, |

| | | |
|---|---|---|
| | | 2H) |
| *Cap-115* |  | $^1$HNMR (400 MHz, $CDCl_3$) δ 5.13 (s, br, 1H), 4.13 (s, br, 1H), 3.69 (s, 3H), 2.61 (d, $J$ = 5.0 Hz, 2H), 1.28 (d, $J$ = 9.1 Hz, 3H). |
| *Cap-116* |  | $^1$HNMR (400 MHz, $CDCl_3$) δ 5.10 (d, $J$ = 8.6 Hz, 1H), 3.74 – 3.83 (m, 1H), 3.69 (s, 3H), 2.54 – 2.61 (m, 2H), 1.88 (sept, $J$ = 7.0 Hz, 1H), 0.95 (d, $J$ = 7.0 Hz, 6H). |

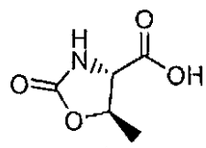
*Cap-117 to Cap-123*

For the preparation of *Cap*-117 to *Cap*-123 the Boc amino acids were obtained from commercially sources and were deprotected by treatment with 25% TFA in $CH_2Cl_2$. After complete reaction as judged by LCMS the solvents were removed *in vacuo* and the corresponding TFA salt of the amino acid was carbamoylated with methyl chloroformate according to the procedure described for *Cap*-51.

| Cap | Structure | LCMS |
|---|---|---|
| *Cap-117* |  | LCMS: Anal. Calcd. for $C_{12}H_{15}NO_4$: 237; found: 238 $(M+H)^+$. |

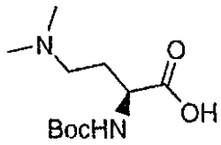
| | | |
|---|---|---|
| *Cap-118* |  | LCMS: Anal. Calcd. for $C_{10}H_{13}NO_4S$: 243; found: 244 $(M+H)^+$. |
| *Cap-119* |  | LCMS: Anal. Calcd. for $C_{10}H_{13}NO_4S$: 243; found: 244 $(M+H)^+$. |
| *Cap-120* |  | LCMS: Anal. Calcd. for $C_{10}H_{13}NO_4S$: 243; found: 244 $(M+H)^+$. |
| *Cap-121* |  | $^1$HNMR (400 MHz, $CDCl_3$) δ 4.06 – 4.16 (m, 1H), 3.63 (s, 3H), 3.43 (s, 1H), 2.82 and 2.66 (s, br, 1H), 1.86 – 2.10 (m, 3H), 1.64 – 1.76 (m, 2H), 1.44 – 1.53 (m, 1H). |
| *Cap-122* |  | $^1$HNMR profile is similar to that of its enantiomer, Cap-121. |
| *Cap-123* |  | LCMS: Anal. Calcd. for $C_{27}H_{26}N_2O_6$: 474; found: 475 $(M+H)^+$. |

*Cap*-124



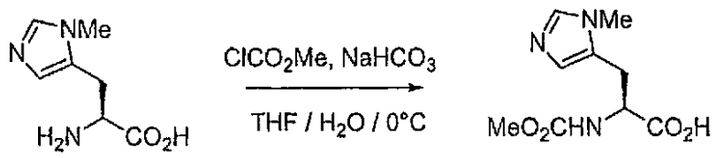
The hydrochloride salt of L-threonine tert-butyl ester was carbamoylated according to the procedure for *Cap*-51. The crude reaction mixture was acidified with 1N HCl to pH~1 and the mixture was extracted with EtOAc (2X50 mL). The combined organic phases were concentrated *in vacuo* to give a colorless oil which solidified on standing. The aqueous layer was concentrated *in vacuo* and the resulting mixture of product and inorganic salts was triturated with EtOAc-$CH_2Cl_2$-MeOH (1:1:0.1) and then the organic phase concentrated *in vacuo* to give a colorless oil which was shown by LCMS to be the desired product. Both crops were combined to give 0.52 g of a solid. $^1$HNMR (400 MHz, $CD_3OD$) δ 4.60 (m, 1H), 4.04 (d, $J$ = 5.0 Hz, 1H), 1.49 (d, $J$ = 6.3 Hz, 3H). LCMS: Anal. Calcd. for $C_5H_7NO_4$: 145; found: 146 $(M+H)^+$.

*Cap*-125



To a suspension of $Pd(OH)_2$, (20%, 100 mg), aqueous formaldehyde (37% wt, 4 ml), acetic acid, (0.5 mL) in methanol (15 mL) was added (S)-4-amino-2-(tert-butoxycarbonylamino)butanoic acid (1 g, 4.48 mmol). The reaction was purged several times with hydrogen and was stirred overnight with an hydrogen balloon room temp. The reaction mixture was filtered through a pad of diatomaceous earth (Celite®), and the volatile component was removed in vacuo. The resulting crude material was used as is for the next step. LC/MS: Anal. Calcd. for $C_{11}H_{22}N_2O_4$: 246; found: 247 $(M+H)^+$.

*Cap*-126

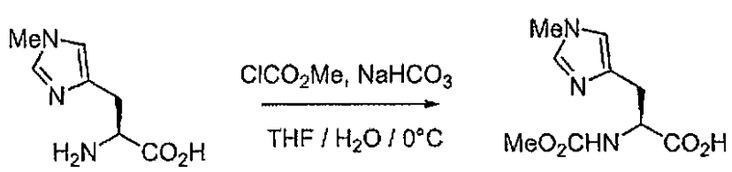



*cj-25* *cap-126*

This procedure is a modification of that used to prepare *Cap*-51. To a suspension of 3-methyl-L-histidine (0.80 g, 4.70 mmol) in THF (10mL) and $H_2O$ (10 mL) at 0°C was added $NaHCO_3$ (0.88 g, 10.5 mmol). The resulting mixture was treated with $ClCO_2Me$ (0.40 mL, 5.20 mmol) and the mixture allowed to stir at 0°C. After stirring for ca. 2h LCMS showed no starting material remaining. The reaction was acidified to pH 2 with 6 N HCl.

The solvents were removed *in vacuo* and the residue was suspended in 20 mL of 20% MeOH in $CH_2Cl_2$. The mixture was filtered and concentrated to give a light yellow foam (1.21 g,). LCMS and $^1$H NMR showed the material to be a 9:1 mixture of the methyl ester and the desired product. This material was taken up in THF (10mL) and $H_2O$ (10mL), cooled to 0°C and LiOH (249.1 mg, 10.4 mmol) was added. After stirring ca. 1h LCMS showed no ester remaining. Therefore the mixture was acidified with 6N HCl and the solvents removed *in vacuo*. LCMS and $^1$H NMR confirm the absence of the ester. The title compound was obtained as its HCl salt contaminated with inorganic salts (1.91 g, >100%). The compound was used as is in subsequent steps without further purification. $^1$HNMR (400 MHz, $CD_3OD$) δ 8.84, (s, 1H), 7.35 (s, 1H), 4.52 (dd, $J$ = 5.0, 9.1 Hz, 1H), 3.89 (s, 3H), 3.62 (s, 3H), 3.35 (dd, $J$ = 4.5, 15.6 Hz, 1H, partially obscured by solvent), 3.12 (dd, $J$ = 9.0, 15.6 Hz, 1H).LCMS: Anal. Calcd. for $C_9H_{13}N_3O_4$: 227.09; found: 228.09 $(M+H)^+$.

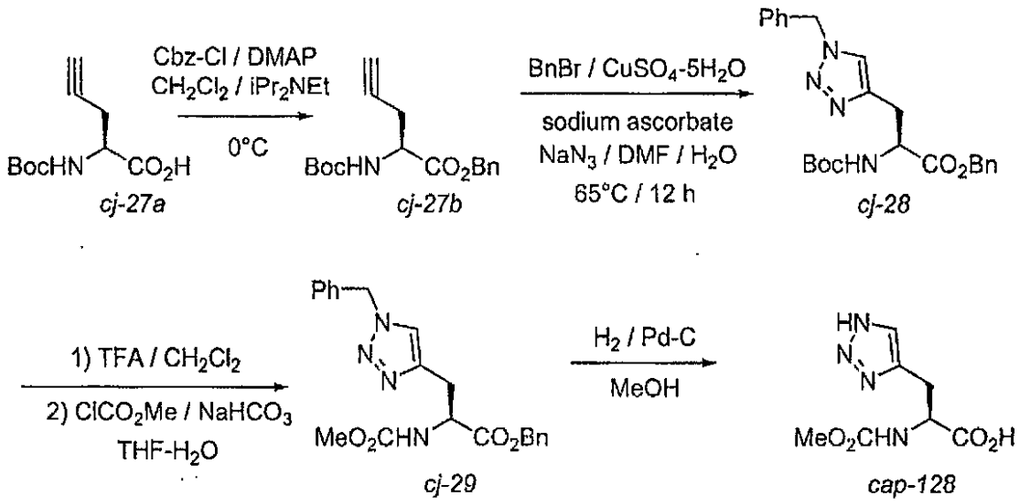
*Cap*-127



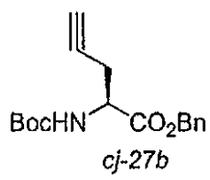

*cj-26* *cap-127*

*Cap*-127 was prepared according to the method for *Cap*-126 above starting from (S)-2-amino-3-(1-methyl-1H-imidazol-4-yl)propanoic acid (1.11 g, 6.56 mmol), $NaHCO_3$ (1.21 g, 14.4 mmol) and $ClCO_2Me$ (0.56 mL, 7.28 mmol). The title compound was obtained as its HCl salt (1.79 g, >100%) contaminated with inorganic salts. LCMS and $^1H$ NMR showed the presence of ca. 5% of the methyl ester. The crude mixture was used as is without further purification. $^1$HNMR (400 MHz, $CD_3OD$) δ 8.90 (s, 1H), 7.35 (s, 1H), 4.48 (dd, $J$ = 5.0, 8.6 Hz, 1H), 3.89 (s, 3H), 3.62 (s, 3H), 3.35 (m, 1H), 3.08 (m, 1H); LCMS: Anal. Calcd. for $C_9H_{13}N_3O_4$: 227.09; found: 228 $(M+H)^+$.

*Preparation of Cap*-128




*Step 1*. Preparation of (S)-benzyl 2-(tert-butoxycarbonylamino)pent-4-ynoate (cj-27b).

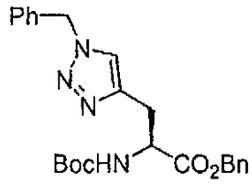



*cj-27b*

To a solution of *cj-27a* (1.01 g, 4.74 mmol), DMAP (58 mg, 0.475 mmol) and $iPr_2NEt$ (1.7 mL, 9.8 mmol) in $CH_2Cl_2$ (100 mL) at 0°C was added Cbz-Cl (0.68 mL, 4.83 mmol). The solution was allowed to stir for 4 h at 0°C, washed (1N $KHSO_4$, brine), dried ($Na_2SO_4$), filtered, and concentrated *in vacuo*. The residue was purified

by flash column chromatography (TLC 6:1 hex:EtOAc) to give the title compound (1.30 g, 91%) as a colorless oil. $^1$HNMR (400 MHz, $CDCl_3$) δ 7.35 (s, 5H), 5.35 (d, br, $J$ = 8.1 Hz, 1H), 5.23 (d, $J$ = 12.2 Hz, 1H), 5.17 (d, $J$ = 12.2 Hz, 1H), 4.48 – 4.53 (m, 1H), 2.68 – 2.81 (m, 2H), 2.00 (t, $J$ = 2.5 Hz, 1H), 1.44 (s, 9H). LCMS: Anal. Calcd. for $C_{17}H_{21}NO_4$: 303; found: 304 $(M+H)^+$.

*Step 2.* Preparation of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(tert-butoxycarbonylamino)propanoate (cj-28).

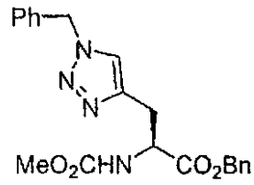



*cj-28*

To a mixture of (S)-benzyl 2-(tert-butoxycarbonylamino)pent-4-ynoate (0.50 g, 1.65 mmol), sodium ascorbate (0.036 g, 0.18 mmol), $CuSO_4$-$5H_2O$ (0.022 g, 0.09 mmol) and $NaN_3$ (0.13 g, 2.1 mmol) in DMF-$H_2O$ (5 mL, 4:1) at rt was added BnBr (0.24 mL, 2.02 mmol) and the mixture was warmed to 65°C. After 5h LCMS indicated low conversion. A further portion of $NaN_3$ (100 mg) was added and heating was continued for 12h. The reaction was poured into EtOAc and $H_2O$ and shaken. The layers were separated and the aqueous layer extracted 3x with EtOAc and the combined organic phases washed ($H_2O$ x3, brine), dried ($Na_2SO_4$), filtered, and concentrated. The residue was purified by flash (Biotage, 40+M 0-5% MeOH in $CH_2Cl_2$; TLC 3% MeOH in $CH_2Cl_2$) to afford a light yellow oil which solidified on standing (748.3 mg, 104%). The NMR was consistent with the desired product but suggests the presence of DMF. The material was used as is without further purification. $^1$HNMR (400 MHz, DMSO-$d_6$) δ 7.84 (s, 1H), 7.27 – 7.32 (m, 10H), 5.54 (s, 2H), 5.07 (s, 2H), 4.25 (m, 1H), 3.16 (dd, $J$ = 1.0, 5.3 Hz, 1H), 3.06 (dd, $J$ = 5.3, 14.7 Hz), 2.96 (dd, $J$ = 9.1, 14.7 Hz, 1H), 1.31 (s, 9H).

LCMS: Anal. Calcd. for $C_{24}H_{28}N_4O_4$: 436; found: 437 $(M+H)^+$.

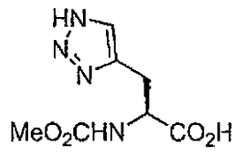
*Step 3.* Preparation of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(methoxycarbonylamino)propanoate (cj-29).



*cj-29*

A solution of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(tert-butoxycarbonylamino)propanoate (0.52 g, 1.15 mmol) in $CH_2Cl_2$ was added TFA (4 mL). The mixture was allowed to stir at room temperature for 2h. The mixture was concentrated *in vacuo* to give a colorless oil which solidified on standing. This material was dissolved in THF-$H_2O$ and cooled to 0°C. Solid $NaHCO_3$ (0.25 g, 3.00 mmol) was added followed by $ClCO_2Me$ (0.25 mL, 3.25 mmol). After stirring for 1.5h the mixture was acidified to pH~2 with 6N HCl and then poured into $H_2O$-EtOAc. The layers were separated and the aq phase extracted 2x with EtOAc. The combined org layers were washed ($H_2O$, brine), dried ($Na_2SO_4$), filtered, and concentrated *in vacuo* to give a colorless oil (505.8 mg, 111%, NMR suggested the presence of an unidentified impurity) which solidified while standing on the pump. The material was used as is without further purification. $^1$HNMR (400 MHz, DMSO-$d_6$) δ 7.87 (s, 1H), 7.70 (d, $J$ = 8.1 Hz, 1H), 7.27 – 7.32 (m, 10H), 5.54 (s, 2H), 5.10 (d, $J$ = 12.7 Hz, 1H), 5.06 (d, $J$ = 12.7 Hz, 1H), 4.32 – 4.37 (m, 1H), 3.49 (s, 3H), 3.09 (dd, $J$ = 5.6, 14.7 Hz, 1H), 2.98 (dd, $J$ = 9.6, 14.7 Hz, 1H). LCMS: Anal. Calcd. for $C_{21}H_{22}N_4O_4$: 394; found: 395 $(M+H)^+$.

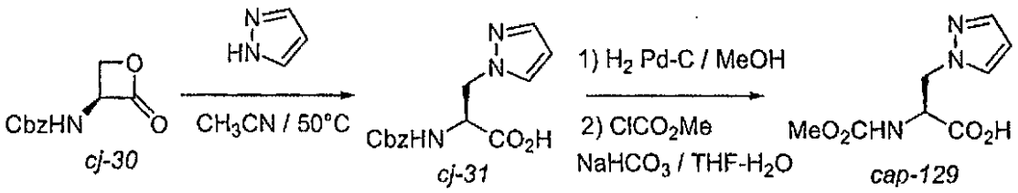
*Step 4.* Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-1,2,3-triazol-4-yl)propanoic acid (*Cap*-128).



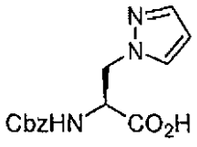
*Cap-128*

(S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(methoxycarbonylamino)propanoate (502 mg, 1.11 mmol) was hydrogenated in the presence of Pd-C (82 mg) in MeOH (5 mL) at atmospheric pressure for 12h. The mixture was filtered through diatomaceous earth (Celite®) and concentrated *in vacuo*. (S)-2-(methoxycarbonylamino)-3-(1H-1,2,3-triazol-4-yl)propanoic acid was obtained as a colorless gum (266 mg, 111%) which was contaminated with ca. 10% of the methyl ester. The material was used as is without further purification. $^1$HNMR (400 MHz, DMSO-$d_6$) δ 12.78 (s, br, 1H), 7.59 (s, 1H), 7.50 (d, $J$ = 8.0 Hz, 1H), 4.19 – 4.24 (m, 1H), 3.49 (s, 3H), 3.12 (dd, $J$ = 4.8 Hz, 14.9 Hz, 1H), 2.96 (dd, $J$ = 9.9, 15.0 Hz, 1H). LCMS: Anal. Calcd. for $C_7H_{10}N_4O_4$: 214; found: 215 $(M+H)^+$.

*Preparation of Cap-129*




*Step 1.* Preparation of (S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (cj-31).

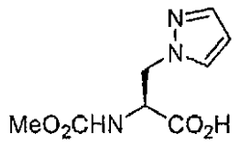



*cj-31*

A suspension of (S)-benzyl 2-oxooxetan-3-ylcarbamate (0.67 g, 3.03 mmol), and pyrazole (0.22 g, 3.29 mmol) in $CH_3CN$ (12 mL) was heated at 50 °C for 24h. The mixture was cooled to rt overnight and the solid filtered to afford (S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (330.1 mg). The filtrate was concentrated *in vacuo* and then triturated with a small amount of $CH_3CN$ (ca. 4 mL) to afford a second crop (43.5 mg). Total yield 370.4 mg (44%). m.p. 165.5 – 168°C. lit m.p. 168.5 – 169.5 [Vederas et al. *J. Am. Chem. Soc.* 1985, *107*, 7105]. $^1$HNMR (400 MHz, $CD_3OD$) δ 7.51 (d, $J$ = 2.0, 1H), 7.48 (s, $J$ = 1.5 Hz, 1H), 7.24 – 7.34 (m, 5H), 6.23 m, 1H), 5.05 (d, 12.7 H, 1H), 5.03 (d, $J$ = 12.7 Hz,

1H), 4.59 – 4.66 (m, 2H), 4.42 – 4.49 (m, 1H). LCMS: Anal. Calcd. for $C_{14}H_{15}N_3O_4$: 289; found: 290 $(M+H)^+$.

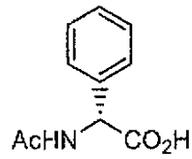
*Step 2.* Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (*Cap-129*).



*cap-129*

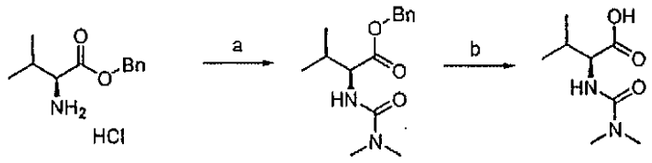
(S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (0.20 g, 0.70 mmol) was hydrogenated in the presence of Pd-C (45 mg) in MeOH (5 mL) at atmospheric pressure for 2h. The product appeared to be insoluble in MeOH, therefore the reaction mixture was diluted with 5mL $H_2O$ and a few drops of 6N HCl. The homogeneous solution was filtered through diatomaceous earth (Celite®), and the MeOH removed *in vacuo*. The remaining solution was frozen and lyophyllized to give a yellow foam (188.9 mg). This material was suspended in THF-$H_2O$ (1:1, 10mL) and then cooled to 0°C. To the cold mixture was added $NaHCO_3$ (146.0 mg, 1.74 mmol) carefully (evolution of $CO_2$). After gas evolution had ceased (ca. 15 min) $ClCO_2Me$ (0.06 mL, 0.78 mmol) was added dropwise. The mixture was allowed to stir for 2h and was acidified to pH~2 with 6N HCl and poured into EtOAc. The layers were separated and the aqueous phase extracted with EtOAC (x5). The combined organic layers were washed (brine), dried ($Na_2SO_4$), filtered, and concentrated to give the title compound as a colorless solid (117.8 mg, 79%). $^1$HNMR (400 MHz, DMSO-$d_6$) δ 13.04 (s, 1H), 7.63 (d, $J$ = 2.6 Hz, 1H), 7.48 (d, $J$ = 8.1 Hz, 1H), 7.44 (d, $J$ = 1.5 Hz, 1H), 6.19 (app t, $J$ = 2.0 Hz, 1H), 4.47 (dd, $J$ = 3.0, 12.9 Hz, 1H), 4.29 – 4.41 (m, 2H), 3.48 (s, 3H). LCMS: Anal. Calcd. for $C_8H_{11}N_3O_4$: 213; found: 214 $(M+H)^+$.

*Cap*-130




*Cap*-130 was prepared by acylation of commercially available (R)-phenylglycine analgous to the procedure given in: Calmes, M.; Daunis, J.; Jacquier, R.; Verducci, J. *Tetrahedron*, 1987, *43*(10), 2285.

*Cap-131*

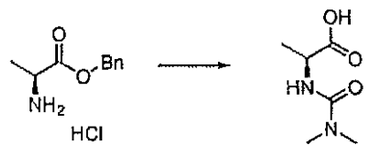



*Step a:* Dimethylcarbamoyl chloride (0.92 mL, 10 mmol) was added slowly to a solution of (S)-benzyl 2-amino-3-methylbutanoate hydrochloride (2.44 g; 10 mmol) and Hunig's base (3.67 mL, 21 mmol) in THF (50 mL). The resulting white suspension was stirred at room temperature overnight (16 hours) and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography, eluting with ethyl acetate:hexanes (1:1). Collected fractions were concentrated under vacuum providing 2.35 g (85%) of clear oil. $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 0.84 (d, *J*=6.95 Hz, 3H), 0.89 (d, *J*=6.59 Hz, 3H), 1.98-2.15 (m, 1H), 2.80 (s, 6H), 5.01-5.09 (m, *J*=12.44 Hz, 1H), 5.13 (d, *J*=12.44 Hz, 1H), 6.22 (d, *J*=8.05 Hz, 1H), 7.26-7.42 (m, 5H). LC (Cond. 1): RT = 1.76 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{16}H_{22}N_2O_3$: 279.17; found 279.03.

*Step b*: To a MeOH (50 mL) solution of the intermediate prepared above (2.35 g; 8.45 mmol) was added Pd/C (10%; 200 mg) and the resulting black suspension was flushed with $N_2$ (3x) and placed under 1 atm of $H_2$. The mixture was stirred at room temperature overnight and filtered though a microfiber filter to remove the catalyst. The resulting clear solution was then concentrated under reduced pressure to obtain 1.43 g (89%) of *Cap-131* as a white foam, which was used

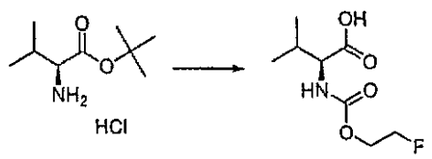
without further purification. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 0.87 (d, *J*=4.27 Hz, 3H), 0.88 (d, *J*=3.97 Hz, 3H), 1.93-2.11 (m, 1H), 2.80 (s, 6H), 3.90 (dd, *J*=8.39, 6.87 Hz, 1H), 5.93 (d, *J*=8.54 Hz, 1H), 12.36 (s, 1H). LC (Cond. 1): RT = 0.33 min; MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{17}N_2O_3$: 189.12; found 189.04.

*Cap-132*



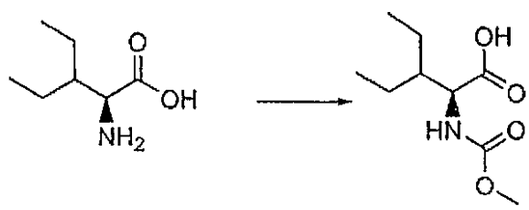

*Cap-132* was prepared from (S)-benzyl 2-aminopropanoate hydrochloride according to the method described for *Cap-131*. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 1.27 (d, *J*=7.32 Hz, 3H), 2.80 (s, 6H), 4.06 (qt, 1H), 6.36 (d, *J*=7.32 Hz, 1H), 12.27 (s, 1H). LC (Cond. 1): RT = 0.15 min; MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{13}N_2O_3$: 161.09; found 161.00.

*Cap-133*



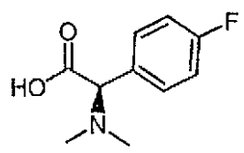

*Cap-133* was prepared from (S)-*tert*-butyl 2-amino-3-methylbutanoate hydrochloride and 2-fluoroethyl chloroformate according to the method described for *Cap-47*. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 0.87 (t, *J* = 6.71 Hz, 6H), 1.97-2.10 (m, 1H), 3.83 (dd, *J*=8.39, 5.95 Hz, 1H), 4.14-4.18 (m, 1H), 4.20-4.25 (m, 1H), 4.50-4.54 (m, 1H), 4.59-4.65 (m, 1H), 7.51 (d, *J* = 8.54 Hz, 1H), 12.54 (s, 1H).

*Cap-134*



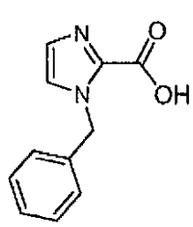
*Cap-134* was prepared from (S)-diethyl alanine and methyl chloroformate according to the method described for *Cap-51*. $^1$H NMR (500 MHz, DMSO-$d_6$) δ ppm 0.72-0.89 (m, 6H), 1.15-1.38 (m, 4H), 1.54-1.66 (m, 1H), 3.46-3.63 (m, 3H), 4.09 (dd, $J$ = 8.85, 5.19 Hz, 1H), 7.24 (d, $J$ = 8.85 Hz, 1H), 12.55 (s, 1H). LC (Cond. 2): RT = 0.66 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{18}NO_4$: 204.12; found 204.02.

*Cap-135*




A solution of D-2-amino-(4-fluorophenyl)acetic acid (338 mg, 2.00 mmol), 1*N* HCl in diethylether (2.0 mL, 2.0 mmol) and formalin (37%, 1 mL) in methanol (5 mL) was subjected to balloon hydrogenation over 10% palladium on carbon (60 mg) for 16 h at 25 °C. The mixture was then filtered through Celite to afford the HCl salt of *Cap-135* as a white foam (316 mg, 80%). $^1$H NMR (300 MHz, MeOH-$d_4$) δ 7.59 (dd, $J$ = 8.80, 5.10 Hz, 2H), 7.29 (t, $J$ = 8.6 Hz, 2H), 5.17 (s, 1H), 3.05 (v br s, 3H), 2.63 (v br s, 3H); $R_t$ = 0.19 min (Cond.-MS-W5); 95% homogenity index; LRMS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{13}FNO_2$: 198.09; found: 198.10.

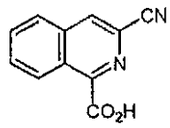
*Cap-136*



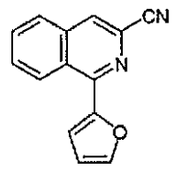

To a cooled (-50 °C) suspension of 1-benzyl-1*H*-imidazole (1.58 g, 10.0 mmol) in anhydrous diethyl ether (50 mL) under nitrogen was added *n*-butyl lithium (2.5 M in hexanes, 4.0 mL, 10.0 mmol) dropwise. After being stirred for 20 min at -50 °C, dry carbon dioxide (passed through Drierite) was bubbled into the reaction mixture for 10 min before it was allowed to warm up to 25 °C. The heavy precipitate which formed on addition of carbon dioxide to the reaction mixture was filtered to

yield a hygroscopic, white solid which was taken up in water (7 mL), acidified to pH = 3, cooled, and induced to crystallize with scratching. Filtration of this precipitate gave a white solid which was suspended in methanol, treated with 1*N* HCl/diethyl ether (4 mL) and concentrated *in vacuo*. Lyophilization of the residue from water (5 mL) afforded the HCl salt of *Cap-136* as a white solid (817 mg, 40%). $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7.94 (d, $J$ = 1.5 Hz, 1H), 7.71 (d, $J$ = 1.5 Hz, 1H), 7.50-7.31 (m, 5H), 5.77 (s, 2H); $R_t$ = 0.51 min (Cond.-MS-W5); 95% homogenity index; LRMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{12}N_2O_2$: 203.08; found: 203.11.

*Cap-137*




*Cap-137, step a*



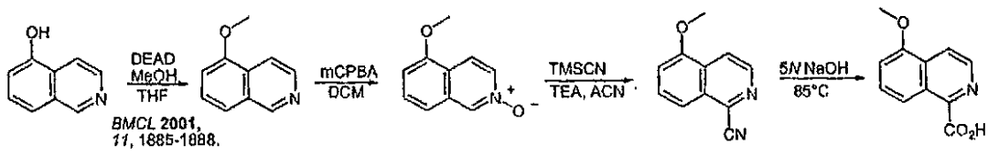

A suspension of 1-chloro-3-cyanoisoquinoline (188 mg, 1.00 mmol; prepared according to the procedure in WO 2003/ 099274) (188 mg, 1.00 mmol), cesium fluoride (303.8 mg, 2.00 mmol), bis(tri-*tert*-butylphosphine)palladium dichloride (10 mg, 0.02 mmol) and 2-(tributylstannyl)furan (378 μL, 1.20 mmol) in anhydrous dioxane (10 mL) under nitrogen was heated at 80 °C for 16 h before it was cooled to 25 °C and treated with saturated, aqueous potassium fluoride solution with vigorous stirring for 1 h. The mixture was partitioned between ethyl acetate and water and the organic phase was separated, washed with brine, dried over $Na_2SO_4$, filtered and concentrated. Purification of the residue on silica gel (elution with 0% to 30% ethyl acetate/hexanes) afforded *Cap-137, step a* (230 mg, 105%) as a white solid which was carried forward directly. $R_t$ = 1.95 min (Cond.-MS-W2); 90% homogeneity index; LRMS: Anal. Calc. for $[M+H]^+$ $C_{14}H_8N_2O$: 221.07; found: 221.12.

*Cap-137*

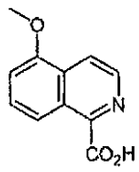
To a suspension of *Cap 137, step a*, (110 mg, 0.50 mmol) and sodium periodate (438 mg, 2.05 mmol) in carbon tetrachloride (1 mL), acetonitrile (1 mL) and water (1.5 mL) was added ruthenium trichloride hydrate (2 mg, 0.011 mmol). The mixture was stirred at 25 °C for 2 h and then partitioned between dichloromethane and water. The aqueous layer was separated, extracted twice more with dichloromethane and the combined dichloromethane extracts were dried over $Na_2SO_4$, filtered and concentrated. Trituration of the residue with hexanes afforded *Cap-137* (55 mg, 55%) as a grayish-colored solid. $R_t$ = 1.10 min (Cond.-MS-W2); 90% homogeneity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_8N_2O_2$: 200.08; found: 200.08.

*Caps 138* to *158*

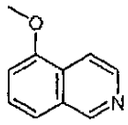
Synthetic Strategy. Method A.




*Cap-138*



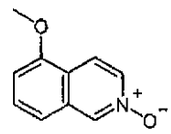

*Cap-138, step a*



To a stirred suspension of 5-hydroxyisoquinoline (prepared according to the procedure in WO 2003/ 099274) (2.0 g, 13.8 mmol) and triphenylphosphine (4.3 g, 16.5 mmol) in dry tetrahydrofuran (20 mL) was added dry methanol (0.8 mL) and

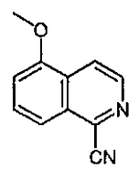
diethyl azodicarboxylate (3.0 mL, 16.5 mmol) portionwise. The mixture was stirred at room temperature for 20 h before it was diluted with ethyl acetate and washed with brine, dried over $Na_2SO_4$, filtered and concentrated. The residue was preabsorbed onto silica gel and chromatographed (elution with 40% ethyl acetate/hexanes) to afford *Cap-138, step a* (1.00 g, 45%) as a light yellow solid. $^1$H NMR ($CDCl_3$, 500 MHz) δ 9.19 (s, 1H), 8.51 (d, $J$ = 6.0 Hz, 1H), 7.99 (d, $J$ = 6.0 Hz, 1H), 7.52-7.50 (m, 2H), 7.00-6.99 (m, 1H), 4.01 (s, 3H); $R_t$ = 0.66 min (Cond.-D2); 95% homogeneity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_{10}NO$: 160.08; found 160.1.

*Cap-138, step b*



To a stirred solution of *Cap 138, step a* (2.34 g, 14.7 mmol) in anhydrous dichloromethane (50 mL) at room temperature was added *meta*-chloroperbenzoic acid (77%, 3.42 g, 19.8 mmol) in one portion. After being stirred for 20 h, powdered potassium carbonate (2.0 g) was added and the mixture was stirred for 1 h at room temperature before it was filtered and concentrated *in vacuo* to afford *Cap-138, step b* (2.15 g, 83%) as a pale, yellow solid which was sufficiently pure to carry forward directly. $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.73 (d, $J$ = 1.5 Hz, 1H), 8.11 (dd, $J$ = 7.3, 1.7 Hz, 1H), 8.04 (d, $J$=7.1 Hz, 1H), 7.52 (t, $J$ = 8.1 Hz, 1H), 7.28 (d, $J$ = 8.3 Hz, 1H), 6.91 (d, $J$ = 7.8 Hz, 1H), 4.00 (s, 3H); $R_t$ = 0.92 min, (Cond.-D1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_{10}NO_2$: 176.07; found: 176.0.

*Cap-138, step c*



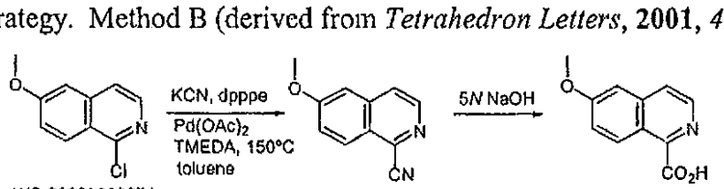
To a stirred solution of *Cap 138, step b* (0.70 g, 4.00 mmol) and triethylamine (1.1 mL, 8.00 mmol) in dry acetonitrile (20 mL) at room temperature under nitrogen

was added trimethylsilylcyanide (1.60 mL, 12.00 mmol). The mixture was heated at 75 °C for 20 h before it was cooled to room temperature, diluted with ethyl acetate and washed with saturated sodium bicarbonate solution and brine prior to drying over $Na_2SO_4$ and solvent concentration. The residue was flash chromatographed on silica gel (gradient elution with 5% ethyl acetate in hexanes to 25% ethyl acetate in hexanes) to afford *Cap-138, step c* (498.7 mg, 68%) as a white, crystalline solid along with 223 mg (30%) of additional *Cap-138, step c* recovered from the filtrate. $^1H$ NMR ($CDCl_3$, 500 MHz) δ 8.63 (d, $J$ = 5.5 Hz, 1H), 8.26 (d, $J$ = 5.5 Hz, 1H), 7.88 (d, $J$ = 8.5 Hz, 1H), 7.69 (t, $J$ = 8.0 Hz, 1H), 7.08 (d, $J$ = 7.5 Hz, 1H), 4.04 (s, 3H); $R_t$ = 1.75 min, (Cond.-D1); 90% homogeneity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_9N_2O$: 185.07; found: 185.10.

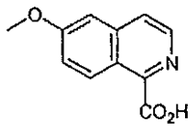
*Cap-138*

*Cap-138, step c* (0.45 g, 2.44 mmol) was treated with 5*N* sodium hydroxide solution (10 mL) and the resulting suspension was heated at 85 °C for 4 h, cooled to 25 °C, diluted with dichloromethane and acidified with 1*N* hydrochloric acid. The organic phase was separated, washed with brine, dried over $Na_2SO_4$, concentrated to ¼ volume and filtered to afford *Cap-138* (0.44g, 88.9%) as a yellow solid. $^1H$ NMR (DMSO-$d_6$, 400 MHz) δ 13.6 (br s, 1H), 8.56 (d, $J$ = 6.0 Hz, 1H), 8.16 (d, $J$ = 6.0 Hz, 1H), 8.06 (d, $J$ = 8.8 Hz, 1H), 7.71-7.67 (m, 1H), 7.30 (d, $J$ = 8.0 Hz, 1H), 4.02 (s, 3H); $R_t$ = 0.70 min (Cond.-D1); 95% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.05.

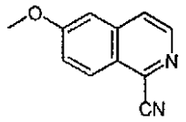
Synthetic Strategy. Method B (derived from *Tetrahedron Letters*, **2001**, *42*, 6707).



*Cap-139*



*Cap-139, step a*

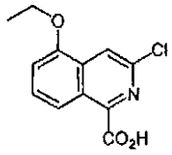


To a thick-walled, screw-top vial containing an argon-degassed suspension of 1-chloro-6-methoxyisoquinoline (1.2 g, 6.2 mmol; prepared according to the procedure in WO 2003/ 099274), potassium cyanide (0.40 g, 6.2 mmol), 1,5-bis(diphenylphosphino)pentane (0.27 g, 0.62 mmol) and palladium (II) acetate (70 mg, 0.31 mmol) in anhydrous toluene (6 mL) was added *N,N,N',N'*-tetramethylethylenediamine (0.29 mL, 2.48 mmol). The vial was sealed, heated at 150 °C for 22 h and then allowed to cool to 25 °C. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over $Na_2SO_4$, filtered and concentrated. The residue was purified on silica gel (gradient elution with 5% ethyl acetate/hexanes to 25% ethyl acetate/hexanes) to afford *Cap-139, step a* (669.7 mg, 59%) as a white solid. $^1$H NMR ($CDCl_3$, 500 MHz) δ 8.54 (d, $J$ = 6.0 Hz, 1H), 8.22 (d, $J$ = 9.0 Hz, 1H), 7.76 (d, $J$ = 5.5 Hz, 1H), 7.41-7.39 (m, 1H), 7.13 (d, $J$ = 2.0 Hz, 1H), 3.98 (s, 3H); $R_t$ = 1.66 min (Cond.-D1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_9N_2O$: 185.07; found: 185.2.

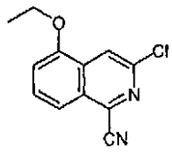
*Cap-139*

*Cap-139* was prepared from the basic hydrolysis of *Cap-139, step a* with 5*N* NaOH according to the procedure described for *Cap 138*. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.63 (v br s, 1H), 8.60 (d, $J$ = 9.3 Hz, 1H), 8.45 (d, $J$ = 5.6 Hz, 1H), 7.95 (d, $J$ = 5.9 Hz, 1H), 7.49 (d, $J$ = 2.2 Hz, 1H), 7.44 (dd, $J$ = 9.3, 2.5 Hz, 1H), 3.95 (s, 3H); $R_t$ = 0.64 min (Cond.-D1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.05.

*Cap-140*



*Cap-140, step a*

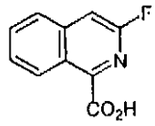


To a vigorously-stirred mixture of 1,3-dichloro-5-ethoxyisoquinoline (482 mg, 2.00 mmol; prepared according to the procedure in WO 2005/ 051410), palladium (II) acetate (9 mg, 0.04 mmol), sodium carbonate (223 mg, 2.10 mmol) and 1,5-bis(diphenylphosphino)pentane (35 mg, 0.08 mmol) in dry dimethylacetamide (2 mL) at 25 °C under nitrogen was added N,N,N',N'-tetramethylethylenediamine (60 mL, 0.40 mmol). After 10 min, the mixture was heated to 150 °C, and then a stock solution of acetone cyanohydrin (prepared from 457 µL of acetone cyanohydrin in 4.34 mL DMA) was added in 1 mL portions over 18 h using a syringe pump. The mixture was then partitioned between ethyl acetate and water and the organic layer was separated, washed with brine, dried over $Na_2SO_4$, filtered and concentrated. The residue was purified on silica gel (gradient elution with 10% ethyl acetate in hexanes to 40% ethyl acetate in hexanes) to afford *Cap-140, step a* (160 mg, 34%) as a yellow solid. $R_t$ = 2.46 min (Cond.-MS-W2); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_9ClN_2O$: 233.05; found: 233.08.

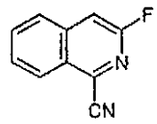
*Cap-140*

*Cap-140* was prepared by the acid hydrolysis of *Cap-140, step a* with 12*N* HCl as described in the procedure for the preparation of *Cap 141*, described below. $R_t$ = 2.24 min (Cond.-MS-W2); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{11}ClNO_3$: 252.04; found: 252.02.

*Cap-141*



*Cap-141, step a*

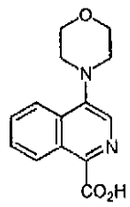


*Cap-141, step a* was prepared from 1-bromo-3-fluoroisoquinoline (prepared from 3-amino-1-bromoisoquinoline using the procedure outlined in *J. Med. Chem.* **1970**, *13*, 613) as described in the procedure for the preparation of *Cap-140, step a* (*vide supra*). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, $J$ = 8.5 Hz, 1H), 7.93 (d, $J$ = 8.5 Hz, 1H), 7.83 (t, $J$ = 7.63 Hz, 1H), 7.77-7.73 (m, 1H), 7.55 (s, 1H); $R_t$ = 1.60 min (Cond.-D1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_6FN_2$: 173.05; found: 172.99.

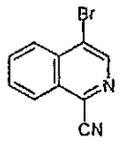
*Cap-141*

*Cap-141, step a* (83 mg, 0.48 mmol) was treated with 12*N* HCl (3 mL) and the resulting slurry was heated at 80 °C for 16 h before it was cooled to room temperature and diluted with water (3 mL). The mixture was stirred for 10 min and then filtered to afford *Cap-141* (44.1 mg, 48%) as an off-white solid. The filtrate was diluted with dichloromethane and washed with brine, dried over $Na_2SO_4$, and concentrated to afford additional *Cap-141* (29.30 mg, 32%) which was sufficiently pure to be carried forward directly. $^1$H NMR (DMSO-$d_6$, 500 MHz) δ 14.0 (br s, 1H), 8.59-8.57 (m, 1H), 8.10 (d, $J$ = 8.5 Hz, 1H), 7.88-7.85 (m, 2H), 7.74-7.71 (m, 1H); $R_t$ = 1.33 min (Cond.-D1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; found: 191.97.

*Cap-142*

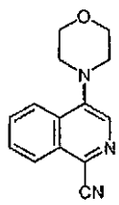


*Cap-142, step a*



*Cap-142, step a* was prepared from 4-bromoisoquinoline N-oxide as described in the two-step procedure for the preparation of *Cap-138, steps b and c*. $R_t$ = 1.45 min (Cond.-MS-W1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_6BrN_2$: 232.97; found: 233.00.

*Cap-142, step b*

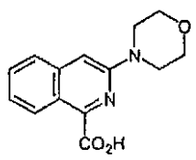


To an argon-degassed suspension of *Cap-142, step a* (116 mg, 0.50 mmol), potassium phosphate tribasic (170 mg, 0.80 mmol), palladium (II) acetate (3.4 mg, 0.015 mmol) and 2-(dicyclohexylphosphino)biphenyl (11 mg, 0.03 mmol) in anhydrous toluene (1 mL) was added morpholine (61 μL, 0.70 mmol). The mixture was heated at 100 °C for 16 h, cooled to 25 °C, filtered through diatomaceous earth (Celite®) and concentrated. Purification of the residue on silica gel (gradient elution with 10% to 70% ethyl acetate in hexanes) afforded *Cap-142, step b* (38 mg, 32%) as a yellow solid which was carried forward directly. $R_t$ = 1.26 min (Cond.-MS-W1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{14}H_{14}N_3O$: 240.11; found: 240.13.

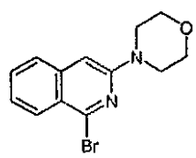
*Cap-142*

*Cap-142* was prepared from *Cap-142, step b* with 5*N* sodium hydroxide as described in the procedure for *Cap 138*. $R_t$ = 0.72 min (Cond.-MS-W1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{14}H_{15}N_2O_3$: 259.11; found: 259.08.

*Cap-143*



*Cap-143, step a*



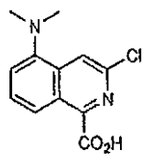
To a stirred solution of 3-amino-1-bromoisoquinoline (444 mg, 2.00 mmol) in anhydrous dimethylformamide (10 mL) was added sodium hydride (60%, unwashed, 96 mg, 2.4 mmol) in one portion. The mixture was stirred at 25 °C for 5 min before 2-bromoethyl ether (90%, 250 µL, 2.00 mmol) was added. This mixture was stirred further at 25 °C for 5 h and at 75 °C for 72 h before it was cooled to 25 °C, quenched with saturated ammonium chloride solution and diluted with ethyl acetate. The organic layer was separated, washed with water and brine, dried over $Na_2SO_4$, filtered and concentrated. Purification of the residue on silica gel (gradient elution with 0% to 70% ethyl acetate in hexanes) afforded *Cap-143, step a* (180 mg, 31%) as a yellow solid. $R_t$ = 1.75 min (Cond.-MS-W1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{13}H_{14}BrN_2O$: 293.03; found: 293.04.

*Cap-143*

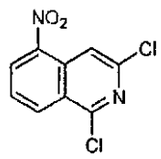
To a cold (-60 °C) solution of *Cap-143, step a* (154 mg, 0.527 mmol) in anhydrous tetrahydrofuran (5 mL) was added a solution of *n*-butyllithium in hexanes (2.5 M, 0.25 mL, 0.633 mmol). After 10 min, dry carbon dioxide was bubbled into

the reaction mixture for 10 min before it was quenched with 1*N* HCl and allowed to warm to 25 °C. The mixture was then extracted with dichloromethane (3 x 30 mL) and the combined organic extracts were concentrated *in vacuo*. Purification of the residue by reverse phase HPLC (MeOH/water/TFA) afforded *Cap-143* (16 mg, 12%). $R_t$ = 1.10 min (Cond.-MS-W1); 90% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{14}H_{15}N_2O_3$: 259.11; found: 259.08.

*Cap-144*

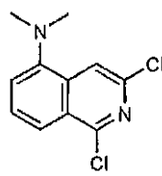


*Cap-144, step a*



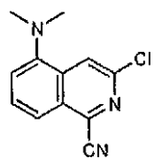
1,3-Dichloroisoquinoline (2.75 g, 13.89 mmol) was added in small portions to a cold (0 °C) solution of fuming nitric acid (10 mL) and concentrated sulfuric acid (10 mL). The mixture was stirred at 0 °C for 0.5 h before it was gradually warmed to 25 °C where it stirred for 16 h. The mixture was then poured into a beaker containing chopped ice and water and the resulting suspension was stirred for 1 h at 0 °C before it was filtered to afford *Cap-144, step a* (2.73 g, 81%) as a yellow solid which was used directly. $R_t$ = 2.01 min (Cond.-D1); 95% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_9H_5Cl_2N_2O_2$: 242.97; found: 242.92.

*Cap-144, step b*



*Cap-144, step a* (0.30 g, 1.23 mmol) was taken up in methanol (60 mL) and treated with platinum oxide (30 mg), and the suspension was subjected to Parr hydrogenation at 7 psi $H_2$ for 1.5 h before formalin (5 mL) and additional platinum oxide (30 mg) were added. The suspension was resubjected to Parr hydrogenation at 45 psi $H_2$ for 13 h before it was suction-filtered through diatomaceous earth (Celite®) and concentrated down to ¼ volume. Suction-filtration of the ensuing precipitate afforded the title compound as a yellow solid which was flash chromatographed on silica gel (gradient elution with 5% ethyl acetate in hexanes to 25% ethyl acetate in hexanes) to afford *Cap-144, step b* (231 mg, 78%) as a pale, yellow solid. $R_t$ = 2.36 min (Cond.-D1); 95% homogenity index; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.57-7.53 (m, 1H), 7.30 (d, *J* = 7.3 Hz, 1H), 2.88 (s, 6H); LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{11}Cl_2N_2$: 241.03; found: 241.02. HRMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{11}Cl_2N_2$: 241.0299; found: 241.0296.

*Cap-144, step c*




*Cap-144, step c* was prepared from *Cap-144, step b* according to the procedure described for the preparation of *Cap-139, step a*. $R_t$ = 2.19 min (Cond.-D1); 95% homogenity index; LCMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{11}ClN_3$: 232.06; found: 232.03. HRMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{11}ClN_3$: 232.0642; found: 232.0631.

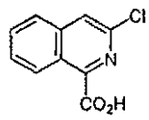
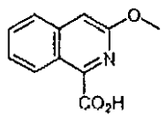
*Cap-144*

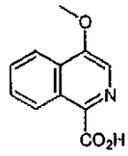
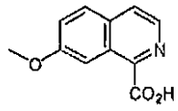
*Cap-144* was prepared according to the procedure described for *Cap-141*. $R_t$ = 2.36 min (Cond.-D1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{12}ClN_2O_2$: 238.01; found: 238.09.

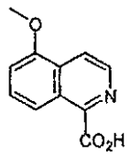
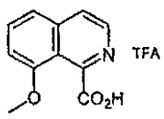
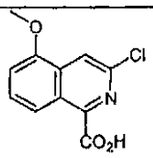
*Caps-145 to -162*

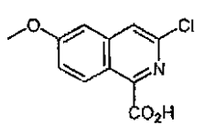
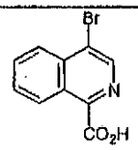
*Caps-145* to *162* were prepared from the appropriate 1-chloroisoquinolines according to the procedure described for the preparation of *Cap-138* (Method A) or *Cap-139* (Method B) unless noted otherwise as outlined below.

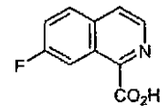
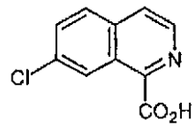
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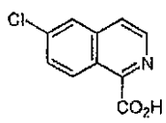
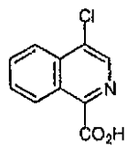
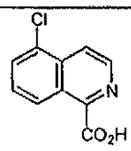
| *Cap #* | Cap | Method | Hydrolysis | $R_t$ (LC-Cond.); % homogeneity index; MS data |
|---|---|---|---|---|
| *Cap-145* |  Prepared from commercially available 1,3-dichloroisoquinoline | B | 12*N* HCl | 1.14 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; found: 208.00. |
| *Cap-146* |  Prepared from commercially available 3-hydroxyisoquinoline | A | 5*N* NaOH | 1.40 min (Cond.-D1); 95%; LCMS: Anal. |

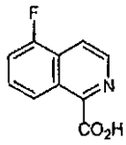
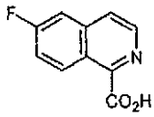
| | | | | |
|---|---|---|---|---|
| | | | | Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.06. |
| *Cap-147* |  Prepared from commercially available 1-chloro-4-hydroxyisoquinoline | B | 5*N* NaOH | 0.87 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.05. |
| *Cap-148* |  Prepared from commercially available 7-hydroxyisoquinoline | A | 5*N* NaOH | 0.70 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; |

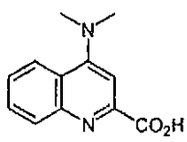
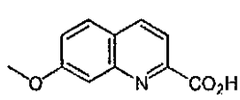
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| | | | | found: 204.05. |
| *Cap-149* |  Prepared from commercially available 5-hydroxyisoquinoline | A | 5*N* NaOH | 0.70 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.05. |
| *Cap-150* |  Prepared from 8-methoxy-1-chloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 099274 | A | 12*N* HCl | 0.26 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 204.04. |
| *Cap-151* |  | B | 12*N* HCl | 1.78 min (Cond.-D1); |

| | | | | |
|---|---|---|---|---|
| | Prepared from 5-methoxy-1,3-dichloroisoquinoline, which can be synthesized following the procedure in WO 2005 / 051410. | | | 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_9ClNO_3$: 238.03; found: 238.09. |
| *Cap-152* |  Prepared from commercially available 6-methoxy-1,3-dichloroisoquinoline | B | 12*N* HCl | 1.65 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_9ClNO_3$: 238.00; found: 238.09. |
| *Cap-153* |  Prepared from 4-bromoisoquinoline, which can be synthesized following the procedure in WO 2003/ 062241 | A | 6*N* HCl | 1.18 min (Cond.-MS-W1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ |

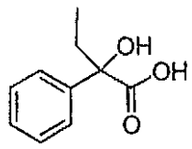
| | | | | |
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| | | | | $C_{10}H_7BrNO_2$: 251.97; found: 251.95. |
| *Cap-154* |  Prepared from 7-fluoro-1-chloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 099274 | B | 5*N* NaOH | 0.28 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; found: 192.03. |
| *Cap-155* |  Prepared from 1,7-dichloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 099274 | B | 5*N* NaOH | 0.59 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; found: 208.00. |

| | | | | |
|---|---|---|---|---|
| *Cap-156* |  Prepared from 1,6-dichloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 099274 | B | 5*N* NaOH | 0.60 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; found: 208.03. |
| *Cap-157* |  Prepared from 1,4-dichloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 062241 | B | 12*N* HCl | 1.49 min (Cond.-D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_{17}ClNO$: 208.02; found: 208.00. |
| *Cap-158* |  Prepared from 1,5-dichloroisoquinoline, | B | 5*N* NaOH | 0.69 min (Cond.-MS-W1); 90%; LCMS: |

| | | | | |
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| | which can be synthesized following the procedure in WO 2003/ 099274 | | | Anal. Calc. for $[M+H]^+$ $C_{10}H_7ClNO_2$: 208.02; found: 208.01. |
| *Cap-159* |  Prepared from 5-fluoro-1-chloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 099274 | B | 5*N* NaOH | 0.41 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7FNO_2$: 192.05; found: 192.03. |
| *Cap-160* |  Prepared from 6-fluoro-1-chloroisoquinoline, which can be synthesized following the procedure in WO 2003/ 099274 | B | 5*N* NaOH | 0.30 min (Cond.-MS-W1); 90%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{10}H_7FNO_2$: |

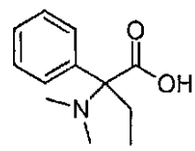
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| | | | | 192.05; found: 192.03. |
| *Cap-161* |  Prepared from 4-bromoquinoline-2-carboxylic acid and dimethylamine (DMSO, 100 °C) | -- | -- | 0.70 min (Cond. D1); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{12}H_{13}N_2O_2$: 217.10; found: 217.06. |
| *Cap-162* |  Prepared from *m*-anisidine following the procedure described in *J. Hetero. Chem.* **1993**, 17 and *Heterocycles*, **2003**, *60*, 953. | -- | -- | 0.65 min (Cond.-M3); 95%; LCMS: Anal. Calc. for $[M+H]^+$ $C_{11}H_{10}NO_3$: 204.07; found: 203.94. |

*Cap-163*



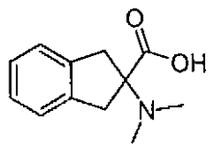

To a solution of 2-ketobutyric acid (1.0 g, 9.8 mmol) in diethylether (25 ml) was added phenylmagnesium bromide (22 ml, 1M in THF) dropwise. The reaction was stirred at ~25 °C under nitrogen for 17.5h. The reaction was acidified with 1N HCl and the product was extracted with ethyl acetate (3 x 100 ml). The combined organic layer was washed with water followed by brine and dried over $MgSO_4$. After concentration *in vacuo*, a white solid was obtained. The solid was recrystallized from hexanes/ethyl acetate to afford *Cap-163* as white needles (883.5 mg). $^1$H NMR (DMSO-$d_6$, $\delta$ = 2.5 ppm, 500 MHz): 12.71 (br s, 1 H), 7.54-7.52 (m, 2H), 7.34-7.31 (m, 2H), 7.26-7.23 (m, 1H), 5.52-5.39 (br s, 1H), 2.11 (m, 1H), 1.88 (m, 1H), 0.79 (app t, J = 7.4 Hz, 3H).

*Cap-164*



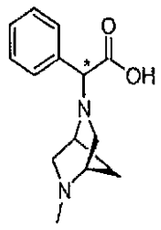

A mixture of 2-amino-2-phenylbutyric acid (1.5 g, 8.4 mmol), formaldehyde (14 mL, 37% in water), 1N HCl (10 mL) and 10% Pd/C (0.5 mg) in MeOH (40 mL) was exposed to $H_2$ at 50 psi in a Parr bottle for 42 h. The reaction was filtered over Celite and concentrated *in vacuo*, the residue was taken up in MeOH (36 mL) and the product was purified with a reverse phase HPLC (MeOH/$H_2O$/TFA) to afford the TFA salt of *Cap-164* as a white solid (1.7 g). $^1$H NMR (DMSO-$d_6$, $\delta$ = 2.5 ppm, 500 MHz) 7.54-7.47 (m, 5H), 2.63 (m, 1H), 2.55 (s, 6H), 2.31 (m, 1H), 0.95 (app t, J = 7.3 Hz, 3H).

*Cap-165*



To a mixture of 2-amino-2-indanecarboxylic acid (258.6 mg, 1.46 mmol) and formic acid (0.6 ml, 15.9 mmol) in 1,2-dichloroethane (7 ml) was added formaldehyde (0.6 ml, 37% in water). The mixture was stirred at ~25 °C for 15 min then heated at 70 °C for 8h. The volatile component was removed *in vacuo*, and the residue was dissolved in DMF (14 mL) and purified by a reverse phase HPLC (MeOH/$H_2O$/TFA) to afford the TFA salt of *Cap-165* as a viscous oil (120.2 mg). $^1H$ NMR (DMSO-$d_6$, δ = 2.5 ppm, 500 MHz): 7.29-7.21 (m, 4 H), 3.61 (d, J = 17.4 Hz, 2H), 3.50 (d, J = 17.4 Hz, 2H), 2.75 (s, 6H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_2$: 206.12; found: 206.07.

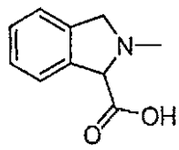
*Cap-166a and -166b*



*Cap-166a*: Diastereomer-1
*Cap-166b*: Diastereomer-2

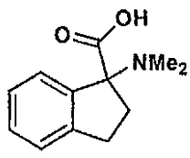
*Caps-166a* and *-166b* were prepared from (1S, 4S)-(+)-2-methyl-2,5-diazabicyclo[2.2.1]heptane (2HBr) according to the method described for the synthesis of *Cap-7a and Cap-7b*, with the exception that the benzyl ester intermediate was separated using a semi-prep Chrialcel OJ column, 20 x 250 mm, 10 μm eluting with 85:15 heptane/ethanol mixture at 10 mL/min elution rate for 25 min. *Cap-166b*: $^1H$ NMR (DMSO-$d_6$, δ = 2.5 ppm, 500 MHz): 7.45 (d, J = 7.3 Hz, 2H), 7.27-7.19 (m, 3H), 4.09 (s, 1H), 3.34 (app br s, 1H), 3.16 (app br s, 1H), 2.83 (d, *J*=10.1 Hz, 1H), 2.71 (m, 2H), 2.46 (m, 1H), 2.27 (s, 3H), 1.77 (d, J = 9.8 Hz, 1H), 1.63 (d, J = 9.8 Hz, 1H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{19}N_2O_2$: 247.14; found: 247.11.

*Cap-167*



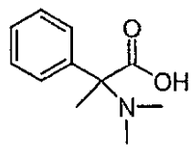
A solution of racemic Boc-1,3-dihydro-2H-isoindole carboxylic acid (1.0g, 3.8 mmol) in 20% TFA/$CH_2Cl_2$ was stirred at ~25 °C for 4h. All the volatile component was removed *in vacuo*. A mixture of the resultant crude material, formaldehyde (15 mL, 37% in water), 1N HCl (10 mL) and 10% Pd/C (10 mg) in MeOH was exposed to $H_2$ (40 PSI) in a Parr bottle for 23 h. The reaction mixture was filtered over Celite and concentrated *in vacuo* to afford *Cap-167* as a yellow foam (873.5 mg). $^1$H NMR (DMSO-$d_6$, $\delta$ = 2.5 ppm, 500 MHz) 7.59-7.38 (m, 4H), 5.59 (s, 1H), 4.84 (d, J = 14 Hz, 1H), 4.50 (d, J = 14.1 Hz, 1H), 3.07 (s, 3H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{12}NO_2$: 178.09; found: 178.65.

*Cap-168*



Racemic *Cap-168* was prepared from racemic Boc-aminoindane-1-carboxylic acid according to the procedure described for the preparation of *Cap-167*. The crude material was employed as such.

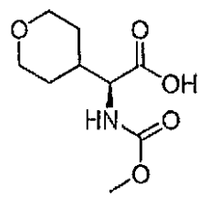
*Cap-169*



A mixture of 2-amino-2-phenylpropanoic acid hydrochloride (5.0 g, 2.5 mmol), formaldehyde (15 ml, 37% in water), 1N HCl (15 ml), and 10% Pd/C (1.32 g) in MeOH (60 mL) was placed in a Parr bottle and shaken under hydrogen (55 PSI) for 4 days. The reaction mixture was filtered through diatomaceous earth (Celite®) and concentrated *in vacuo*. The residue was taken up in MeOH and purified by reverse

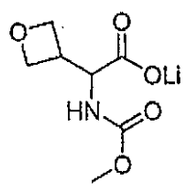
phase prep-HPLC (MeOH/water/TFA) to afford the TFA salt of *Cap-169* as a viscous semi-solid (2.1 g). $^1$H NMR ($CDCl_3$, δ = 7.26 ppm, 500 MHz): 7.58-7.52 (m, 2 H), 7.39-7.33 (m, 3H), 2.86 (br s, 3H), 2.47 (br s, 3H), 1.93 (s, 3H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.12; found: 194.12.

*Cap-170*



To (*S*)-2-amino-2-(tetrahydro-2*H*-pyran-4-yl)acetic acid (505mg; 3.18mmol; obtained from Astatech) in water (15ml) was added sodium carbonate (673mg; 6.35mmol), and the resultant mixture was cooled to 0 °C and then methyl chloroformate (0.26ml; 3.33mmol) was added dropwise over 5 minutes. The reaction was allowed to stir for 18 hours while allowing the bath to thaw to ambient temperature. The reaction mixture was then partitioned between 1N HCl and ethyl acetate. The organic layer was removed and the aqueous layer was further extracted with 2 additional portions of ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford *Cap-170* a colorless residue. $^1$H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 12.65 (1 H, br s), 7.44 (1 H, d, *J*=8.24 Hz), 3.77 - 3.95 (3 H, m), 3.54 (3 H, s), 3.11 - 3.26 (2 H, m), 1.82 - 1.95 (1 H, m), 1.41 - 1.55 (2 H, m), 1.21 - 1.39 (2 H, m); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{16}NO_5$: 218.1; found 218.1.

*Cap-171*

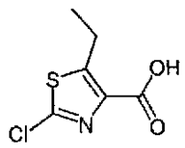


A solution of methyl 2-(benzyloxycarbonylamino)-2-(oxetan-3-ylidene)acetate (200 mg, 0.721 mmol; Il Farmaco (2001), 56, 609–613) in ethyl

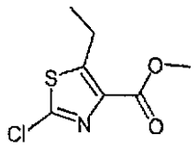
acetate (7 ml) and $CH_2Cl_2$ (4.00 ml) was degassed by bubbling nitrogen for 10min. Dimethyl dicarbonate (0.116 ml, 1.082 mmol) and Pd/C (20 mg, 0.019 mmol) were then added, the reaction mixture was fitted with a hydrogen balloon and allowed to stir at ambient temperature overnight at which time TLC (95:5 $CH_2Cl_2$ / MeOH: visulalized with stain made from 1g $Ce(NH_4)_2SO_4$, 6g ammonium molybdate, 6ml sulfuric acid, and 100ml water) indicated complete conversion. The reaction was filtered through celite and concentrated. The residue was purified via Biotage® (load with dichloromethane on 25 samplet; elute on 25S column with dichloromethane for 3CV then 0 to 5% MeOH / dichloromethane over 250ml then hold at 5% MeOH / dichloromethane for 250ml; 9ml fractions). Collected fractions containing desired material and concentrated to 120mg (81%) of methyl 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetate as a colorless oil. $^1$H NMR (500 MHz, CHLOROFORM-D) δ ppm 3.29 - 3.40 (m, *J*=6.71 Hz, 1 H) 3.70 (s, 3 H) 3.74 (s, 3 H) 4.55 (t, *J*=6.41 Hz, 1 H) 4.58 - 4.68 (m, 2 H) 4.67 - 4.78 (m, 2 H) 5.31 (br s, 1 H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{14}NO_5$: 204.2; found 204.0.

To methyl 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetate (50 mg, 0.246 mmol) in THF (2 mL) and water (0.5 mL) was added lithium hydroxide monohydrate (10.33 mg, 0.246 mmol). The resultant solution was allowed to stir overnite at ambient temperature. TLC (1:1 EA / Hex; Hanessian stain [1g $Ce(NH_4)_2SO_4$, 6g ammonium molybdate, 6ml sulfuric acid, and 100ml water]) indicated ~10% starting material remaining. Added an additional 3mg LiOH and allowed to stir overnight at which time TLC showed no starting material remaining. Concentrated *in vacuo* and placed on high vac overnite providing 55mg lithium 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetate as a colorless solid. $^1$H NMR (500 MHz, MeOD) δ ppm 3.39 - 3.47 (m, 1 H) 3.67 (s, 3 H) 4.28 (d, *J*=7.93 Hz, 1 H) 4.64 (t, *J*=6.26 Hz, 1 H) 4.68 (t, *J*=7.02 Hz, 1 H) 4.73 (d, *J*=7.63 Hz, 2 H).

*Cap-172*



*Cap-172, step a*

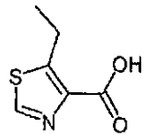


The following diazotization step was adapted from Barton, A.; Breukelman, S. P.; Kaye, P. T.; Meakins, G. D.; Morgan, D. J. *J. C. S. Perkin Trans I* **1982**, 159-164: A solution of $NaNO_2$ (166 mg, 2.4 mmol) in water (0.6 mL) was added slowly to a stirred, cold (0 °C) solution of methyl 2-amino-5-ethyl-1,3-thiazole-4-carboxylate (186 mg, 1.0 mmol), $CuSO_4 \cdot 5H_2O$ (330 mg, 1.32 mmol), NaCl (260 mg, 4.45 mmol) and $H_2SO_4$ (5.5 mL) in water (7.5 mL). The mixture was stirred at 0 °C for 45 min and allowed to warm up to room temperature where it stirred further for 1 h before CuCl (118 mg) was added. This mixture was stirred further at room temperature for 16 h before it was diluted with brine and extracted with ether twice. The organic layers were combined, dried over $MgSO_4$ and concentrated to give methyl 2-chloro-5-ethylthiazole-4-carboxylate (i.e. *Cap-172, step a*) (175 mg, 85%) as an orange oil (80% pure) which was used directly in the next reaction. $R_t$ = 1.99 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_7H_9ClNO_2S$: 206.01; found: 206.05.

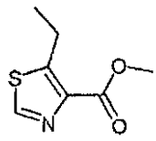
*Cap-172*

To a solution of methyl 2-chloro-5-ethylthiazole-4-carboxylate (175 mg) in THF/$H_2O$/MeOH (20 mL/ 3 mL/ 12 mL) was added LiOH (305 mg, 12.76 mmol). The mixture was stirred at room temperature overnight before it was concentrated down and neutralized with 1*N* HCl in ether (25 mL). The residue was extracted twice with ethyl acetate and the organic layers were combined, dried over $MgSO_4$ and evaporated to yield *Cap-172* (60 mg, 74%) as a red solid which was used without further purification. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ ppm 13.03-13.42 (1 H, m), 3.16 (2 H, q, $J$ = 7.4 Hz), 1.23 (3 H, t, $J$ = 7.5 Hz). $R_t$ = 1.78 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_6H_7ClNO_2S$: 191.99; found: 191.99.

*Cap-173*



*Cap-173, step a*



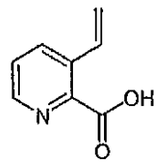
The following diazotization step was adapted from Barton, A.; Breukelman, S. P.; Kaye, P. T.; Meakins, G. D.; Morgan, D. J. *J. C. S. Perkin Trans I* **1982**, 159-164: A solution of $NaNO_2$ (150 mg, 2.17 mmol) in water (1.0 mL) was added dropwise to a stirred, cold (0 °C) solution of methyl 2-amino-5-ethyl-1,3-thiazole-4-carboxylate (186 mg, 1.0 mmol) in 50% $H_3PO_2$ (3.2 mL). The mixture was stirred at 0 °C for 1 h and allowed to warm up to room temperature where it stirred further for 2h. After recooling to 0 °C, the mixture was treated slowly with a solution of NaOH (85 mg) in water (10 mL). The mixture was then diluted with saturated $NaHCO_3$ solution and extracted twice with ether. The organic layers were combined, dried over $MgSO_4$ and concentrated to give methyl 5-ethylthiazole-4-carboxylate (i.e. *Cap-173, step a*) (134 mg, 78%) as an orange oil (85% pure) which was used directly in the next reaction. $R_t$ = 1.58 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_7H_{10}NO_2S$: 172.05; found: 172.05.

*Cap-173*

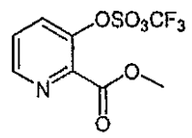
To a solution of methyl 5-ethylthiazole-4-carboxylate (134 mg) in THF/$H_2O$/MeOH (18 mL/ 2.7 mL/ 11 mL) was added LiOH (281 mg, 11.74 mmol). The mixture was stirred at room temperature overnight before it was concentrated down and neutralized with 1*N* HCl in ether (25 mL). The residue was extracted twice with ethyl acetate and the organic layers were combined, dried over $MgSO_4$ and evaporated to yield *Cap-173* (90 mg, 73%) as an orange solid which was used without further purification. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ ppm 12.74-13.04 (1

H, m), 3.20 (2 H, q, $J$ = 7.3 Hz), 1.25 (3 H, t, $J$ = 7.5 Hz). $R_t$ = 1.27 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_6H_8NO_2S$: 158.03; found: 158.04.

*Cap-174*




*Cap-174, step a*



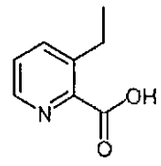

Triflic anhydride (5.0 g, 18.0 mmol) was added dropwise to a cold (0 °C) solution of methyl 3-hydroxypicolinate (2.5 g, 16.3 mmol) and TEA (2.5 mL, 18.0 mmol) in $CH_2Cl_2$ (80 mL). The mixture was stirred at 0 °C for 1h before it was allowed to warm up to room temperature where it stirred for an additional 1 h. The mixture was then quenched with saturated $NaHCO_3$ solution (40 mL) and the organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated to give methyl 3-(trifluoromethylsulfonyloxy)picolinate (*i.e. Cap-174, step a*) (3.38 g, 73%) as a dark brown oil (>95% pure) which was used directly without further purification. $^1H$ NMR (300 MHz, $CDCl_3$) δ ppm 8.72-8.79 (1 H, m), 7.71 (1 H, d, $J$ = 1.5 Hz), 7.58-7.65 (1 H, m), 4.04 (3 H, s). $R_t$ = 1.93 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_7F_3NO_5S$: 286.00; found: 286.08.

*Cap-174*

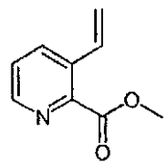
To a solution of methyl 3-(trifluoromethylsulfonyloxy)picolinate (570 mg, 2.0 mmol) in DMF (20 mL) was added LiCl (254 mg, 6.0 mmol), tributyl(vinyl)stannane (761 mg, 2.4 mmol) and bis(triphenylphosphine)palladium dichloride (42 mg, 0.06 mmol). The mixture was heated at 100 °C overnight before a saturated solution of KF (20 mL) was added to the reaction mixture at room temperature. This mixture was stirred for 4 h before it was filtered through diatomaceous earth (Celite®) and the

pad was washed with ethyl acetate. The aqueous phase of the filtrate was then separated and concentrated down *in vacuo*. The residue was treated with 4*N* HCl in dioxanes (5 mL) and the resulting mixture was extracted with methanol, filtered and evaporated to afford *Cap-174* (260 mg) as a green solid which was slightly contaminated with inorganic salts but was used without further purification. $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 8.21 (1 H, d, $J$ = 3.7 Hz), 7.81-7.90 (1 H, m), 7.09 (1 H, dd, $J$ = 7.7, 4.8 Hz), 6.98 (1 H, dd, $J$ = 17.9, 11.3 Hz), 5.74 (1 H, dd, $J$ = 17.9, 1.5 Hz), 5.20 (1 H, d, $J$ = 11.0 Hz). $R_t$ = 0.39 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_8NO_2$: 150.06; found: 150.07.

*Cap-175*



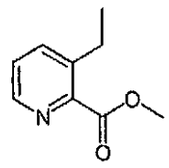

*Cap-175, step a*




To a solution of methyl 3-(trifluoromethylsulfonyloxy)picolinate (*i.e. Cap 173, step a*) (570 mg, 2.0 mmol), an intermediate in the preparation of *Cap-174*, in DMF (20 mL) was added LiCl (254 mg, 6.0 mmol), tributyl(vinyl)stannane (761 mg, 2.4 mmol) and bis(triphenylphosphine)palladium dichloride (42 mg, 0.06 mmol). The mixture was heated at 100 °C for 4 h before the solvent was removed *in vacuo*. The residue was taken up in acetonitrile (50 mL) and hexanes (50 mL) and the resulting mixture was washed twice with hexanes. The acetonitrile layer was then separated, filtered through Celite, and evaporated. Purification of the residue by flash chromatography on a Horizon instrument (gradient elution with 25% ethyl acetate in hexanes to 65% ethyl acetate in hexanes) afforded methyl 3-vinylpicolinate (i.e. *Cap-175, step a*) (130 mg, 40%) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 8.60 (1 H, dd, $J$ = 4.6, 1.7 Hz), 7.94 (1 H, d, $J$ = 7.7 Hz), 7.33-7.51 (2 H, m), 5.72 (1 H, d,

$J$ = 17.2 Hz), 5.47 (1 H, d, $J$ = 11.0 Hz), 3.99 (3 H, s). $R_t$ = 1.29 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{10}NO_2$: 164.07; found: 164.06.

*Cap-175, step b*

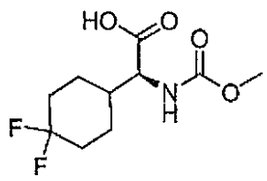


Palladium on carbon (10%, 25 mg) was added to a solution of methyl 3-vinylpicolinate (120 mg, 0.74 mmol) in ethanol (10 mL). The suspension was stirred at room temperature under an atmosphere of hydrogen for 1 h before it was filtered through Celite and the pad of diatomaceous earth (Celite®) was washed with methanol. The filtrate was concentrated down to dryness to yield methyl 3-ethylpicolinate (i.e. *Cap-175, step b*) which was taken directly into the next reaction. $R_t$ = 1.15 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{12}NO_2$: 166.09; found: 166.09.

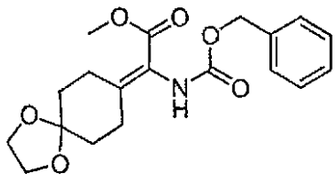
*Cap-175*

To a solution of methyl 3-ethylpicolinate in THF/$H_2O$/MeOH (5 mL/ 0.75 mL/ 3 mL) was added LiOH (35 mg, 1.47 mmol). The mixture was stirred at room temperature for 2 d before additional LiOH (80 mg) was added. After an additional 24 h at room temperature, the mixture was filtered and the solvent was removed *in vacuo*. The residue was then treated with 4*N* HCl in dioxanes (5 mL) and the resulting suspension was concentrated down to dryness to yield *Cap-175* as a yellow solid which was used without further purification. $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 8.47 (1 H, dd, $J$ = 4.8, 1.5 Hz), 7.82-7.89 (1 H, m), 7.53 (1 H, dd, $J$ = 7.7, 4.8 Hz), 2.82 (2 H, q, $J$ = 7.3 Hz), 1.17 (3 H, t, $J$ = 7.5 Hz). $R_t$ = 0.36 min (Cond.-MD1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{10}NO_2$: 152.07; found: 152.10.

*Cap-176*

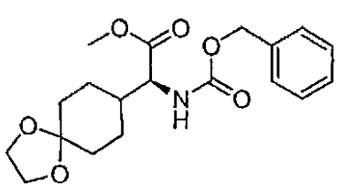


*Cap-176, step a*



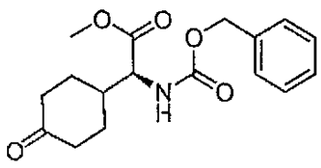
A solution of 1,4-dioxaspiro[4.5]decan-8-one (15 g, 96 mmol) in EtOAc (150 mL) was added to a solution of methyl 2-(benzyloxycarbonylamino)-2-(dimethoxyphosphoryl)acetate (21.21 g, 64.0 mmol) in 1,1,3,3-tetramethylguanidine (10.45 mL, 83 mmol) and EtOAc (150 mL). The resulting solution was the stirred at ambient temperature for 72 h and then it was diluted with EtOAc (25 mL). The organic layer was washed with 1N HCl (75 mL), $H_2O$ (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified via Biotage (5% to 25 % EtOAc/Hexanes; 300g column). The combined fractions containing the product were then concentrated under vacuum and the residue was re-crystallized from hexanes/EtOAc to give white crystals that corresponded to methyl 2-(benzyloxycarbonylamino)-2-(1,4-dioxaspiro[4.5]decan-8-ylidene)acetate (6.2 g) $^1$H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 7.30 - 7.44 (5 H, m), 6.02 (1 H, br. s.), 5.15 (2 H, s), 3.97 (4 H, s), 3.76 (3 H, br. s.), 2.84 - 2.92 (2 H, m), 2.47 (2 H, t, *J*=6.40 Hz), 1.74 - 1.83 (4 H, m). LC (Cond. OL1): $R_t$ = 2.89 min. LC/MS: Anal. Calcd. For $[M+Na]^+$ $C_{19}H_{23}NNaO_6$: 745.21; found: 745.47.

*Cap 176, step b*



Ester *Cap 176, step b* was prepared from alkene *Cap 176, step a* according to the method of Burk, M. J.; Gross, M. F. and Martinez J. P. (*J. Am. Chem. Soc.*, **1995**, *117*, 9375-9376 and references therein): A 500 mL high-pressure bottle was charged with alkene *Cap 176, step a* (3.5 g, 9.68 mmol) in degassed MeOH (200 mL) under a blanket of $N_2$. The solution was then charged with (-)-1,2-Bis((2S,5S)-2,5-dimethylphospholano)ethane(cyclooctadiene)rhodium (I) tetrafluoroborate (0.108 g, 0.194 mmol) and the resulting mixture was flushed with $N_2$ (3x) and charged with $H_2$ (3x). The solution was shaken vigorously under 70 psi of $H_2$ at ambient temperature for 72 h. The solvent was removed under reduced pressure and the remaining residue was taken up in EtOAc. The brownish solution was then filtered through a plug of Silica Gel and eluted with EtOAc. The solvent was concentrated under vacuum to afford a clear oil corresponding to ester *Cap 176, step b* (3.4 g) .$^1$H NMR (500 MHz, $CDCl_3$-*d*) δ ppm 7.28 - 7.43 (5 H, m), 5.32 (1 H, d, *J*=9.16 Hz), 5.06 - 5.16 (2 H, m), 4.37 (1 H, dd, *J*=9.00, 5.04 Hz), 3.92 (4 H, t, *J*=3.05 Hz), 3.75 (3 H, s), 1.64 - 1.92 (4 H, m), 1.37 - 1.60 (5 H, m). LC (Cond. OL1): $R_t$ = 1.95 min. LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{19}H_{26}NO_6$: 364.18; found: 364.27.

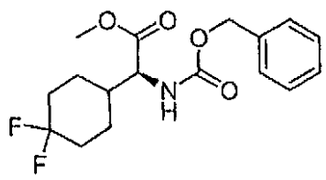
*Cap 176, step c*



Ester *Cap 176, step b* (4.78 g, 13.15 mmol) was dissolved in THF (15 mL) followed by sequential addition of water (10 mL), glacial acetic acid (26.4 mL, 460 mmol) and dichloroacetic acid (5.44 mL, 65.8 mmol). The resulting mixture was stirred for 72 h at ambient temperature, and the reaction was quenched by slow addition of solid $Na_2CO_3$ with vigorous stirring until the release of gas was no longer visible. Crude product was extracted into 10% ethyl acetate-dichloromethane and the organic layers were combined, dried ($MgSO_4$) filtered and concentrated. The resulting residue was purified via Biotage (0 to 30% EtOAc/Hex; 25 g column) to afford ketone *Cap 176, step c* (3.86g) as a clear oil. $^1$H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 7.28 - 7.41 (5 H, m), 5.55 (1 H, d, *J*=8.28 Hz), 5.09 (2 H, s), 4.46 (1 H, dd,

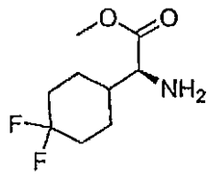
*J*=8.16, 5.14 Hz), 3.74 (3 H, s), 2.18 - 2.46 (5 H, m), 1.96 - 2.06 (1 H, m), 1.90 (1 H, ddd, *J*=12.99, 5.96, 2.89 Hz), 1.44 - 1.68 (2 H, m, *J*=12.36, 12.36, 12.36, 12.36, 4.77 Hz). LC (Cond. OL1): $R_t$ = 1.66 min. LC/MS: Anal. Calcd. For $[M+Na]^+$ $C_{17}H_{21}NNaO_5$: 342.13; found: 342.10.

*Cap 176, step d*



Deoxo-Fluor® (3.13 mL, 16.97 mmol) was added to a solution of ketone *Cap 176, step c* (2.71 g, 8.49 mmol) in $CH_2Cl_2$ (50 mL) followed by addition of a catalytic ammount of EtOH (0.149 mL, 2.55 mmol). The resulting yellowish solution was stirred at rt overnight. The reaction was quenched by addition of sat. aq. $NaHCO_3$ (25 mL) and the mixture was extracted with EtOAc (3X75 mL)). The combined organic layers were dried ($MgSO_4$), filtered and dried to give a yellowish oil. The residue was purified via Biotage chromatography (2% to 15% EtOAc/Hex; 90g column) and a white solid corresponding to the difluoro amino acid dilforide *Cap 176, step d* (1.5 g) was recovered. $^1$H NMR (400 MHz, , $CDCl_3$-*d*) δ ppm 7.29 - 7.46 (5 H, m), 5.34 (1 H, d, *J*=8.28 Hz), 5.12 (2 H, s), 4.41 (1 H, dd, *J*=8.66, 4.89 Hz), 3.77 (3 H, s), 2.06 - 2.20 (2 H, m), 1.83 - 1.98 (1 H, m), 1.60 - 1.81 (4 H, m), 1.38 - 1.55 (2 H, m). $^{19}$F NMR (376 MHz, $CDCl_3$-*d*) δ ppm -92.15 (1 F, d, *J*=237.55 Hz), -102.44 (1 F, d, *J*=235.82 Hz). LC (Cond. OL1): $R_t$ = 1.66 min. LC/MS: Anal. Calcd. For $[2M+Na]^+$ $C_{34}H_{42}F_4N_2NaO_8$: 705.28; found: 705.18.

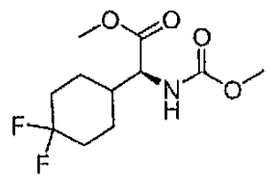
*Cap 176, step e*



Difluoride *Cap 176, step d* (4 g, 11.72 mmol) was dissolved in MeOH (120 mL) and charged with Pd/C (1.247 g, 1.172 mmol). The suspension was flushed with

$N_2$ (3x) and the reaction mixture was placed under 1 atm of $H_2$ (balloon). The mixture was stirred at ambient temperature for 48 h. The suspension was then filtered though a plug of Celite and concentrated under vacuum to give an oil that corresponded to amino acid *Cap 176, step e* (2.04 g) and that was used without further purification. $^1$H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 3.62 (3 H, s), 3.20 (1 H, d, *J*=5.77 Hz), 1.91 - 2.09 (2 H, m), 1.50 - 1.88 (7 H, m), 1.20 - 1.45 (2 H, m). $^{19}$F NMR (376 MHz, *DMSO-d*$_6$) δ ppm -89.39 (1 F, d, *J*=232.35 Hz), -100.07 (1 F, d, *J*=232.35 Hz). $^{13}$C NMR (101 MHz, *DMSO-d*$_6$) δ ppm 175.51 (1 C, s), 124.10 (1 C, t, *J*=241.21, 238.90 Hz), 57.74 (1 C, s), 51.39 (1 C, s), 39.23 (1 C, br. s.), 32.02 - 33.83 (2 C, m), 25.36 (1 C, d, *J*=10.02 Hz), 23.74 (1 C, d, *J*=9.25 Hz). LC (Cond. OL2): $R_t$ = 0.95 min. LC/MS: Anal. Calcd. For $[2M+H]^+$ $C_{18}H_{31}F_4N_2O_2$: 415.22; found: 415.40.

*Cap 176, step f*



Methyl chloroformate (1.495 mL, 19.30 mmol) was added to a solution of amino acid *Cap 176, step e* (2 g, 9.65 mmol) and DIEA (6.74 mL, 38.6 mmol) in $CH_2Cl_2$ (100 mL). The resulting solution was stirred at rt for 3 h and volatiles were removed under reduced pressure. The residue was purified via Biotage (0% to 20% EtOAc/Hex; 90g column). A clear oil that solidified upon standing under vacuum and corresponding to carbamate *Cap-176, step f* (2.22 g) was recovered. $^1$H NMR (500 MHz, $CDCl_3$-*d*) δ ppm 5.27 (1 H, d, *J*=8.55 Hz), 4.39 (1 H, dd, *J*=8.85, 4.88 Hz), 3.77 (3 H, s), 3.70 (3 H, s), 2.07 - 2.20 (2 H, m), 1.84 - 1.96 (1 H, m), 1.64 - 1.82 (4 H, m), 1.39 - 1.51 (2 H, m). $^{19}$F NMR (471 MHz, $CDCl_3$-*d*) δ ppm -92.55 (1 F, d, *J*=237.13 Hz), -102.93 (1 F, d, *J*=237.12 Hz). $^{13}$C NMR (126 MHz, $CDCl_3$-*d*) δ ppm 171.97 (1 C, s), 156.69 (1 C, s), 119.77 - 125.59 (1 C, m), 57.24 (1 C, br. s.), 52.48 (1 C, br. s.), 52.43 (1 C, s), 39.15 (1 C, s), 32.50 - 33.48 (2 C, m), 25.30 (1 C, d,

*J*=9.60 Hz), 24.03 (1 C, d, *J*=9.60 Hz). LC (Cond. OL1): $R_t$ = 1.49 min. LC/MS: Anal. Calcd. For $[M+Na]^+$ $C_{11}H_{17}F_2NNaO_4$: 288.10; found: 288.03.

*Cap-176*

A solution of LiOH (0.379 g, 15.83 mmol) in Water (25 mL) was added to a solution of carbamate *Cap-176, step f* (2.1 g, 7.92 mmol) in THF (75 mL) and the resulting mixture was stirred at ambient temperature for 4 h. THF was removed under vacuum and the remaining aqueous phase was acidified with 1N HCl solution (2 mL) and then extracted with EtOAc (2 X 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to give a white foam corresponding to *Cap-176* (1.92 g). $^1$H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 12.73 (1 H, s), 7.50 (1 H, d, *J*=8.78 Hz), 3.97 (1 H, dd, *J*=8.53, 6.02 Hz), 3.54 (3 H, s), 1.92 - 2.08 (2 H, m), 1.57 - 1.90 (5 H, m), 1.34 - 1.48 (1 H, m), 1.27 (1 H, qd, *J*=12.72, 3.26 Hz). $^{19}$F NMR (376 MHz, *DMSO-d*$_6$) δ ppm -89.62 (1 F, d, *J*=232.35 Hz), -99.93 (1 F, d, *J*=232.35 Hz). LC (Cond. OL2): $R_t$ = 0.76 min. LC/MS: Anal. Calcd. For $[M-H]^+$ $C_{10}H_{14}F_2NO_4$: 250.09; found: 250.10.

BIOLOGICAL ACTIVITY

An HCV Replicon assay was utilized in the present disclosure, and was prepared, conducted and validated as described in commonly owned PCT/US2006/022197 and in O'Boyle et. al. *Antimicrob Agents Chemother.* **2005** Apr;49(4):1346-53. Assay methods incorporating luciferase reporters have also been used as described (Apath.com).

HCV-neo replicon cells and replicon cells containing mutations in the NS5A region were used to test the currently described family of compounds. The compounds were determined to have more than 10-fold less inhibitory activity on cells containing mutations than wild-type cells. Thus, the compounds of the present disclosure can be effective in inhibiting the function of the HCV NS5A protein and are understood to be as effective in combinations as previously described in application PCT/US2006/022197 and commonly owned WO/O4014852. Further, the compounds of the present disclosure can be effective against the HCV 1b genotype.

It should also be understood that the compounds of the present disclosure can inhibit multiple genotypes of HCV. Table 2 shows the $EC_{50}$ (Effective 50% inhibitory concentration) values of representative compounds of the present disclosure against the HCV 1b genotype. In one embodiment, compounds of the present disclosure are inhibitory versus 1a, 1b, 2a, 2b, 3a, 4a, and 5a genotypes. $EC_{50}$ values against HCV 1b are as follows A (10-350 nM); B (1-9.9 nM); C (0.1-0.99 nM); D (0.002-0.099 nM).

| Compound No. | 1b EC50 (nM) | Range | Name |
|---|---|---|---|
| OL-1 | | B | (1R)-2-((2S)-2-(4-(4-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenoxy) phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine |
| OL-2 | 9.1 | B | (1R)-2-((2S)-2-(4-(4-(4-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenoxy)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanol |
| OL-3 | | B | dimethyl (oxybis(4,1-phenylene-1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate |
| OL-4 | 0.07 | D | (1R)-2-((2S)-2-(4-(3-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenoxy) phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine |
| OL-5 | 80 | A | (1R)-2-((2S)-2-(4-(3-(4-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenoxy)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanol |

| Compound No. | 1b EC50 (nM) | Range | Name |
|---|---|---|---|
| OL-6 | | D | methyl ((1R)-2-((2S)-2-(4-(3-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenoxy)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate |
| OL-7 | | D | (1R)-2-((2S)-2-(4-(4-((4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)benzyl)oxy) phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine |
| OL-8 | | D | methyl ((1R)-2-((2S)-2-(4-(4-((4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)benzyl)oxy)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate |
| OL-9 | | D | (1R)-2-((2S)-2-(4-(4-(2-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)ethyl) phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine |
| OL-10 | | D | (1R,1'R)-2,2'-(1,2-ethanediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl))bis(2-oxo-1-phenylethanol) |
| OL-11 | | D | dimethyl (1,2-ethanediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl ((1R)-2-oxo-1-phenyl-2,1-ethanediyl))) biscarbamate |

| Compound No. | 1b EC50 (nM) | Range | Name |
|---|---|---|---|
| OL-12 | | D | N′,N‴-(1,2-ethanediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl ((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-ethylurea) |
| OL-13 | | D | 1-cyclopentyl-3-((1R)-2-((2S)-2-(4-(4-(2-(4-(2-((2S)-1-((2R)-2-((cyclopentylcarbamoyl) amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)ethyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)urea |
| OL-14 | | C | (1R)-2-((2S)-2-(4-(4-(((4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)benzyl)oxy) methyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine |
| OL-15 | 1.1 | B | (1R)-2-((2S)-2-(4-(4-(((4-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)benzyl)oxy)methyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanol |
| OL-16 | | D | dimethyl (oxybis(methylene-4,1-phenylene-1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl ((1R)-2-oxo-1-phenyl-2,1-ethanediyl))) biscarbamate |

| Compound No. | 1b EC50 (nM) | Range | Name |
|---|---|---|---|
| OL-17 | | D | 1-methyl-3-((1R)-2-((2S)-2-(4-(4-(((4-(2-((2S)-1-((2R)-2-((methylcarbamoyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)benzyl)oxy)methyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)urea |
| OL-18 | | D | 1-ethyl-3-((1R)-2-((2S)-2-(4-(4-(((4-(2-((2S)-1-((2R)-2-((ethylcarbamoyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)benzyl)oxy)methyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)urea |
| OL-19 | | B | 1-cyclopentyl-3-((1R)-2-((2S)-2-(4-(4-(((4-(2-((2S)-1-((2R)-2-((cyclopentylcarbamoyl) amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)benzyl)oxy)methyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)urea |
| OL-20 | | C | (1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)benzyl)oxy) methyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine |
| OL-21 | | C | (1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)benzyl)oxy)methyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanol |

| Compound No. | 1b EC50 (nM) | Range | Name |
|---|---|---|---|
| OL-22 | | D | (methyl ((1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)benzyl)oxy)methyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate |
| OL-23 | | C | 1-methyl-3-((1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-((methylcarbamoyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)benzyl)oxy)methyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)urea |
| OL-24 | | D | 1-ethyl-3-((1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-((ethylcarbamoyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)benzyl)oxy)methyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)urea |
| OL-25 | | D | 1-cyclopentyl-3-((1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-((cyclopentylcarbamoyl) amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)benzyl)oxy)methyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)urea |
| D-1 | | D | dimethyl (1,1':4',1''-terphenyl-4,4''-diylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl ((1R)-2-oxo-1-phenyl-2,1-ethanediyl))) biscarbamate |

| Compound No. | 1b EC50 (nM) | Range | Name |
|---|---|---|---|
| D-2 | | C | (1R)-2-((2S)-2-(4-(4''-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-1,1':4',1''-terphenyl-4-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine |
| D-3 | .0.006 | D | methyl ((1S)-1-(((2S)-2-(4-(4-((2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate |
| D-4 | | D | methyl ((1R)-2-((2S)-2-(4-(4-((2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate |
| D-5 | | D | methyl ((1R)-2-((2S)-2-(7-((4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate |

| Compound No. | 1b EC50 (nM) | Range | Name |
|---|---|---|---|
| D-6 | | D | methyl ((1S)-1-(((2S)-2-(4-(4-((2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate |
| D-7 | | D | methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate |
| D-8 | 0.005 | D | methyl ((1R)-2-((1R,3S,5R)-3-(7-((4-(2-((1R,3S,5R)-2-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-phenylethyl)carbamate |
| D-9 | | D | methyl ((1S)-1-(((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate |

| Compound No. | 1b EC50 (nM) | Range | Name |
|---|---|---|---|
| D-10 | | D | methyl ((1S)-1-(((1R,3S,5R)-3-(7-((2-((3S)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate |
| D-11 | | D | methyl ((1S)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate |
| M1 | | D | methyl ((1S)-1-(((2S)-2-(4-(4-((4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl) carbamate |
| M2 | 0.24 | C | dimethyl (1,2-ethynediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl ((1R)-2-oxo-1-phenyl-2,1-ethanediyl))) biscarbamate |
| M2.1 | | D | dimethyl (1,2-ethynediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate |

| Compound No. | 1b EC50 (nM) | Range | Name |
|---|---|---|---|
| M3 | | D | methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-((4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl) amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0] hex-3-yl)-1H-imidazol-4-yl)phenyl)ethynyl) phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0] hex-2-yl)carbonyl)-2-methylpropyl)carbamate |
| M4 | | D | dimethyl (1,2-ethynediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo [3.1.0]hexane-3,2-diyl((2S)-1-oxo-1,2-butanediyl)))biscarbamate |
| M5 | | C | dimethyl (1,2-ethynediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo [3.1.0]hexane-3,2-diyl((1S)-1-cyclobutyl-2-oxo-2,1-ethanediyl)))biscarbamate |
| M6 | 0.0033 | D | dimethyl (1,2-ethynediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo [3.1.0]hexane-3,2-diyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate |
| M7 | | D | methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-((4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl) amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate |

| Compound No. | 1b EC50 (nM) | Range | Name |
|---|---|---|---|
| M8 | | D | methyl ((1S)-1-(((1R,3S,5R)-3-(4-chloro-5-(4-((4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate |
| M9 | | D | methyl ((1S)-1-(((1R,3S,5R)-3-(4-chloro-5-(4-((4-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate |
| M9.1 | | D | methyl ((1S)-2-((1R,3S,5R)-3-(4-(4-((4-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate |
| M9.2 | | D | dimethyl (1,2-ethynediylbis(4,1-phenylene(4-chloro-1H-imidazole-5,2-diyl)(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate |

| Compound No. | 1b EC50 (nM) | Range | Name |
|---|---|---|---|
| M9.3 | | D | methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-((1S,2S)-2-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)cyclopropyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate |
| M9.4 | | D | dimethyl ((1S,2S)-1,2-cyclopropanediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate |
| M9.5 | | D | methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-((1R,2R)-2-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)cyclopropyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate |
| M9.6 | | D | dimethyl ((1R,2R)-1,2-cyclopropanediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate |

| Compound No. | 1b EC50 (nM) | Range | Name |
|---|---|---|---|
| M9.7 | | D | methyl ((1S)-1-(((2S,4S)-2-(4-(4-((1S,2S)-2-(4-(2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)cyclopropyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate |
| M9.8 | | D | dimethyl ((1S,2S)-1,2-cyclopropanediylbis(4,1-phenylene-1H-imidazole-4,2-diyl((2S,4S)-4-methyl-2,1-pyrrolidinediyl)((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate |
| M10 | | D | methyl ((1S)-1-(((2S,5S)-2-(4-(4-((4-(2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl) carbonyl)-2-methylpropyl)carbamate |
| M11 | | D | dimethyl (1,2-ethynediylbis(4,1-phenylene-1H-imidazole-4,2-diyl((2S,5S)-5-methyl-2,1-pyrrolidinediyl)((2S)-1-oxo-1,2-butanediyl))) biscarbamate |
| M12 | | D | dimethyl (1,2-ethynediylbis(4,1-phenylene-1H-imidazole-4,2-diyl((2S,5S)-5-methyl-2,1-pyrrolidinediyl)((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate |

| Compound No. | Ib EC50 (nM) | Range | Name |
|---|---|---|---|
| M12.1 | | D | methyl ((1S)-1-(((2S,5S)-2-(4-(4-((4-(2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate |
| M12.2 | | D | methyl ((1S)-1-(((2S,4S)-2-(4-(4-((4-(2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate |
| M12.3 | 0.014 | D | dimethyl (1,2-ethynediylbis(4,1-phenylene-1H-imidazole-4,2-diyl((2S,4S)-4-methyl-2,1-pyrrolidinediyl)((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate |
| M12.4 | | D | methyl ((1S)-1-(((2S,4S)-2-(4-(4-((4-(4-chloro-2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate |

| Compound No. | 1b EC50 (nM) | Range | Name |
|---|---|---|---|
| M12.5 | | D | methyl ((1S)-1-(((2S,4S)-2-(4-chloro-5-(4-((4-(4-chloro-2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate |
| M12.6 | | D | methyl ((1S)-2-((2S,4S)-2-(4-(4-((4-(4-chloro-2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate |
| M12.7 | 0.061 | D | dimethyl (1,2-ethynediylbis(4,1-phenylene(4-chloro-1H-imidazole-5,2-diyl)((2S,4S)-4-methyl-2,1-pyrrolidinediyl)((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate |
| M12.8 | | D | methyl ((1S)-2-((2S,4S)-2-(4-(4-((4-(2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate |

| Compound No. | 1b EC50 (nM) | Range | Name |
|---|---|---|---|
| M12.9 | | D | methyl ((1S)-1-(((1S,3S,5S)-3-(4-(4-((4-(2-((1S,3S,5S)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-5-methyl-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate |
| M13 | | D | methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-((E)-2-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)vinyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate |
| M14 | 0.017 | D | dimethyl ((E)-1,2-ethenediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl))) biscarbamate |
| M15 | | D | methyl ((1S)-2-((1R,3S,5R)-3-(4-(4-((E)-2-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)vinyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate |

| Compound No. | 1b EC50 (nM) | Range | Name |
|---|---|---|---|
| N1 | | D | methyl ((1S)-1-(((2S)-2-(4-(4-((4-(2-((2S)-4,4-difluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate |
| N2 | | D | dimethyl (ethyne-1,2-diylbis(4,1-phenylene-1H-imidazole-5,2-diyl((2S)-4,4-difluoropyrrolidine-2,1-diyl)((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl)))biscarbamate |
| N3 | 0.25 | A | methyl ((1R)-2-((2S)-2-(5-(4-((4-(2-((2S)-4,4-difluoro-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-4,4-difluoropyrrolidin-1-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate |
| N4 | 0.18 | A | dimethyl (ethyne-1,2-diylbis(4,1-phenylene-1H-imidazole-5,2-diyl((2S)-4,4-difluoropyrrolidine-2,1-diyl)((1R)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl)))biscarbamate |
| N5 | | D | methyl ((1S)-1-(((3S)-3-(4-(4-((4-(2-((3S)-4-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-3-morpholinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-4-morpholinyl)carbonyl)-2-methylpropyl)carbamate |

| Compound No. | 1b EC50 (nM) | Range | Name |
|---|---|---|---|
| N6 | | A | methyl ((1S)-1-(((2S)-2-(4-(4-((4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-piperidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-piperidinyl)carbonyl)-2-methylpropyl)carbamate |
| N7 | | D | methyl ((1S)-1-(((2S,4S)-4-hydroxy-2-(4-(4-((4-(2-((2S,4S)-4-hydroxy-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate |
| N7.1 | | | methyl ((1S)-1-(((2S)-2-(4-(4-((4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methylene-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-4-methylene-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate |
| N7.2 | | | methyl ((1S)-1-(((2S,4R)-4-hydroxy-2-(4-(4-((4-(2-((2S,4R)-4-hydroxy-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate |

| Compound No. | 1b EC50 (nM) | Range | Name |
|---|---|---|---|
| N8 | | A | methyl((1S)-1-(((1S,3S,5S)-3-(4-(4-((4-(2-((1S,3S,5S)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate |
| N9 | | D | dimethyl (1,2-ethynediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate |
| J1 | | D | methyl ((1S)-1-(((2S)-2-(4-(3-((3-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate |
| J1.1 | 338.8 | A | methyl ((1S)-2-methyl-1-(((2S)-2-(4-(3-((3-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate |
| J2 | 0.12 | C | dimethyl (1,2-ethynediylbis(3,1-phenylene-1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate |

| Compound No. | 1b EC50 (nM) | Range | Name |
|---|---|---|---|
| J3 | | D | methyl ((1S)-1-(((1R,3S,5R)-3-(4-(3-((3-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate |
| J4 | | D | dimethyl (1,2-ethynediylbis(3,1-phenylene-1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate |
| J5 | | D | methyl ((1S)-1-(((2S)-2-(4-(4'-((4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate |

The compounds of the present disclosure may inhibit HCV by mechanisms in addition to or other than NS5A inhibition. In one embodiment the compounds of the present disclosure inhibit HCV replicon and in another embodiment the compounds of the present disclosure inhibit NS5A.

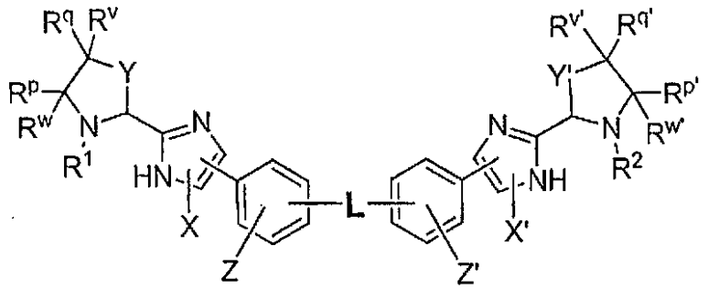
It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing

examples, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

CLAIMS

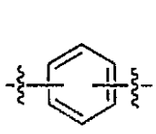
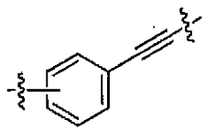
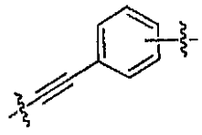
WHAT IS CLAIMED IS:

1. A compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

L is selected from –O–, –$CH_2CH_2$–, –CH=CH–, –C≡C–, –$OCH_2$–, -$CH_2O$–, -$CH_2OCH_2$–,  ,  ,  , and  ;

X is hydrogen (H) or halogen and Z is hydrogen; or

X and Z, together with the carbon atoms to which they are attached, form a five- to eight-membered aromatic or non-aromatic fused ring optionally containing one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the five- to eight-membered ring is optionally substituted with one, two, or three substitutents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylsulfonyl, aryl, arylalkyl, arylsulfonyl, carboxy, formyl, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, -$NR^aR^b$, ($NR^aR^b$)alkyl, ($NR^aR^b$)carbonyl, oxo, and spirocycle;

X' is hydrogen (H) or halogen and Z' is hydrogen; or

X' and Z', together with the carbon atoms to which they are attached, form a five- to eight-membered aromatic or non-aromatic fused ring optionally

containing one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein the five- to eight-membered ring is optionally substituted with one, two, or three substitutents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylsulfonyl, aryl, arylalkyl, arylsulfonyl, carboxy, formyl, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, -$NR^aR^b$, ($NR^aR^b$)alkyl, ($NR^aR^b$)carbonyl, oxo, and spirocycle;

Y and Y' are each independently -$CH_2$-, -$CH_2CH_2$-, or -$CH_2O$-, wherein the -$CH_2O$- is drawn such that the oxygen atom is bound to the carbon atom substituted with $R^v$ and $R^q$ or $R^{v'}$ and $R^{q'}$;

$R^p$ is hydrogen or $C_1$ to $C_4$ alkyl;

$R^q$ is hydrogen, alkyl, or halo; or

$R^p$ and $R^q$, together with the carbon atoms to which they are attached, form a cycloalkyl ring;

$R^v$ is selected from hydrogen, alkyl, halo, and hydroxy; or

$R^v$ and $R^q$, together with the carbon atom to which they are attached, form an ethylenyl group or a cycloalkyl ring;

$R^{p'}$ is hydrogen or $C_1$ to $C_4$ alkyl;

$R^{q'}$ is hydrogen, alkyl, or halo; or

$R^{p'}$ and $R^{q'}$, together with the carbon atoms to which they are attached, form a cycloalkyl ring;

$R^{v'}$ are independently selected from hydrogen, alkyl, halo, and hydroxy; or

$R^{v'}$ and $R^{q'}$, together with the carbon atom to which they are attached, form an ethylenyl group or a cycloalkyl ring;

$R^w$ and $R^{w'}$ are independently selected from hydrogen and alkyl;

$R^1$ is hydrogen or –$C(O)R^x$;

$R^2$ is hydrogen or –$C(O)R^y$;

$R^x$ and $R^y$ are independently selected from cycloalkyl, heteroaryl, heterocyclyl, alkoxy, and alkyl, said alkyl being substituted by one or more substituents independently selected from aryl, alkenyl, cycloalkyl, heterocyclyl, heteroaryl, -$OR^3$, -$C(O)OR^4$, -$NR^aR^b$, and -$C(O)NR^cR^d$,

wherein any said aryl and heteroaryl may optionally be substituted with one or more substituents independently selected from alkenyl, alkyl, haloalkyl, arylalkyl, heterocyclyl, heterocyclylalkyl, halogen, cyano, nitro, -C(O)OR$^4$, -OR$^5$, -NR$^a$R$^b$, (NR$^a$R$^b$)alkyl, and (MeO)(HO)P(O)O-, and

wherein any said cycloalkyl and heterocyclyl may optionally be fused onto an aromatic ring and may optionally be substituted with one or more substituents independently selected from alkyl, hydroxyl, halogen, aryl, -NR$^a$R$^b$, oxo, and -C(O)OR$^4$;

R$^3$ is hydrogen, alkyl, or arylalkyl;

R$^4$ is alkyl or arylalkyl;

R$^5$ is hydrogen, alkyl, or arylalkyl;

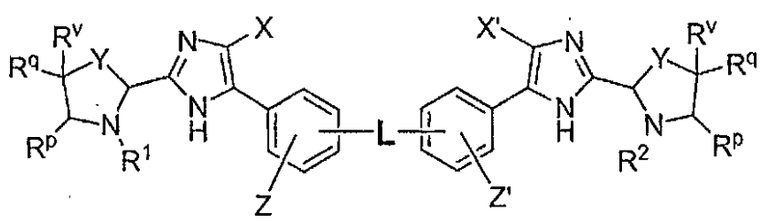
R$^a$ and R$^b$ are independently selected from hydrogen, alkyl, cycloalkyl, arylalkyl, heteroaryl, -C(O)R$^6$, -C(O)OR$^7$, –C(O)NR$^c$R$^d$, and (NR$^c$R$^d$)alkyl, or alternatively, R$^a$ and R$^b$, together with the nitrogen atom to which they are attached, form a five- or six-membered ring or bridged bicyclic ring structure, wherein said five- or six-membered ring or bridged bicyclic ring structure optionally may contain one or two additional heteroatoms independently selected from nitrogen, oxygen, and sulfur and may contain one, two, or three substituents independently selected from $C_1$ to $C_6$ alkyl, $C_1$ to $C_4$ haloalkyl, aryl, hydroxyl, $C_1$ to $C_6$ alkoxy, $C_1$ to $C_4$ haloalkoxy, and halogen;

R$^6$ is alkyl;

R$^7$ is alkyl, arylalkyl, cycloalkyl, or haloalkyl; and

R$^c$ and R$^d$ are independently selected from hydrogen, alkyl, arylalkyl, and cycloalkyl.

2. The compound of claim 1, further characterized by Formula (Ia):



(Ia),

or a pharmaceutically acceptable salt or a tautomer thereof, wherein:

X is hydrogen or chloro (Cl) and Z is hydrogen; or

X and Z, together with the carbon atoms to which they are attached, form a six-membered aromatic or non-aromatic fused ring;

X' is hydrogen or chloro (Cl) and Z' is hydrogen; or

X' and Z', together with the carbon atoms to which they are attached, form a six-membered aromatic or non-aromatic fused ring;

Y is $-CH_2-$, $-CH_2CH_2-$, or $-CH_2O-$, wherein the $-CH_2O-$ is drawn such that the oxygen atom is bound to the carbon atom substituted with $R^v$ and $R^q$;

$R^p$ is hydrogen or $C_1$ to $C_4$ alkyl;

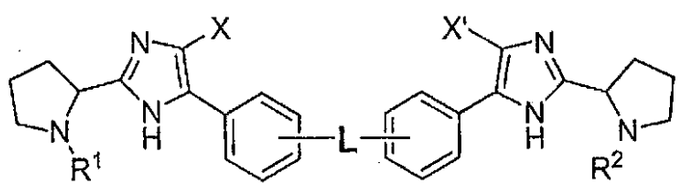
$R^q$ is hydrogen, alkyl, or haloalkyl; or

$R^p$ and $R^q$, together with the carbon atoms to which they are attached, form a cycloalkyl ring; and

$R^v$ is selected from hydrogen, alkyl, halo, and hydroxy; or

$R^v$ and $R^q$, together with the carbon atom to which they are attached, form an ethylenyl group or a cycloalkyl ring.

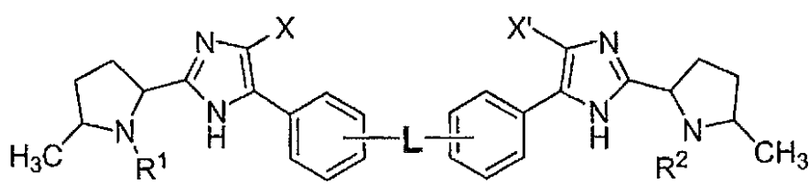
3. The compound of claim 2 further characterized by Formula (Ib):



(Ib),

or a pharmaceutically acceptable salt or a tautomer thereof.

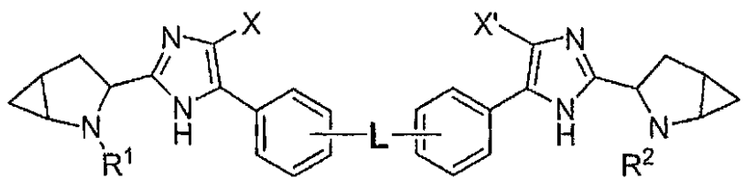
4. The compound of claim 2, further characterized by Formula (Ic):



(Ic),

or a pharmaceutically acceptable salt or a tautomer thereof.

5. The compound of claim 2, further characterized by Formula (Id):



(Id),

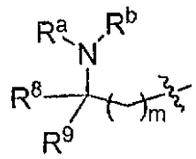
or a pharmaceutically acceptable salt or a tautomer thereof.

6. The compound of claim 2, or a pharmaceutically acceptable salt or a tautomer thereof, wherein:

$R^1$ is $-C(O)R^x$;

$R^2$ is $-C(O)R^y$;

$R^x$ and $R^y$ are independently alkyl substituted by at least one $-NR^aR^b$, characterized by Formula (A):



(A),

wherein:

m is 0 or 1;

$R^8$ is hydrogen or alkyl;

$R^9$ is selected from hydrogen, cycloalkyl, aryl, heteroaryl, heterocyclyl, and alkyl optionally substituted with a substituent selected from aryl, alkenyl, cycloalkyl, heterocyclyl, heteroaryl, heterobicyclyl, $-OR^3$, $-C(O)OR^4$, $-NR^aR^b$, and $-C(O)NR^cR^d$,

wherein any said aryl and heteroaryl may optionally be substituted with one or more substituents independently selected from alkyl, haloalkyl, arylalkyl, heterocyclyl, heterocyclylalkyl, halogen, cyano, nitro, $-C(O)OR^4$, $-OR^5$, $-NR^aR^b$, $(NR^aR^b)$alkyl, and (MeO)(HO)P(O)O-, and

wherein any said cycloalkyl and heterocyclyl may optionally be fused onto an aromatic ring and may optionally be substituted with one or more substituents independently selected from alkyl, hydroxyl, halogen, aryl, $-NR^aR^b$, oxo, and $-C(O)OR^4$; and

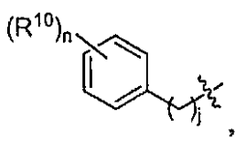
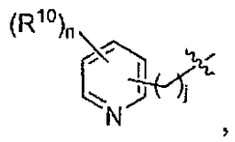
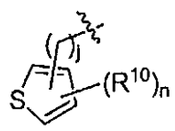
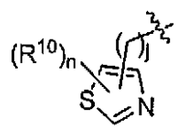
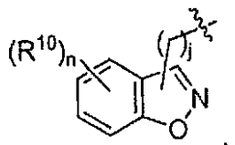
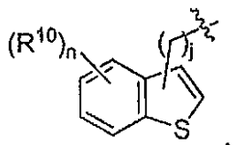
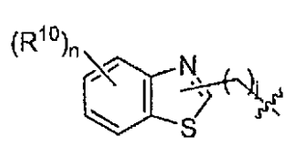
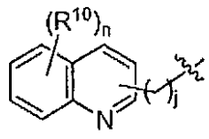
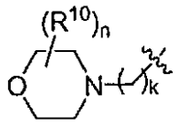
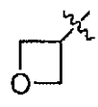
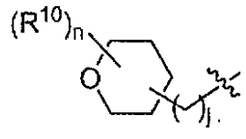
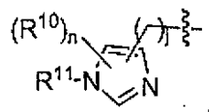
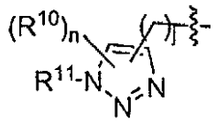
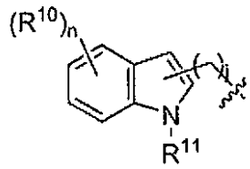
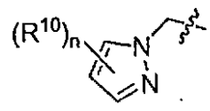
$R^3$, $R^4$, $R^5$, $R^a$, $R^b$, $R^c$, and $R^d$ are defined as in claim 1.

7. The compound of claim 6, or a pharmaceutically acceptable salt or a tautomer thereof, wherein:

m is 0;

$R^8$ is hydrogen or $C_1$ to $C_4$ alkyl;

$R^9$ is selected from hydrogen, $C_1$ to $C_6$ alkyl optionally substituted with $-OR^{12}$, $C_3$ to $C_6$ cycloalkyl, allyl, $-CH_2C(O)NR^cR^d$, $(NR^cR^d)$alkyl,


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, and

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wherein j is 0 or 1;

k is 1, 2, or 3;

n is 0 or an integer selected from 1 through 4;

each $R^{10}$ is independently hydrogen, $C_1$ to $C_4$ alkyl, $C_1$ to $C_4$ haloalkyl, halogen, nitro, -OBn, or (MeO)(OH)P(O)O-;

$R^{11}$ is hydrogen, $C_1$ to $C_4$ alkyl, or benzyl;

$R^{12}$ is hydrogen, $C_1$ to $C_4$ alkyl, or benzyl;

$R^a$ is hydrogen or $C_1$ to $C_4$ alkyl;

$R^b$ is $C_1$ to $C_4$ alkyl, $C_3$ to $C_6$ cycloalkyl, benzyl, 3-pyridyl, pyrimidin-5-yl, acetyl, $-C(O)OR^7$, or $-C(O)NR^cR^d$;

$R^7$ is $C_1$ to $C_4$ alkyl or $C_1$ to $C_4$ haloalkyl;

$R^c$ is hydrogen or $C_1$ to $C_4$ alkyl; and

$R^d$ is hydrogen, $C_1$ to $C_4$ alkyl, or $C_3$ to $C_6$ cycloalkyl.

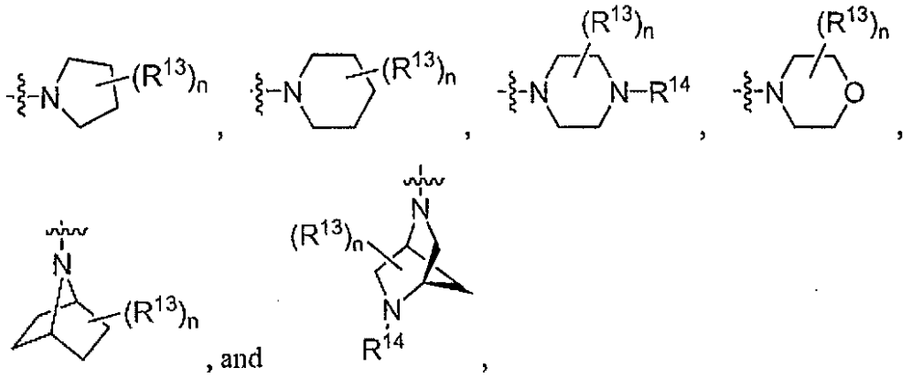
8. The compound of claim 6, or a pharmaceutically acceptable salt or a tautomer thereof, wherein:

m is 0;

$R^8$ is hydrogen;

$R^9$ is phenyl optionally substituted with one up to five substituents independently selected from $C_1$ to $C_6$ alkyl, $C_1$ to $C_4$ haloalkyl, halogen, $C_1$ to $C_6$ alkoxy, hydroxyl, cyano, and nitro; and

$NR^aR^b$ is a heterocyclyl or heterobicyclyl group selected from:



wherein n is 0, 1, or 2;

each $R^{13}$ is independently selected from $C_1$ to $C_6$ alkyl, phenyl, trifluoromethyl, halogen, hydroxyl, methoxy, and oxo; and

$R^{14}$ is $C_1$ to $C_6$ alkyl, phenyl, benzyl, or -C(O)$OR^{15}$ group, wherein $R^{15}$ is $C_1$ to $C_4$ alkyl, phenyl, or benzyl.

9. The compound of claim 6, or a pharmaceutically acceptable salt or a tautomer thereof, wherein:

m is 1;

$R^8$ is hydrogen;

$R^9$ is $C_1$ to $C_6$ alkyl, arylalkyl, or heteroarylalkyl;

$R^a$ is hydrogen; and

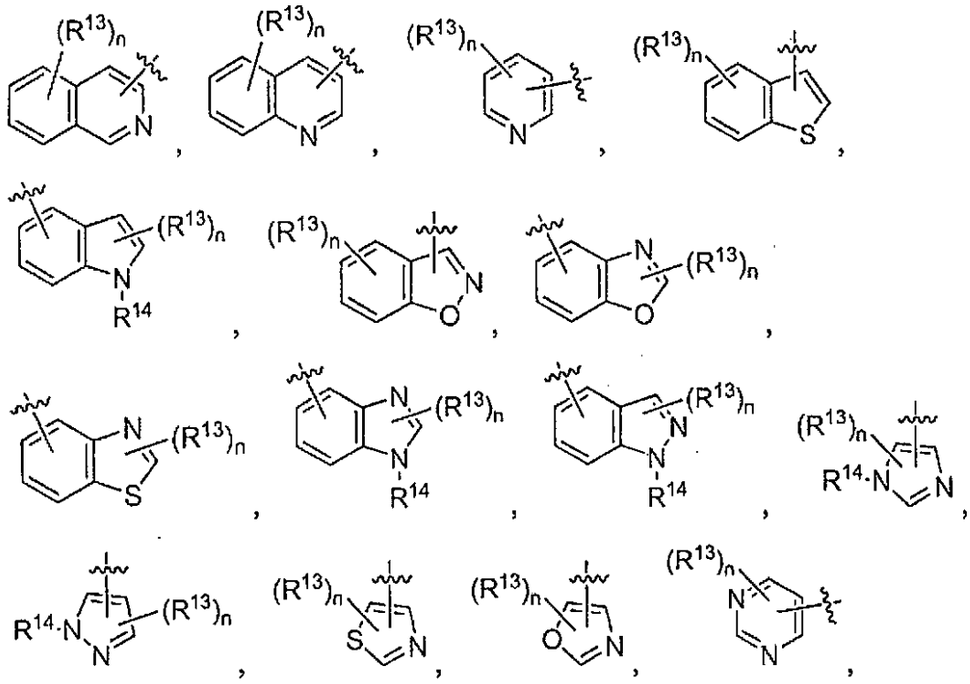
$R^b$ is –C(O)$OR^7$, wherein $R^7$ is $C_1$ to $C_6$ alkyl.

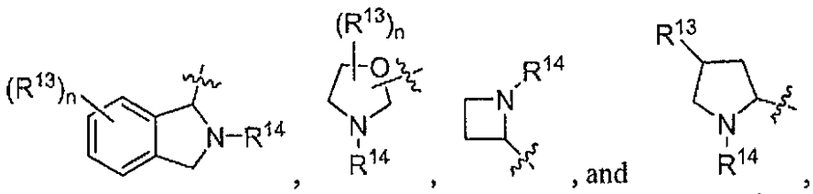
10. The compound of claim 2, or a pharmaceutically acceptable salt or a tautomer thereof, wherein:

$R^1$ is –C(O)$R^x$;

$R^2$ is –C(O)$R^y$;

$R^x$ and $R^y$ are heteroaryl or heterocyclyl independently selected from:





wherein n is 0 or an integer selected from 1 through 4;

each $R^{13}$ is independently selected from hydrogen, $C_1$ to $C_6$ alkyl, $C_1$ to $C_4$ haloalkyl, phenyl, benzyl, $C_1$ to $C_6$ alkoxy, $C_1$ to $C_4$ haloalkoxy, heterocyclyl, halogen, $NR^cR^d$, hydroxyl, cyano, and oxo, where $R^c$ and $R^d$ are independently hydrogen or $C_1$ to $C_4$ alkyl; and

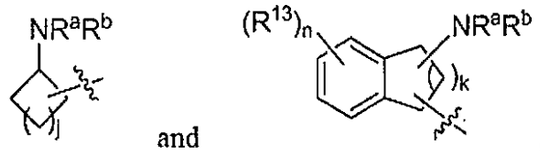
$R^{14}$ is hydrogen (H), $C_1$ to $C_6$ alkyl, benzyl, or $-C(O)OR^4$, wherein $R^4$ is $C_1$ to $C_6$ alkyl.

11. The compound of claim 2, or a pharmaceutically acceptable salt or a tautomer thereof, wherein:

$R^1$ is $-C(O)R^x$;

$R^2$ is $-C(O)R^y$;

$R^x$ and $R^y$ are cycloalkyl independently selected from:



wherein

j is 0, 1, 2, or 3;

k is 0, 1, or 2;

n is 0 or an integer selected from 1 through 4;

each $R^{13}$ is independently selected from hydrogen, $C_1$ to $C_6$ alkyl, $C_1$ to $C_4$ haloalkyl, $C_1$ to $C_6$ alkoxy, halogen, hydroxyl, cyano, and nitro; and

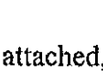
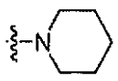
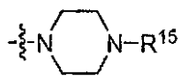
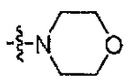
$R^a$ and $R^b$ are each independently hydrogen, $C_1$ to $C_6$ alkyl, or $-C(O)OR^7$, wherein $R^7$ is $C_1$ to $C_6$ alkyl.

12. The compound of claim 2, or a pharmaceutically acceptable salt or a tautomer thereof, wherein:

$R^1$ is $-C(O)R^x$;

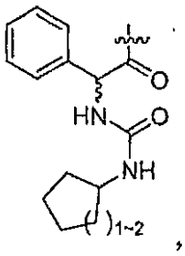
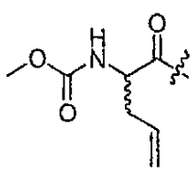
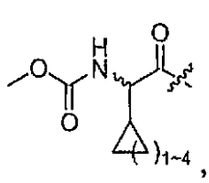
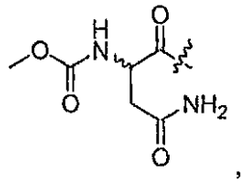
$R^2$ is $-C(O)R^y$;

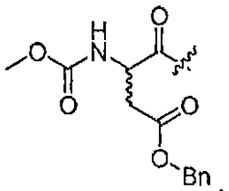
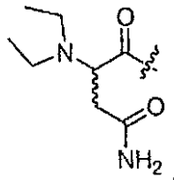
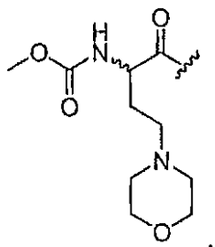
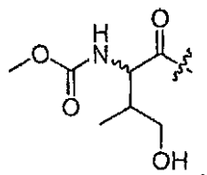
$R^x$ and $R^y$ are independently arylalkyl, wherein aryl part of said arylalkyl may optionally be substituted with $(NR^aR^b)$alkyl; and

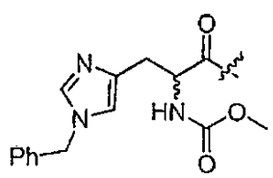
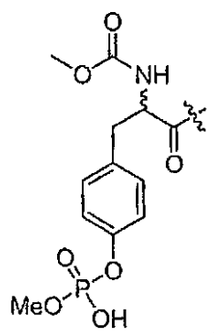
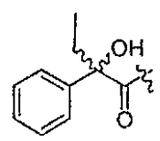
$R^a$ and $R^b$ are independently hydrogen, $C_1$ to $C_6$ alkyl, or benzyl, or alternatively, $R^a$ and $R^b$, together with the nitrogen atom to which they are attached, form a five- or six-membered ring selected from  ,  ,  , and  , wherein $R^{15}$ is hydrogen, $C_1$ to $C_6$ alkyl, or benzyl.

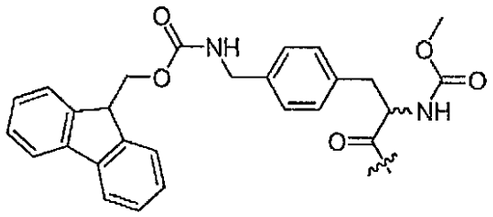
13. The compound of claim 2, or a pharmaceutically acceptable salt or a tautomer thereof, wherein:

$R^1$ and $R^2$ are the same and are selected from the group consisting of:

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 ,  ,  ,  ,

 ,  ,  , and



,

wherein a squiggle bond ( ~~~ ) in the structure indicates that a stereogenic center to which the bond is attached can take either (R)- or (S)- configuration so long as chemical bonding principles are not violated.

14. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

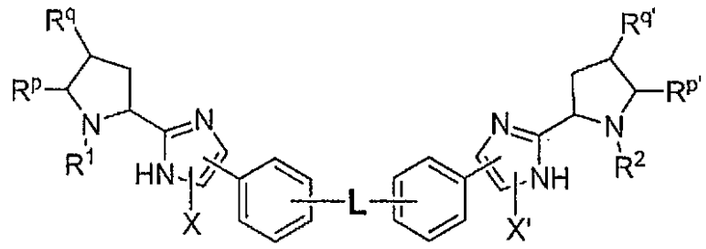
$R^1$ is $-C(O)R^x$;

$R^2$ is $-C(O)R^y$; and

$R^x$ and $R^y$ are both t-butoxy.

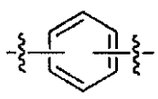
15. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein $R^1$ and $R^2$ are both hydrogen.

16. A compound of Formula (II):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

L is selected from $-O-$, $-CH_2CH_2-$, $-CH=CH-$, $-C\equiv C-$, $-OCH_2-$, $-CH_2O-$, $-CH_2OCH_2-$,  , and  ;

X and X′ are independently hydrogen (H) or halogen;

$R^p$ is hydrogen or $C_1$ to $C_4$ alkyl, and $R^q$ is hydrogen, or alternatively, $R^p$ and $R^q$, together with the carbon atoms to which they are attached, form a cyclopropyl ring;

$R^{p'}$ is hydrogen or $C_1$ to $C_4$ alkyl, and $R^{q'}$ is hydrogen, or alternatively, $R^{p'}$ and $R^{q'}$, together with the carbon atoms to which they are attached, form a cyclopropyl ring;

$R^1$ is hydrogen or $-C(O)R^x$;

$R^2$ is hydrogen or $-C(O)R^y$;

$R^x$ and $R^y$ are independently selected from cycloalkyl, heteroaryl, heterocyclyl, alkoxy, and alkyl, said alkyl being substituted by one or more substituents independently selected from aryl, alkenyl, cycloalkyl, heterocyclyl, heteroaryl, $-OR^3$, $-C(O)OR^4$, $-NR^aR^b$, and $-C(O)NR^cR^d$, wherein any said aryl and heteroaryl may optionally be substituted with one or more substituents independently selected from alkyl, haloalkyl, arylalkyl, heterocyclyl, heterocyclylalkyl, halogen, cyano, nitro, $-C(O)OR^4$, $-OR^5$, $-NR^aR^b$, $(NR^aR^b)$alkyl, and (MeO)(HO)P(O)O-, and

wherein any said cycloalkyl and heterocyclyl may optionally be fused onto an aromatic ring and may optionally be substituted with one or more substituents independently selected from alkyl, hydroxyl, halogen, aryl, $-NR^aR^b$, oxo, and $-C(O)OR^4$;

$R^3$ is hydrogen, alkyl, or arylalkyl;

$R^4$ is alkyl or arylalkyl;

$R^5$ is hydrogen, alkyl, or arylalkyl;

$R^a$ and $R^b$ are independently selected from hydrogen, alkyl, cycloalkyl, arylalkyl, heteroaryl, $-C(O)R^6$, $-C(O)OR^7$, $-C(O)NR^cR^d$, and $(NR^cR^d)$alkyl, or alternatively, $R^a$ and $R^b$, together with the nitrogen atom to which they are attached, form a five- or six-membered ring or bridged bicyclic ring structure, wherein said five- or six-membered ring or bridged bicyclic ring structure optionally may contain one or two additional heteroatoms independently selected from nitrogen, oxygen, and sulfur and may contain one, two, or three

substituents independently selected from $C_1$ to $C_6$ alkyl, $C_1$ to $C_4$ haloalkyl, aryl, hydroxyl, $C_1$ to $C_6$ alkoxy, $C_1$ to $C_4$ haloalkoxy, and halogen;

$R^6$ is alkyl;

$R^7$ is alkyl, arylalkyl, or haloalkyl; and

$R^c$ and $R^d$ are independently selected from hydrogen, alkyl, arylalkyl, and cycloalkyl.

17. A compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

(1R)-2-((2S)-2-(4-(4-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenoxy) phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(4-(4-(4-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenoxy)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanol;

dimethyl (oxybis(4,1-phenylene-1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

(1R)-2-((2S)-2-(4-(3-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenoxy) phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(4-(3-(4-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenoxy)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanol;

methyl ((1R)-2-((2S)-2-(4-(3-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenoxy)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

(1R)-2-((2S)-2-(4-(4-((4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)benzyl)oxy) phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

methyl ((1R)-2-((2S)-2-(4-(4-((4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)benzyl)oxy)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

(1R)-2-((2S)-2-(4-(4-(2-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)ethyl) phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R,1'R)-2,2'-(1,2-ethanediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl))bis(2-oxo-1-phenylethanol);

dimethyl (1,2-ethanediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl ((1R)-2-oxo-1-phenyl-2,1-ethanediyl))) biscarbamate;

N',N'''-(1,2-ethanediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl ((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-ethylurea);

1-cyclopentyl-3-((1R)-2-((2S)-2-(4-(4-(2-(4-(2-((2S)-1-((2R)-2-((cyclopentylcarbamoyl) amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)ethyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)urea;

(1R)-2-((2S)-2-(4-(4-(((4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)benzyl)oxy) methyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(4-(4-(((4-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)benzyl)oxy)methyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanol;

dimethyl (oxybis(methylene-4,1-phenylene-1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl ((1R)-2-oxo-1-phenyl-2,1-ethanediyl))) biscarbamate;

1-methyl-3-((1R)-2-((2S)-2-(4-(4-(((4-(2-((2S)-1-((2R)-2-((methylcarbamoyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)benzyl)oxy)methyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)urea;

1-ethyl-3-((1R)-2-((2S)-2-(4-(4-(((4-(2-((2S)-1-((2R)-2-((ethylcarbamoyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-

yl)benzyl)oxy)methyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)urea;

1-cyclopentyl-3-((1R)-2-((2S)-2-(4-(4-(((4-(2-((2S)-1-((2R)-2-((cyclopentylcarbamoyl) amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)benzyl)oxy)methyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)urea;

(1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)benzyl)oxy) methyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

(1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)benzyl)oxy)methyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanol;

(methyl ((1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)benzyl)oxy)methyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

1-methyl-3-((1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-((methylcarbamoyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)benzyl)oxy)methyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)urea;

1-ethyl-3-((1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-((ethylcarbamoyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)benzyl)oxy)methyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)urea;

1-cyclopentyl-3-((1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-((cyclopentylcarbamoyl) amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)benzyl)oxy)methyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)urea;

dimethyl (1,1':4',1''-terphenyl-4,4''-diylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl ((1R)-2-oxo-1-phenyl-2,1-ethanediyl))) biscarbamate;

(1R)-2-((2S)-2-(4-(4''-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-1,1':4',1''-terphenyl-4-yl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine;

methyl ((1S)-1-(((2S)-2-(4-(4-((2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1R)-2-((2S)-2-(4-(4-((2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1R)-2-((2S)-2-(7-((4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(4-((2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1R)-2-((1R,3S,5R)-3-(7-((4-(2-((1R,3S,5R)-2-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-phenylethyl)carbamate;

methyl ((1S)-1-(((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-4,5-dihydro-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((1R,3S,5R)-3-(7-((2-((3S)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-

naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-naphtho[1,2-d]imidazol-7-yl)ethynyl)-1H-naphtho[1,2-d]imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(4-((4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl) carbamate;

dimethyl (1,2-ethynediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl ((1R)-2-oxo-1-phenyl-2,1-ethanediyl))) biscarbamate;

dimethyl (1,2-ethynediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-((4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl) amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0] hex-3-yl)-1H-imidazol-4-yl)phenyl)ethynyl) phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0] hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

dimethyl (1,2-ethynediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo [3.1.0]hexane-3,2-diyl((2S)-1-oxo-1,2-butanediyl)))biscarbamate;

dimethyl (1,2-ethynediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo [3.1.0]hexane-3,2-diyl((1S)-1-cyclobutyl-2-oxo-2,1-ethanediyl)))biscarbamate;

dimethyl (1,2-ethynediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo [3.1.0]hexane-3,2-diyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-((4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl) amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((1R,3S,5R)-3-(4-chloro-5-(4-((4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((1R,3S,5R)-3-(4-chloro-5-(4-((4-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((1R,3S,5R)-3-(4-(4-((4-(4-chloro-2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate;

dimethyl (1,2-ethynediylbis(4,1-phenylene(4-chloro-1H-imidazole-5,2-diyl)(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-((1S,2S)-2-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)cyclopropyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

dimethyl ((1S,2S)-1,2-cyclopropanediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-((1R,2R)-2-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)cyclopropyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

dimethyl ((1R,2R)-1,2-cyclopropanediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-1-(((2S,4S)-2-(4-(4-((1S,2S)-2-(4-(2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-

4-yl)phenyl)cyclopropyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S,5S)-2-(4-(4-((4-(2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl) carbonyl)-2-methylpropyl)carbamate;

dimethyl (1,2-ethynediylbis(4,1-phenylene-1H-imidazole-4,2-diyl((2S,5S)-5-methyl-2,1-pyrrolidinediyl)((2S)-1-oxo-1,2-butanediyl))) biscarbamate;

dimethyl (1,2-ethynediylbis(4,1-phenylene-1H-imidazole-4,2-diyl((2S,5S)-5-methyl-2,1-pyrrolidinediyl)((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-1-(((2S,5S)-2-(4-(4-((4-(2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S,4S)-2-(4-(4-((4-(2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

dimethyl (1,2-ethynediylbis(4,1-phenylene-1H-imidazole-4,2-diyl((2S,4S)-4-methyl-2,1-pyrrolidinediyl)((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-1-(((2S,4S)-2-(4-(4-((4-(4-chloro-2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S,4S)-2-(4-chloro-5-(4-((4-(4-chloro-2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S,4S)-2-(4-(4-((4-(4-chloro-2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate;

dimethyl (1,2-ethynediylbis(4,1-phenylene(4-chloro-1H-imidazole-5,2-diyl)((2S,4S)-4-methyl-2,1-pyrrolidinediyl)((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-2-((2S,4S)-2-(4-(4-((4-(2-((2S,4S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-4-methyl-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate;

methyl ((1S)-1-(((1S,3S,5S)-3-(4-(4-((4-(2-((1S,3S,5S)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-5-methyl-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4-((E)-2-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl) amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0] hex-3-yl)-1H-imidazol-4-yl)phenyl)vinyl) phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0] hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

dimethyl ((E)-1,2-ethenediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo [3.1.0]hexane-3,2-diyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl))) biscarbamate;

methyl ((1S)-2-((1R,3S,5R)-3-(4-(4-((E)-2-(4-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl) amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0] hex-3-yl)-1H-imidazol-4-yl)phenyl)vinyl) phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0] hex-2-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(4-((4-(2-((2S)-4,4-difluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

dimethyl (ethyne-1,2-diylbis(4,1-phenylene-1H-imidazole-5,2-diyl((2S)-4,4-difluoropyrrolidine-2,1-diyl)((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl)))biscarbamate;

methyl ((1R)-2-((2S)-2-(5-(4-((4-(2-((2S)-4,4-difluoro-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-4,4-difluoropyrrolidin-1-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate;

dimethyl (ethyne-1,2-diylbis(4,1-phenylene-1H-imidazole-5,2-diyl((2S)-4,4-difluoropyrrolidine-2,1-diyl)((1R)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl)))biscarbamate;

methyl ((1S)-1-(((3S)-3-(4-(4-((4-(2-((3S)-4-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-3-morpholinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-4-morpholinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(4-((4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-piperidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-piperidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S,4S)-4-hydroxy-2-(4-(4-((4-(2-((2S,4S)-4-hydroxy-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl((1S)-1-(((1S,3S,5S)-3-(4-(4-((4-(2-((1S,3S,5S)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

dimethyl (1,2-ethynediylbis(4,1-phenylene-1H-imidazole-4,2-diyl(1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-1-(((2S)-2-(4-(3-((3-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-

yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(4-(3-((3-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

dimethyl (1,2-ethynediylbis(3,1-phenylene-1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-1-(((1R,3S,5R)-3-(4-(3-((3-(2-((1R,3S,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

dimethyl (1,2-ethynediylbis(3,1-phenylene-1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate;

dimethyl ((1S,2S)-1,2-cyclopropanediylbis(4,1-phenylene-1H-imidazole-4,2-diyl((2S,4S)-4-methyl-2,1-pyrrolidinediyl)((1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-1-(((2S)-2-(4-(4-((4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-4-methylene-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-4-methylene-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S,4R)-4-hydroxy-2-(4-(4-((4-(2-((2S,4R)-4-hydroxy-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(4'-((4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)ethynyl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate; and corresponding stereoisomers and tautomers thereof.

18. A composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

19. A method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

Traducción Solicitud Internacional

# INHIBIDORES DEL VIRUS DE LA HEPATITIS C

## REFERENCIA A SOLICITUDES DE PATENTE RELACIONADAS

La presente solicitud de patente reivindica la prioridad de la solicitud de patente provisional de Estados Unidos con número de serie 61/164.531 presentada el 30 de marzo de 2009.

## CAMPO DE LA DIVULGACIÓN

La presente divulgación se refiere de forma general a compuestos antivirales, y más específicamente a compuestos que pueden inhibir la función de la proteína NS5A codificada por el virus de la hepatitis C (VHC), composiciones que comprenden dichos compuestos, y procedimientos para inhibir la función de la proteína NS5A.

## ANTECEDENTES DE LA DIVULGACIÓN

El VHC es un importante patógeno humano, que se estima que ha infectado a 170 millones de personas en todo el mundo - aproximadamente cinco veces el número de personas infectadas por el virus de la inmunodeficiencia humano de tipo 1. Una fracción sustancial de estos individuos infectados por VHC desarrolla una enfermedad hepática progresiva grave, que incluye cirrosis y carcinoma hepatocelular.

El tratamiento de referencia actual para VHC, que emplea una combinación de interferón pegilado y ribavirina, presenta una tasa de éxito subóptima para conseguir una respuesta vírica mantenida y provoca numerosos efectos secundarios. Por lo tanto, existe una clara necesidad, sentida desde hace mucho tiempo, de desarrollar terapias eficaces para cubrir esta necesidad médica no

satisfecha.

VHC es un virus de ARN de polaridad positiva. Basándose en una comparación de la secuencia de aminoácidos deducida y la gran similitud en la región 5' no traducida, VHC ha sido clasificado como un género diferente de la familia Flaviviridae. Todos los miembros de la familia Flaviviridae presentan viriones encapsulados que contienen un genoma de ARN de polaridad positiva que codifica todas las proteínas específicas del virus conocidas mediante traducción de un marco de lectura abierto, ininterrumpido y único.

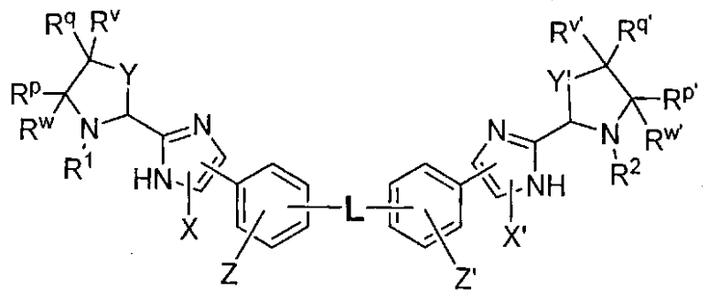
Existe una heterogeneidad considerable en la secuencia de nucleótidos y de aminoácidos codificados por todo el genoma de VHC debido a la alta tasa de errores de la ARN polimerasa dependiente de ARN codificada que carece de capacidad editora. Se han caracterizado al menos seis genotipos principales, y se han descrito más de 50 subtipos distribuidos por todo el mundo. La significación clínica de la heterogeneidad genética de VHC ha demostrado una propensión a la aparición de mutaciones durante el tratamiento con monoterapias, por lo tanto es deseable que puedan usarse opciones de tratamiento adicionales. El posible efecto modulador de los genotipos sobre la patogénesis y terapia sigue sin entenderse.

El genoma de ARN monocatenario de VHC tiene una longitud de aproximadamente 9500 nucleótidos y tiene un único marco de lectura abierto (ORF) que codifica una única poliproteína grande de aproximadamente 3000 aminoácidos. En las células infectadas, esta poliproteína es escindida en múltiples sitios por proteasas celulares y víricas para producir las proteínas estructurales y no estructurales (NS). En el caso de VHC, la generación de proteínas no estructurales maduras (NS2, NS3, NS4A, NS4B, NS5A, y NS5B) es realizada por dos proteasas víricas. Se cree que la primera es una metaloproteasa y escinde la unión entre NS2

y NS3; la segunda es una serina proteasa contenida en la región del extremo N de NS3 (también denominada en el presente documento proteasa NS3) y actúa de mediadora de todas las escisiones posteriores aguas abajo de NS3, tanto en cis, en el sitio de escisión NS3 y NS4A, como en trans, para el resto de los sitios NS4A-NS4B, NS4B-NS5A, NS5A-NS5B. La proteína NS4A parece realizar funciones múltiples, actuando tanto de cofactor para la proteasa NS3 como ayudando en la localización en la membrana de NS3 y otros componentes de las replicasas víricas. Para una actividad de proteasa adecuada es necesaria la formación de un complejo NS3-NS4A lo que supone una eficacia proteolítica mayor de los eventos de escisión. La proteína NS3 también muestra actividades de nucleósido trifosfatasa y ARN helicasa. NS5B (también denominada VHC polimerasa en el presente documento) es una ARN polimerasa dependiente de ARN que está implicada en la replicación de VHC con otras proteínas de VHC, entre otras NS5A, en un complejo de replicasa.

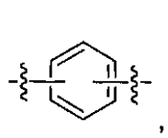
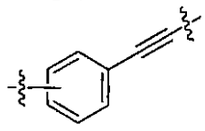
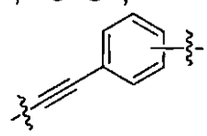
Son deseables compuestos útiles para tratar a pacientes infectados con VHC que inhiban selectivamente la replicación del virus VHC. En particular, son deseables compuestos que sean eficaces para inhibir la función de la proteína NS5A. La proteína NS5A de VHC se describe, por ejemplo, en las siguientes referencias: S. L. Tan, et al., *Virology*, 284:1-12 (2001); K.-J. Park, et al., *J. Biol. Chem.*, 30711-30718 (2003); T. L. Tellinghuisen, et al., *Nature*, **435**, 374 (2005); R. A. Love, et al., *J. Virol*, **83**, 4395 (2009); N. Appel, et al., *J. Biol. Chem.*, **281**, 9833 (2006); L. Huang, *J. Biol. Chem.*, **280**, 36417 (2005); C. Rice, et al., documento WO2006093867.

La presente divulgación proporciona compuestos que inhiben selectivamente la replicación del virus VHC, caracterizados por la Fórmula (I):



(I),

o una sal farmacéuticamente aceptable de los mismos, en la que:

L se selecciona a partir de –O–, $–CH_2CH_2–$, –CH=CH–, –C≡C–, $–OCH_2–$, $-CH_2O–$, $-CH_2OCH_2–$,  ,  ,  , y  ;

X es hidrógeno (H) o halógeno y Z es hidrógeno; o

X y Z, junto con los átomos de carbono a los que están unidos, forman un anillo condensado aromático o no aromático de cinco a ocho miembros que opcionalmente contiene uno o dos heteroátomos que se seleccionan independientemente a partir de nitrógeno, oxígeno, y azufre; en la que el anillo de cinco a ocho miembros está opcionalmente sustituido con uno, dos, o tres sustituyentes que se seleccionan independientemente a partir de alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, alquilsulfonilo, arilo, arilalquilo, arilsulfonilo, carboxi, formilo, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialquilo, $-NR^aR^b$, $(NR^aR^b)$alquilo, $(NR^aR^b)$carbonilo, oxo, y espirociclo;

X' es hidrógeno (H) o halógeno y Z' es hidrógeno; o

X' y Z', junto con los átomos de carbono a los que están unidos, forman un anillo condensado aromático o no aromático de cinco a ocho miembros que opcionalmente contiene uno o dos heteroátomos que se

seleccionan independientemente a partir de nitrógeno, oxígeno, y azufre; en la que el anillo de cinco a ocho miembros está opcionalmente sustituido con uno, dos, o tres sustituyentes que se seleccionan independientemente a partir de alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, alquilsulfonilo, arilo, arilalquilo, arilsulfonilo, carboxi, formilo, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialquilo, $-NR^aR^b$, $(NR^aR^b)$alquilo, $(NR^aR^b)$carbonilo, oxo, y espirociclo;

Y e Y' son cada uno independientemente $-CH_2-$, $-CH_2CH_2-$, o $-CH_2O-$, en los que el

$-CH_2O-$ se dibuja de tal forma que el átomo de oxígeno esté unido al átomo de carbono sustituido con $R^v$ y $R^q$ o $R^{v'}$ y $R^{q'}$;

$R^p$ es hidrógeno o alquilo $C_1$ a $C_4$;

$R^q$ es hidrógeno, alquilo, o halo; o

$R^p$ y $R^q$, junto con los átomos de carbono a los que están unidos, forman un anillo cicloalquilo;

$R^v$ se selecciona a partir de hidrógeno, alquilo, halo, e hidroxi; o

$R^v$ y $R^q$, junto con el átomo de carbono al que están unidos, forman un grupo etilenilo o un anillo cicloalquilo;

$R^{p'}$ es hidrógeno o alquilo $C_1$ a $C_4$;

$R^{q'}$ es hidrógeno, alquilo, o halo; o

$R^{p'}$ y $R^{q'}$, junto con los átomos de carbono a los que están unidos, forman un anillo cicloalquilo;

$R^{v'}$ se seleccionan independientemente a partir de hidrógeno, alquilo, halo, e hidroxi; o

$R^{v'}$ y $R^{q'}$, junto con el átomo de carbono al que están unidos, forman un grupo etilenilo o un anillo cicloalquilo;

$R^w$ y $R^{w'}$ se seleccionan independientemente a partir de hidrógeno y alquilo;

$R^1$ es hidrógeno o $-C(O)R^x$;

$R^2$ es hidrógeno o $-C(O)R^y$;

$R^x$ y $R^y$ se seleccionan independientemente a partir de cicloalquilo, heteroarilo, heterociclilo, alcoxi, y alquilo, estando dicho alquilo sustituido por uno o más sustituyentes que se seleccionan independientemente a partir de arilo, alquenilo, cicloalquilo, heterociclilo, heteroarilo, $-OR^3$, $-C(O)OR^4$, $-NR^aR^b$, y $-C(O)NR^cR^d$,

en los que cualquiera de dichos arilo y heteroarilo puede estar opcionalmente sustituido con uno o más sustituyentes que se seleccionan independientemente a partir de alquenilo, alquilo, haloalquilo, arilalquilo, heterociclilo, heterociclilalquilo, halógeno, ciano, nitro, $-C(O)OR^4$, $-OR^5$, $-NR^aR^b$, $(NR^aR^b)$alquilo, y (MeO)(HO)P(O)O-, y

en los que cualquiera de dichos cicloalquilo y heterociclilo puede opcionalmente estar condensado a un anillo aromático y puede estar opcionalmente sustituido con uno o más sustituyentes que se seleccionan independientemente a partir de alquilo, hidroxilo, halógeno, arilo, $-NR^aR^b$, oxo, y $-C(O)OR^4$;

$R^3$ es hidrógeno, alquilo, o arilalquilo;

$R^4$ es alquilo o arilalquilo;

$R^5$ es hidrógeno, alquilo, o arilalquilo;

$R^a$ y $R^b$ se seleccionan independientemente a partir de hidrógeno, alquilo, cicloalquilo, arilalquilo, heteroarilo, $-C(O)R^6$, $-C(O)OR^7$, $-C(O)NR^cR^d$, y $(NR^cR^d)$alquilo, o de forma alternativa, $R^a$ y $R^b$, junto con el átomo de

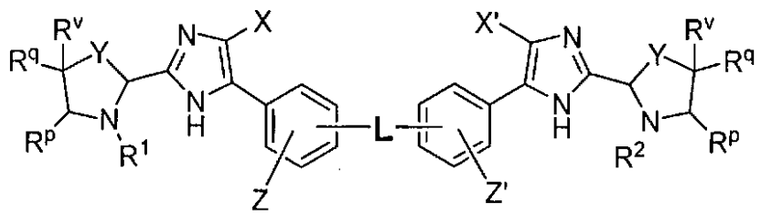
nitrógeno al que están unidos, forman un anillo de cinco o seis miembros o estructura anular bicíclica con puente, en la que dicho anillo de cinco o seis miembros o estructura anular bicíclica con puente opcionalmente pueden contener uno o dos heteroátomos adicionales que se seleccionan independientemente a partir de nitrógeno, oxígeno, y azufre y pueden contener uno, dos, o tres sustituyentes que se seleccionan independientemente a partir de alquilo $C_1$ a $C_6$, haloalquilo $C_1$ a $C_4$, arilo, hidroxilo, alcoxi $C_1$ a $C_6$, haloalcoxi $C_1$ a $C_4$, y halógeno;

$R^6$ es alquilo;

$R^7$ es alquilo, arilalquilo, cicloalquilo, o haloalquilo; y

$R^c$ y $R^d$ se seleccionan independientemente a partir de hidrógeno, alquilo, arilalquilo, y cicloalquilo.

En una primera realización del primer aspecto, la presente divulgación proporciona un compuesto de la Fórmula (I) caracterizado además por la Fórmula (Ia):




(Ia),

o una sal o un tautómero farmacéuticamente aceptable del mismo, en la que:

X es hidrógeno o cloro (Cl) y Z es hidrógeno; o

X y Z, junto con los átomos de carbono a los que están unidos, forman un anillo condensado aromático o no aromático de seis miembros;

X' es hidrógeno o cloro (Cl) y Z' es hidrógeno; o

X' y Z', junto con los átomos de carbono a los que están unidos,

forman un anillo condensado aromático o no aromático de seis miembros;

Y es $-CH_2-$, $-CH_2CH_2-$, o $-CH_2O-$, en los que el $-CH_2O-$ se dibuja de tal forma que el átomo de oxígeno esté unido al átomo de carbono sustituido con $R^v$ y $R^q$;

$R^p$ es hidrógeno o alquilo $C_1$ a $C_4$;

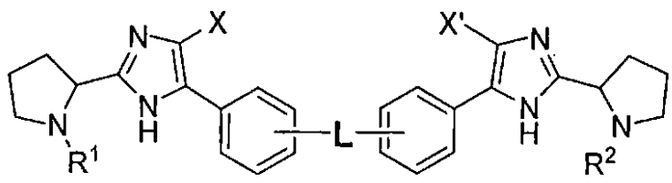
$R^q$ es hidrógeno, alquilo, o halo; o

$R^p$ y $R^q$, junto con los átomos de carbono a los que están unidos, forman un anillo cicloalquilo; y

$R^v$ se selecciona a partir de hidrógeno, alquilo, halo, e hidroxi; o

$R^v$ y $R^q$, junto con el átomo de carbono al que están unidos, forman un grupo etilenilo o un anillo cicloalquilo.

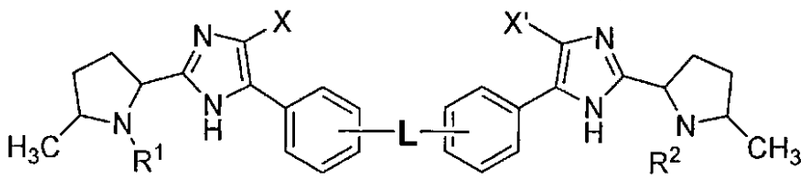
En una segunda realización del primer aspecto, la presente divulgación proporciona un compuesto de la Fórmula (I) caracterizado además por la Fórmula (Ib):




(Ib),

o una sal o un tautómero farmacéuticamente aceptable del mismo.

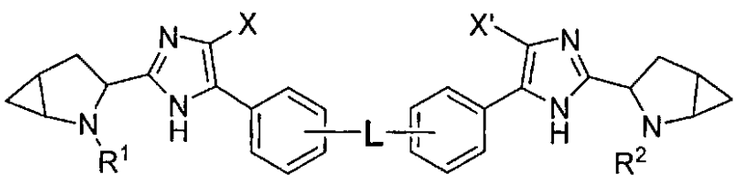
En una tercera realización del primer aspecto, la presente divulgación proporciona un compuesto de la Fórmula (I) caracterizado además por la Fórmula (Ic):



(Ic),

o una sal o un tautómero farmacéuticamente aceptable del mismo.

En una cuarta realización del primer aspecto, la presente divulgación proporciona un compuesto de la Fórmula (I) caracterizado además por la Fórmula (Id):



(Id),

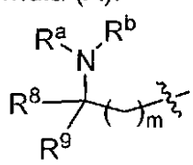
o una sal o un tautómero farmacéuticamente aceptable del mismo.

En una quinta realización del primer aspecto, la presente divulgación proporciona un compuesto de la Fórmula (Ia), o una sal farmacéuticamente aceptable del mismo, en la que:

$R^1$ es $-C(O)R^x$;

$R^2$ es $-C(O)R^y$;

$R^x$ y $R^y$ son independientemente alquilo sustituido por al menos un $-NR^aR^b$, caracterizado por la Fórmula (A):



(A),

en la que:

m es 0 ó 1;

$R^8$ es hidrógeno o alquilo;

$R^9$ se selecciona a partir de hidrógeno, cicloalquilo, arilo, heteroarilo, heterociclilo, y alquilo opcionalmente sustituido con un sustituyente que se selecciona a partir de arilo, alquenilo, cicloalquilo, heterociclilo, heteroarilo, heterobiciclilo, $-OR^3$, $-C(O)OR^4$, $-NR^aR^b$, y $-C(O)NR^cR^d$,

en el que cualquiera de dichos arilo y heteroarilo puede estar opcionalmente sustituido con uno o más sustituyentes que se seleccionan independientemente a partir de alquilo, haloalquilo, arilalquilo, heterociclilo, heterociclilalquilo, halógeno, ciano, nitro, $-C(O)OR^4$, $-OR^5$,

$-NR^aR^b$, $(NR^aR^b)$alquilo, y (MeO)(HO)P(O)O-, y

en el que cualquiera de dichos cicloalquilo y heterociclilo puede opcionalmente estar condensado a un anillo aromático y puede estar opcionalmente sustituido con uno o más sustituyentes que se seleccionan independientemente a partir de alquilo, hidroxilo, halógeno, arilo, $-NR^aR^b$, oxo, y $-C(O)OR^4$; y

$R^3$, $R^4$, $R^5$, $R^a$, $R^b$, $R^c$, y $R^d$ se definen como en la Fórmula (I).

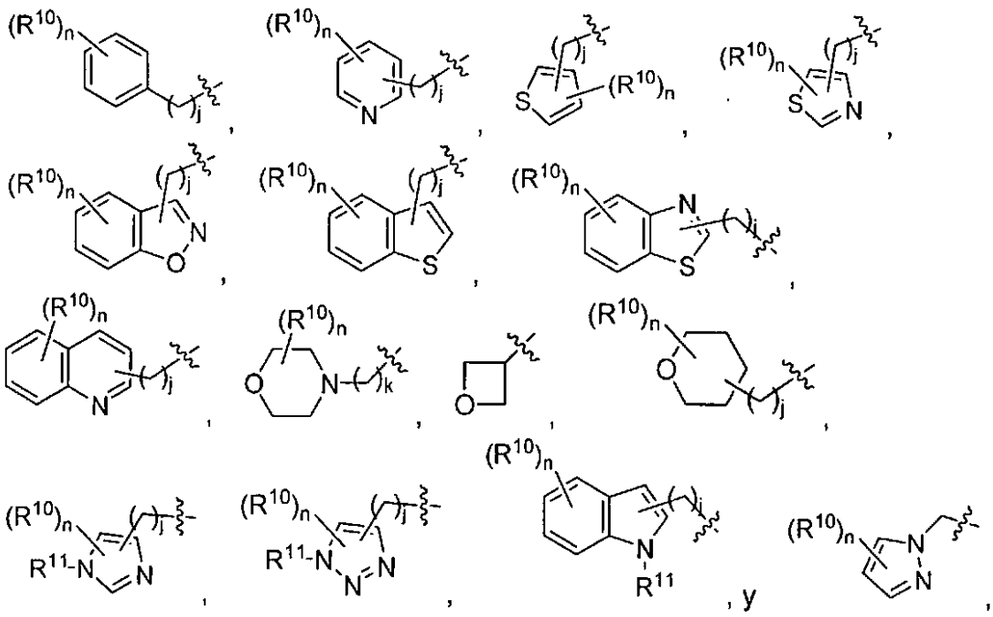
En una sexta realización del primer aspecto, la presente divulgación proporciona un compuesto de la Fórmula (Ia) o una sal farmacéuticamente aceptable del mismo, en la que

m es 0;

$R^8$ es hidrógeno o alquilo $C_1$ a $C_4$;

$R^9$ se selecciona a partir de hidrógeno, alquilo $C_1$ a $C_6$ opcionalmente sustituido con

$-OR^{12}$, cicloalquilo $C_3$ a $C_6$, alilo, $-CH_2C(O)NR^cR^d$, $(NR^cR^d)$alquilo,



en las que j es 0 ó 1;

k es 1, 2 ó 3;

n es 0 o un número entero que se selecciona desde 1 hasta 4;

cada $R^{10}$ es independientemente hidrógeno, alquilo $C_1$ a $C_4$, haloalquilo $C_1$ a $C_4$, halógeno, nitro, -OBn, o (MeO)(OH)P(O)O-;

$R^{11}$ es hidrógeno, alquilo $C_1$ a $C_4$, o bencilo;

$R^{12}$ es hidrógeno, alquilo $C_1$ a $C_4$, o bencilo;

$R^a$ es hidrógeno o alquilo $C_1$ a $C_4$;

$R^b$ es alquilo $C_1$ a $C_4$, cicloalquilo $C_3$ a $C_6$, bencilo, 3-piridilo, pirimidin-5-ilo, acetilo, $-C(O)OR^7$, o $-C(O)NR^cR^d$;

$R^7$ es alquilo $C_1$ a $C_4$ o haloalquilo $C_1$ a $C_4$;

$R^c$ es hidrógeno o alquilo $C_1$ a $C_4$; y

$R^d$ es hidrógeno, alquilo $C_1$ a $C_4$, o cicloalquilo $C_3$ a $C_6$.

En una séptima realización del primer aspecto, la presente divulgación proporciona un compuesto de la Fórmula (Ia) o una sal farmacéuticamente

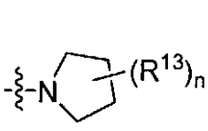
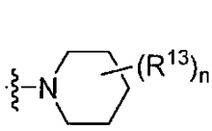
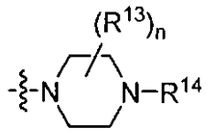
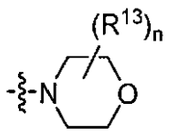
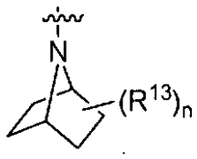
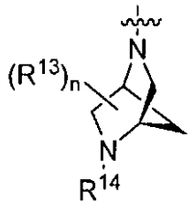
aceptable del mismo, en la que

m es 0;

$R^8$ es hidrógeno;

$R^9$ es fenilo opcionalmente sustituido con de uno hasta cinco sustituyentes que se seleccionan independientemente a partir de alquilo $C_1$ a $C_6$, haloalquilo $C_1$ a $C_4$, halógeno, alcoxi $C_1$ a $C_6$, hidroxilo, ciano, y nitro; y

$NR^aR^b$ es un grupo heterociclilo o heterobiciclilo que se selecciona a partir de:


,

,

,

,

, y

,

en las que n es 0, 1 ó 2;

cada $R^{13}$ se selecciona independientemente a partir de alquilo $C_1$ a $C_6$, fenilo, trifluorometilo, halógeno, hidroxilo, metoxi, y oxo; y

$R^{14}$ es alquilo $C_1$ a $C_6$, fenilo, bencilo, o un grupo $-C(O)OR^{15}$, en el que $R^{15}$ es alquilo $C_1$ a $C_4$, fenilo, o bencilo.

En una octaba realización del primer aspecto, la presente divulgación proporciona un compuesto de la Fórmula (Ia) o una sal farmacéuticamente aceptable del mismo, en la que

m es 1;

$R^8$ es hidrógeno;

$R^9$ es alquilo $C_1$ a $C_6$, arilalquilo, o heteroarilalquilo;

$R^a$ es hidrógeno; y

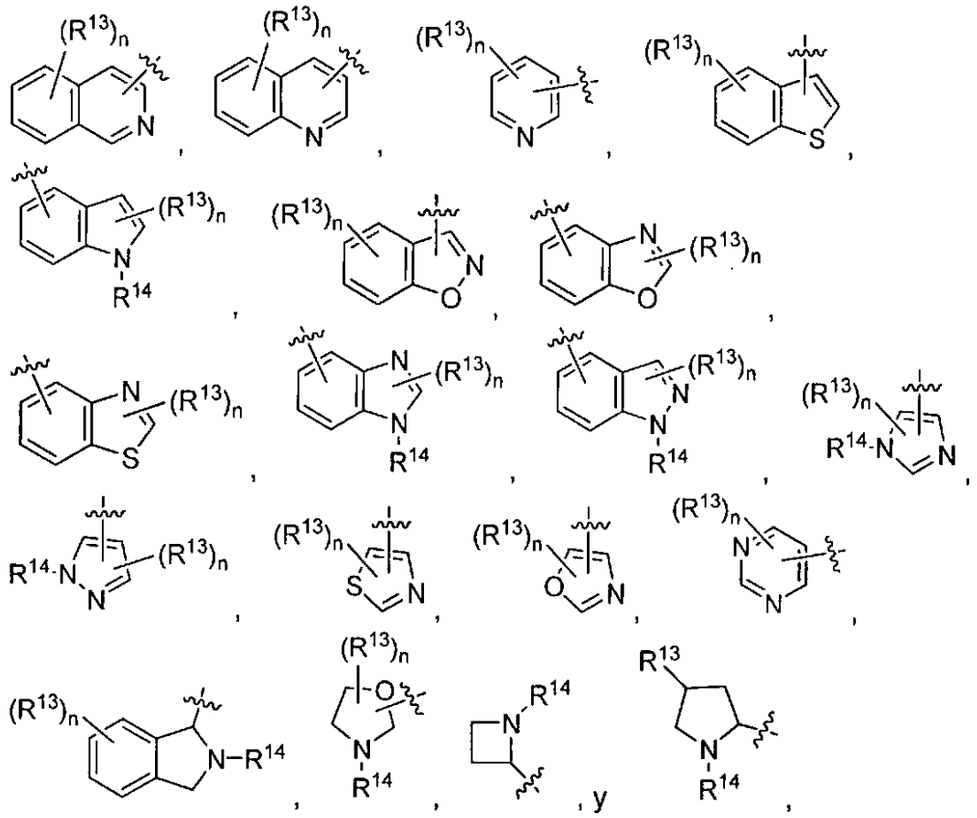
$R^b$ es $-C(O)OR^7$, en el que $R^7$ es alquilo $C_1$ a $C_6$.

En una novena realización del primer aspecto, la presente divulgación proporciona un compuesto de la Fórmula (Ia) o una sal farmacéuticamente aceptable del mismo, en la que

$R^1$ es $-C(O)R^x$;

$R^2$ es $-C(O)R^y$;

$R^x$ y $R^y$ son heteroarilo o heterociclilo que se selecciona independientemente a partir de:



en las que n es 0 o un número entero que se selecciona desde 1 hasta 4;

cada $R^{13}$ se selecciona independientemente a partir de hidrógeno, alquilo $C_1$ a $C_6$, haloalquilo $C_1$ a $C_4$, fenilo, bencilo, alcoxi $C_1$ a $C_6$, haloalcoxi $C_1$ a $C_4$, heterociclilo, halógeno, $NR^cR^d$, hidroxilo, ciano, y oxo, donde $R^c$ y $R^d$ son independientemente hidrógeno o alquilo $C_1$ a $C_4$; y

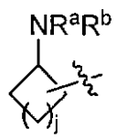
$R^{14}$ es hidrógeno (H), alquilo $C_1$ a $C_6$, bencilo, o $-C(O)OR^4$, en el que $R^4$ es alquilo $C_1$ a $C_6$.

En una décima realización del primer aspecto, la presente divulgación proporciona un compuesto de la Fórmula (Ia) o una sal farmacéuticamente aceptable del mismo, en la que

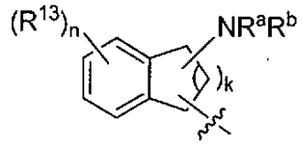
$R^1$ es $-C(O)R^x$;

$R^2$ es $-C(O)R^y$;

$R^x$ y $R^y$ son cicloalquilo que se selecciona independientemente a partir de:




y




en las que

j es 0, 1, 2 ó 3;

k es 0, 1 ó 2;

n es 0 o un número entero que se selecciona desde 1 hasta 4;

cada $R^{13}$ se selecciona independientemente a partir de hidrógeno, alquilo $C_1$ a $C_6$, haloalquilo $C_1$ a $C_4$, alcoxi $C_1$ a $C_6$, halógeno, hidroxilo, ciano, y nitro; y

$R^a$ y $R^b$ son cada uno independientemente hidrógeno, alquilo $C_1$ a $C_6$, o $-C(O)OR^7$, en el que $R^7$ es alquilo $C_1$ a $C_6$.

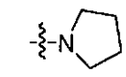
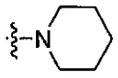
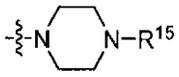
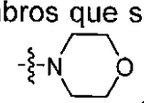
En una undécima realización del primer aspecto, la presente divulgación

proporciona un compuesto de la Fórmula (Ia) o una sal farmacéuticamente aceptable del mismo, en la que

$R^1$ es $-C(O)R^x$;

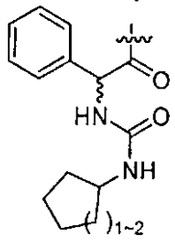
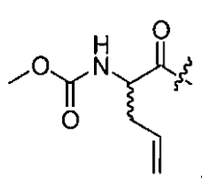
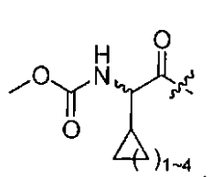
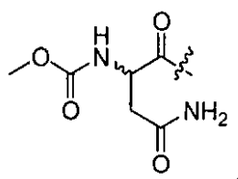
$R^2$ es $-C(O)R^y$;

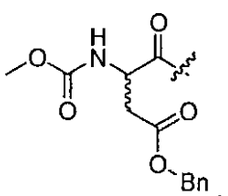
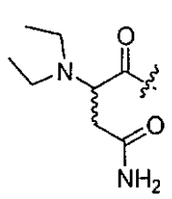
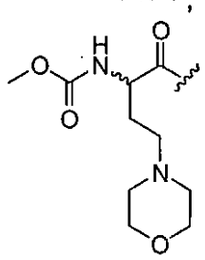
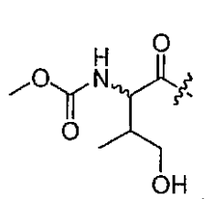
$R^x$ y $R^y$ son independientemente arilalquilo, en los que la parte arilo de dicho arilalquilo puede estar opcionalmente sustituida con $(NR^aR^b)$alquilo; y

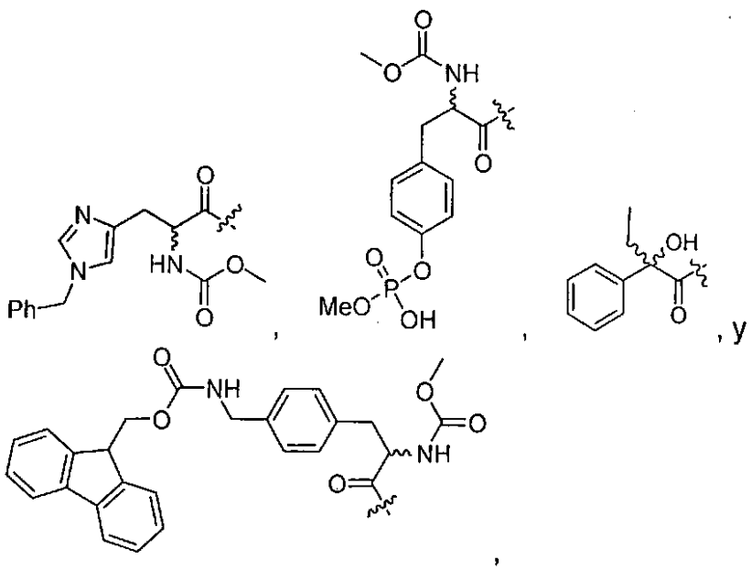
$R^a$ y $R^b$ son independientemente hidrógeno, alquilo $C_1$ a $C_6$, o bencilo, o de forma alternativa, $R^a$ y $R^b$, junto con el átomo de nitrógeno al que están unidos, forman un anillo de cinco o seis miembros que se selecciona a partir de  ,  ,  , y  , en la que $R^{15}$ es hidrógeno, alquilo $C_1$ a $C_6$, o bencilo.

En una duodécima realización del primer aspecto, la presente divulgación proporciona un compuesto de la Fórmula (Ia) o una sal farmacéuticamente aceptable del mismo, en la que

$R^1$ y $R^2$ son iguales y se seleccionan a partir del grupo constituido por:

 ,  ,  ,  ,

 ,  ,  ,  ,



en las que un enlace ondulado (〰) en la estructura indica que un centro estereógeno al que está unido el enlace puede tomar la configuración (R)- o (S)- siempre que no se incumplan los principios del enlace químico.

En una decimotercera realización del primer aspecto, la presente divulgación proporciona un compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo, en la que

$R^1$ es $-C(O)R^x$;

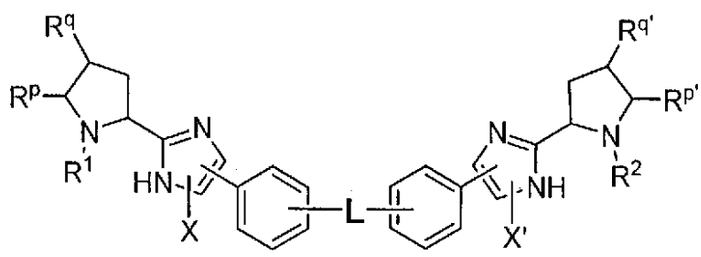
$R^2$ es $-C(O)R^y$; y

$R^x$ y $R^y$ son ambos t-butoxi.

En una decimocuarta realización del primer aspecto, la presente divulgación proporciona un compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo, en la que

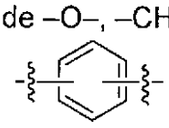
$R^1$ y $R^2$ son ambos hidrógeno.

En un segundo aspecto la presente divulgación proporciona un compuesto de la Fórmula (II):



(I),

o una sal farmacéuticamente aceptable de los mismos, en la que:

L se selecciona a partir de –O–, $–CH_2CH_2–$, –CH=CH–, –C≡C–, –$OCH_2–$, $-CH_2O–$, $-CH_2OCH_2–$,  , y  ;

X y X' son independientemente hidrógeno (H) o halógeno;

$R^p$ es hidrógeno o alquilo $C_1$ a $C_4$, y $R^q$ es hidrógeno, o de forma alternativa, $R^p$ y $R^q$, junto con los átomos de carbono a los que están unidos, forman un anillo ciclopropilo;

$R^{p'}$ es hidrógeno o alquilo $C_1$ a $C_4$, y $R^{q'}$ es hidrógeno, o de forma alternativa, $R^{p'}$ y $R^{q'}$, junto con los átomos de carbono a los que están unidos, forman un anillo ciclopropilo;

$R^1$ es hidrógeno o $–C(O)R^x$;

$R^2$ es hidrógeno o $–C(O)R^y$;

$R^x$ y $R^y$ se seleccionan independientemente a partir de cicloalquilo, heteroarilo, heterociclilo, alcoxi, y alquilo, estando dicho alquilo sustituido por uno o más sustituyentes que se seleccionan independientemente a partir de arilo, alquenilo, cicloalquilo, heterociclilo, heteroarilo, $-OR^3$, $-C(O)OR^4$, $-NR^aR^b$, y $-C(O)NR^cR^d$,

en el que cualquiera de dichos arilo y heteroarilo puede estar opcionalmente sustituido con uno o más sustituyentes que se seleccionan

independientemente a partir de alquilo, haloalquilo, arilalquilo, heterociclilo, heterociclilalquilo, halógeno, ciano, nitro, $-C(O)OR^4$, $-OR^5$,

$-NR^aR^b$, $(NR^aR^b)$alquilo, y (MeO)(HO)P(O)O-, y

en los que cualquiera de dichos cicloalquilo y heterociclilo puede opcionalmente estar condensado a un anillo aromático y puede estar opcionalmente sustituido con uno o más sustituyentes que se seleccionan independientemente a partir de alquilo, hidroxilo, halógeno, arilo, $-NR^aR^b$, oxo, y $-C(O)OR^4$;

$R^3$ es hidrógeno, alquilo, o arilalquilo;

$R^4$ es alquilo o arilalquilo;

$R^5$ es hidrógeno, alquilo, o arilalquilo;

$R^a$ y $R^b$ se seleccionan independientemente a partir de hidrógeno, alquilo, cicloalquilo, arilalquilo, heteroarilo, $-C(O)R^6$, $-C(O)OR^7$, $-C(O)NR^cR^d$, y $(NR^cR^d)$alquilo, o de forma alternativa, $R^a$ y $R^b$, junto con el átomo de nitrógeno al que están unidos, forman un anillo de cinco o seis miembros o estructura anular bicíclica con puente, en la que dicho anillo de cinco o seis miembros o estructura anular bicíclica con puente opcionalmente pueden contener uno o dos heteroátomos adicionales que se seleccionan independientemente a partir de nitrógeno, oxígeno, y azufre y pueden contener uno, dos, o tres sustituyentes que se seleccionan independientemente a partir de alquilo $C_1$ a $C_6$, haloalquilo $C_1$ a $C_4$, arilo, hidroxilo, alcoxi $C_1$ a $C_6$, haloalcoxi $C_1$ a $C_4$, y halógeno;

$R^6$ es alquilo;

$R^7$ es alquilo, arilalquilo, o haloalquilo; y

$R^c$ y $R^d$ se seleccionan independientemente a partir de hidrógeno,

alquilo, arilalquilo, y cicloalquilo.

En un tercer aspecto, la presente divulgación proporciona una composición que comprende un compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo, y un vehículo farmacéuticamente aceptable, en la que la Fórmula (I) se define de acuerdo con cualquiera de las realizaciones que se describen anteriormente en el primer aspecto de la presente divulgación.

En una primera realización del tercer aspecto, la composición además comprende al menos un compuesto adicional que presenta actividad contra VHC.

En una segunda realización del tercer aspecto, al menos uno de los compuestos adicionales es un interferón o una ribavirina.

En una tercera realización del tercer aspecto, el interferón se selecciona a partir de interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A, e interferón tau linfoblastoide.

En una cuarta realización del tercer aspecto la presente divulgación proporciona una composición que comprende un compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo, un vehículo farmacéuticamente aceptable, y al menos un compuesto adicional que presenta actividad contra VHC, en la que al menos uno de los compuestos adicionales se selecciona a partir de interleucina 2, interleucina 6, interleucina 12, un compuesto que potencia el desarrollo de una respuesta de linfocitos T cooperadores de tipo 1, ARN de interferencia, ARN no codificante, Imiqimod, ribavirina, un inhibidor de inosina 5'-monofosfato deshidrogenasa, amantadina y rimantadina.

En una quinta realización del tercer aspecto, la presente divulgación proporciona una composición que comprende un compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo, un vehículo farmacéuticamente

aceptable, y al menos un compuesto adicional que tiene actividad contra VHC, en la que al menos uno de los compuestos adicionales es eficaz para inhibir la función de una diana que se selecciona a partir de metaloproteasa de VHC, serina proteasa de VHC, polimerasa de VHC, helicasa de VHC, proteína NS4B de VHC, entrada de VHC, ensamblaje de VHC, migración de VHC, proteína NS5A de VHC e IMPDH para el tratamiento de una infección por VHC.

En un cuarto aspecto, la presente divulgación proporciona un procedimiento de tratamiento de una infección por VHC en un paciente, que comprende administrar al paciente una cantidad terapéuticamente eficaz de un compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo, en la que la Fórmula (I) se define de acuerdo con cualquiera de las realizaciones que se describen anteriormente en el primer aspecto de la presente divulgación.

En una primera realización del cuarto aspecto, el procedimiento comprende además administrar al menos un compuesto adicional que tenga actividad contra VHC antes, después o simultáneo al compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo.

En una segunda realización del cuarto aspecto, al menos uno de los compuestos adicionales es un interferón o una ribavirina.

En una tercera realización del cuarto aspecto, el interferón se selecciona a partir de interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A, e interferón tau linfoblastoide.

En una cuarta realización del cuarto aspecto, la presente divulgación proporciona un procedimiento de tratamiento de una infección por VHC en un paciente, que comprende administrar al paciente una cantidad terapéuticamente eficaz de un compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable

del mismo, y al menos un compuesto adicional que tenga actividad contra VHC antes, después o simultáneo al compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo, en la que al menos uno de los compuestos adicionales se selecciona a partir de interleucina 2, interleucina 6, interleucina 12, un compuesto que potencia el desarrollo de una respuesta de linfocitos T cooperadores de tipo 1, ARN de interferencia, ARN no codificante, Imiqimod, ribavirina, un inhibidor de inosina 5'-monofosfato deshidrogenasa, amantadina y rimantadina.

En una quinta realización del cuarto aspecto, la presente divulgación proporciona un procedimiento de tratamiento de una infección por VHC en un paciente, que comprende administrar al paciente una cantidad terapéuticamente eficaz de un compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo, y al menos un compuesto adicional que tenga actividad contra VHC antes, después o simultáneo al compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo, en la que al menos uno de los compuestos adicionales es eficaz para inhibir la función de una diana que se selecciona a partir de metaloproteasa de VHC, serina proteasa de VHC, polimerasa de VHC, helicasa de VHC, proteína NS4B de VHC, entrada de VHC, ensamblaje de VHC, migración de VHC, proteína NS5A de VHC e IMPDH para el tratamiento de una infección por VHC.

Los compuestos de la presente divulgación pueden ser eficaces para inhibir la función de la proteína NS5A de VHC. En particular, los compuestos de la presente divulgación pueden ser eficaces para inhibir el genotipo 1b de VHC o múltiples genotipos de VHC. Por lo tanto, esta divulgación también engloba: (1) composiciones que comprenden un compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo, y un vehículo farmacéuticamente

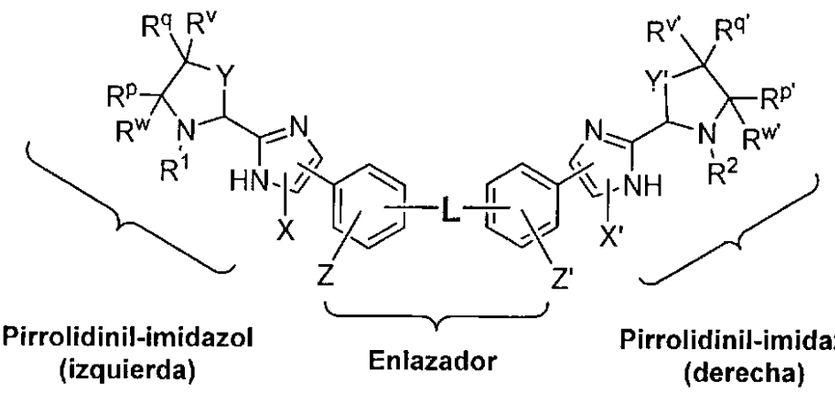
aceptable; y (2) un procedimiento de tratamiento de una infección por VHC en un paciente, que comprende administrar al paciente una cantidad terapéuticamente eficaz de un compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo.

Otros aspectos de la presente divulgación pueden incluir combinaciones adecuadas de realizaciones descritas en el presente documento.

Todavía pueden encontrarse otros aspectos y realizaciones en la descripción que se proporciona en el presente documento.

La descripción de la presente divulgación en el presente documento debe interpretarse de forma congruente con las leyes y principios de los enlaces químicos. En algunos casos, puede ser necesario eliminar un átomo de hidrógeno para acomodar un sustituyente en cualquier lugar dado.

A continuación se ilustran ciertas características de la estructura de la Fórmula (I):



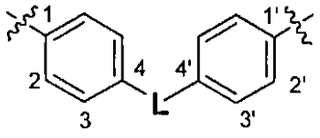

(I).

En la Fórmula (I), tal como se ilustra anteriormente, el resto "pirrolidinil-imidazol" a la izquierda del "enlazador" es independiente del resto "pirrolidinil-imidazol" a la derecha del grupo enlazador en lo que respecta, por ejemplo a , (1)

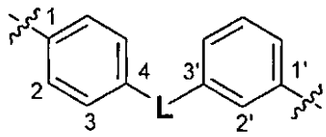
tautómero del anillo imidazol, (2) configuración absoluta de los centros estereógenos del anillo pirrolidina, y (3) sustituyentes del nitrógeno de la pirrolidina, es decir, $R^1$ y $R^2$ son independientes el uno del otro, aunque en algunas circunstancias son preferentemente iguales.

Debe entenderse que la representación de un resto pirrolidina a la "izquierda" o a la "derecha" es únicamente ilustrativo, que en modo alguno limita el alcance de la divulgación.

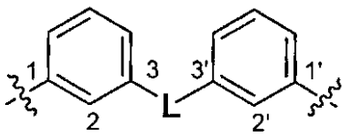
En el grupo enlazador de la Fórmula (I), el enlace entre "L" y los dos anillos benceno engloba todas las combinaciones siguientes:



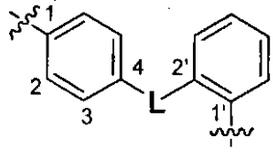
(para-para),



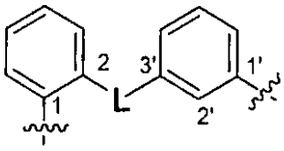
(para-meta),



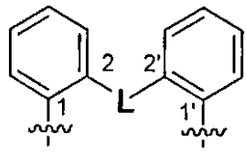
(meta-meta),



(para-orto),

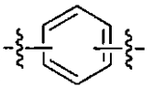


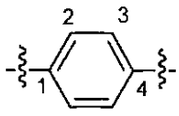
(meta-orto), y



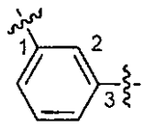
(orto-orto),

en las que son preferentes los enlaces "para-para," "para-meta," y "meta-meta".

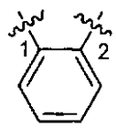
Del mismo modo, en la Fórmula (I), cuando L es un grupo fenileno (  ), puede unirse a los dos anillos benceno adyacentes de la forma siguiente:



(para),



(meta), y

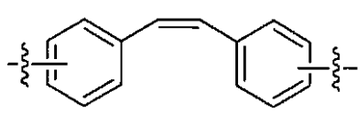
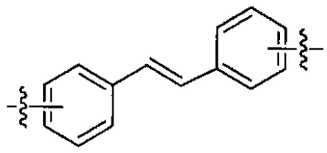


(orto),

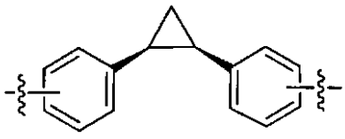
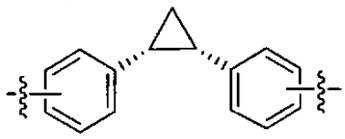
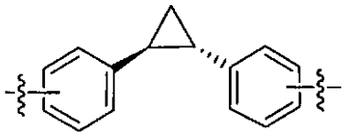
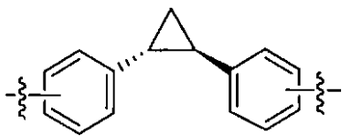
en las que son preferentes las disposiciones "para" y "meta", y la disposición

"para" es la más preferente.

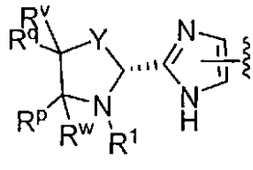
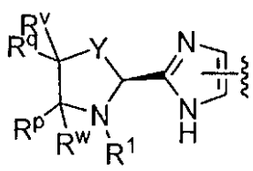
En la Fórmula (I), cuando L es un grupo vinileno (-CH=CH-), puede tomar la configuración trans- o cis-, tal como se ilustra a continuación:


(cis-),

(trans-).

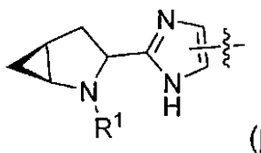
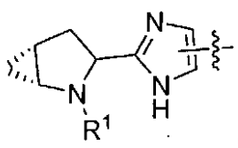
En la Fórmula (I), cuando L es un grupo ciclopropileno (  ), los dos sustituyentes benceno pueden estar en posición trans- o cis- el uno con respecto al otro, formando una de las cuatro configuraciones siguientes:


(cis-),

(cis-),

(trans-),

(trans-).

En un anillo pirrolidina de un resto pirrolidinil-imidazol, el centro de carbono estereógeno al que está unido el grupo imidazol puede tomar la configuración (R)- o (S)- tal como se ilustra a continuación:

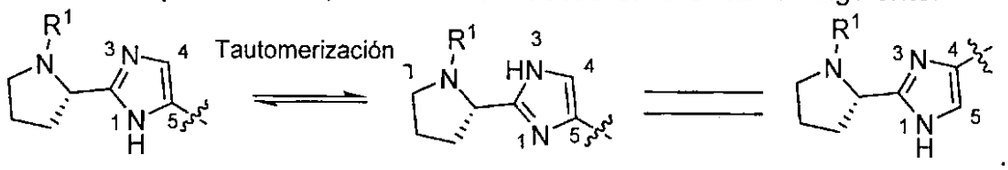

(R-)

(S-)

Cuando un anillo ciclopropilo está condensado a un anillo pirrolidina de un resto pirrolidinil-imidazol, es decir, cuando ($R^p$, $R^q$) juntos son $-CH_2-$, el grupo $CH_2$ del anillo ciclopropilo condensado puede tomar la posición $\alpha$- o $\beta$- relativa al anillo pirrolidina, tal como se ilustra a continuación:


(β-),

(α-).

Por lo tanto, se pretende que esta divulgación abarque todos los estereoisómeros posibles incluso cuando se describa un único estereoisómero, o cuando no se defina la estereoquímica, de una estructura.

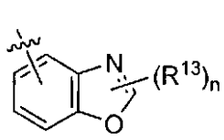
En la Fórmula (I), el enlace entre un anillo benceno del grupo enlazador y un anillo imidazol de un resto pirrolidinil-imidazol puede tener lugar en la posición C-4 o la C-5 (véase más adelante) del anillo imidazol. Tal como entedería una persona de experiencia ordinaria en la técnica, debido a la tautomerización del anillo imidazol, el enlace de un anillo benceno a la posición C-4 puede ser equivalente a la unión del anillo benceno a la posición C-5, tal como se muestra en la ecuación siguiente:



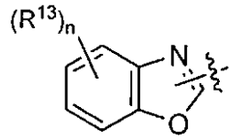

El mismo principio es aplicable también a un sustituyente X o X'.

Por lot anto, esta divulgación se pretende que abarque todos los tautómeros posibles incluso cuando una estructura represente sólo uno de ellos.

En esta divulgación, un enlace flotante (por ejemplo,  ) o un sustituyente flotante (por ejemplo, $-R^{13}$) en una estructura indica que el enlace o sustituyente puede unirse a cualquier posición disponible de la estructura por eliminación de un hidrógeno de la posición disponible. Debe entenderse que en una estructura anular bicíclica o policíclica, a no ser que se defina de otra manera, la posición de un enlace flotante o de una sustituyente flotante no limita la posición de dicho enlace o sustituyente en un anillo específico. Por lo tanto, debe interpretarse que los dos sustituyentes siguientes son equivalentes:




y




Debe entenderse que los compuestos que engloba la presente divulgación son los que son adecuadamente estables para usar como agente farmacéutico.

Se pretende que la definición de cualquier sustituyente o variable en una localización particular de la molécula sea independiente de sus definiciones en cualquier otra parte de esa molécula. Por ejemplo, para el sustituyente $(R^{10})_n$, cuando n es 2, cada uno de los dos grupos $R^{10}$ puede ser igual o diferente.

Todas las patentes, solicitudes de patente y referencias de la bibliografía citadas en la memoria descriptiva se incorporan al presente documento por referencia en su totalidad. En el caso de incoherencias, prevalecerá la presente divulgación, incluidas las definiciones.

## DEFINICIONES

Anteriormente se han proporcionado definiciones para cada uno de los grupos definidos. Además, se usarán las siguientes definiciones.

Tal como se usa en el presente documento, las formas en singular "uno", "una", y "la" "el" incluyen las referencias en plural a no ser que el contexto claramente indique lo contrario.

A no ser que se indique lo contrario, todos los grupos arilo, cicloalquilo, heteroarilo, y heterociclilo de la presente divulgación pueden estar sustituidos como se describe en cada una de sus definiciones respectivas. Por ejemplo, la parte arilo de un grupo arilalquilo puede estar sustituida como se describe en la definición del término "arilo."

El término "acetilo," tal como se usa en el presente documento, se refiere a –

$C(O)CH_3$.

El término "alquenilo," tal como se usa en el presente documento, se refiere a una cadena de hidrocarburo monovalente, lineal o ramificada que tiene uno o más, preferentemente uno a dos, enlaces dobles en ella. El enlace doble de un grupo alquenilo puede no estar conjugado o estar conjugado a otro grupo insaturado. Los grupos alquenilo adecuados incluyen, pero sin limitación, grupos alquenilo $C_2$ a $C_{10}$, como por ejemplo vinilo, alilo, butenilo, pentenilo, hexenilo, butadienilo, pentadienilo, hexadienilo, 2-etilhexenilo, 2-propil-2-butenilo, 4-(2-metil-3-buteno)pentenilo. Un grupo alquenilo puede no estar sustituido o estar sustituido con uno o dos sustituyentes adecuados.

El término "alcoxi," tal como se usa en el presente documento, se refiere a un grupo alquilo unido a un resto molecular progenitor mediante un átomo de oxígeno. Los ejemplos representativos de grupos alcoxi incluyen, pero sin limitación, metoxi ($CH_3O$-), etoxi ($CH_3CH_2O$-), y t-butoxi ($(CH_3)_3CO$-).

El término "alcoxialquilo," tal como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos, o tres grupos alcoxi.

El término "alcoxicarbonilo," tal como se usa en el presente documento, se refiere a un grupo alcoxi unido a un resto molecular progenitor mediante un grupo carbonilo.

El término "alquilo," tal como se usa en el presente documento, se refiere a a grupo derivado de un hidrocarburo saturado de cadena lineal o ramificada mediante eliminación de un hidrógeno de uno de los carbonos saturados. El grupo alquilo preferentemente contiene de uno a diez átomos de carbono. Los ejemplos representativos de grupo alquilo incluyen, pero sin limitación, metilo, etilo, isopropilo, y *terc*-butilo.

El término "alquilcarbonilo," tal como se usa en el presente documento, se refiere a un grupo alquilo unido a un resto molecular progenitor mediante un grupo carbonilo. Los ejemplos representativos de grupo alquilcarbonilo incluyen, pero sin limitación, acetilo ($-C(O)CH_3$), propanoilo ($-C(O)CH_2CH_3$), n-butirilo ($-C(O)CH_2CH_2CH_3$), y 2,2-dimetilpropanoilo o pivaloilo ($-C(O)C(CH_3)_3$).

El término "alquilsulfonilo," tal como se usa en el presente documento, se refiere a un grupo alquilo unido a un resto molecular progenitor mediante un grupo sulfonilo.

El término "alilo," tal como se usa en el presente documento, se refiere al grupo $-CH_2CH=CH_2$.

El término "arilo," tal como se usa en el presente documento, se refiere a un grupo derivado de un carbociclo aromático por eliminación de un átomo de hidrógeno de un anillo aromático. El grupo arilo puede ser monocíclico, bicíclico o policíclico, en el que en el grupo arilo bicíclico o policíclico, el carbociclo aromático puede estar condensado a otro carbociclo aromático o no aromático de cuatro a seis miembros. Los ejemplos representativos de grupos arilo incluyen, pero sin limitación, fenilo, indanilo, indenilo, naftilo, y 1,2,3,4-tetrahidronaft-5-ilo.

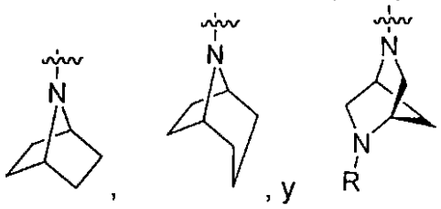
El término "arilalquilo," tal como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos, o tres grupos arilo, en el que la parte arilo del grupo arilalquilo puede estar opcionalmente sustituido por de uno a cinco sustituyentes que se seleccionan independientemente a partir de grupos alquilo $C_1$ a $C_6$, haloalquilo $C_1$ a $C_4$, alcoxi $C_1$ a $C_6$, halógeno, ciano, y nitro. Los ejemplos representados de arilalquilo incluyen, pero sin limitación, bencilo, 2-fenil-1-etilo ($PhCH_2CH_2$-), (naft-1-il)metilo, y (naft-2-il)metilo.

El término "arilsulfonilo," tal como se usa en el presente documento, se refiere

a un grupo arilo unido a un resto molecular progenitor mediante un grupo sulfonilo.

El término "bencilo," tal como se usa en el presente documento, se refiere a un grupo metilo en el que se ha reemplazado uno de los átomos de hidrógeno por un grupo fenilo, en el que dicho grupo fenilo puede estar opcionalmente sustituido por de uno a cinco sustituyentes que se seleccionan independientemente a partir de metilo, trifluorometilo (-$CF_3$), metoxi (-$OCH_3$), halógeno, y nitro (-$NO_2$). Los ejemplos representativos de grupo bencilo incluyen, pero sin limitación, $PhCH_2$-, 4-MeO-$C_6H_4CH_2$-, y 2,4,6-tri-metil-$C_6H_4CH_2$-.

El término "anillo bicíclico con puente," tal como se usa en el presente documento, se refiere a una estructura anular que comprende una cabeza de puente entre dos de los miembros del anillo, en el que el anillo y la cabeza de puente opcionalmente pueden comprender independientemente uno o más, preferentemente uno a dos, heteroátomos que se seleccionan independientemente a partir de nitrógeno, oxígeno, y azufre. Los ejemplos ilustrados de una estructura anular bicíclica con puente incluyen, pero sin limitación:




, , y .

Los términos "Cap" y "cap," tal como se usan en el presente documento, se refieren al grupo que está situado en el átomo de nitrógeno del anillo pirrolidina en los compuestos de la fórmula (I). Debe entenderse que "Cap" o "cap" también puede referirse al reactivo que es precursor de la "cap" final en los compuestos de la fórmula (I) y se usa como uno de los materiales iniciales de la reacción para unir un grupo del nitrógeno de la pirrolidina que da como resultado el producto final, un compuesto que contiene la pirrolidina funcionalizada que estará presente en el

compuesto de la fórmula (I).

El término "carbonilo," tal como se usa en el presente documento, se refiere a -C(O)-.

El término "carboxilo," o "carboxi," tal como se usa en el presente documento, se refiere a -CO2H.

El término "ciano," tal como se usa en el presente documento, se refiere a -CN.

El término "cicloalquilo," tal como se usa en el presente documento, se refiere a un grupo derivado de un carbociclo saturado, que tiene preferentemente de tres a ocho átomos de carbono, por eliminación de un átomo de hidrógeno del carbociclo saturado, en el que el carbociclo saturado opcionalmente puede estar condensado a otro u otros dos carbociclos aromáticos o no aromáticos. Los ejemplos representativos de grupos cicloalquilo incluyen, pero sin limitación, ciclopropilo, ciclopentilo, ciclohexilo, y 1,2,3,4-tetrahidronaft-1-ilo.

El término "formilo," tal como se usa en el presente documento, se refiere a -CHO.

Los términos "halo" y "halógeno," tal como se usa en el presente documento, se refieren a F, Cl, Br, o I.

El término "haloalcoxi," tal como se usa en el presente documento, se refiere a un grupo haloalquilo unido a un resto molecular progenitor mediante un átomo de oxígeno.

El término "haloalquilo," tal como se usa en el presente documento, se refiere a un grupo alquilo sustituido por al menos un átomo de halógeno. El grupo haloalquilo puede ser un grupo alquilo del cual todos los átomos de hidrógeno están sustituidos por halógenos. Los ejemplos representativos de haloalquilo incluyen,

pero sin limitación, trifluorometilo ($CF_3$-), 1-cloroetilo ($ClCH_2CH_2$-), y 2.2.2-trifluoroetilo ($CF_3CH_2$-).

El término "heteroarilo," tal como se usa en el presente documento, se refiere un grupo derivado de un compuesto monocíclico, bicíclico, o policíclico que comprende al menos un anillo aromático que comprende uno o más, preferentemente uno a tres, heteroátomos que se seleccionan independientemente a partir de nitrógeno, oxígeno, y azufre, por eliminación de un átomo de hidrógeno de un anillo aromático del mismo. Como es sabido por los expertos en la técnica, los anillos heteroarilo tienen un carácter menos aromático que sus homólogos con todo carbonos. Por lo tanto, para los fines de la divulgación, un grupo heteroarilo sólo necesita tener cierto grado de carácter aromático. Los ejemplos ilustrativos de grupos heteroarilo incluyen, pero sin limitación, piridilo, piridazinilo, pirimidilo, pirazilo, triazinilo, pirrolilo, pirazolilo, imidazolilo, (1,2,3,)- y (1,2,4)-triazolilo, pirazinilo, pirimidinilo, tetrazolilo, furilo, tienilo, isoxazolilo, tiazolilo, isoxazolilo, oxazolilo, indolilo, quinolinilo, isoquinolinilo, bencisoxazolilo, benzotiazolilo, benzotienilo, y pirrolopiridinilo.

El término "heteroarilalquilo," tal como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos, o tres grupos heteroarilo.

El término "heterobiciclilo," tal como se usa en el presente documento, se refiere a una estructura anular que comprende dos anillos condensados o con puente que incluyen carbono y uno o más, preferentemente uno a tres, heteroátomos que se seleccionan independientemente a partir de nitrógeno, oxígeno, y azufre. La estructura de anular heterobicíclica es un subconjunto de anillo heterocíclico y puede estar saturado o insaturado. Los ejemplos de estructuras anulares heterobicíclicas incluyen, pero sin limitación, tropano, quinuclidina, y 7-

azabiciclo[2.2.1]heptano.

El término "heterociclilo," tal como se usa en el presente documento, se refiere a un grupo derivado de un compuesto monocíclico, bicíclico, o policíclico que comprende al menos un anillo no aromático que comprende uno o más, preferentemente uno a tres, heteroátomos que se seleccionan independientemente a partir de nitrógeno, oxígeno, y azufre, por eliminación de un átomo de hidrógeno del anillo no aromático. El grupo heterociclilo engloba el grupo heterobiciclilo. Los grupos heterociclilo de la presente divulgación pueden estar unidos a un resto molecular progenitor mediante un átomo de carbono o un átomo de nitrógeno del grupo. Los ejemplos de grupos heterociclilo incluyen, pero sin limitación, morfolinilo, oxazolidinilo, piperazinilo, piperidinilo, pirrolidinilo, tetrahidrofurilo, tiomorfolinilo e indolinilo.

El término "heterociclilalquilo," tal como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos, o tres grupos heterociclilo.

Los términos "hidroxi" o "hidroxilo," tal como se usan en el presente documento, se refieren a -OH.

El término "hidroxialquilo," tal como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos, o tres grupos hidroxi.

El término "nitro," tal como se usa en el presente documento, se refiere a $-NO_2$.

El término "$-NR^aR^b$," tal como se usa en el presente documento, se refiere a dos grupos, $R^a$ y $R^b$, que están unidos a un resto molecular progenitor mediante un átomo de nitrógeno, o de forma alternativa $R^a$ y $R^b$, junto con el átomo de nitrógeno al que están unidos, forman una estructura anular bicíclica condensada o con puente de 5 ó 6 miembros que opcionalmente contiene uno, dos, o tres

heteroátomos adicionales que se seleccionan independientemente a partir de nitrógeno, oxígeno, y azufre. El término "-$NR^cR^d$" se define de forma similar.

El término "($NR^aR^b$)alquilo," tal como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos, o tres grupos –$NR^aR^b$. El término "($NR^cR^d$)alquilo" se define de forma similar.

El término "oxo," tal como se usa en el presente documento, se refiere a =O.

El término "sulfonilo," tal como se usa en el presente documento, se refiere a -$SO_2$-.

El término "trialquilsililo," tal como se usa en el presente documento, se refiere a -$SiR_3$, en el que cada R es alquilo $C_1$ a $C_4$ o fenilo. Los tres grupos R pueden ser iguales o diferentes. Los ejemplos representativos de "trialquilsililo" incluyen, pero sin limitación, trimetilsililo (TMS), *terc*-butildifenilsililo (TBDPS), *terc*-butildimetilsililo (TBS o TBDMS), y triisopropilsililo (TIPS).

Existen centros asimétricos en los compuestos de la presente divulgación. Estos centros se designan con los símbolos "R" o "S", dependiendo de la configuración de los sustituyentes alrededor del átomo de carbono quiral. Debe entenderse que la divulgación engloba todas las formas isoméricas estereoquímicas, o sus mezclas, que poseen la capacidad de inhibir NS5A. Pueden prepararse estereoisómeros individuales de los compuestos sintéticamente a partir de materiales iniciales comercialmente disponibles que contienen centros quirales o por preparación de mezclas de productos enantioméricos seguido de separación como por ejemplo conversión a una mezcla de diastereoisómeros seguido de separación o recristalización, técnicas cromatográficas o separación directa de enantiómeros en columnas cromatográficas quirales. Los compuestos iniciales de estereoquímica particular o bien están comercialmente disponibles o pueden

prepararse y resolverse mediante técnicas conocidas en la técnica.

Ciertos compuestos de la presente divulgación también pueden existir en formas con conformación estable que puedan separarse. La asimetría de torsión debida a una rotación restringida en torno a un enlace único asimétrico, por ejemplo debido a impedimentos estéricos o a tensión anular, puede permitir la separación de los diferentes confórmeros. La presente divulgación incluye cada isómero conformacional de estos compuestos y sus mezclas.

El término "compuestos de la presente divulgación", y expresiones equivalentes, se pretende que engloben compuestos de la Fórmula (I), y sus enantiómeros, diastereómeros y sales farmacéuticamente aceptables. De forma similar, las referencias a los intermedios se pretende que engloben sus sales cuando el contexto lo permita.

Se pretende que la presente divulgación incluya todos los isótopos de los átomos que aparecen en los presentes compuestos. Los isótopos incluyen los átomos que tienen el mismo número atómico pero diferentes números másicos. Como ejemplo general y sin limitación, los isótopos de hidrógeno incluyen deuterio y tritio. Los isótopos de carbono incluyen $^{13}C$ y $^{14}C$. Los compuestos marcados isotópicamente de la invención generalmente pueden prepararse mediante técnicas convencionales conocidas por los expertos en la técnica o mediante procesos análogos a los descritos en el presente documento, usando un reactivo marcado isotópicamente apropiado en lugar del reactivo no marcado que se emplea en otros casos. Dichos compuestos pueden tener una variedad de usos potenciales, por ejemplo como patrones y reactivos para determinar la actividad biológica. En el caso de los isótopos estables, dichos compuestos pueden tener el potencial de modificar favorablemente propiedades biológicas, farmacológicas o

farmacocinéticas.

Los compuestos de la presente divulgación pueden existir en forma de sales farmacéuticamente aceptables. El término "sal farmacéuticamente aceptable," tal como se usa en el presente documento, representa sales o formas zwiteriónicas de los compuestos de la presente divulgación que son solubles o dispersables en agua o aceite, que sean, según el alcance del criterio médico leal, adecuados para usar en contacto con los tejidos de los pacientes sin una excesiva toxicidad, irritación, respuesta alérgica u otro problema o complicación correspondiente a una proporción beneficio/riesgo razonable y que sea eficaz para el uso que se pretenda. Las sales pueden prepararse durante el aislamiento y purificación finales de los compuestos o por separado haciendo reaccionar un átomo de nitrógeno adecuado con un ácido adecuado. Las sales de adición de ácidos adecuadas incluyen acetato, adipato, alginato, citrato, aspartato, benzoato, bencenosulfonato, bisulfato, butirato, alcanforato, alcanforsulfonato; digluconato, glicerofosfato, hemisulfato, heptanoato, hexanoato, formato, fumarato, clorhidrato, bromhidrato, yodhidrato, 2-hidroxietanosulfonato, lactato, maleato, mesitilenosulfonato, metanosulfonato, naftilenosulfonato, nicotinato, 2-naftalenosulfonato, oxalato, palmoato, pectinato, persulfato, 3-fenilproprionato, picrato, pivalato, propionato, succinato, tartrato, tricloroacetato, trifluoroacetato, fosfato, glutamato, bicarbonato, para-toluenosulfonato, y undecanoato. Los ejemplos de ácidos que pueden emplearse para formar sales de adición farmacéuticamente aceptables incluyen ácidos inorgánicos como por ejemplo clorhídrico, bromhídrico, sulfúrico y fosfórico y ácidos orgánicos como por ejemplo oxálico, maleico, succínico y cítrico.

Las sales de adición básicas pueden prepararse durante la etapa de aislamiento y purificación finales de los compuestos haciendo reaccionar un grupo

carboxi con una base adecuada como por ejemplo el hidróxido, carbonato o bicarbonato de un catión metálico o con amoniaco o una amina primaria, secundaria o terciaria orgánica. Los cationes de sales farmacéuticamente aceptables incluyen litio, sodio, potasio, calcio, magnesio y aluminio, así como cationes de aminas cuaternarias no tóxicas como por ejemplo amonio, tetrametilamonio, tetraetilamonio, metilamina, dimetilamina, trimetilamina, trietilamina, dietilamina, etilamina, tributilamina, piridina, N,N-dimetilanilina, N-metilpiperidina, N-metilmorfolina, diciclohexilamina, procaína, dibencilamina, N,N-dibencilfenetilamina, y N,N'-dibenciletilendiamina. Otras aminas orgánicas representativas útiles para la formación de sales de adición de bases incluyen etilendiamina, etanolamina, dietanolamina, piperidina, y piperazina.

Aunque es posible que, para usar en terapia, puedan administrarse cantidades terapéuticamente eficaces de un compuesto de la Fórmula (I), así como sus sales farmacéuticamente aceptables, en forma de la sustancia química en bruto, es posible presentar el principio activo en forma de una composición farmacéutica. Por consiguiente, la divulgación proporciona además composiciones farmacéuticas, que incluyen cantidades terapéuticamente eficaces de compuestos de la Fórmula (I) o sus sales farmacéuticamente aceptables, y uno o más, preferentemente de uno a tres, vehículos, diluyentes, o excipientes farmacéuticamente aceptables. El término "cantidad terapéuticamente eficaz," tal como se usa en el presente documento, se refiere a la cantidad total de cada componente activo que es suficiente para demostrar un beneficio significativo para el paciente, por ejemplo, una reducción mantenida de la carga vírica. Cuando se aplica a un principio activo individual, administrado solo, el término se refiere a ese ingrediente solo. Cuando se aplica a una combinación, el término se refiere a cantidades combinadas de los principios

activos que provoca el efecto terapéutico, ya se administren combinados, en serie o de forma simultanea. Los compuestos de la Fórmula (I) y sus sales farmacéuticamente aceptables, son tal como se describen anteriormente. Los vehículo(s), diluyente(s) o excipiente(s) deben ser aceptables en el sentido de que sean compatibles con los otros ingredientes de la formulación y no sean perjudiciales para el receptor de los mismos. De acuerdo con otro aspecto de la presente divulgación, también se proporciona un proceso para la preparación de una formulación farmacéutica que incluye mezclar un compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo, con uno o más, preferentemente uno a tres, vehículos, diluyentes, o excipientes farmacéuticamente aceptables. El término "farmacéuticamente aceptable" tal como se usa en el presente documento, se refiere a aquellos compuestos, materiales, composiciones, y/o formas farmacéuticas que son, según el alcance del criterio médico leal, adecuados para usar en contacto con los tejidos de pacientes sin una excesiva toxicidad, irritación, respuesta alérgica u otros problemas o complicaciones, que corresponde a una relación beneficio/riesgo razonable, y son eficaces para el uso que se pretende.

Las formulaciones farmacéuticas pueden presentarse en formas monodosis que contienen una cantidad predeterminada de principio activo por monodosis. Los niveles de dosis de entre aproximadamente 0,01 y aproximadamente 250 miligramos por kilogramo ("mg/kg") de peso corporal al día, preferentemente entre aproximadamente 0,05 y aproximadamente 100 mg/kg de peso corporal al día de los compuestos de la presente divulgación son habituales en una monoterapia para la prevención y el tratamiento de la enfermedad mediada por VHC. Habitualmente, las composiciones farmacéuticas de esta divulgación se administrarán desde aproximadamente 1 a aproximadamente 5 veces al día o de forma alternativa, en

forma de infusión continua. Dicha administración puede usarse como terapia crónica o aguda. La cantidad de principio activo que puede combinarse con los materiales de vehículo para producir una única forma farmacéutica variará dependiendo de la afección que se esté tratando, de la gravedad de la afección, del tiempo de administración, la vía de administración, la velocidad de excreción del compuesto empleado, la duración del tratamiento, y la edad, sexo, peso y afección del paciente. Las formulaciones monodosis son las que contienen una dosis o subdosis diaria, tal como se indica anteriormente en el presente documento, o una fracción apropiada de las mismas de un principio activo. Generalmente, el tratamiento se inicia con dosis pequeñas sustancialmente por debajo de la dosis óptima del compuesto. Después, la dosis se aumenta en pequeños incrementos hasta que se alcanza el efecto óptimo en las circunstancias dadas. En general, el compuesto se administra, de la forma más deseable a un nivel de concentración que generalmente conseguirá resultados antiviralmente eficaces sin provocar efectos secundarios dañinos ni perjudiciales.

Cuando las composiciones de esta divulgación comprenden una combinación de un compuesto de la presente divulgación y uno o más agentes terapéuticos o profilácticos adicionales, tanto el compuesto como el agente adicional habitualmente están presentes a niveles de dosis de entre aproximadamente 10 a 150%, y más preferentemente entre aproximadamente 10 y 80% de la dosis que normalmente se administra en una pauta de monoterapia.

Las formulaciones farmacéuticas pueden adaptarse para la administración por cualquier vía apropiada, por ejemplo por vía oral (que incluye bucal o sublingual), rectal, nasal, tópica (que incluye bucal, sublingual o transdérmica), vaginal o parenteral (que incluye inyecciones o infusiones subcutánea, intracutánea,

intramuscular, intraarticular, intrasinovial, intrasternal, intratecal, intralesional, intravenosa o intradérmica). Dichas formulaciones pueden prepararse mediante cualquier procedimiento conocido en la técnica de la farmacia, por ejemplo asociando el principio activo con los vehículo(s) o excipiente(s). Son preferentes la administración oral o la administración mediante inyección.

Las formulaciones farmacéuticas adaptadas para la administración oral pueden presentarse en forma de unidades separadas tales como cápsulas o comprimidos; polvos o gránulos; soluciones o suspensiones en líquidos acuosos o no acuosos; espumas o batidos comestibles, emulsiones líquidas de aceite en agua o emulsiones de agua en aceite.

Por ejemplo, para la administración oral en forma de un comprimido o cápsula, el componente medicamentoso activo puede combinarse con un vehículo inerte, oral, no tóxico farmacéuticamente aceptable tal como etanol, glicerol, agua y similares. Los polvos se preparan moliendo el compuesto a un tamaño adecuado y mezclando con un vehículo farmacéutico molido de forma similar tal como un carbohidrato comestible, como por ejemplo, almidón o manitol. También puede haber presentes aromas, conservantes, dispersantes y agentes colorantes.

Las cápsulas se elaboran preparando una mezcla en polvo, tal como se describe anteriormente, y cargando vainas de gelatina formadas. Pueden añadirse deslizantes y lubricantes tales como sílice coloidal, talco, estearato de magnesio, estearato de calcio o polietilenglicol sólido a la mezcla en polvo antes de la operación de llenado. También puede añadirse un agente disgregante o solubilizante tal como agar-agar, carbonato cálcico o carbonato sódico para mejorar la disponibilidad del medicamento cuando se ingiere la cápsula.

Además, cuando se desee o sea necesario, también pueden incorporarse

aglutinantes, lubricantes, agentes disgregantes y agentes colorantes adecuados a la mezcla. Los aglutinantes adecuados incluyen almidón, gelatina, azúcares naturales tales como glucosa o beta-lactosa, edulcorantes de maíz, gomas naturales y sintéticas tales como goma arábiga, tragacanto, o alginato sódico, carboximetilcelulosa, polietilenglicol y similares. Los lubricantes que se usan en estas formas farmacéuticas incluyen oleato sódico, cloruro sódico, y similares. Los desintegradores incluyen, sin limitación, almidón, metilcelulosa, agar, bentonita, goma xantana, y similares. Los comprimidos se formulan, por ejemplo, preparando una mezcla en polvo, granulando o formando pepitas, añadiendo un lubricante y disgregante y dándole forma de comprimidos. Se prepara una mezcla en polvo mezclando el compuesto pulverizado de forma adecuada con un diluyente o base tal como se describe anteriormente, y de forma opcional, con un aglutinante tal como carboximetilcelulosa, un alginato, gelatina, o polivinilpirrolidona, un retardante de la solución tal como parafina, un acelerador de la resorción tal como una sal cuaternaria y/o un agente de absorción tal como bentonita, caolín o fosfato dicálcico. La mezcla en polvo puede granularse humedeciendo con un aglutinante tal como sirope, pasta de almidón, mucílago de acacia o soluciones de materiales celulósicos o poliméricos y haciéndolos pasar por un tamiz. Como alternativa al granulado, la mezcla en polvo puede pasarse por la máquina de comprimidos produciendo pepitas de forma imperfecta que se descomponen en gránulos. Los gránulos pueden lubricarse para evitar que se peguen al comprimido formando moldes mediante la adición de ácido esteárico, una sal de estearato, talco o aceite mineral. La mezcla lubricada se comprime después en forma de comprimidos. Los compuestos de la presente divulgación también pueden combinarse con un vehículo inerte fluido y darles forma de comprimidos directamente sin pasar por las etapas de granulado o

formación de pellas. Puede proporcionarse un recubrimiento protector transparente u opaco formado por una capa sellante de laca, un recubrimiento de azúcar o material polimérico y un recubrimiento pulido de cera. Pueden añadirse tintes a estos recubrimientos para distinguir entre las diferentes monodosis.

Los líquidos orales como soluciones, jarabes y elixires pueden prepararse en forma monodosis de forma que una cantidad dada contenga una cantidad predeterminada del compuesto. Los jarabes pueden prepararse disolviendo el compuesto en una solución acuosa aromatizada de forma adecuada, mientras que los elixires se preparan mediante el uso de un vehiculo no tóxico. También pueden añadirse solubilizantes y emulsionantes tales como alcoholes de isostearilo etoxilados y éteres de polioxietilen sorbitol, conservantes, aditivos aromatizantes tales como aceite de menta o edulcorantes naturales o sacarina u otros edulcorantes artificiales y similares.

Cuando sea apropiado, pueden microencapsularse las composiciones monodosis para la administración oral. La formulación también puede prepararse para prolongar o mantener la liberación como por ejemplo recubriendo o embebiendo el material particulado en polímeros, cera o similares.

Los compuestos de la Fórmula (I), y sus sales farmacéuticamente aceptables, también pueden administrarse en forma de sistemas de administración de liposomas, tales como vesículas unilaminares, vesículas unilaminares grandes y vesículas multilaminares. Los liposomas pueden formarse a partir de una variedad de fosfolípidos, tales como colesterol, estearilamina, o fosfatidilcolinas.

Los compuestos de la Fórmula (I) y sus sales farmacéuticamente aceptables también pueden administrarse usando anticuerpos monoclonales como vehículos individuales a los que se acoplan las moléculas de compuesto. Los compuestos

también pueden acoplarse con polímeros solubles como vehículos para fármacos dirigibles. Dichos polímeros pueden incluir polivinilpirrolidona, copolímero de pirano, polihidroxipropilmetacrilamida-fenol, polihidroxietilaspartamidafenol, o poli(óxido de etileno)polilisina sustituido con restos palmitoilo. Además, los compuestos pueden acoplarse a una clase de polímeros biodegradables de utilidad para lograr la liberación controlada de un fármaco, por ejemplo, ácido poliláctico, polépsilon caprolactona, ácido polihidroxibutírico, poliortoésteres, poliacetales, polidihidropiranos, policianoacrilatos y copolímeros de bloque anfipáticos de hidrogeles .

Las formulaciones farmacéuticas adaptadas para la administración transdérmica pueden presentarse en forma de parches separados para poner en contacto íntimo con la epidermis del receptor durante un periodo de tiempo prolongado. Por ejemplo, el principio activo puede administrarse con el parche mediante iontoforesis tal como se describe de forma general en *Pharm. Res.*, 3(6):318 (1986).

Las formulaciones farmacéuticas adaptadas para la administración tópica pueden formularse en forma de ungüentos, cremas, suspensiones, lociones, polvos, soluciones, pastas, geles, sprays, aerosoles o aceites.

Para los tratamientos oculares o de otros tejidos externos, por ejemplo la boca y la piel, las formulaciones preferiblemente se aplican en forma de un ungüento o crema tópicos. Cuando se formulan en forma de ungüento, el principio activo puede emplearse con una base de un ungüento parafínico o miscible en agua. De forma alternativa, el principio activo puede formularse en una crema con una base en crema de aceite en agua o una base de agua en aceite.

Las formulaciones farmacéuticas adaptadas para las administraciones tópicas

oculares incluyen colirios, en los que se disuelve o suspende el principio activo en un vehículo adecuado, especialmente un disolvente acuoso.

Las formulaciones farmacéuticas que se adaptan para la administración tópica bucal incluyen tabletas, pastillas y colutorios.

Las formulaciones farmacéuticas adaptadas para la administración rectal pueden presentarse en forma de supositorios o de enemas.

Las formulaciones farmacéuticas adaptadas para la administración nasal en la que el vehículo es sólido incluyen un polvo basto que tiene un tamaño de partícula por ejemplo en el intervalo de 20 a 500 micrómetros que se administra en la forma en la que se inhala el rape, es decir mediante inhalación rápida por las vías nasales a partir de un contenedor del polvo que se sujeta próximo a la nariz. Las formulaciones adecuadas en las que el vehículo es un líquido, para la administración en forma de un spray nasal o en forma de gotas nasales, incluyen soluciones acuosas u oleosas del principio activo.

Las formulaciones farmacéuticas adaptadas para la administración por inhalación incluyen polvos o pulverizaciones de partículas finas, que pueden generarse por medio de diversos tipos de aerosoles, nebulizadores o insufladores presurizados dosificados.

Las formulaciones farmacéuticas adaptadas para la administración vaginal pueden presentarse en forma de pesarios, tampones, cremas, geles, pastas, espumas o formulaciones en spray.

Las formulaciones farmacéuticas adaptadas para la administración parenteral incluyen soluciones inyectables estériles acuosas y no acuosas que pueden contener antioxidantes, tampones, bacterioestáticos y solutos que hacen que la formulación sea isotónica con la sangre del receptor que se pretenda; y

suspensiones estériles acuosas y no acuosas que pueden incluir agentes de suspensión y agentes espesantes. Las formulaciones pueden presentarse en envases monodosis o multidosis, por ejemplo ampollas y viales sellados, y pueden almacenarse en estado liofilizado que requiera únicamente la adición de vehículo líquido estéril, por ejemplo agua inyectable, antes de su uso. Las soluciones y suspensiones inyectables inmediatas pueden prepararse a partir de polvos, gránulos y comprimidos estériles.

Debe entenderse que además de los ingredientes que se mencionan de forma particular anteriormente, las formulaciones pueden incluir otros agentes convencionales en la técnica dependiendo del tipo de formulación en cuestión, por ejemplo, los adecuados para la administración oral pueden incluir agentes aromatizantes.

El término "paciente" incluye tanto seres humanos como otros mamíferos.

El término "tratar" se refiere a: (i) prevenir la aparición de una enfermedad, trastorno o afección en un paciente que pueda estar predispuesto a la enfermedad, trastorno, y/o afección pero todavía no ha sido diagnosticado como que la padece; (ii) inhibir la enfermedad, trastorno, o afección, es decir, detener su desarrollo; y (iii) aliviar la enfermedad, trastorno, o afección, es decir, provocar la regresión de la enfermedad, trastorno, y/o afección.

Los compuestos de la presente divulgación también pueden administrarse con una ciclosporina, por ejemplo, ciclosporina A. Se ha demostrado que la ciclosporina A es activa contra VHC en ensayos clínicos (*Hepatology*, 38:1282 (2003); *Biochem. Biophys. Res. Commun.*, 313:42 (2004); *J. Gastroenterol.*, 38:567 (2003)).

La Tabla 1 a continuación enumera algunos ejemplos ilustrativos de

compuestos que pueden administrarse con los compuestos de esta divulgación. Los compuestos de la divulgación pueden administrarse con otros compuestos con actividad contra VHC en politerapia, bien de forma conjunta o por separado o combinando los compuestos para formar una composición.

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*Tabla 1*

| Nombre comercial | Clase fisiológica | Tipo de inhibidor o diana | Compañía proveedora |
|---|---|---|---|
| NIM811<br>Debio-025 | | Inhibidores de ciclofilina | Novartis Debiopharm |
| Zadaxin | | Inmunomodulador | SciClone |
| Suvus | | Azul de metileno | Bioenvision |
| Actilon (CPG10101) | | Agonista de TLR9 | Coley |
| Batabulin (T67) | Anticanceroso | Inhibidor de β-tubulina | Tularik Inc., South San Francisco, CA |
| ISIS 14803 | Antiviral | No codificante | ISIS Pharmaceuticals Inc, Carlsbad, CA / Elan Pharmaceuticals Inc., New York, NY |
| Summetrel | Antiviral | Antiviral | Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA |
| GS-9132 (ACH-806) | Antiviral | Inhibidor de VHC | Achillion / Gilead |

| Nombre comercial | Clase fisiológica | Tipo de inhibidor o diana | Compañía proveedora |
|---|---|---|---|
| Compuestos y sales de pirazolopirimidina Del documento WO 2005/047288 26 de mayo de 2005 | Antiviral | Inhibidores de VHC | Arrow Therapeutics Ltd. |
| Levovirina | Antiviral | Inhibidor de IMPDH | Ribapharm Inc., Costa Mesa, CA |
| Merimepodib (VX-497) | Antiviral | Inhibidor de IMPDH | Vertex Pharmaceuticals Inc., Cambridge, MA |
| XTL-6865 (XTL-002) | Antiviral | Anticuerpo monoclonal | XTL Biopharmaceuticals Ltd., Rehovot, Israel |
| Telaprevir (VX-950, LY-570310) | Antiviral | Inhibidor de la serina protesasa NS3 | Vertex Pharmaceuticals Inc., Cambridge, MA / Eli Lilly y Co., Inc., Indianapolis, IN |
| HCV-796 | Antiviral | Inhibidor de la replicasa NS5B | Wyeth / Viropharma |
| NM-283 | Antiviral | Inhibidor de la replicasa NS5B | Idenix / Novartis |

| Nombre comercial | Clase fisiológica | Tipo de inhibidor o diana | Compañía proveedora |
|---|---|---|---|
| GL-59728 | Antiviral | Inhibidor de la replicasa NS5B | Gene Labs / Novartis |
| GL-60667 | Antiviral | Inhibidor de la replicasa NS5B | Gene Labs / Novartis |
| 2'C MeA | Antiviral | Inhibidor de la replicasa NS5B | Gilead |
| PSI 6130 | Antiviral | Inhibidor de la replicasa NS5B | Roche |
| R1626 | Antiviral | Inhibidor de la replicasa NS5B | Roche |
| 2'C Metil adenosina | Antiviral | Inhibidor de la replicasa NS5B | Merck |
| JTK-003 | Antiviral | Inhibidor de RdRp | Japan Tobacco Inc., Tokio, Japón |
| Levovirina | Antiviral | Ribavirina | ICN Pharmaceuticals, Costa Mesa, CA |
| Ribavirina | Antiviral | Ribavirina | Schering-Plough Corporation, Kenilworth, NJ |
| Viramidina | Antiviral | Profármaco de ribavirina | Ribapharm Inc., Costa Mesa, CA |

| Nombre comercial | Clase fisiológica | Tipo de inhibidor o diana | Compañía proveedora |
|---|---|---|---|
| Heptazyme | Antiviral | Ribozima | Ribozyme Pharmaceuticals Inc., Boulder, CO |
| BILN-2061 | Antiviral | Inhibidor de serina proteasas | Boehringer Ingelheim Pharma KG, Ingelheim, Alemania |
| SCH 503034 | Antiviral | Inhibidor de serina proteasas | Schering-Plough |
| Zadazim | Inmunomodulador | Inmunomodulador | SciClone Pharmaceuticals Inc., San Mateo, CA |
| Ceplene | Inmunomodulador | Inmunomodulador | Maxim Pharmaceuticals Inc., San Diego, CA |
| CELLCEPT® | Inmunosupresor | IgG inmunosupresora de VHC | F. Hoffmann-La Roche LTD, Basel, Suiza |
| Civacir | Inmunosupresor | IgG inmunosupresora de VHC | Nabi Biopharmaceuticals Inc., Boca Raton, FL |
| Albuferon - α | Interferón | Albúmina IFN-α2b | Human Genome Sciences Inc., Rockville, MD |

| Nombre comercial | Clase fisiológica | Tipo de inhibidor o diana | Compañía proveedora |
|---|---|---|---|
| Infergen A | Interferón | IFN alfa-1 | InterMune Pharmaceuticals Inc., Brisbane, CA |
| Omega IFN | Interferón | IFN-ω | Intarcia Therapeutics |
| IFN-β y EMZ701 | Interferón | IFN-β y EMZ701 | Transición Therapeutics Inc., Ontario, Canadá |
| REBIF® | Interferón | IFN-β1a | Serono, Ginebra, Suiza |
| Roferon A | Interferón | IFN-α2a | F. Hoffmann-La Roche LTD, Basel, Suiza |
| Intrón A | Interferón | IFN-α2b | Schering-Plough Corporation, Kenilworth, NJ |
| Intrón A y Zadaxin | Interferón | IFN-α2b/α1-timosina | RegeneRx Biopharma. Inc., Bethesda, MD / SciClone Pharmaceuticals Inc, San Mateo, CA |

| Nombre comercial | Clase fisiológica | Tipo de inhibidor o diana | Compañía proveedora |
|---|---|---|---|
| Rebetron | Interferón | IFN-α2b / ribavirina | Schering-Plough Corporation, Kenilworth, NJ |
| Actimmune | Interferón | INF-γ | InterMune Inc., Brisbane, CA |
| Interferón-β | Interferón | Interferón-β-1a | Serono |
| Multiferon | Interferón | IFN de acción prolongada | Viragen / Valentis |
| Wellferon | Interferón | IFN-αn1linfoblastoide | GlaxoSmithKline plc, Uxbridge, Reino Unido |
| Omniferon | Interferón | IFN-α natural | Viragen Inc., Plantation, FL |
| Pegasys | Interferón | IFN-α2a pegilado | F. Hoffmann-La Roche LTD, Basel, Suiza |
| Pegasys y Ceplene | Interferón | IFN-α2a PEGilado/inmunomodulador | Maxim Pharmaceuticals Inc., San Diego, CA |
| Pegasys y Ribavirina | Interferón | IFN-α2a PEGilado/ribavirina | F. Hoffmann-La Roche LTD, Basel, Suiza |

| Nombre comercial | Clase fisiológica | Tipo de inhibidor o diana | Compañía proveedora |
|---|---|---|---|
| PEG-Intrón | Interferón | IFN-α2b PEGilado | Schering-Plough Corporation, Kenilworth, NJ |
| PEG-Intrón / ribavirina | Interferón | IFN-α2b PEGilado/ribavirina | Schering-Plough Corporation, Kenilworth, NJ |
| IP-501 | Protección hepática | Antifibrótico | Indevus Pharmaceuticals Inc., Lexington, MA |
| IDN-6556 | Protección hepática | Inhibidor de caspasa | Idun Pharmaceuticals Inc., San Diego, CA |
| ITMN-191 (R-7227) | Antiviral | Inhibidor de serina proteasas | InterMune Pharmaceuticals Inc., Brisbane, CA |
| GL-59728 | Antiviral | Inhibidor de la replicasa NS5B | Genelabs |
| ANA-971 | Antiviral | Agonista de TLR-7 | Anadys |
| Boceprevir | Antiviral | Inhibidor de serina proteasas | Schering-Plough |
| TMS-435 | Antiviral | Inhibidor de serina proteasas | Tibotec BVBA, Mechelen, Bégica |

| Nombre comercial | Clase fisiológica | Tipo de inhibidor o diana | Compañía proveedora |
|---|---|---|---|
| BI-201335 | Antiviral | Inhibidor de serina proteasas | Boehringer Ingelheim Pharma KG, Ingelheim, Germany |
| MK-7009 | Antiviral | Inhibidor de serina proteasas | Merck |
| PF-00868554 | Antiviral | Inhibidor de replicasas | Pfizer |
| ANA598 | Antiviral | Inhibidor no nucleosídico de polimerasa NS5B | Anadys Pharmaceuticals, Inc., San Diego, CA, USA |
| IDX375 | Antiviral | Inhibidor no nucleosídico de replicasa | Idenix Pharmaceuticals, Cambridge, MA, USA |
| BILB 1941 | Antiviral | Inhibidor de polimerasa NS5B | Boehringer Ingelheim Canada Ltd R&D, Laval, QC, Canadá |
| PSI-7851 | Antiviral | Inhibidor nucleosídico de polimerasa | Pharmasset, Princeton, NJ, USA |
| VCH-759 | Antiviral | Inhibidor de polimerasa NS5B | ViroChem Pharma |
| VCH-916 | Antiviral | Inhibidor de polimerasa NS5B | ViroChem Pharma |

| Nombre comercial | Clase fisiológica | Tipo de inhibidor o diana | Compañía proveedora |
|---|---|---|---|
| GS-9190 | Antiviral | Inhibidor de polimerasa NS5B | Gilead |
| Peg-interferón lamda | Antiviral | Interferón | ZymoGenetics / Bristol-Myers Squibb |

Los compuestos de la presente divulgación también pueden emplearse como reactivos de laboratorio. Los compuestos pueden ser una contribución decisiva para proporcionar herramientas de investigación para diseñar ensayos de replicación del virus, validación de sistemas de ensayo en animales y estudios de biología estructural para potenciar más el conocimiento de los mecanismos de la enfermedad de VHC. Además, los compuestos de la presente divulgación son útiles para establecer o determinar el sitio de unión de otros compuestos antivirales, por ejemplo, por inhibición competitiva.

Los compuestos de esta divulgación también pueden usarse para tratar o prevenir la contaminación vírica de materiales y así reducir el riesgo de infección vírica del personal médico o de laboratorio o de los pacientes que entran en contacto con dichos materiales, por ejemplo, sangre, tejidos, instrumentos y prendas quirúrgicos, instrumentos y prendas de laboratorio y aparatos y materiales de extracción o transfusión de sangre.

Esta divulgación se pretende que englobe los compuestos que tienen la Fórmula (I) cuando se preparan mediante procedimientos sintéticos o mediante procesos metabólicos que incluyen los que se producen en el organismo humano o animal (*in vivo*) o los procesos que tienen lugar *in vitro*.

Las abreviaturas que se usan en la presente solicitud de patente, que incluyen en particular los ejemplos ilustrativos siguientes, son notorios para los expertos en la técnica. Algunas de la abreviaturas que se usan son las siguientes: TFA para ácido trifluoroacético; min o min. para minutos; MeCN o ACN para acetonitrilo; LDA para diisopropilamida de litio; DMSO para sulfóxido de dimetilo; h para horas; Boc o BOC para terc-butoxicarbonilo; HATU para hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio; TR o Tr para tiempo de retención o TA para temperatura ambiente; Me para metilo; DMF para N,N-dimetilformamida; $Pd(Ph_3P)_4$ para tetrakistrifenil fosfina paladio; MeOH para metanol; MeOD para $CD_4OD$; TEA para trietilamina; Ph para fenilo; TBDPS para terc-butildifenilsililo; $Et_3N$ o TEA para trietilamina; DMAP para N,N-dimetilaminopiridina; EtOAc para acetato de etilo; TBAF para fluoruro de tetrabutilamonio; THF para tetrahidrofurano; DIEA o DIPEA o $iPr_2NEt$ para diisopropiletilamina; NCS para N-clorosuccinimida; NBS para N-bromosuccinimida; DCM para diclorometano; MEB para 2-(trimetilsilil)etoximetilo; DCE para 1,2-dicloroetano; EDCI para 1-etil-3-(3-dimetilaminopropil)carbodiimida; DBU para 1,8-diazabiciclo[5,4,0]undec-7-eno; $Pd(t\text{-}Bu_3P)_2$ para bis(tributilfosfina) paladio; HMDS para hexametildisilazida; $TMSCHN_2$ para trimetilsilildiazometano; H-D-Ser-OBzl para éster bencílico de D-serina; i-PrOH para isopropanol; LiHMDS para hexametildisilazida de litio; DIBAL o DIBALH para hidruro de diisobutilaluminio; TBDMS para terc-butildimetilsililo; CBz para carbobenciloxi; Bn para bencilo; DEAD para azodicarboxilato de dietilo; mCPBA para ácido meta-cloroperoxibenzoico; TMSCN para cianuro de trimetilsililo; dpppe para 1,5-Bis(difenilfosfino) pentano; TMEDA para tetrametiletilendiamina; OAc para acetato; DMA para N,N-dimetilacetamida; y d para días.

La presente divulgación se describirá ahora relativa a ciertas realizaciones que no se pretende que limiten su alcance. Por el contrario, la presente divulgación abarca todas las alternativas, modificaciones, y equivalentes que pueden incluirse en el alcance de las reivindicaciones. Por lo tanto, los siguientes ejemplos, que incluyen realizaciones específicas, ilustrarán una práctica de la presente divulgación, entendiéndose que los ejemplos tienen fines ilustrativos de ciertas realizaciones y se presentan para proporcionar lo que se cree que es la descripción más útil y fácilmente comprensible de sus procedimientos y aspectos conceptuales.

Los materiales iniciales pueden obtenerse de fuentes comerciales o prepararse mediante procedimientos ya establecidos en la bibliografía conocidos por las personas de experiencia ordinaria en la técnica.

## EJEMPLOS

A no ser que se indique lo contrario, las evaluaciones de la pureza se realizaron en un sistema de CL Shimadzu y la determinación del tiempo de retención ($T_R$) y el análisis de masas de baja resolución se realizaron en un sistema de CL Shimadzu acoplado a un sistema de EM Waters MICROMASS® ZQ. Obsérvese que los tiempos de retención pueden variar ligeramente de un aparato a otro.

Condición 1

Columna = PHENOMENEX®, C18, 3,0 X 50 mm, 10 µm

% inicial de B = 0

% final de B = 100

Tiempo de gradiente = 2 min

Tiempo de terminación = 3 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = 0,1 % de TFA en 10% de metanol/90% de agua

Disolvente B = 0,1 % de TFA en 90% de metanol/10% de agua

Condición 2

Columna = XTERRA®, C18, 3,0 x 50 mm, S7

% inicial de B = 0

% final de B = 100

Tiempo de gradiente = 2 min

Tiempo de terminación = 3 min

Caudal = 5 ml/min

Longitud de onda = 220 nm

Disolvente A = 0,2 % de $H_3PO_4$ en 10% de metanol/90% de agua

Disolvente B = 0,2 % de $H_3PO_4$ en 90% de metanol/10% de agua

Condición 3

Columna = PHENOMENEX®, C18, 3,0 X 50 mm, 10 µm

% inicial de B = 0

% final de B = 100

Tiempo de gradiente = 3 min

Tiempo de terminación = 4 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = 0,1 % de TFA en 10% de metanol/90% de agua

Disolvente B = 0,1 % de TFA en 90% de metanol/10% de agua

Condición 4

Columna = XTERRA®, C18, 3,0 x 50 mm, S7

% inicial de B = 0

% final de B = 100

Tiempo de gradiente = 10 min

Tiempo de terminación = 11 min

Caudal = 5 ml/min

Longitud de onda = 220 nm

Disolvente A = 0,2 % de $H_3PO_4$ en 10% de metanol/90% de agua

Disolvente B = 0,2 % de $H_3PO_4$ en 90% de metanol/10% de agua

Condición 5

Columna = PHENOMENEX®, C18, 3,0 X 50 mm, 10 µm

% inicial de B = 0

% final de B = 100

Tiempo de gradiente = 4 min

Tiempo de terminación = 5 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = 0,1 % de TFA en 10% de metanol/90% de agua

Disolvente B = 0,1 % de TFA en 90% de metanol/10% de agua

Condición 6

Columna = Phenomenex-Luna, C18, 4,6 X 50 mm, S10

% inicial de B = 0

% final de B = 100

Tiempo de gradiente = 3 min

Tiempo de terminación = 4 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = 0,1 % de TFA en 10% de metanol/90% de agua

Disolvente B = 0,1 % de TFA en 90% de metanol/10% de agua

Condición 7

Columna = Phenomenex-Luna, C18, 3,0X 50 mm, S10

% inicial de B = 0

% final de B = 100

Tiempo de gradiente = 2 min

Tiempo de terminación = 3 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = 0,1 % de TFA en 10% de metanol/90% de agua

Disolvente B = 0,1 % de TFA en 90% de metanol/10% de agua

Condición 9

Columna = Waters Sunfire, C18, 4,6X150 mm, 3,5 µm

% inicial de B = 10

% final de B = 50

Tiempo de gradiente = 20 min

Tiempo de terminación = 25 min

Caudal = 1 ml/min

Longitud de onda = 220 y 254 nm

Disolvente A = 0,1% de TFA en 5% de $CH_3CN$/95% de $H_2O$

Disolvente B = 0,1% de TFA en 95% de $CH_3CN$/5% de $H_2O$

Condición 9a

Igual que la Condición 9 a excepción de que el Tiempo de terminación = 35 min

Condición 9a.1

Columna = Waters Sunfire, C18, 4,6X150 mm, 3,5 µm

% inicial de B = 30

% final de B = 100

Tiempo de gradiente = 20 min

Tiempo de terminación = 25 min

Caudal = 1 ml/min

Longitud de onda = 220 y 254 nm

Disolvente A = 0,1% de TFA en 5% de $CH_3CN$/95% de $H_2O$

Disolvente B = 0,1% de TFA en 95% de $CH_3CN$/5% de $H_2O$

Condición 10

Columna = Waters Xbridge phenyl, C18, 4,6X150 mm, 3 µm

% inicial de B = 10

% final de B = 50

Tiempo de gradiente = 20 min

Tiempo de terminación = 25 min

Caudal = 1 ml/min

Longitud de onda = 220 y 254 nm

Disolvente A = 0,1% de TFA en 5% de $CH_3CN$/95% de $H_2O$

Disolvente B = 0,1% de TFA en 95% de $CH_3CN$/5% de $H_2O$

Condición 10a

Igual que la Condición 10 a excepción de que el Tiempo de terminación = 35 min

Condición 10a.1

Columna = Waters Xbridge phenyl, C18, 4,6X150 mm, 3 µm

% inicial de B = 40

% final de B = 100

Tiempo de gradiente = 20 min

Tiempo de terminación = 25 min

Caudal = 1 ml/min

Longitud de onda = 220 y 254 nm

Disolvente A = 0,1% de TFA en 5% de $CH_3CN$/95% de $H_2O$

Disolvente B = 0,1% de TFA en 95% de $CH_3CN$/5% de $H_2O$

Condición 10b

Columna = Sunfire, C18, 3,0 X 150 mm, 3,5 µm

% inicial de B = 10

% final de B = 40

Tiempo de gradiente = 15 min

Tiempo de terminación = 18 min

Caudal = 1 ml/min

Longitud de onda 1 = 220 nm

Longitud de onda 2 = 254 nm

Disolvente A = 0,1 % de TFA en 5% de MeCN/95% de agua

Disolvente B = 0,1 % de TFA en 95% de MeCN/5% de agua

Condición 10c

Columna = Xbridge Phenyl, C18, 3,0 X 150 mm, 3,5 µm

% inicial de B = 10

% final de B = 40

Tiempo de gradiente = 15 min

Tiempo de terminación = 18 min

Caudal = 1 ml/min

Longitud de onda 1 = 220 nm

Longitud de onda 2 = 254 nm

Disolvente A = 0,1 % de TFA en 5% de MeCN/95% de agua

Disolvente B = 0,1 % de TFA en 95% de MeCN/5% de agua

Condición 10d

Columna = PHENOMENEX®-Luna, C18, 2,0 X 50 mm, 3 µm

% inicial de B = 0

% final de B = 100

Tiempo de gradiente = 4 min

Tiempo de terminación = 5 min

Caudal = 0,8 ml/min

Longitud de onda = 220 nm

Disolvente A = 0,1 % de TFA en 10% de metanol/90% de agua

Disolvente B = 0,1 % de TFA en 90% de metanol/10% de agua

Temp. del horno = 40 °C

Condición 10e (sistema de CL Agilent 1200 series)

Columna = Waters Xbridge phenyl, C18, 4,6X150 mm, 3,5 µm

Disolvente A = Tampón: $CH_3CN$ (95:5)

Disolvente B = Tampón: $CH_3CN$ (5:95)

Tampón = 0,05% de TFA en $H_2O$ (pH 2,5, ajustado con amoniaco diluido)

% inicial de B = 10

% final de B = 100

Tiempo de gradiente = 12 min

Tiempo isocrático = 3 min

Tiempo de terminación = 23 min

Caudal = 1 ml/min

Longitud de onda = 220 y 254 nm

Condición 10f (Espectrómetro de masas Agilent LC-1200 series acoplado a 6140 de cuadrante único, modo IES +)

Columna = Zorbax SB, C18, 4,6X50 mm, 5 µm

Disolvente A = MeOH (10%) + 0,1% de TFA en $H_2O$ (90%)

Disolvente B = MeOH (90%) + 0,1% de TFA en $H_2O$ (10%)

% inicial de B = 0

% final de B = 100

Tiempo de gradiente = 3 min

Tiempo isocrático = 1 min

Tiempo de terminación = 5 min

Caudal = 5 ml/min

Longitud de onda = 220 nm

Condición 10g (Espectrómetro de masas Agilent LC-1200 series acoplado a 6140 de cuadrante único, modo IES +)

Columna = Ascentis Express, C-8, 2,1X5 mm, 2,7 µm

Disolvente A = $CH_3CN$ (2%) + $NH_4COOH$ 10 mM en $H_2O$ (98%)

Disolvente B = $CH_3CN$ (98%) + $NH_4COOH$ 10 mM en $H_2O$ (2%)

% inicial de B = 0

% final de B = 100

Tiempo de gradiente = 1,5 min

Tiempo isocrático = 1,7 min

Tiempo de terminación = 4 min

Caudal = 1 ml/min

Longitud de onda = 220 nm

Condición 10h

Columna = PHENOMENEX®-Luna, C18, 4,6 X 30 mm, S10

% inicial de B = 0

% final de B = 100

Tiempo de gradiente = 3 min

Tiempo de terminación = 4 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = 0,1 % de TFA en 10% de metanol/90% de agua

Disolvente B = 0,1 % de TFA en 90% de metanol/10% de agua

Condición 11

Columna = PHENOMENEX®-Luna, C18, 50X2 mm, 3µm

% inicial de B = 0

% final de B = 100

Tiempo de gradiente = 4 min

Tiempo de terminación = 5 min

Caudal = 0,8 ml/min

Longitud de onda = 220 nm

Disolvente A = 5% de metanol/95% de agua : acetato de amonio 10 mM

Disolvente B = 95% de metanol/5% de agua : acetato de amonio 10 mM

Temperatura del horno = 40 °C

Condición 12 (HPLC de Waters Acquity con detección UV-Vis de Waters PDA y sonda para espectrometría Waters SQ MS-ESCI)

Columna = Waters Acquity BEH, C18, 150 X 2,1 mm de DI, 1,7 µm (a 35 °C)

Fase móvil A = 0,05% de TFA en agua

Fase móvil B = 0,05% de TFA en acetonitrilo

Sistema de disolventes: mantener 10% de B: 0-1 min; 10-98% de B: 1-32 min;

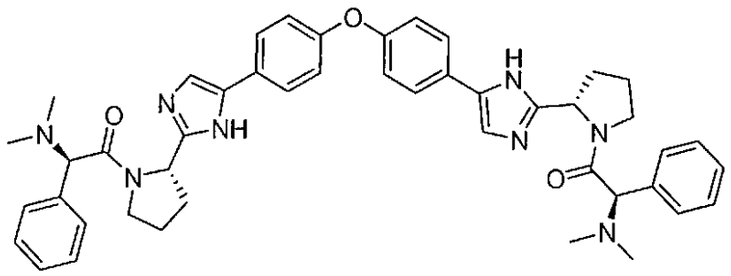
mantener 98% de B: 32-35 min; 98-10% de B: 35-35,3 min; mantener 10% de B: 35,3-40 min

Caudal = 0,35 ml/min

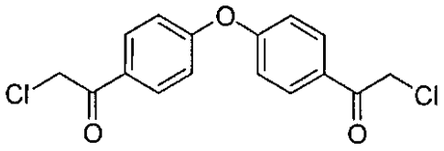
Detección UV = 335 nm

EJEMPLOS

Ejemplo OL-1



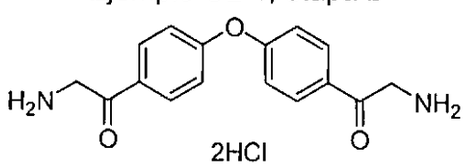
Ejemplo OL-1, etapa a



Se añadió éster dimetílico (1,5 g, 5,24 mmol) a una solución de cloroyodometano (3,05 ml, 41,92 mmol) en tetrahidrofurano (50 ml) y la solución resultante se enfrió a -78 °C. Se añadió gota a gota una solución 1,8 M de LDA (29 ml, 52 mmol) en tetrahidrofurano y la suspensión marrón resultante se agitó a -78 °C durante 15 min. Después se añadió una solución de ácido acético glacial en tetrahidrofurano (10 ml en 50 ml) lentamente y la mezcla marrón se agitó a -78 °C durante 10 min antes de dejar que alcanzara temperatura ambiente. La mezcla se tomó en acetato de etilo y salmuera (1:1, 50 ml) y la fase orgánica después se

separó, se lavó con una solución saturada de bicarbonato sódico y salmuera, se secó ($MgSO_4$), se filtró, y se concentró a vacío. El residuo se sometió a cromatografía ultrarrápida (gel de sílice; 15% de acetato de etilo/hexanos) proporcionando OL-1a en forma de un sólido marrón claro (0,6 g). RMN de $^1H$ (500 MHz, DMSO-$d_6$) δ ppm 5,17 (s, 4 H), 7,22 (d, J=8,85 Hz, 4 H), 8,06 (d, J=8,85 Hz, 4 H). CL (Cond. 2): $T_R$ = 1,53 minutos, 97% de índice de homogeneidad; CLEM: Anal. Calc. para $(M-H)^+$ $C_{16}H_{11}Cl_2O_3$: 321,01; Encontrado: 321,30.

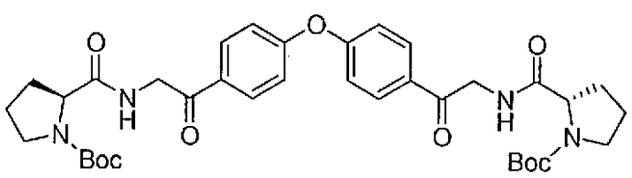
Ejemplo OL-1, etapa b




2HCl

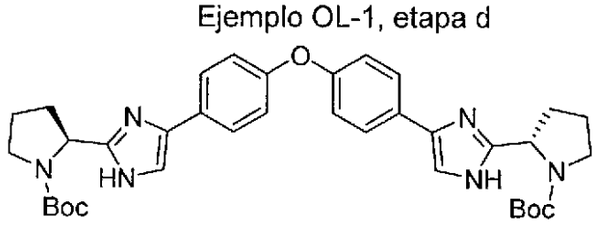
Se calentó a reflujo una mezcla de OL-1a (0,6 g, 1,85 mmol) y diformilamida sódica (0,42 g, 4,45 mmol) en acetonitrilo (20 ml) a reflujo durante 4 h. El disolvente se eliminó después a presión reducida y el residuo restante se volvió a disolver en una solución al 5% de HCl en etanol (30 ml) y se calentó a temperatura de reflujo durante 2 h. La mezcla se enfrió en un baño de agua y hielo y el precipitado resultante se filtró, se lavó con etanol y éter y se secó a vacío. El sólido marrón claro recuperado se usó sin purificación adicional (0,66 g). RMN de $^1H$ (500 MHz, DMSO-$d_6$) δ ppm 4,54 (s, 4 H), 7,25 (d, J=8,85 Hz, 4 H), 8,11 (d, J=8,55 Hz, 4 H), 8,52 (s ancho, 6 H). CL (Cond. 1): $T_R$ = 1,24 min; EMBR: Anal. Calc. para $(M+H)^+$ $C_{16}H_{17}N_2O_3$ 285,12; Encontrado: 285,19.

Ejemplo OL-1, etapa c



Se añadió N,N-diisopropiletilamina (1,13 ml, 6,47 mmol) gota a gota, durante 15 minutos, a una mezcla heterogénea de N-Boc-L-prolina (0,8 g, 3,73 mmol), HATU (1,48 g, 3,88 mmol), OL-1b (0,66 g, 1,85 mmol) y dimetilformamida (15 ml), y se agitó en condiciones ambientales durante 4 h. La mayoría de los componentes volátiles se eliminaron a vacío, y el residuo resultante se fraccionó entre acetato de etilo (30 ml) y agua (20 ml). La fase orgánica se lavó con agua (20 ml) y salmuera, se secó ($MgSO_4$), se filtró, y se concentró a vacío. Se preparó una malla de gel de sílice a partir del residuo y se sometió a cromatografía ultrarrápida (gel de sílice; 65-85 % de acetato de etilo/ hexanos) proporcionando OL-1c en forma de un sólido marrón claro (0,7 g). RMN de $^1H$ (500 MHz, DMSO-$d_6$) δ ppm 1,39/1,34 (rotámeros, s, 18 H), 1,70 - 1,91 (m, 6 H), 2,00 - 2,25 (m, J=8,55 Hz, 2 H), 3,22 - 3,33 (m, 2 H), 3,32 - 3,47 (m, J=10,68, 10,68 Hz, 2 H), 4,08 - 4,26 (m, 2 H), 4,56 (ddd, J=36,93, 18,16, 5,34 Hz, 4 H), 7,19 (d, J=8,85 Hz, 4 H), 8,06 (d, J=7,93 Hz, 4 H), 8,11 - 8,24 (m, J=5,49 Hz, 2 H). CL (Cond. 1): $T_R$ = 2,55 min; EMBR: Anal. Calc. para $(M+H)^+$ $C_{36}H_{47}N_4O_9$ 679,33; Encontrado: 679,44.

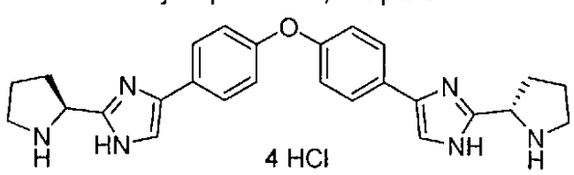
Ejemplo OL-1, etapa d



Una mezcla de OL-1c (0,7 g, 1,025 mmol) y acetato de amonio (0,79 g, 10 mmol) en xilenos (5 ml) se calentó en un tubo sellado a 140 °C durante 1,2 horas

con radiación microondas. El componente volátil se eliminó a vacío, y el residuo se fraccionó cuidadosamente entre acetato de etilo y agua, después de lo cual se añadió suficiente solución saturada de bicarbonato sódico para hacer que el pH de la fase acuosa fuera ligeramente básico después de agitar el sistema bifásico. Las fases se separaron, y la fase acuosa se extrajo con más acetato de etilo. La fase orgánica combinada se lavó con salmuera, se secó ($MgSO_4$), se filtró, y se concentró a vacío. El material resultante se sometió a una cromatografía ultrarrápida (gel de sílice; 15-25% de acetona/diclorometano) proporcionando OL-1d (0,13 g). RMN de $^1H$ (500 MHz, DMSO-$d_6$) δ ppm 1,17/1,48 (rotámeros, s, 18 H), 1,76 - 1,93 (m, 4 H), 1,93 - 2,06 (m, J=10,07 Hz, 2 H), 2,10 - 2,30 (m, 2 H), 3,32 - 3,39 (m, 2 H), 3,45 - 3,62 (m, 2 H), 4,69 - 4,80 (m, 1 H), 4,83 (d, J=7,02 Hz, 1 H), 6,97 (d, J=7,93 Hz, 4 H), 7,00 - 7,22 (m, 1 H), 7,40/7,62 (rotámeros, m, 2 H), 7,73 (d, J=8,55 Hz, 3 H), 11,74/11,81/12,07 (rotámeros, s, 2 H). CL (Cond. 2): $T_R$ = 1,53 minutos, 93% de índice de homogeneidad; CLEM: Anal. Calc. para $(M+H)^+$ $C_{36}H_{44}N_6O_5$: 641,34; Encontrado: 641,50.

Ejemplo OL-1, etapa e




4 HCl

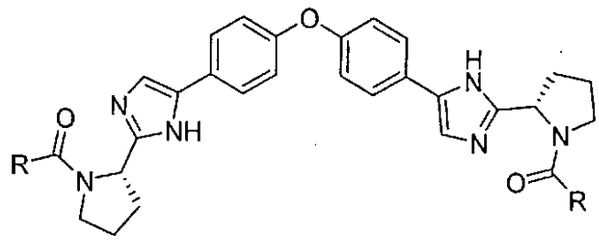
A una solución de OL-1d (0,13 g, 0,2 mmol) en 30 ml diclorometano se añadió 1 ml de una solución 4,0 M de HCl en dioxano. La reacción se agitó durante 2 horas a temperatura ambiente y se concentró a presión reducida. El residuo resultante se volvió a disolver en una cantidad mínima de metanol y el producto deseado se trituró con éter, se filtró y se secó a vacío. Se recuperó un sólido

tostado claro (0,11g) y se usó sin purificación adicional. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 1,92 - 2,07 (m, 2 H), 2,12 - 2,25 (m, 2 H), 2,37 - 2,47 (m, 4 H), 3,30 - 3,47 (m, 4 H), 4,90 - 5,02 (m, 2 H), 7,15 (d, J=8,55 Hz, 4 H), 7,91 (d, J=8,24 Hz, 4 H), 7,97 (s, 2 H), 9,74 (s ancho, 2 H), 10,25 (s ancho, 2 H). Nota: la señal del NH del imidazol era demasiado ancha para asignarle un desplazamiento químico. CL (Cond. 1): $T_R$ = 1,68 min; EMBR: Anal. Calc. para $(M+H)^+$ $C_{26}H_{29}N_6O$ 441,24; Encontrado: 441,30.

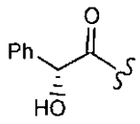
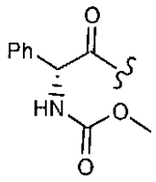
Ejemplo OL-1

Se añadió HATU (52 mg, 0,137 mmol) a una mezcla de OL-1e (35 mg, 0,06 mmol), diisopropiletilamina (58 µl, 0,33 mmol) y Cap-1 (22 mg, 0,12 mmol) en dimetilformamida (3 ml), y la mezcla resultante se agitó a temperatura ambiente durante 3 h. El componente volátil se eliminó a vacío, y el residuo se purificó mediante un sistema de HPLC de fase inversa (agua/metanol/TFA) proporcionando la sal TFA del Ejemplo OL-1 en forma de un sólido blanquecino (32 mg). RMN de $^1$H (500 MHz, DMSO-$D_6$) δ ppm 1,82 - 1,93 (m, 2 H), 1,94 - 2,08 (m, 4 H), 2,14 - 2,24 (m, 2 H), 2,29 - 2,40 (m, 4 H), 2,83 (s, 4 H), 2,97 - 3,07 (m, 4 H), 3,97 (t, J=8,24 Hz, 2 H), 4,89 - 5,20 (m, 2 H), 5,34 - 5,73 (m, 2 H), 7,00 - 7,22 (m, 6 H), 7,49 - 7,64 (m, 9 H), 7,70 - 7,89 (m, 5 H), 10,20 (br.s, 2 H). CL (Cond. 1): $T_R$ = 2,48 min; EMBR: Anal. Calc. para $(M+H)^+$ $C_{46}H_{51}N_8O_3$ 763,41; Encontrado: 763,56; EMAR: Anal. Calc. para $(M+H)^+$ $C_{46}H_{51}N_8O_3$ 763,4084; Encontrado: 763,4109.

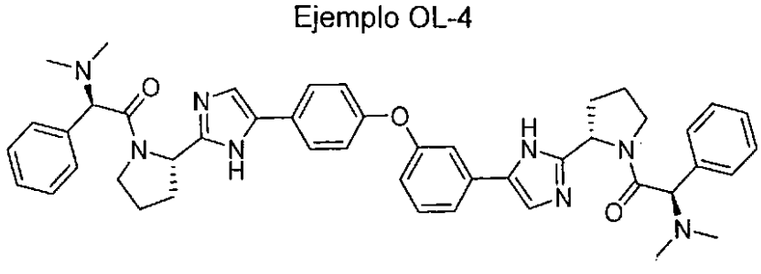
Ejemplos OL-2 y OL-3



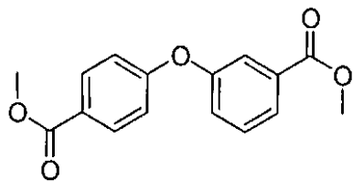
Los Ejemplos OL-2 y OL-3 se prepararon en forma de sales TFA sustituyendo los ácidos respectivos por Cap-1 usando el mismo procedimiento descrito para el Ejemplo OL-1.

| Ejemplo |  Ácido | TR (Cond. de CL); Datos de EM |
|---|---|---|
| OL-2 |  Ácido mandélico | $T_R$ = 2,92 min. CL (Cond. 2); CLEM: Anal. Calc. para $(M+H)^+$ $C_{42}H_{41}N_6O_5$ 709,31; Encontrado: 709,41; EMAR: Anal. Calc. para: $C_{42}H_{41}N_6O_5$ 709,3138; Encontrado: 709,3147 $(M+H)^+$ |
| OL-3 |  Cap-4 | $T_R$ = 3,65 min). CL (Cond. 2); CLEM: Anal. Calc. para $(M+H)^+$ $C_{46}H_{47}N_8O_7$ 823,35; Encontrado: 823,66; EMAR: Anal. Calc. para $(M+H)^+$ $C_{46}H_{47}N_8O_7$ 823,3568; Encontrado: 823,3574 |

Ejemplo OL-4

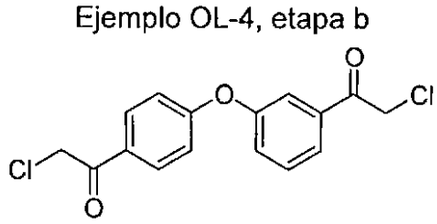


Ejemplo OL-4, etapa a



Se combinaron 3-bromobenzoato de metilo (5 g, 23,2 mmol), 4-hidroxibenzoato de metilo (5,3 g, 34,87 mmol), carbonato de cesio (15,12 g, 46,4 mmol), yoduro de cobre (I) (0,44 g, 2,32 mmol) y clorhidrato de N,N-dimetilo (0,97 g, 6,96 mmol) en dioxano (100 ml) en un tubo sellado y la mezcla resultante se calentó a 90 °C durante 15 h. El disolvente se eliminó a presión reducida y el residuo se tomó en acetato de etilo/agua (1:1, 200 ml). La fase orgánica se lavó con carbonato sódico acuoso saturado, agua y salmuera, se secó ($MgSO_4$), se filtró y se concentró a vacío. El material resultante se purificó por cromatografía ultrarrápida (gel de sílice, 5% de acetato de etilo/hexanos) proporcionando OL-4a en forma de un aceite transparente que solidificó al reposar (5,8 g). RMN de $^1H$ (500 MHz, DMSO-$d_6$) δ ppm 3,83 (s, 6 H), 7,10 (d, J=8,55 Hz, 2 H), 7,43 (dd, J=8,09, 2,59 Hz, 1 H), 7,56 (s, 1 H), 7,61 (t, J=7,93 Hz, 1 H), 7,81 (d, J=7,63 Hz, 1 H), 7,98 (d, J=8,55 Hz, 2 H). CL (Cond. 2): $T_R$ = 1,53 minutos; CLEM: Anal. Calc. para $(M+1)^+$ $C_{16}H_{15}O_5$: 287,01; Encontrado: 287,23.

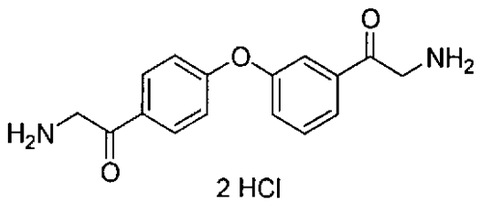
Ejemplo OL-4, etapa b



OL-4b se preparó a partir de OL-4a, de acuerdo con el mismo procedimiento

que se usó para la preparación de OL-1a. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 5,14 (s, 2 H), 5,20 (s, 2 H), 7,13 (d, J=8,85 Hz, 2 H), 7,43 - 7,49 (m, 1 H), 7,64 (t, J=8,09 Hz, 1 H), 7,66 - 7,68 (m, 1 H), 7,85 (d, J=7,93 Hz, 1 H), 8,02 (d, J=8,85 Hz, 2 H). CL (Cond. 1): $T_R$ = 1,51 min; EMBR: Anal. Calc. para $(M+H)^+$ $C_{16}H_{13}Cl_2O_3$ 323,02; Encontrado: 323,07.

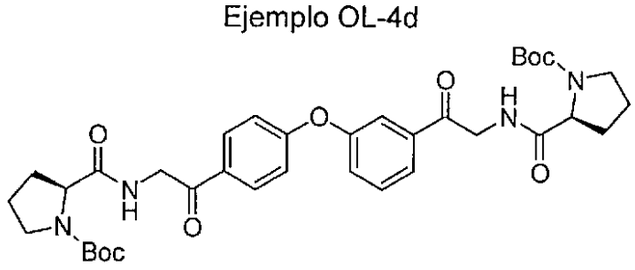
Ejemplo OL-4, etapa c



2 HCl

OL-4c se preparó a partir del Ejemplo OL-4b, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1b. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm. 4,52 (s, 2 H), 4,56 (s, 2 H), 7,16 (d, J=8,85 Hz, 2 H), 7,51 (dd, J=8,24, 2,44 Hz, 1 H), 7,68 (t, J=7,93 Hz, 1 H), 7,71 - 7,75 (m, 1 H), 7,91 (d, J=7,63 Hz, 1 H), 8,07 (d, J=8,85 Hz, 2 H), 8,60 (s, 6 H). CL (Cond. 2): Anal. Calc. para $C_{16}H_{17}N_2O_3$ $(M+H)^+$ 285,12; Encontrado: 285,15.

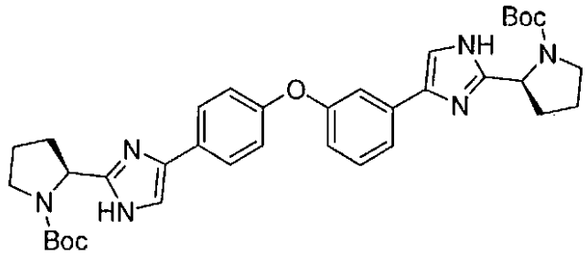
Ejemplo OL-4d



El ejemplo OL-4d se preparó a partir del Ejemplo OL-4c, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1c. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 1,38/1,33 (rotámeros, s, 18 H), 1,69 - 1,91 (m, 6 H),

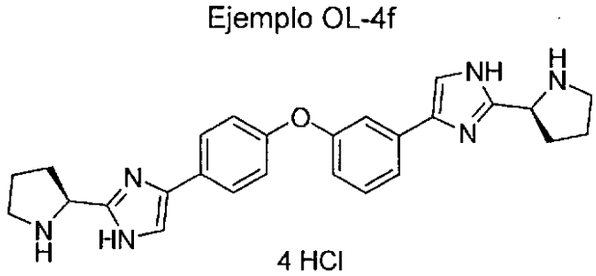
1,95 - 2,19 (m, 2 H), 3,20 - 3,31 (m, 2 H), 3,32 - 3,47 (m, 2 H), 4,08 - 4,23 (m, 2 H), 4,43 - 4,68 (m, 4 H), 7,10 (d, J=8,55 Hz, 2 H), 7,42 (dd, J=8,09, 1,98 Hz, 1 H), 7,57 - 7,70 (m, 2 H), 7,86 (d, J=7,02 Hz, 1 H), 8,03 (d, J=7,93 Hz, 2 H), 8,08 - 8,24 (m, 2 H). CL (Cond. 1): $T_R$ = 2,53 min; EMBR: Anal. Calc. para $C_{36}H_{47}N_4O_9$ $(M+H)^+$ 679,33; Encontrado: 679,42.

Ejemplo OL-4e




El ejemplo OL-4e se preparó a partir del Ejemplo OL-4d, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1d. RMN de $^1H$ (500 MHz, DMSO-$d_6$) δ ppm 1,14/1,17 /1,38/1,40 (rotámeros, s, 18 H), 1,71 - 2,06 (m, 6 H), 2,09 - 2,28 (m, J=25,79, 13,89 Hz, 2 H), 3,31 - 3,40 (m, 2 H), 3,51 (s, 2 H), 4,65 - 4,89 (m, 2 H), 6,80 (t, J=8,39 Hz, 1 H), 6,91 - 7,10 (m, 2 H), 7,28 - 7,55 (m, 5 H), 7,58 - 7,80 (m, 2 H), 11,66 - 12,21 (m, 2 H). CL (Cond. 1): $T_R$ = 2,98 min; EMBR: Anal. Calc. para $C_{36}H_{45}N_6O_5$ $(M+H)^+$ 641,34; Encontrado: 641,39.

Ejemplo OL-4f



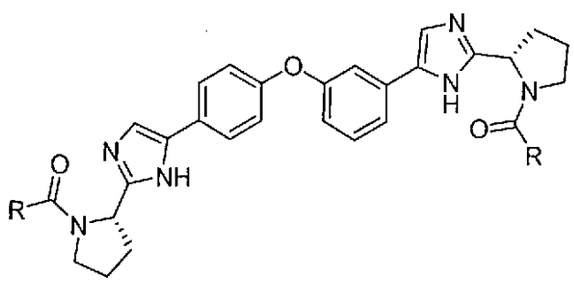

4 HCl

El Ejemplo OL-4f se preparó a partir del Ejemplo OL-4e, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1e. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 1,94 - 2,06 (m, 2 H), 2,09 - 2,23 (m, 2 H), 2,28 - 2,38 (m, 1 H), 2,37 - 2,47 (m, 3 H), 3,27 - 3,50 (m, 4 H), 4,90 (s ancho, 1 H), 4,99 (s ancho, 1 H), 7,00 (d, J=7,93 Hz, 1 H), 7,13 (d, J=8,55 Hz, 2 H), 7,49 (t, J=7,93 Hz, 1 H), 7,62 (s, 1 H), 7,69 (d, J=7,63 Hz, 1 H), 7,92 (d, J=8,55 Hz, 2 H), 7,99 (s, 2 H), 9,58 (s ancho, 1 H), 9,84 (s ancho, 1 H), 10,25 (br. d, J=22,28 Hz, 2 H). Nota: la señal del NH del imidazol era demasiado ancha para asignarle un desplazamiento químico. CL (Cond. 1): $T_R$ = 1,72 min; EMBR: Anal. Calc. para $C_{26}H_{29}N_6O$ $(M+H)^+$ 441,24; Encontrado: 441,29.

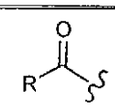
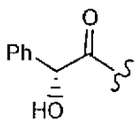
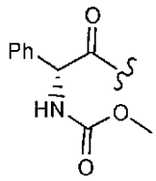
Ejemplo OL-4

El Ejemplo OL-4 se preparó a partir del Ejemplo OL-4f de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 1,83 - 1,92 (m, 4 H), 1,95 - 2,09 (m, 8 H), 2,11 - 2,23 (m, 4 H), 2,75 - 2,88 (m, 2 H), 2,92 (s, 1 H), 2,96 - 3,12 (m, 2 H), 3,97 (t, J=8,39 Hz, 2 H), 5,14 (dd, J=17,70, 7,02 Hz, 2 H), 5,41 (s, 2 H), 6,91 - 7,11 (m, J=49,75 Hz, 2 H), 7,14 (d, J=7,93 Hz, 2 H), 7,44 - 7,68 (m, 12 H), 7,79 (d, J=8,54 Hz, 2 H), 7,84 - 8,02 (m, J=9,16 Hz, 2 H), 10,21 (s, 1 H). Nota: la señal del NH del imidazol era demasiado ancha para asignarle un desplazamiento químico. CL (Cond. 1): $T_R$ = 1,78 min; EMBR: Anal. Calc. para $C_{46}H_{51}N_8O_3$ $(M+H)^+$ 763,41; Encontrado: 763,56. EMAR: Anal. Calc. para $C_{46}H_{51}N_8O_3$ $(M+H)^+$ 763,4084; Encontrado: 763,4067.

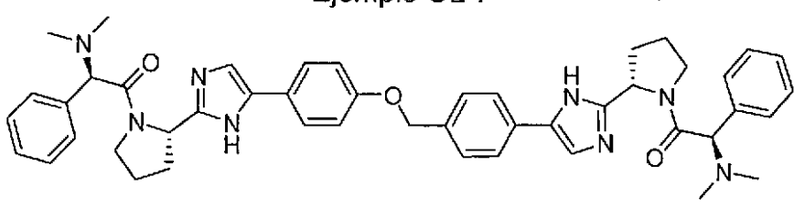
Ejemplos OL-5 y OL-6



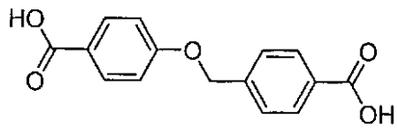
Los Ejemplos OL-5 a OL-6 se prepararon en forma de sales TFA sustituyendo los ácidos respectivos por Cap-1 de acuerdo con el mismo procedimiento descrito para el Ejemplo OL-4.

| Ejemplo |  Ácido | TR (Cond. de CL); Datos de EM |
|---|---|---|
| OL-5 |  Ácido mandélico | $T_R$ = 1,78 min. CL (Cond. 2); CLEM: Anal. Calc. para: $C_{42}H_{41}N_6O_5$ $(M+H)^+$ 709,31; Encontrado: 709,42; EMAR: Anal. Calc. para: $C_{42}H_{41}N_6O_5$ $(M+H)^+$ 709,3138; Encontrado: 709,3130 |
| OL-6 |  Cap-4 | $T_R$ = 1,96 min. CL (Cond. 2); CLEM: Anal. Calc. para: $C_{46}H_{47}N_8O_7$ $(M+H)^+$ 823,36; Encontrado: 823,51; EMAR: Anal. Calc. para: $C_{46}H_{47}N_8O_7$ $(M+H)^+$ 823,3568; Encontrado: 823,3588 |

Ejemplo OL-7

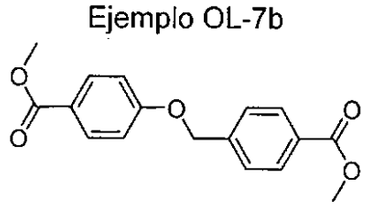


Ejemplo OL-7a



A una solución de ácido 4-(clorometil)benzoico (8,53 g, 50 mmol) e hidróxido sódico (10 g, 0,25 mol) en agua (40 ml) se añadió una solución de ácido 4-hidroxibenzoico (6,9 g, 50 mmol) e hidróxido sódico (6 g, 0,15 mol) en agua (50 ml). La mezcla resultante se calentó a temperatura de reflujo durante 15 h y, después de enfriar a temperatura ambiente, se filtró y se acidificó con una solución de ácido sulfúrico en agua (1:1, 200 ml). El precipitado resultante se eliminó por filtración, se lavó con agua y se secó a vacío. El sólido blanquecino (9,3 g) se usó sin purificación adicional. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 5,27 (s, 1 H), 7,10 (d, J=8,85 Hz, 2 H), 7,56 (d, J=8,24 Hz, 2 H), 7,89 (d, J=8,85 Hz, 2 H), 7,96 (d, J=8,24 Hz, 2 H), 12,36 (s ancho, 2 H). CL (Cond. 2), Nota: La molécula no se ionizó bien en el sistema de CL/EM y por lo tanto no se obtuvo una masa exacta.

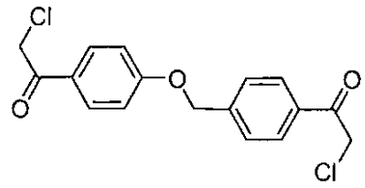
Ejemplo OL-7b



Se añadió (diazometil)trimetilsilano (15 ml, 30 mmol, 2 M en hexanos) gota a gota a una suspensión del Ejemplo OL-7a (2,04 g, 7,5 mmol) en metanol (30 ml) a 5 °C (baño de agua y hielo). Cuando se completó la adición, se extrajo del baño helado y la mezcla se agitó a temperatura ambiente toda la noche. El disolvente se eliminó a presión reducida y el residuo restante se tomó en acetato de etilo, se lavó

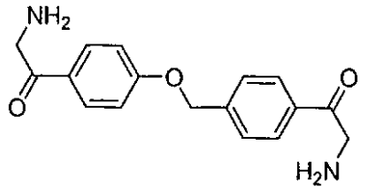
con agua, bicarbonato sódico y salmuera, se secó ($MgSO_4$), se filtró y se concentró a vacío. El material resultante se purificó por cromatografía ultrarrápida (gel de sílice, 10% de acetato de etilo/hexanos) proporcionando el Ejemplo OL-7b en forma de un sólido blanco (1,5 g). RMN de $^1H$ (500 MHz, DMSO-$d_6$) δ ppm 3,80 (s, 3 H), 3,85 (s, 3 H), 5,29 (s, 2 H), 7,13 (d, J=8,85 Hz, 2 H), 7,59 (d, J=8,24 Hz, 2 H), 7,91 (d, J=9,16 Hz, 2 H), 7,98 (d, J=8,24 Hz, 2 H). CL (Cond. 1): $T_R$ = 2,56 min; EMBR: Anal. Calc. para $C_{17}H_{16}O_5$ $(M+H)^+$ 301,11; Encontrado: 301,22.

Ejemplo OL-7c




El Ejemplo OL-7c se preparó a partir del Ejemplo OL-7b, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1a. RMN de $^1H$ (500 MHz, DMSO-$d_6$) δ ppm 5,09 (s, 2 H), 5,18 (s, 2 H), 5,34 (s, 2 H), 7,15 (d, J=8,85 Hz, 2 H), 7,62 (d, J=8,55 Hz, 2 H), 7,95 (d, J=9,16 Hz, 2 H), 8,00 (d, J=8,55 Hz, 2 H). CL (Cond. 1): $T_R$ = 2,36 min; EMBR: Anal. Calc. para $C_{17}H_{15}Cl_2O_3$ $(M+H)^+$ 337,04 Encontrado: 337,09.

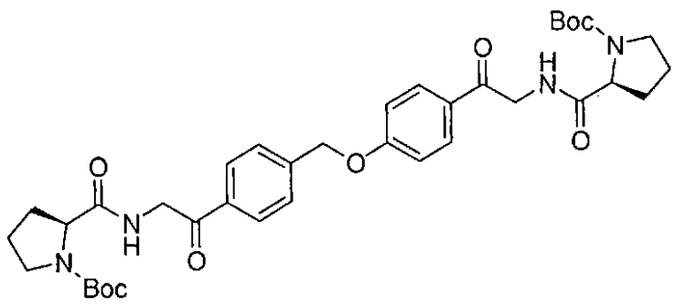
Ejemplo OL-7d




El Ejemplo OL-7d se preparó a partir del Ejemplo OL-7c, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1b. RMN de

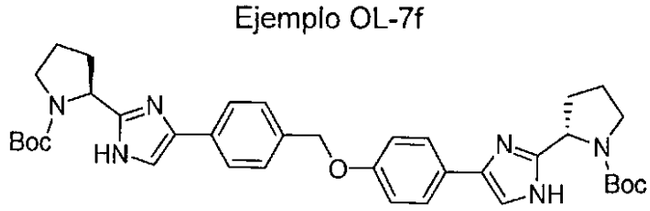
$^1$H (500 MHz, DMSO-$d_6$) δ ppm 4,49 (s, 2 H), 4,57 (s, 2 H), 5,38 (s, 2 H), 7,19 (d, J=8,85 Hz, 2 H), 7,66 (d, J=8,24 Hz, 2 H), 8,00 (d, J=8,85 Hz, 2 H), 8,05 (d, J=8,24 Hz, 2 H), 8,45 (s, 6 H). CL (Cond. 1): $T_R$ = 1,26 min; EMBR: Anal. Calc. para $C_{17}H_{19}NI_2O_3$ $(M+H)^+$ 299,14 Encontrado: 299,19.

Ejemplo OL-7e




El Ejemplo OL-7e se preparó a partir del Ejemplo OL-7d, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1c. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 1,30 - 1,47 (m, 18 H), 1,65 - 1,89 (m, 6 H), 2,01 - 2,20 (m, 2 H), 3,24 - 3,34 (m, 2 H), 3,34 - 3,43 (m, 2 H), 4,09 - 4,25 (m, 2 H), 4,44 - 4,68 (m, 4 H), 5,33 (s, 2 H), 7,13 (d, J=8,85 Hz, 2 H), 7,60 (d, J=8,24 Hz, 2 H), 7,99 (dd, J=20,29, 8,09 Hz, 4 H), 8,04 - 8,22 (m, J=31,74 Hz, 2 H). CL (Cond. 2): $T_R$ = 1,53 minutos, 97% de índice de homogeneidad; CLEM: Anal. Calc. para $C_{37}H_{49}N_4O_9$ $(M+1)^+$ 693,35; Encontrado: 693,32.

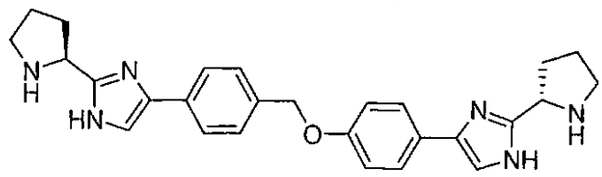
Ejemplo OL-7f




El Ejemplo OL-7f se preparó a partir del Ejemplo OL-7e, de acuerdo con el

mismo procedimiento que se usó para la preparación del Ejemplo OL-1d. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 1,06 - 1,52 (m, 18 H), 1,69 - 2,08 (m, 6 H), 2,08 - 2,30 (m, 2 H), 3,33 - 3,43 (m, 2 H), 3,52 (s, 2 H), 4,75 (s, 1 H), 4,83 (s, 1 H), 5,06 (s, 2 H), 6,92 - 7,10 (m, J=7,63 Hz, 2 H), 7,20 - 7,33 (m, 1 H), 7,40 (d, J=7,63 Hz, 2 H), 7,46 (d, J=8,55 Hz, 1 H), 7,64 (d, J=7,63 Hz, 2 H), 7,75 (d, J=7,93 Hz, 2 H), 11,47 - 12,18 (m, 2 H). CL (Cond. 1): $T_R$ = 2,94 min; EMBR: Anal. Calc. para $C_{37}H_{47}N_6O_3$ $(M+H)^+$ 655,36 Encontrado: 655,39.

Ejemplo OL-7g



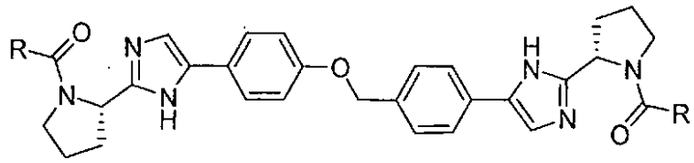
El Ejemplo OL-7g se preparó a partir del Ejemplo OL-7fe, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1e. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 1,93 - 2,07 (m, 2 H), 2,13 - 2,26 (m, 2 H), 2,40 - 2,48 (m, 3 H), 3,31 - 3,52 (m, 5 H), 4,91 - 5,09 (m, 2 H), 5,21 (s, 2 H), 7,17 (d, J=8,85 Hz, 2 H), 7,57 (d, J=8,24 Hz, 2 H), 7,87 (d, J=8,85 Hz, 2 H), 7,93 (d, J=8,24 Hz, 2 H), 8,03 (d, J=16,79 Hz, 2 H), 9,78 (s, 1 H), 9,95 (s, 1 H), 10,31 (s, 2 H). Nota: la señal del NH del imidazol era demasiado ancha para asignarle un desplazamiento químico. CL (Cond. 2): $T_R$ = 0,62 minutos; CLEM: Anal. Calc. para $C_{27}H_{31}N_6O$ $(M+1)^+$ 455,26; Encontrado: 455,34.

Ejemplo OL-7

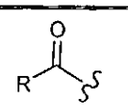
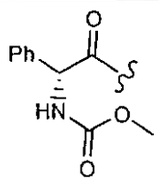
El Ejemplo OL-7 se preparó a partir del Ejemplo OL-7g de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1. RMN de $^1$H

(500 MHz, DMSO-$d_6$) δ ppm 1,90 (d, J=2,44 Hz, 2 H), 2,04 (d, J=3,66 Hz, 4 H), 2,21 (s, 2 H), 2,36 (d, J=1,83 Hz, 2 H), 2,42 - 2,46 (m, 4 H), 2,83 (s ancho, 4 H), 2,99 - 3,11 (m, 2 H), 3,98 (d, J=7,02 Hz, 2 H), 5,18 (s, 4 H), 5,42 (d, J=8,55 Hz, 2 H), 7,08 - 7,28 (m, 3 H), 7,50 - 7,67 (m, 11 H), 7,73 (d, J=7,32 Hz, 2 H), 7,80 (d, J=7,93 Hz, 2 H), 7,85 - 7,98 (m, J=10,38 Hz, 1 H). Nota: la señal del NH del imidazol era demasiado ancha para asignarle un desplazamiento químico. CL (Cond. 3): $T_R$ = 2,94 min; EMBR: Anal. Calc. para $C_{47}H_{52}N_8O_3$ $(M+H)^+$ 777,42 Encontrado: 777,51; EMAR: Anal. Calc. para $C_{47}H_{53}N_8O_3$ $(M+H)^+$ 777,4241 Encontrado: 777,4265.

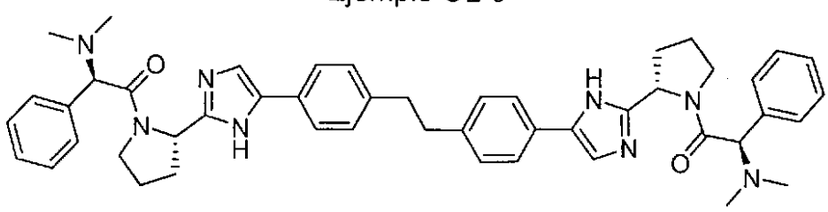
Ejemplo OL-8



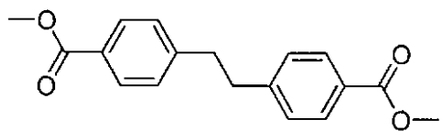
El Ejemplo OL-8 se preparó en forma de sal TFA sustituyendo el ácido respectivo por Cap-1 de acuerdo con el mismo procedimiento descrito para el Ejemplo OL-7.

| Ejemplo |  Ácido | TR (Cond. de CL); Datos de EM |
|---|---|---|
| OL-8 |  Cap-4 | $T_R$ = 3,70 min. CL (Cond. 4); CLEM: Anal. Calc. para $C_{47}H_{49}N_8O_7$ $(M+H)^+$ 837,37; Encontrado: 837,54; EMAR: Anal. Calc. para: $C_{47}H_{49}N_8O_7$ $(M+H)^+$ 837,3724; Encontrado: 837,3715 |

Ejemplo OL-9

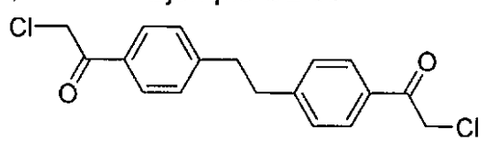


Ejemplo OL-9a



Se añadió paladio sobre carbono (10%, 300 mg) a una solución de 4,4'-(eteno-1,2-diil)dibenzoato de dimetilo (2g, 6,76 mmol) en metanol (100 ml). La suspensión se purgó con $N_2$, se introdujo en 1 atm de $H_2$ (globo) y se agitó a temperatura ambiente toda la noche. La mezcla después se filtró a través de una capa de tierra de diatomeas (CELITE®) y el disolvente se concentró a presión reducida. Se recuperó un sólido blanco (1,42 g) y se usó sin purificación adicional. RMN de $^1H$ (500 MHz, $CDCl_3$) δ ppm 2,98 (s, 4 H), 3,90 (s, 6 H), 7,18 (d, J=7,32 Hz, 4 H), 7,93 (d, J=7,32 Hz, 4 H). CL (Cond. 1): $T_R$ = 2,65 min; EMBR: Anal. Calc. para $C_{18}H_{19}O_4$ $(M+H)^+$ 299,13 Encontrado: 299,21.

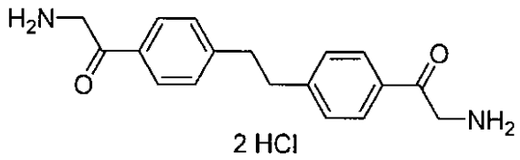
Ejemplo OL-9b



El Ejemplo OL-9b se preparó a partir del Ejemplo OL-9a, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1a. RMN de $^1H$ (500 MHz, $CDCl_3$) δ ppm 3,02 (s, 4 H), 4,67 (s, 4 H), 7,25 (d, J=8,24 Hz, 4,H),

7,86 (d, J=8,24 Hz, 4 H). CL (Cond. 2): $T_R$ = 0,62 min; CLEM: Anal. Calc. para $C_{18}H_{17}Cl_2O_2$ $(M+1)^+$ 335,06; Encontrado: 335,12.

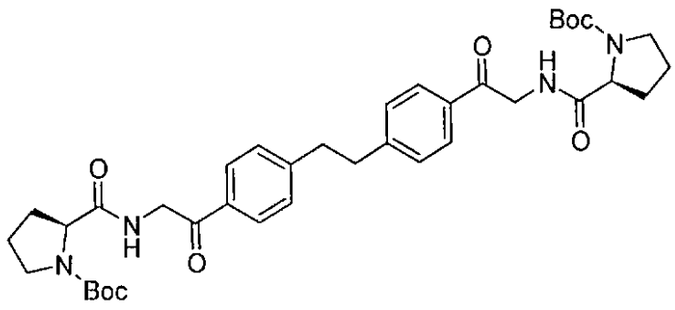
Ejemplo OL-9c




2 HCl

El Ejemplo OL-9c se preparó a partir del Ejemplo OL-9b, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1b. RMN de $^1H$ (500 MHz, DMSO-$d_6$) δ ppm 3,03 (s, 4 H), 4,51 (s, 4 H), 7,43 (d, J=8,55 Hz, 4 H), 7,92 (d, J=8,24 Hz, 4 H), 8,50 (s, 6 H). CL (Cond. 3): $T_R$ = 1,90 min; EMBR: Anal. Calc. para $C_{18}H_{21}N_2O_2$ $(M+H)^+$ 297,16 Encontrado: 297,24.

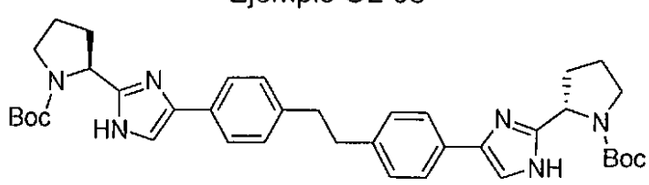
Ejemplo OL-9d




El Ejemplo OL-9d se preparó a partir del Ejemplo OL-9c, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1c. RMN de $^1H$ (500 MHz, $CDCl_3$) δ ppm 1,38 - 1,56 (m, 18 H), 1,83 - 2,00 (m, 4 H), 2,08 - 2,38 (m, 4 H), 3,01 (s, 4 H), 3,32 - 3,65 (m, 4 H), 4,28 (s ancho, 1 H), 4,39 (s ancho, 1 H), 4,63 - 4,71 (m, 2 H), 4,72 - 4,84 (m, J=4,58 Hz, 2 H), 7,01 (s, 1 H), 7,18 - 7,33 (m, 4 H), 7,47 (s, 1 H), 7,87 (d, J=7,93 Hz, 4 H). CL (Cond. 1): $T_R$ = 2,56 min; EMBR:

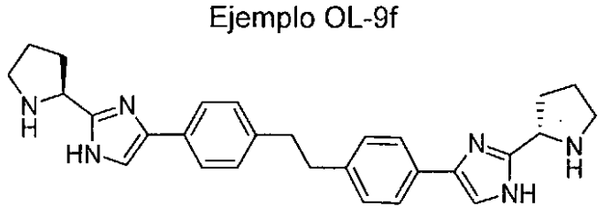
Anal. Calc. para $C_{38}H_{51}N_4O_8$ $(M+H)^+$ 691,37, Encontrado: 691,48.

Ejemplo OL-9e




El Ejemplo OL-9e se preparó a partir del Ejemplo OL-9d, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1d. RMN de $^1H$ (500 MHz, DMSO-$d_6$) δ ppm 1,15/1,39(rotámeros, s, 18 H), 1,75 - 1,92 (m, 3 H), 1,96 (s, 3 H), 2,09 - 2,27 (m, J=32,04 Hz, 2 H), 2,81 - 2,90 (m, 4 H), 3,31 - 3,40 (m, 2 H), 3,52 (s, 2 H), 4,66 - 4,88 (m, J=35,40 Hz, 2 H), 7,14 (d, J=7,02 Hz, 4 H), 7,21 (s, 1 H), 7,31 - 7,41 (m, 1 H), 7,51 (d, J=6,41 Hz, 1 H), 7,61 (d, J=7,93 Hz, 3 H), 11,62 - 12,08 (m, 2 H). CL (Cond. 1): $T_R$ = 2,20 min; EMBR: Anal. Calc. para $C_{38}H_{49}N_6O_4$ $(M+H)^+$ 653,38, Encontrado: 653,47.

Ejemplo OL-9f



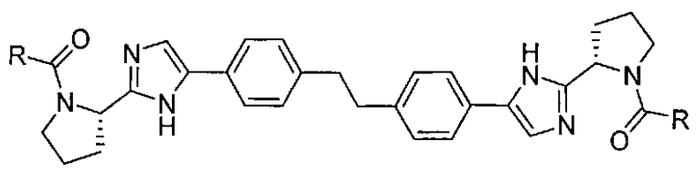

El Ejemplo OL-9f se preparó a partir del Ejemplo OL-9e, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1e. RMN de $^1H$ (500 MHz, DMSO-$d_6$) δ ppm 1,92 - 2,05 (m, 2 H), 2,11 - 2,25 (m, 2 H), 2,40 - 2,47 (m, 4 H), 2,89 - 3,03 (m, 4 H), 3,32 - 3,39 (m, 2 H), 3,40 - 3,49 (m, 2 H), 5,02 (t, J=7,78 Hz, 2 H), 7,32 (d, J=8,24 Hz, 4 H), 7,80 (d, J=8,24 Hz, 4 H), 9,91 (s, 2 H), 10,32 (s, 2 H). Nota: la señal del NH del imidazol era demasiado ancha para

asignarle un desplazamiento químico. CL (Cond. 5): $T_R$ = 2,52 min; EMBR: Anal. Calc. para $C_{28}H_{33}N_6$ $(M+H)^+$ 453,28, Encontrado: 453,31.

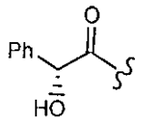
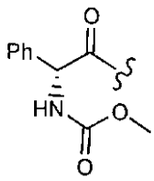
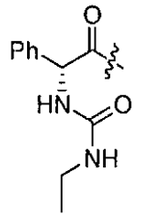
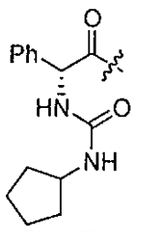
Ejemplo OL-9

El Ejemplo OL-9 se preparó a partir del Ejemplo OL-9f, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1. RMN de $^1H$ (500 MHz, DMSO-$d_6$) δ ppm 1,82 - 1,95 (m, 2 H), 1,97 - 2,10 (m, 4 H), 2,15 - 2,27 (m, J=4,58 Hz, 2 H), 2,28 - 2,45 (m, 4 H), 2,72 - 2,88 (m, 4 H), 2,94 (s, 5 H), 2,98 - 3,07 (m, 2 H), 3,97 (t, J=9,77 Hz, 2 H), 5,17 (d, J=6,10 Hz, 2 H), 5,41 (s, 2 H), 7,12 (s, 1 H), 7,38 (d, J=7,32 Hz, 4 H), 7,51 - 7,62 (m, 9 H), 7,69 (d, J=7,93 Hz, 4 H), 7,93 (s, 2 H). Nota: la señal del NH del imidazol era demasiado ancha para asignarle un desplazamiento químico. CL (Cond. 5): $T_R$ = 2,87 min; EMBR: Anal. Calc. para $C_{48}H_{55}N_8O_2$ $(M+H)^+$ 775,44 Encontrado: 775,51; EMAR: Anal. Calc. para $C_{48}H_{55}N_8O_2$ $(M+H)^+$ 775,4448 Encontrado: 775,4454.

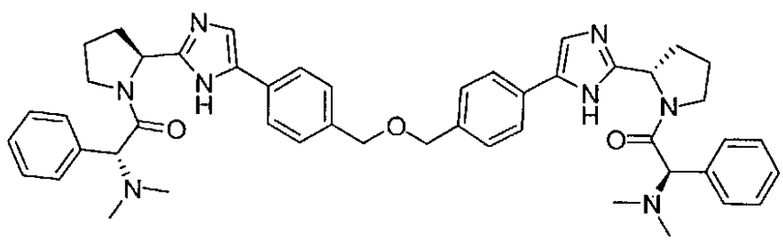
Ejemplos OL-10 a OL-13



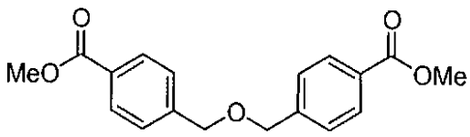
Los Ejemplos OL-10 a OL-13 se prepararon en forma de sales TFA sustituyendo los ácidos respectivos por Cap-1 de acuerdo con el mismo procedimiento descrito para el Ejemplo OL-9.

| Ejemplo |  Ácido | TR (Cond. de CL); Datos de EM |
|---|---|---|
| OL-10 |  Ácido mandélico | $T_R$ = 2,64 min. CL (Cond. 4); CLEM: Anal. Calc. para: $C_{44}H_{45}N_6O_4$ $(M+H)^+$ 721,35; Encontrado: 721,42; EMAR: Anal. Calc. para $C_{44}H_{45}N_6O_4$ $(M+H)^+$ 721,3502; Encontrado: 721,3518 |
| OL-11 |  Cap-4 | $T_R$ = 2,88 min. CL (Cond. 4); CLEM: Anal. Calc. para: $C_{48}H_{51}N_8O_6$ $(M+H)^+$ 835,39; Encontrado: 835,49; EMAR: Anal. Calc. para: $C_{48}H_{50}N_8O_6$ $(M+H)^+$ 835,3932; Encontrado: 835,3939 |
| OL-12 |  **Cap-46** | $T_R$ = 4,20 min. CL (Cond. 4); CLEM: Anal. Calc. para: $C_{50}H_{57}N_{10}O_4$ $(M+H)^+$ 861,45; Encontrado: 861,50; EMAR: Anal. Calc. para: $C_{50}H_{57}N_{10}O_4$ $(M+H)^+$ 861,4564; Encontrado: 861,4562 |
| OL-13 |  **Cap-48** | $T_R$ = 5,11 min. CL (Cond. 4); CLEM: Anal. Calc. para: $C_{56}H_{64}N_{10}O_4$ $(M+H)^+$ 941,52; Encontrado: 941,71; EMAR: Anal. Calc. para: $C_{56}H_{65}N_{10}O_4$ $(M+H)^+$ 941,5190; Encontrado: 941,5162 |

Ejemplo OL-14

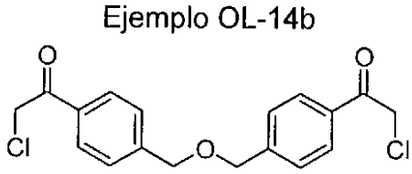


Ejemplo OL-14a



Se añadió trietilsilano (5,84 ml, 36,55 mmol) gota a gota a una solución de 4-formilbenzoato de metilo (5 g, 30,46 mmol) y tribromuro de bismuto (0,273 g, 0,61 mmol) en acetonitrilo (75 ml) y la solución opaca se agitó a temperatura ambiente durante 15 min. Los volátiles se eliminaron a presión reducida y el residuo restante se tomó en acetato de etilo. La fase orgánica después se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y se concentró a vacío. El sólido recuperado después se sometió a cromatografía ultrarrápida (gel de sílice; 10-20% de acetato de etilo/hexanos) proporcionando OL-14a (3,05 g). RMN de $^1H$ (500 MHz, $CDCl_3$) δ ppm 3,84 (s, 6 H), 4,65 (s, 4 H), 7,51 (d, J=8,24 Hz, 4 H), 7,95 (d, J=8,24 Hz, 4 H). CL (Cond. 2): $T_R$ = 1,68 min; CLEM: Anal. Calc. para $C_{18}H_{19}O_5$ $(M+H)^+$ 315,12; Encontrado: 315,26.

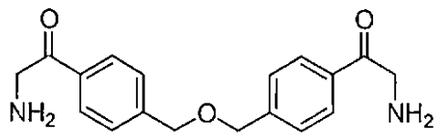
Ejemplo OL-14b



El Ejemplo OL-14b se preparó a partir del Ejemplo OL-14a, de acuerdo con el

mismo procedimiento que se usó para la preparación del Ejemplo OL-1a. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 4,67 (s, 4 H), 5,19 (s, 4 H), 7,55 (d, J=8,24 Hz, 4 H), 7,98 (d, J=8,24 Hz, 4 H). CL (Cond. 5): $T_R$ = 3,85 min; EMBR: Anal. Calc. para $C_{18}H_{17}Cl_2O_3$ $(M+H)^+$ 351,05, Encontrado: 351,06.

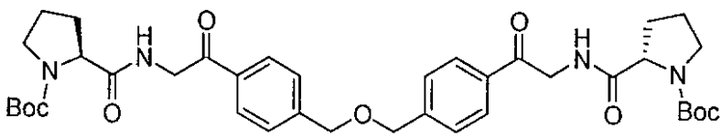
Ejemplo OL-14c



2 HCl

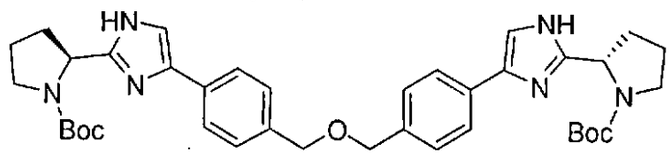
El Ejemplo OL-14c se preparó a partir del Ejemplo OL-14b, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1b. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 4,55 (s, 4 H), 4,69 (s, 4 H), 7,57 (d, J=8,24 Hz, 4 H), 8,02 (d, J=8,55 Hz, 4 H), 8,53 (s, 6 H). CL (Cond. 1): $T_R$ = 1,29 min; EMBR: Anal. Calc. para $C_{18}H_{21}N_2O_3$ $(M+H)^+$ 313,15, Encontrado: 313,21.

Ejemplo OL-14d



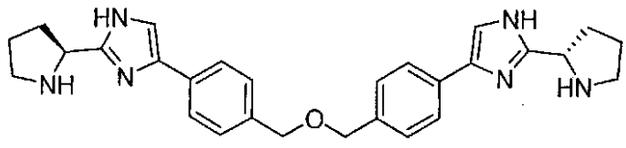
El Ejemplo OL-14d se preparó a partir del Ejemplo OL-14c, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1c. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 1,34/1,40 (rotámeros, s, 18 H), 1,70 - 1,92 (m, 6 H), 1,99 - 2,20 (m, 2 H), 3,24 - 3,33 (m, 2 H), 3,35 - 3,44 (m, 2 H), 4,11 - 4,25 (m, 2 H), 4,50 - 4,65 (m, 4 H), 4,66 (s, 4 H), 7,53 (d, J=8,24 Hz, 4 H), 7,99 (d, J=7,93 Hz, 4 H), 8,09 - 8,23 (m, 2 H). CL (Cond. 1): $T_R$ = 2,49 min; EMBR: Anal. Calc. para $C_{38}H_{51}N_4O_9$ $(M+H)^+$ 707,36 Encontrado: 707,50.

Ejemplo OL-14e




El Ejemplo OL-14e se preparó a partir del Ejemplo OL-14d, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1d. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 1,14/ 1,39 (rotámeros, s, 18 H), 1,76 - 2,06 (m, 6 H), 2,08 - 2,30 (m, 2 H), 3,31 - 3,41 (m, 2 H), 3,52 (s, 2 H), 4,49 (s, 4 H), 4,70 - 4,78 (m, 1 H), 4,79 - 4,90 (m, 1 H), 7,29/7,35 (rotámeros, d, J=7,93 Hz, 4 H), 7,40 - 7,54 (m, 2 H), 7,71/761 (rotámeros, d, J=7,93 Hz, 4 H), 11,72 - 12,19 (m, 2 H). CL (Cond. 1): $T_R$ = 2,14 min; EMBR: Anal. Calc. para $C_{38}H_{49}N_6O_5$ $(M+H)^+$669,38, Encontrado: 669,53.

Ejemplo OL-14f

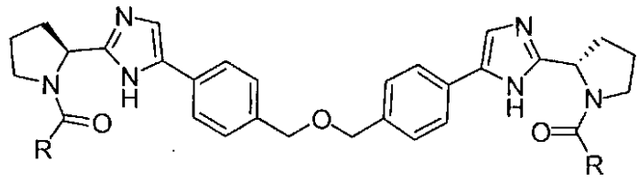



El Ejemplo OL-14f se preparó a partir del Ejemplo OL-14e, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1e. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 1,94 - 2,06 (m, 2 H), 2,11 - 2,25 (m, 2 H), 2,38 - 2,48 (m, 4 H), 3,32 - 3,50 (m, 4 H), 4,60 (s, 4 H), 4,92 - 5,06 (m, 2 H), 7,48 (d, J=7,93 Hz, 4 H), 7,89 (d, J=7,93 Hz, 4 H), 8,04 (s, 2 H), 9,78 (s, 2 H), 10,28 (s, 2 H). Nota: la señal del NH del imidazol era demasiado ancha para asignarle un desplazamiento químico. CL (Cond. 1): TR =1,69 min; EMBR: Anal. Calc. para $C_{28}H_{33}N_6O$ $(M+H)^+$ 469,27 Encontrado: 469,34.

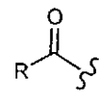
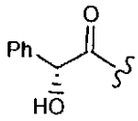
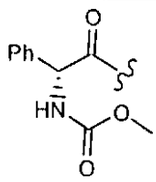
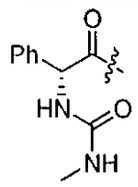
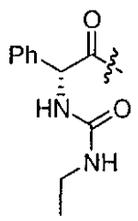
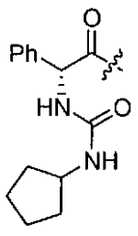
Ejemplo OL-14

El Ejemplo OL-14 se preparó a partir del Ejemplo OL-14f, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 1,82 - 2,11 (m, 6 H), 2,18 (d, J=6,10 Hz, 2 H), 2,31 - 2,47 (m, 4 H), 2,98 - 3,10 (m, 2 H), 3,92 - 4,07 (m, 2 H), 4,59 (s, 4 H), 5,10 - 5,22 (m, 2 H), 5,42 (s, 2 H), 7,07 - 7,13 (m, 2 H), 7,40 - 7,51 (m, 4 H), 7,54 - 7,67 (m, 10 H), 7,75 (d, J=7,32 Hz, 4 H). Nota: la señal del NH del imidazol era demasiado ancha para asignarle un desplazamiento químico. Las señales para los grupos Me del cap quedaron por debajo del pico del disolvente. CL (Cond. 4): $T_R$ = 1,83 min; EMBR: Anal. Calc. para $C_{48}H_{55}N_8O_3$ $(M+H)^+$ 791,44; Encontrado: 791,60. EMAR: Anal. Calc. para $C_{48}H_{55}N_8O_3$ $(M+H)^+$ 791,4397; Encontrado: 791,4406.

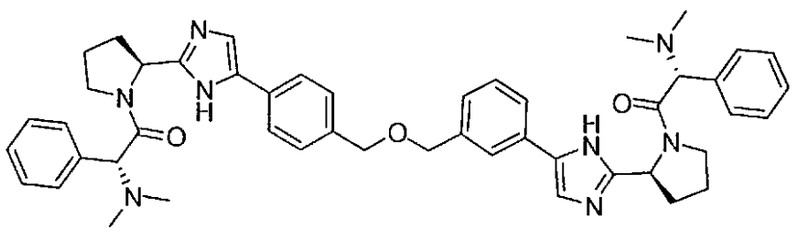
Ejemplos OL-15 a OL-19



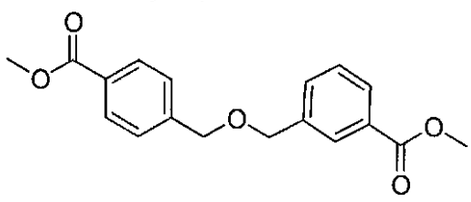
Los Ejemplos OL-15 a OL-19 se prepararon en forma de sales TFA sustituyendo los ácidos respectivos por Cap-1 de acuerdo con el mismo procedimiento descrito para el Ejemplo OL-14.

| Ejemplo |  Ácido | TR (Cond. de CL); Datos de EM |
|---|---|---|
| OL-15 |  Ácido mandélico | $T_R$ = 2,86 min. CL (Cond. 4); CLEM: Anal. Calc. para: $C_{44}H_{45}N_6O_5$ $(M+H)^+$ 737,34; Encontrado: 737,38; EMAR: Anal. Calc. para: $C_{44}H_{45}N_6O_5$ $(M+H)^+$ 737,3451; Encontrado: 737,3452 |
| OL-16 |  Cap-4 | $T_R$ = 3,45 min. CL (Cond. 4); CLEM: Anal. Calc. para: $C_{48}H_{51}N_8O_7$ $(M+H)^+$ 851,39; Encontrado: 851,40; EMAR: Anal. Calc. para: $C_{48}H_{51}N_8O_7$ $(M+H)^+$ 851,3881; Encontrado: 851,3910 |
| OL-17 |  Cap-45a | $T_R$ = 1,16 min. CL (Cond. 2); CLEM: Anal. Calc. para: $C_{48}H_{53}N_{10}O_5$ $(M+H)^+$ 849,42; Encontrado: 849,61; EMAR: Anal. Calc. para: $C_{48}H_{53}N_{10}O_5$ $(M+H)^+$ 849,4200; Encontrado: 849,4182 |
| OL-18 |  Cap-46 | $T_R$ = 1,24 min. CL (Cond. 2); CLEM: Anal. Calc. para: $C_{50}H_{56}N_{10}O_5$ $(M+H)^+$ 877,45; Encontrado: 877,70; EMAR: Anal. Calc. para: $C_{50}H_{57}N_{10}O_5$ $(M+H)^+$ 877,4513; Encontrado: 877,4506 |
| OL-19 |  Cap-48 | $T_R$ = 1,43 min. CL (Cond. 2); CLEM: Anal. Calc. para: $C_{56}H_{65}N_{10}O_5$ $(M+H)^+$ 957,51; Encontrado: 957,84; EMAR: Anal. Calc. para: $C_{56}H_{65}N_{10}O_5$ $(M+H)^+$ 957,5139; Encontrado: 957,5142 |

Ejemplo OL-20

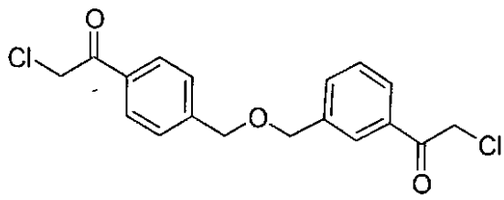


Ejemplo OL-20a



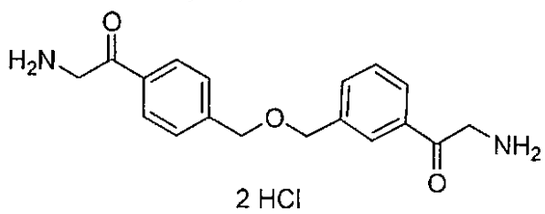
Se añadió hidruro sódico (0,76 g, 18,95 mmol, 60% en peso) lentamente a una solución de 4-(hidroximetil)benzoato de metilo (3 g, 18,05 mmol) en dimetilformamida (25 ml). La solución azul oscuro resultante se agitó a temperatura ambiente durante 15 min y se añadió 3-(bromometil)benzoato de metilo (3,76g, 16,41 mmol) en una porción. La solución amarilla resultante se agitó a temperatura ambiente durante 1 h y después se eliminaron las sustancias volátiles a presión reducida. El residuo se tomó en acetato de etilo y se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y se concentró a vacío. El residuo se sometió a cromatografía ultrarrápida (gel de sílice; 20% de acetato de etilo/hexanos) proporcionando el Ejemplo OL-20a en forma de un aceite transparente que solidificó al reposar (2,49 g). RMN de $^1H$ (300 MHz, $CDCl_3$) δ ppm 3,91 (d, J=1,83 Hz, 6 H), 4,61 (d, J=2,56 Hz, 4 H), 7,39 - 7,49 (m, 3 H), 7,54 - 7,61 (m, 1 H), 7,93 - 8,00 (m, 1 H), 7,99 - 8,07 (m, 3 H). CL (Cond. 1): TR =2,56 min; EMBR: Anal. Calc. para $C_{18}H_{19}O_5$ $(M+H)^+$ 315,12 Encontrado: 315,22.

Ejemplo OL-20b



El Ejemplo OL-20b se preparó a partir del Ejemplo OL-20a, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1a. RMN de $^1$H (500 MHz, $CDCl_3$) δ ppm 4,65 (d, J=4,58 Hz, 4 H), 4,69 (d, J=3,36 Hz, 4 H), 7,47 - 7,54 (m, J=7,63, 7,63 Hz, 3 H), 7,62 (d, J=7,63 Hz, 1 H), 7,89 (d, J=7,93 Hz, 1 H), 7,93 - 8,00 (m, 3 H). CL (Cond. 1): TR =2,34 min; EMBR: Anal. Calc. para $C_{18}H_{17}Cl_2O_3$ $(M+H)^+$ 351,05 Encontrado: 351,12.

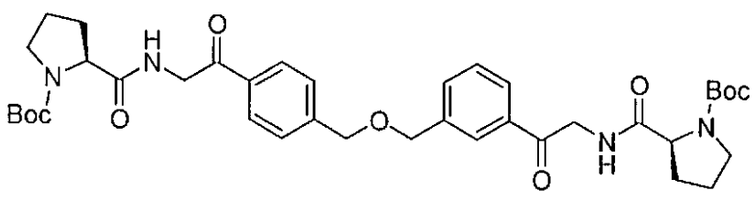
Ejemplo OL-20c



2 HCl

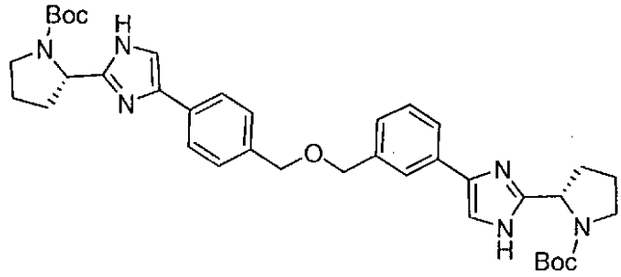
El Ejemplo OL-20c se preparó a partir del Ejemplo OL-20b, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1b. RMN de $^1$H (300 MHz, DMSO-$d_6$) δ ppm 4,57 (d, J=2,93 Hz, 4 H), 4,68 (d, J=5,85 Hz, 4 H), 7,52 - 7,67 (m, J=8,60, 8,60 Hz, 3 H), 7,73 (d, J=7,68 Hz, 1 H), 7,90 - 8,10 (m, 4 H), 8,53 (s, 6 H). CL (Cond. 1): TR =1,32 min; EMBR: Anal. Calc. para $C_{18}H_{21}N_2O_3$ $(M+H)^+$ 313,15 Encontrado: 313,24.

Ejemplo OL-20d



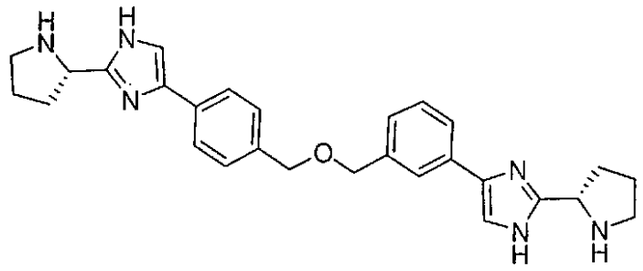
El Ejemplo OL-20d se preparó a partir del Ejemplo OL-20c, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1c. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 1,39/1,34 (rotámeros, s, 18 H), 1,69 - 1,95 (m, 6 H), 2,00 - 2,18 (m, J=23,80 Hz, 2 H), 3,23 - 3,33 (m, 2 H), 3,34 - 3,43 (m, 2 H), 4,11 - 4,23 (m, 2 H), 4,50 - 4,63 (m, 4 H), 4,65 (d, J=6,71 Hz, 4 H), 7,48 - 7,56 (m, 3 H), 7,66 (d, J=7,63 Hz, 1 H), 7,89 - 8,02 (m, 4 H), 8,06 - 8,25 (m, 2 H). CL (Cond. 1): TR =2,53 min; EMBR: Anal. Calc. para $C_{38}H_{51}N_4O_9$ $(M+H)^+$ 707,36 Encontrado: 707,44.

Ejemplo OL-20e



El Ejemplo OL-20e se preparó a partir del Ejemplo OL-20d, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1d. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 1,14/1,39 (rotámeros, s, 18 H), 1,76 - 2,07 (m, 6 H), 2,08 - 2,29 (m, 2 H), 3,31 - 3,40 (m, 2 H), 3,52 (s ancho, 2 H), 4,44 - 4,59 (m, J=8,55 Hz, 4 H), 4,75 (s ancho, 1 H), 4,83 (s ancho, 1 H), 7,08 - 7,23 (m, 2 H), 7,30 (d, J=7,63 Hz, 2 H), 7,34 - 7,50 (m, 2 H), 7,53 - 7,67 (m, 1 H), 7,68 - 7,79 (m, 3 H), 11,70 - 12,22 (m, 2 H). CL (Cond. 1): TR =2,19 min; EMBR: Anal. Calc. para $C_{38}H_{48}N_6O_5$ $(M+H)^+$ 669,39, Encontrado: 669,40.

Ejemplo OL-20f



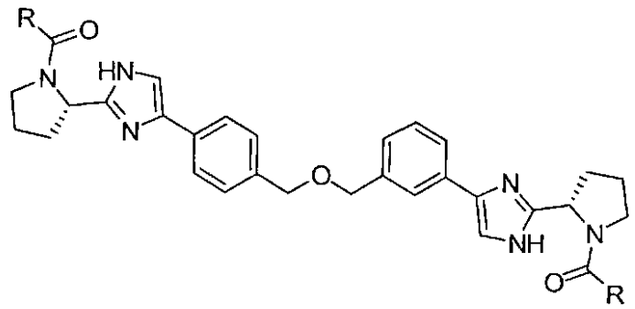
El Ejemplo OL-20f se preparó a partir del Ejemplo OL-20e, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1e. RMN de $^1$H (500 MHz, DMSO-D6) δ ppm 1,94 - 2,08 (m, 2 H), 2,12 - 2,24 (m, 2 H), 2,39 - 2,48 (m, J=5,19 Hz, 4 H), 3,27 - 3,49 (m, 4 H), 4,61 (d, J=4,88 Hz, 4 H), 4,94 - 5,09 (m, J=7,93 Hz, 2 H), 7,38 (d, J=7,32 Hz, 1 H), 7,45 - 7,53 (m, 3 H), 7,83 (d, J=7,63 Hz, 1 H), 7,90 (d, J=7,02 Hz, 3 H), 8,07 (s, 2 H), 9,86 (s ancho, 2 H), 10,33 (s ancho, 2 H). Nota: la señal del NH del imidazol era demasiado ancha para asignarle un desplazamiento químico. CL (Cond. 1): $T_R$ = 1,75 min; EMBR: Anal. Calc. para $C_{28}H_{32}N_6O$ $(M+H)^+$ 469,27, Encontrado: 469,23.

Ejemplo OL-20

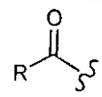
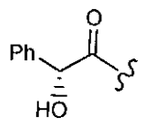
El Ejemplo OL-20 se preparó a partir del Ejemplo OL-20f, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 1,84 - 1,95 (m, J=5,19 Hz, 2 H), 1,95 - 2,09 (m, J=8,24 Hz, 4 H), 2,15 - 2,28 (m, 2 H), 3,02 (q, J=7,73 Hz, 2 H), 3,93 - 4,05 (m, 2 H), 4,61 (s ancho, 4 H), 5,12 - 5,22 (m, 2 H), 5,42 (br.s, 2 H), 7,12 (s ancho, 1 H), 7,39 (s, 1 H), 7,45 - 7,51 (m, J=7,32 Hz, 3 H), 7,53 - 7,64 (m, 9 H), 7,66 - 7,82 (m, 4 H), 7,96 (s, 2 H). Nota: la señal del NH del imidazol era demasiado ancha para asignarle un

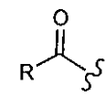
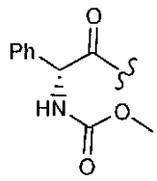
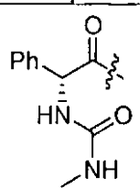
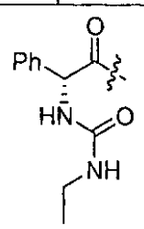
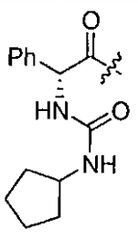
desplazamiento químico. Las señales para los grupos Me del cap quedaron por debajo del pico del disolvente. CL (Cond. 4): $T_R$ = 1,93 min; EMBR: Anal. Calc. para $C_{48}H_{55}N_8O_3$ $(M+H)^+$ 791,44; Encontrado: 791,57. EMAR: Anal. Calc. para $C_{48}H_{55}N_8O_3$ $(M+H)^+$. 791,4397; Encontrado: 791,4373.

Ejemplos OL-21 a OL-25

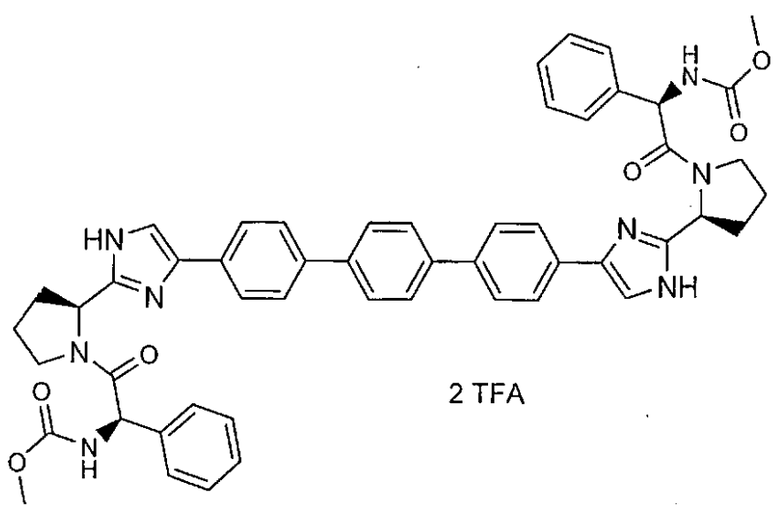


Los Ejemplos OL-21 a OL-25 se prepararon en forma de sales TFA sustituyendo los ácidos respectivos por Cap-1 de acuerdo con el mismo procedimiento descrito para el Ejemplo OL-20.

| Ejemplo |  Ácido | TR (Cond. de CL); Datos de EM |
|---|---|---|
| OL-21 |  Ácido mandélico | $T_R$ = 2,97 min. CL (Cond. 4); CLEM: Anal. Calc. para: $C_{44}H_{45}N_6O_5$ $(M+H)^+$ 737,34; Encontrado: 737,46; EMAR: Anal. Calc. para: $C_{44}H_{45}N_6O_5$ $(M+H)^+$ 737,3451; Encontrado: 737,3459 |

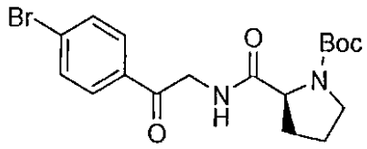
| Ejemplo |  Ácido | TR (Cond. de CL); Datos de EM |
|---|---|---|
| OL-22 |  Cap-4 | $T_R$ = 3,59 min. CL (Cond. 4); CLEM: Anal. Calc. para: $C_{48}H_{51}N_8O_7$ $(M+H)^+$ 851,38; Encontrado: 851,50; EMAR: Anal. Calc. para: $C_{48}H_{51}N_8O_7$ $(M+H)^+$ 851,3881; Encontrado: 851,3893 |
| OL-23 |  Cap-45a | $T_R$ = 1,15 min. CL (Cond. 2); CLEM: Anal. Calc. para: $C_{48}H_{52}N_{10}O_5$ $(M+H)^+$ 849,42; Encontrado: 849,46; EMAR: Anal. Calc. para: $C_{48}H_{53}N_{10}O_5$ $(M+H)^+$ 849,4200; Encontrado: 849,4185 |
| OL-34 |  Cap-46 | $T_R$ = 1,24 min. CL (Cond. 2); CLEM: Anal. Calc. para: $C_{50}H_{56}N_{10}O_5$ $(M+H)^+$ 877,45 Encontrado: 877,69; EMAR: Anal. Calc. para: $C_{50}H_{57}N_{10}O_5$ $(M+H)^+$ 877,4513; Encontrado: 877,4510 |
| OL-25 |  Cap-48 | $T_R$ = 4,89 min. CL (Cond. 4); CLEM: Anal. Calc. para: $C_{56}H_{64}N_{10}O_5(M+H)^+$ 957,51; Encontrado: 957,82; EMAR: Anal. Calc. para: $C_{56}H_{65}N_{10}O_5$ $(M+H)^+$ 957,5139; Encontrado: 957,5150 |

Ejemplo D-1



2 TFA

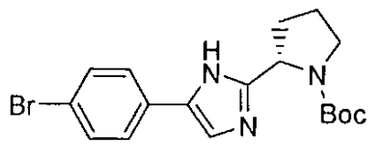
Ejemplo D-1, etapa a



Se añadió *N,N*-diisopropiletilamina (18 ml, 103,3 mmol) gota a gota, durante 15 minutos, a una mezcla heterogénea de *N*-Boc-L-prolina (7,14 g, 33,17 mmol), HATU (13,32 g, 35,04 mmol), la sal HCl de 2-amino-1-(4-bromofenil)etanona (8,13 g, 32,44 mmol), y DMF (105 ml), y se agitó en condiciones ambientales durante 55 minutos. La mayoría de los componentes volátiles se eliminaron a vacío, y el residuo resultante se fraccionó entre acetato de etilo (300 ml) y agua (200 ml). La fase orgánica se lavó con agua (200 ml) y salmuera, se secó ($MgSO_4$), se filtró, y se concentró a vacío. Se preparó una malla de gel de sílice a partir del residuo y se sometió a cromatografía ultrarrápida (gel de sílice; 50-60 % de acetato de etilo/hexanos) proporcionando D-1a en forma de un sólido blanco (12,8 g). RMN de $^1H$ (500 MHz, DMSO-$d_6$) δ ppm 1,40/1,34 (dos ap br s, 9 H), 1,90-1,70 (m, 3 H), 2,18-2,20 (m, 1 H), 3,30-3,23 (m, 1 H), 3,43-3,35 (m, 1 H), 4,22-4,12 (m, 1 H), 4,53

(dd, *J*=18,1, 5,6, 1 H), 4,61 (dd, *J*=18,3, 5,7, 1 H), 7,75 (d ancho, *J*=8,6, 2 H), 7,92 (d ancho, *J*=8,0, 2 H), 8,25-8,14 (m, 1H). CL (Cond. 7): $T_R$ = 1,70 min; EMBR: Anal. Calc. para $(M+Na)^+$ $C_{18}H_{23}BrN_2NaO_4$: 433,07 encontrado 433,09.

Ejemplo D-1, etapa b




Una mezcla de D-1a (12,8 g, 31,12 mmol) y $NH_4OAc$ (12,0 g, 155,7 mmol) en xilenos (155 ml) se calentó en un tubo sellado a 140 °C durante 2 horas. El componente volátil se eliminó a vacío, y el residuo se fraccionó cuidadosamente entre acetato de etilo y agua, después de lo cual se añadió suficiente solución saturada de $NaHCO_3$ para hacer que el pH de la fase acuosa fuera ligeramente básico después de agitar el sistema bifásico. Las fases se separaron, y la fase acuosa se extrajo con más acetato de etilo. La fase orgánica combinada se lavó con salmuera, se secó ($MgSO_4$), se filtró, y se concentró a vacío. El material resultante se recristalizó de acetato de etilo/hexanos proporcionando dos cosechas de imidazol D-1b en forma de un sólido denso, amarillo claro que pesaba 5,85 g. El licor madre se concentró a vacío y se sometió a una cromatografía ultrarrápida (gel de sílice; 30% de acetato de etilo/hexanos) proporcionando un 2,23 g más del Ejemplo D-1b. RMN de $^1H$ (500 MHz, DMSO-$d_6$) δ ppm 1,40/1,15 (s ancho aparente, 9 H), 2,30-1,75 (m, 4 H), 3,36 (m, 1 H), 3,52 (s ancho aparente, 1 H), 4,86-4,70 (m, 1 H), 7,72-7,46/7,28 (m, 5 H), 12,17/11,92/11,86 (m, 1 H). CL (Cond. 7): $T_R$ = 1,71 min; EMBR: Anal. Calc. para $[M+H]^+$ $C_{18}H_{23}BrN_3O_2$: 392,10; encontrado 391,96; EMAR: Anal. Calc. para $[M+H]^+$ $C_{18}H_{23}BrN_3O_2$: 392,0974; encontrado 392,0959.

Se evaluó la pureza óptica de las dos muestras del Ejemplo D-1b de acuerdo con las condiciones de HPLC siguientes (ee > 99% para las cosechas combinadas; ee = 96,7% para la muestra de la cromatografía ultrarrápida):

Columna: Chiralpak AD, 10 µm, 4,6 x 50 mm

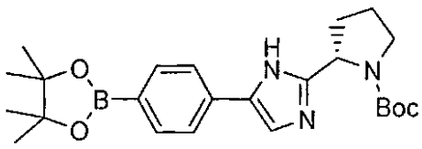
Disolvente: 2% de etanol/heptano (isocrático)

Caudal: 1 ml/min

Longitud de onda: 220 ó 254 nm

Tiempo de retención relativo: 2,83 minutos (*R*), 5,34 minutos (*S*).

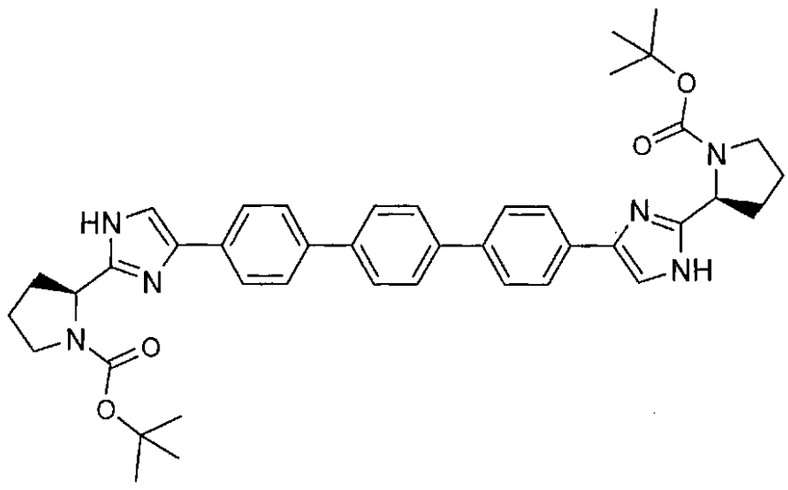
Ejemplo D-1, etapa c




Se añadió $Pd(Ph_3P)_4$ (469 mg, 0,41 mmol) a un tubo a presión que contenía una mezcla de D-1b (4,01 g, 10,22 mmol), bis(pinacolato)diboro (5,42 g, 21,35 mmol), acetato potásico (2,57 g, 26,21 mmol) y 1,4-dioxano (80 ml). El tubo a presión se purgó con nitrógeno, se tapó y se calentó en un baño de aceite a 80 °C durante 16,5 horas. La mezcla de reacción se filtró y el filtrado se concentró a vacío. El residuo en bruto se fraccionó cuidadosamente entre $CH_2Cl_2$ (150 ml) y un medio acuoso (50 ml de agua y 10 ml de solución saturada de $NaHCO_3$). La fase acuosa se extrajo con $CH_2Cl_2$, y la fase orgánica combinada se secó ($MgSO_4$), se filtró, y se concentró a vacío. El material resultante se purificó con cromatografía ultrarrápida (la muestra se cargó con disolvente de elución; 20-35% de acetato de etilo/$CH_2Cl_2$) proporcionando el Ejemplo D-1c, contaminado con pinacol, en forma de un sólido denso blanquecino; la proporción molar relativa entre el Ejemplo D-1c y pinacol era

de aproximadamente 10:1 (RMN de $^1$H). La muestra pesaba 3,925 g después de ~2,5 días de exposición a vacío elevado. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 1,45-1,10 (m, 21H), 2,27-1,77 (m, 4H), 3,36 (m, 1H), 3,52 (s ancho aparente, 1H), 4,86-4,70 (m, 1H), 7,79-7,50/ 7,34-7,27 (m, 5H), 12,22/11,94/ 11,87 (m, 1H). CL (Cond. 7): $T_R$ = 1,64 min; EMBR: Anal. Calc. para $[M+H]^+$ $C_{24}H_{35}BN_3O_4$: 440,27; encontrado 440,23.

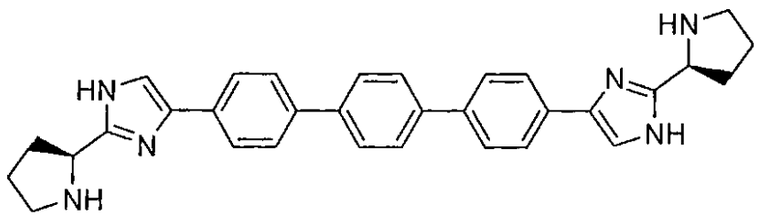
Ejemplo D-1, etapa d



Se añadió tetrakistrifenilfosfina paladio (17,5 mg, 0,015 mmol) en una porción a una suspensión en agitación de D-1c (320 mg, 0,85 mmol), 1,4- diyodobenceno (100 mg, 0,30 mmol) y bicarbonato sódico (180 mg, 2,18 mmol) en dimetoxietano (2,4 ml) y agua (7 ml) y se calentó a 90 °C durante 2 h. La reacción se diluyó con acetato de etilo y se lavó con bicarbonato sódico saturado. La fase orgánica se secó sobre sulfato sódico, se filtró y se concentró a vacío. El filtrado se tomó en metanol, se filtró a través de un filtro de jeringuilla de nylon y después se purificó mediante HPLC preparativa proporcionando D-1d en forma de un sólido blanco (101,1 mg, 20% de rendimiento). RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 1,17 (s

ancho, 9 H), 1,41 (s ancho, 9 H), 1,80 - 2,06 (m, 4 H), 2,13 - 2,32 (m, 4 H), 3,35 - 3,43 (m, 2 H), 3,56 (br. s., 2 H), 4,80 (s ancho, 2 H), 7,54 (d, *J*=10,07 Hz, 2 H), 7,73 (d, *J*=7,63 Hz, 4 H), 7,79 (s, 4 H), 7,83 (d, *J*=8,24 Hz, 4 H). CL (Cond. 6): $T_R$ = 2,55 min; EMAR: Anal. Calc. para $(M+H)^+$ $C_{42}H_{49}N_6O_4$ 701,3815; Encontrado: 701,3790.

Ejemplo D-1, etapa e



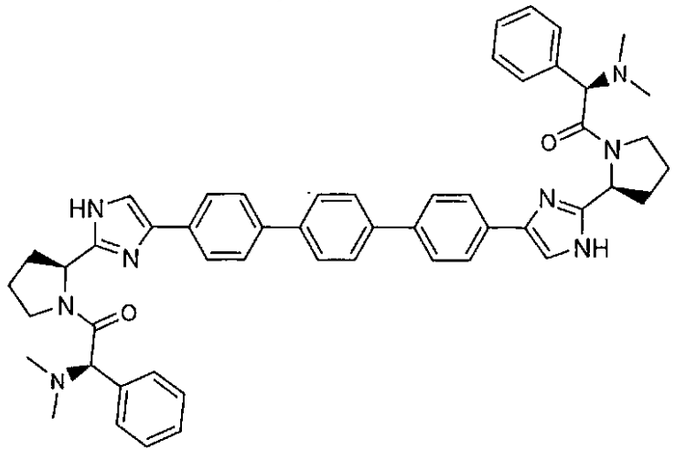

D-1e se preparó a partir de D-1d, de acuerdo con el mismo procedimiento que se usó para la preparación de OL-1e excepto que se usó metanol (1 ml) en lugar de diclorometano. Esto proporcionó D-1e en forma de un sólido tostado y en forma de una sal clorhidrato (101,5 mg, 96 % de rendimiento). RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 1,93 - 2,30 (m, 9 H), 2,32 - 2,44 (m, 3 H), 4,69 - 4,86 (m, 2 H), 7,68 - 7,87 (m, 12 H), 7,90 (d, *J* = 8,24 Hz, 2 H), 9,48 - 9,75 (m, 2 H). CL (*Cond. 6*): $T_R$ = 1,99 min; EMAR: Anal. Calc. para $(M+H)^+$ $C_{32}H_{33}N_6$ 501,2767; Encontrado: 501,2753.

Ejemplo D-1

El Ejemplo D-1 (sal TFA) se preparó a partir de D-1e, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1. Esto proporcionó el Ejemplo D-1 en forma de un sólido tostado (37,8 mg, 54 % de rendimiento). RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 2,05 (d, *J*=8,55 Hz, 8 H), 3,49 - 3,57 (m, 10 H), 3,94 (s ancho, 2 H), 5,52 (d, *J*=7,63 Hz, 2 H), 7,31 - 7,47 (m, 10 H),

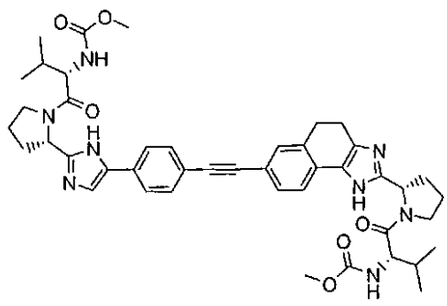
7,72 (d, *J*=7,02 Hz, 2 H), 7,87 - 8,01 (m, 12 H). CL (*Cond. 6*): $T_R$ = 2,41 min; EMAR: Anal. Calc. para $(M+H)^+$ $C_{52}H_{51}N_8O_6$ 883,3932; Encontrado: 883,3947.

Ejemplo D-2

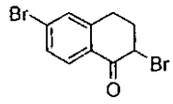


El Ejemplo D-2 (sal TFA) se preparó a partir de la pirrolidina D-1e, de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1. Esto proporcionó el Ejemplo D-2 en forma de un sólido amarillo claro (15,4 mg, 38% de rendimiento). RMN de $^1H$ (500 MHz, DMSO-$d_6$) δ ppm 2,50-1,70 (m, 14 H), 2,98-2,62 (m, 6 H), 4,05-2,98 (m, 4 H), 5,79-5,12 (m, 4 H), 8,20-7,10 (m, 24 H), 10,25 (s ancho, 2 H). Nota: la señal del NH del imidazol era demasiado ancha para asignarle un desplazamiento químico. CL (*Cond. 6*): $T_R$ = 2,08 min; EMAR: Anal. Calc. para $(M+H)^+$ $C_{52}H_{55}N_8O_2$ 823,4448; Encontrado: 823,4467.

Ejemplo D-3



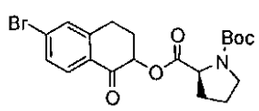
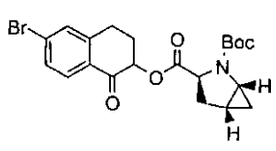
Ejemplo D-3, etapa a



Se añadió gota a gota una solución de bromo (683 µl, 13,33 mmol) en ácido acético (7 ml) a una solución fría (10 °C) de 6-bromo-3,4-dihidronaftalen-1(2*H*)-ona (adquirido en *J* & W Pharmlab, LLC) (3,00 g, 13,33 mmol) y 48% de bromuro de hidrógeno (20 µl, 13,33 mmol) en ácido acético (120 ml). La mezcla se dejó calentar temperatura ambiente después de completar la adición y se dejó agitar a temperatura ambiente durante 1 h antes de diluir con diclorometano y se lavó con agua (3x), solución saturada de bicarbonato sódico, se secó sobre sulfato sódico anhidro y se concentró. Se aisló D-3a (4,19 g, 97% de rendimiento) en forma de un aceite incoloro que solidificó al reposar a vacío elevado proporcionando un sólido blanco. Este material se usó sin purificación adicional. RMN de $^1$H (500 MHz, *DMSO-d*$_6$) δ ppm 7,85 (1 H, d, *J*=8,5 Hz), 7,71 (1 H, s), 7,62 (1 H, dd, *J*=8,5, 1,8 Hz), 5,06 (1 H, dd, *J*=6,1, 3,7 Hz), 2,93 - 3,15 (2 H, m), 2,55 - 2,64 (1 H, m), 2,32 - 2,42 (1 H, m). $T_R$ = 2,67 min (Cond. 6); CL/EM: Anal. Calc. para $[M+H]^+$ $C_{10}H_9{}^{79}Br_2O$: 304,90; Encontrado: 304,91.

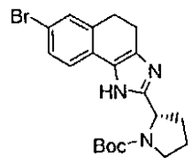
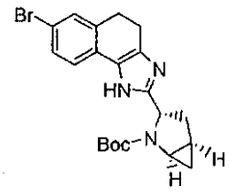
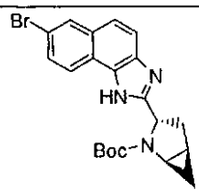
Ejemplos D-3b1 y D-3b2 (etapa b)

D-3b1 y D-3b2 se prepararon a partir de D-3a y las prolinas protegidas con Boc apropiadas de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo M3, etapa g.

| | | |
|---|---|---|
| **D-3b1** |  | **$T_R$ = 3,00 y 3,19 min (Cond. 3); CL/EM: Anal. Calc. para $[M+Na]^+$ $C_{20}H_{25}{}^{79}BrNO_5$: 460,08; Encontrado: 460,10.** |
| **D-3b2** |  | **$T_R$ = 2,99 y 3,17 min (Cond. 3), CLEM: Calc para $C_{21}H_{25}{}^{79}BrNO_5$ $[M+Na]^+$ 472,07; Encontrado: 472,10** |

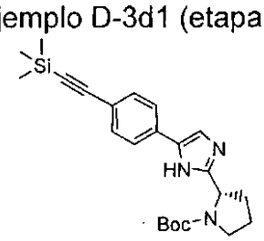
Ejemplos D-3c1 y D-3c2 (etapa c)

D-3c1 y D-3c2 se prepararon a partir de D-3b1 y D-3b2 respectivamente de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo M3, etapa h.

| | | |
|---|---|---|
| D-3c1 |  A partir de D-3b1 | RMN de $^1$H (500 MHz, *MeOD,* falta el N-H del imidazol) δ ppm 7,32 - 7,43 (3 H, m), 4,86 -4,97 (1 H, m), 3,63 - 3,74 (1 H, m), 3,47 - 3,57 (1 H, m), 2,98 - 3,07 (2 H, m), 2,83 (2 H, d, *J*=8,2 Hz), 2,25 - 2,45 (1 H, m), 2,00 - 2,11 (2 H, m), 1,93 - 1,99 (1 H, m), 1,25 - 1,48 (9 H, 2s). $T_R$ = 2,24 min (Cond. 3); CL/EM: Anal. Calc. para $[M+H]^+$ $C_{20}H_{25}{}^{79}BrN_3O_2$: 418,13; Encontrado: 418,10. EMAR: Anal. Calc. para $[M+H]^+$ $C_{21}H_{25}{}^{79}BrN_3O_2$: 430,1125; encontrado 430,1124. |
| D-3c2 |  A partir de D-3b2 | $T_R$ = 2,28 min (Cond. 3); CL/EM: Anal. Calc. para $[M+H]^+$ $C_{21}H_{25}{}^{79}BrN_3O_2$: 430,11; Encontrado: 430,16. EMAR: Anal. Calc. para $[M+H]^+$ $C_{21}H_{25}{}^{79}BrN_3O_2$: 430,1125; encontrado 430,1123. |
| D-3c3 |  Preparado a partir de D- | $T_R$ = 2,06 min (Cond. 3); CL/EM: Anal. Calc para $C_{21}H_{23}{}^{81}BrN_3O_2$ $(M+H)^+$ 430,10; Encontrado: 429,98. |

| | | |
|---|---|---|
| | **3c2 de acuerdo con el mismo procedimiento que se usó para la preparación de D-3g1** | |

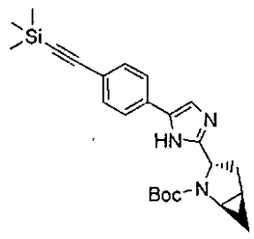
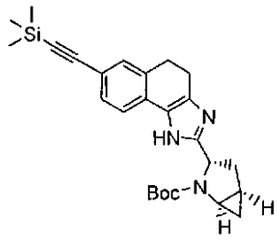
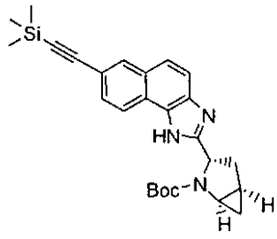
Ejemplo D-3d1 (etapa d)



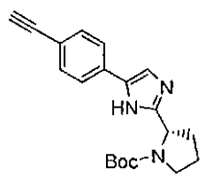

Se añadió etiniltrimetilsilano (0,59 ml, 4,25 mmol) a una solución de D-1b (1,5 g, 3,82 mmol), trifenilfosfina (0,20 g, 0,77 mmol), dietilamina (4,25 ml, 40,70 mmol), yoduro de cobre (I) (40 mg, 0,21 mmol) y *trans*-dicloro(bis-trifenilfosfina)paladio (II) (149 mg, 0,21 mmol) en DMF seca (1,4 ml) a temperatura ambiente en un recipiente microondas. El recipiente se tapó y se radió durante 25 min a 120 °C. Se realizaron dos reacciones idénticas de 1,5 g en tándem. Las mezclas de reacción se diluyeron con éter y acetato de etilo, se combinaron y se agitaron con HCl 0,1*N*. Después de reposar durante 20 min, la suspensión se filtró por succión y la capa se lavó con éter y acetato de etilo. La fase orgánica después se separó, se lavó con salmuera, se secó sobre sulfato sódico, y se concentró. Se aisló el producto en bruto (4,2 g) en forma de una espuma marrón rojiza que se tomó en diclorometano y se añadió directamente a una columna Thompson de 110 g de gel de sílice. La elución en gradiente del residuo con 20% de acetato de etilo en diclorometano a 100% de acetato de etilo proporcionó D-3d1 (2,8 g, 40% de rendimiento) en forma de un sólido amarillo después de la evaporación del eluyente que se llevó a la siguiente

etapa directamente. $T_R$ = 2,37 min (Cond. 3); CL/EM: Anal. Calc para $C_{23}H_{32}N_3O_2Si$ $[M+H]^+$ 410,23; Encontrado: 410,12.

D-3d2 a D-3d4 se prepararon de acuerdo con los procedimientos que se describen para D-3d1.

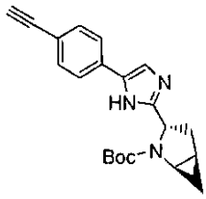
| | | |
|---|---|---|
| **D-3d2** |  **A partir de M3, etapa h** | **$T_R$ = 2,34 min (Cond. 3); CL/EM: Anal. Calc para $C_{24}H_{32}N_3O_2Si$ $[M+H]^+$ 422,22; Encontrado: 421,85.** |
| **D-3d3** |  **A partir de D-3c2** | **$T_R$ = 2,43 min (Cond. 3); CL/EM: Anal. Calc para $C_{26}H_{34}N_3O_2Si$ $[M+H]^+$ 448,24; Encontrado: 448,82.** |
| **D-3d4** |  **A partir de D-3c3** | **$T_R$ = 2,51 min (Cond. 3); CL/EM: Anal. Calc para $C_{26}H_{32}N_3O_2Si$ $(M+H)^+$ 446,23; Encontrado: 446,05.** |

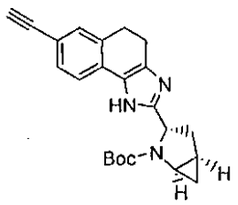
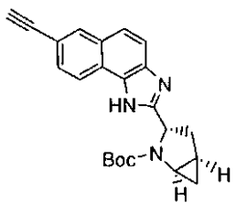
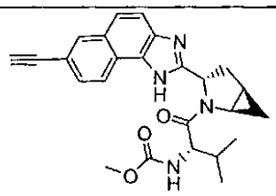
Ejemplo D-3e1 (etapa e)



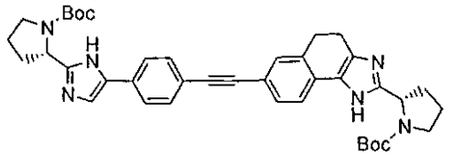
Se añadió carbonato potásico (91 mg, 0,66 mmol) en una porción a una solución en agitación de D-3d1 (2,7 g, 6,6 mmol) en MeOH (60 ml) a temperatura ambiente. La mezcla se agitó durante 1 h antes de concentrar a vacío. El residuo se tomó en diclorometano y se añadió directamente a una columna Thompson de 130 g de gel de sílice. La elución en gradiente del residuo con 15% de acetato de etilo en hexanos a 100% de acetato de etilo proporcionó D-3e1 (2,04 g, 87% de rendimiento) en forma de una espuma amarilla después de la evaporación del eluente. Después se sometió una pequeña cantidad (aprox. 20 mg) del producto a HPLC preparativa para lograr una muestra más pura de D-3e1 en forma de un sólido blanquecino. RMN de $^1$H (500 MHz, *MeOD,* falta el N-H del imidazol) δ ppm 7,68 (2 H, d, *J*=7,9 Hz), 7,46 (2 H, d, *J*=8,2 Hz), 7,34 - 7,40 (1 H, m), 4,89 (1 H, m), 3,64 - 3,73 (1 H, m), 3,49 (1 H, m), 3,49 (1 H, s), 3,31 - 3,34 (1 H, m), 2,25 - 2,44 (1 H, m), 1,99 - 2,11 (3 H, m), 1,25 y 1,47 (9 H, 2s). $T_R$ = 1,63 min (Cond. 3), CL/EM: Anal. Calc para $C_{20}H_{24}N_3O_2$ $(M+H)^+$ 338,19; Encontrado: 338,12.

D-3e2 a D-3e5 se prepararon de acuerdo con los procedimientos que se describen para el alquino D-3e1.

| | | |
|---|---|---|
| **D-3e2** |  **A partir de D-3d2** | **$T_R$ = 1,65 min (Cond. 3); CL/EM: Anal. Calc para $C_{21}H_{24}N_3O_2$ $[M+H]^+$ 350,19; Encontrado: 350,10.** |

| | | |
|---|---|---|
| **D-3e3** |  **A partir de D-3d3** | **$T_R$ = 1,81 min (Cond. 3); CL/EM: Anal. Calc para $C_{23}H_{26}N_3O_2$ $[M+H]^+$ 376,20; Encontrado: 376,20.** |
| **D-3e4** |  **A partir de D-3d4** | **$T_R$ = 1,88 min (Cond. 3); CL/EM: Anal. Calc para $C_{23}H_{24}N_3O_2$ $(M+H)^+$ 374,19; Encontrado: 374,04.** |
| **D-3e5** |  **Preparado a partir de D-3e4 y Cap-51 usando los procedimientos descritos para D-3h1 y el Ejemplo OL-1** | **$T_R$ = 1,75 min (Cond. 3); CL/EM: Anal. Calc para $C_{25}H_{27}N_4O_3$ $[M+H]^+$ 431,21; Encontrado: 431,09.** |

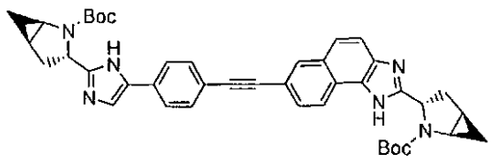
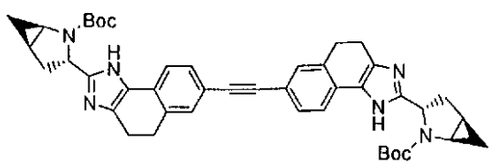
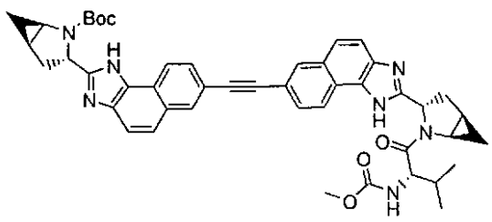
Ejemplo D-3f1 (etapa f)



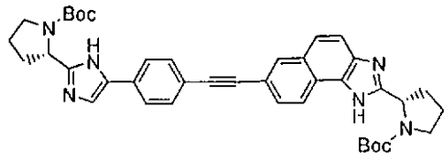
Se añadió tetrakis(trifenilfosfina)paladio (83 mg, 0,072 mmol) en una porción a una mezcla desgasificada con argón agitada del Ejemplo D-3c1 (300 mg, 0,717

mmol), D-3e1 (315 mg, 0,932 mmol), trietilamina (0,40 ml, 2,87 mmol) y yoduro de cobre (I) (13,7 mg, 0,072 mmol) en DMF anhidra (6 ml) a temperatura ambiente en un vial con tapón a rosca de paredes gruesas. La mezcla se agitó a temperatura ambiente durante 16 h y a 40 °C durante 16 h antes de añadir más CuI (10 mg), TEA (0,4 ml) y catalizador $Pd(PPh_3)_4$ (40 mg) dado que la reacción no se había completado después de 32 h según se determinó por CLEM. La mezcla se agitó más a 60 °C durante 10 h antes de enfriar a temperatura ambiente, se diluyó con acetato de etilo, THF y agua y se filtró con succión. La fase orgánica del filtrado se separó, se lavó con solución saturada de bicarbonato sódico y salmuera antes de secar sobre sulfato sódico anhidro y evaporar. El residuo se tomó en diclorometano y se añadió directamente a una columna Thompson de 80 g de gel de sílice. La elución en gradiente del residuo con 30% de acetato de etilo en hexanos a 100% de acetato de etilo seguido de 0% de metanol en acetato de etilo a 20% de metanol en acetato de etilo proporcionó D-3f1 (366,7 mg, 68% de rendimiento) en forma de una espuma marrón dorada después de la evaporación del eluente. Después se sometió una pequeña cantidad (aprox. 20 mg) del producto a HPLC preparativa para lograr una muestra más pura del Ejemplo D-3f1 en forma de un sólido tostado. RMN de $^1H$ (500 MHz, *MeOD*, falta el N-H del imidazol) δ ppm 7,73 (2 H, d, *J*=8,2 Hz), 7,47 - 7,57 (4 H, m), 7,41 (2 H, br s), 4,96 - 5,09 (1 H, m), 4,89 - 4,96 (1 H, m), 3,69 (2 H, br s), 3,54 (2 H, br s), 3,04 - 3,13 (2 H, m), 2,83 - 2,94 (2 H, m), 2,30 - 2,50 (2 H, m), 1,94 - 2,17 (6 H, m), 1,27 - 1,49 (18 H, 2s). $T_R$ = 2,06 min (Cond. 3); CL/EM: Anal. Calc para $C_{40}H_{47}N_6O_4$ $(M+H)^+$ 675,37; Encontrado: 675,26.

D-3f2 a D-3f4 se prepararon de acuerdo con el procedimiento descrito para D-3f1.

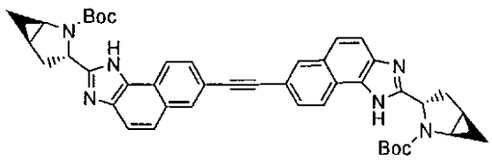
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|---|---|---|
| D-3f2 |  D-3e2 y D-3c3 | $T_R$ = 2,12 min (Cond. 3); CL/EM: Anal. Calc para $C_{42}H_{45}N_6O_4$ $[M+H]^+$ 697,35; Encontrado: 697,25. |
| D-3f3 |  A partir de D-3e3 y D-3c2 | $T_R$ = 2,14 min (Cond. 3); CL/EM: Anal. Calc para $C_{44}H_{49}N_6O_4$ $[M+H]^+$ 725,38; Encontrado: 725,25. |
| D-3f4 |  A partir de D-3c3 y D-3e5 | CLEM: 2,18 min (Cond. 3); CL/EM: Anal. Calc para $C_{45}H_{48}N_7O_5$ $(M+H)^+$ 778,37; Encontrado: 778,22. |

Ejemplo D-3g1 (etapa g)



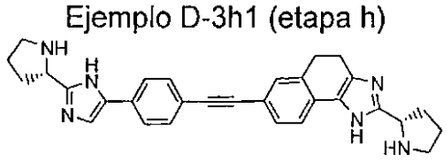
Se añadió dióxido de manganeso activado (2,0 g, 23,12 mmol) en una porción a una solución en agitación de D-3f1 (260 mg, 0,39 mmol) en diclorometano seco (5 ml). La suspensión se agitó a temperatura ambiente durante 6 h antes de añadir más dióxido de manganeso activado (1,0 g). La suspensión se agitó durante 14 h más a temperatura ambiente antes de filtrar con succión a través de una capa de Celite con MeOH y la capa se lavó con más MeOH varias veces. El filtrado después se concentró a vacío proporcionando D-3g1 (225,1 mg, 82% de rendimiento) en forma de un sólido amarillo. Después se sometió una pequeña cantidad (aprox. 20 mg) del producto a HPLC preparativa para lograr una muestra más pura de D-3g1 en forma de un sólido tostado claro. RMN de $^1$H (500 MHz, *MeOD*, falta el N-H del imidazol) δ ppm 8,43 (1 H, d, *J*=8,5 Hz), 8,19 (1 H, br s), 7,68 - 7,78 (5 H, m), 7,62 (2 H, d, *J*=8,2 Hz), 7,54 (1 H, s), 4,90 - 5,27 (2 H, m), 3,76 - 3,85 (1 H, m), 3,66 - 3,74 (1 H, m), 3,51 - 3,66 (2 H, m), 2,35 - 2,60 (2 H, m), 1,94 - 2,21 (6 H, m), 1,49 (6 H, br s), 1,27 (6 H, br s), 1,14 (6 H, br s). $T_R$ = 2,12 min (Cond. 3); CL/EM: Anal. Calc para $C_{40}H_{45}N_6O_4$ $(M+H)^+$ 673,35; Encontrado: 673,30.

D-3g2 se preparó de acuerdo con el procedimiento descrito para D-3g1.

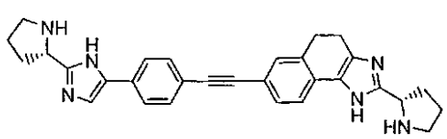
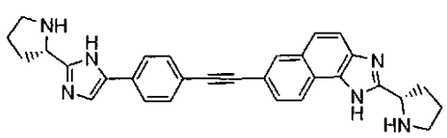
| | | |
|---|---|---|
| **D-3g2** |  **A partir de D-3f3** | **CLEM: 2,27 min (Cond. 3); CL/EM: Anal. Calc para $C_{44}H_{45}N_6O_4$** |

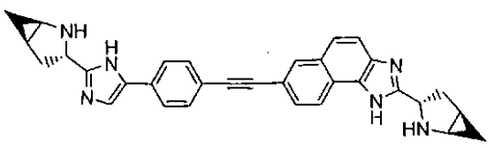
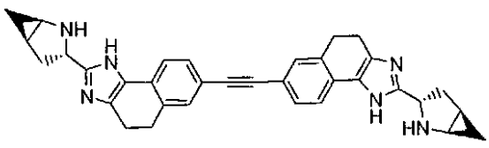
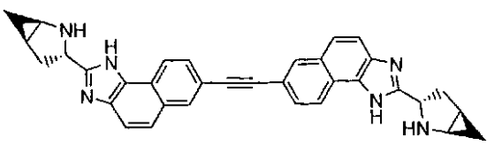
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|---|---|---|
| | | **$(M+H)^+$ 721,35; Encontrado: 721,25.** |

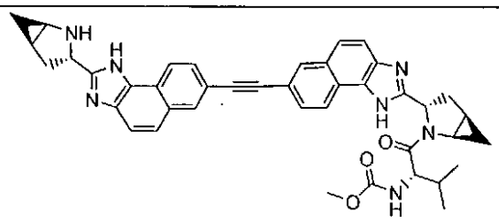
Ejemplo D-3h1 (etapa h)



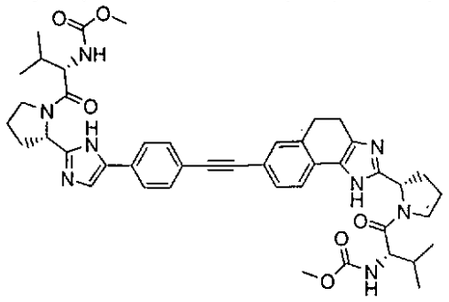
D-3h1 a D-3h6 se prepararon a partir de D-3f1, D-3g1, D-3f2, D-3f3, D-3g2 y D-3f4, respectivamente, de acuerdo con el mismo procedimiento que se usó para la preparación de OL-1e excepto que se usó metanol (1 ml) en lugar de diclorometano. Esto proporcionó D-3h1 a D-3h6 en forma de sales clorhidrato (o sales TFA cuando se purificó posteriormente con HPLC preparativa) tras la concentración del disolvente(s) a vacío.

| | | |
|---|---|---|
| **D-3h1** |  **A partir de D-3f1** | **$T_R$ = 1,44 min (Cond. 3); CL/EM: Anal. Calc para $C_{30}H_{31}N_6$ $[M+H]^+$ 475,26; Encontrado: 475,16.** |
| **D-3h2** |  **A partir de D-3g1** | **RMN de $^1H$ (500 MHz, *MeOD*, falta el N-H del imidazol) δ ppm 8,46 (1 H, d, *J*=8,5 Hz), 8,21 (1 H, s), 7,84 (2 H, d, *J*=8,2 Hz), 7,70** |

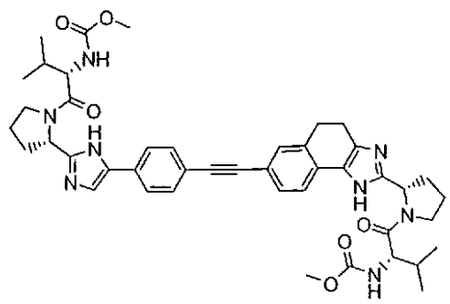
| | | |
|---|---|---|
| | | - 7,80 (4 H, m), 7,64 (2 H, d, *J*=8,5 Hz), 5,15 (1 H, s), 4,97 (1 H, s), 3,62 - 3,70 (1 H, m), 3,56 (3 H, s), 2,65 - 2,75 (1 H, m), 2,55 - 2,64 (1 H, m), 2,17 - 2,53 (6 H, series de m). $T_R$ = 1,61 min (Cond. 3); CL/EM: Anal. Calc para $C_{30}H_{29}N_6$ $(M+H)^+$ 473,25; Encontrado: 473,13. |
| D-3h3 |  A partir de D-3f2 | $T_R$ = 1,62 min (Cond. 3); CL/EM: Anal. Calc para $C_{32}H_{29}N_6$ $(M+H)^+$ 497,25; Encontrado: 497,13. |
| D-3h4 |  A partir de D-3f3 | $T_R$ = 1,62 min (Cond. 3); CL/EM: Anal. Calc para $C_{34}H_{33}N_6$ $[M+H]^+$ 525,28; Encontrado: 525,13. |
| D-3h5 |  A partir de D-3g2 | CLEM: 1,78 min (Cond. 3); CL/EM: Anal. Calc para $C_{34}H_{29}N_6$ $(M+H)^+$ 521,25; Encontrado: 521,13. |

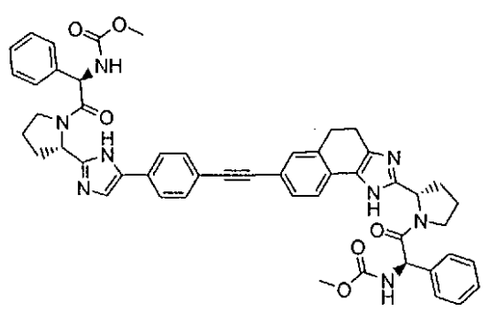
| | | |
|---|---|---|
| **D-3h6** |  **A partir de D-3f4** | **CLEM: 1,95 min (Cond. 3); CL/EM: Anal. Calc para $C_{41}H_{40}N_7O_3$ $(M+H)^+$ 678,32; Encontrado: 678,45.** |

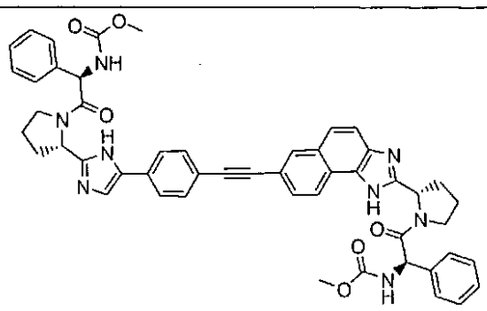
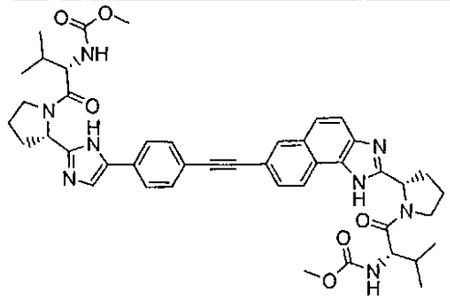
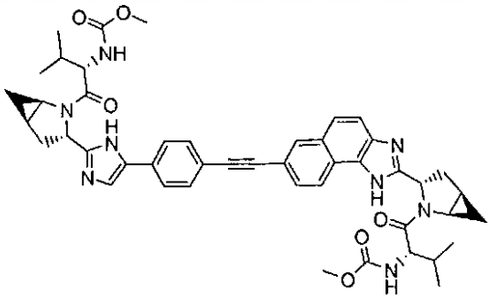
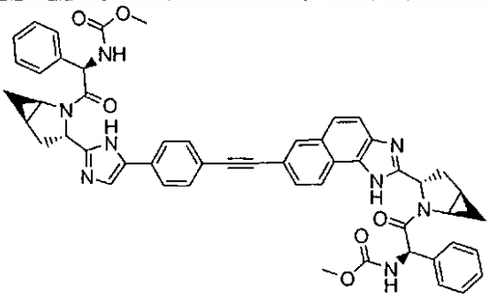
Ejemplo D-3 a D-11 (etapa final)

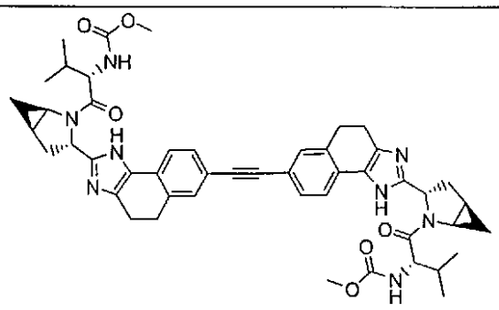
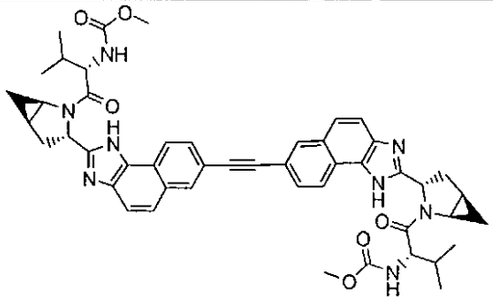
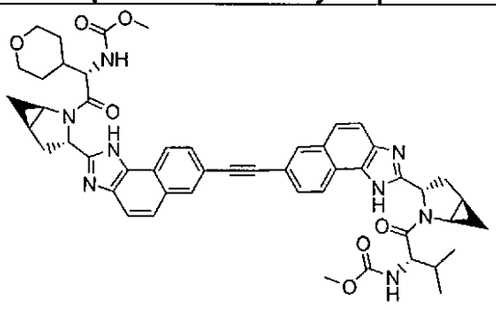


Los Ejemplos D-3 a D-11 se prepararon a partir de D-3h1 a D-3h6 y los ácidos apropiados de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo OL-1. Esto proporcionó los Ejemplos D-3 a D-11 en forma de sales TFA después de la purificación por HPLC.

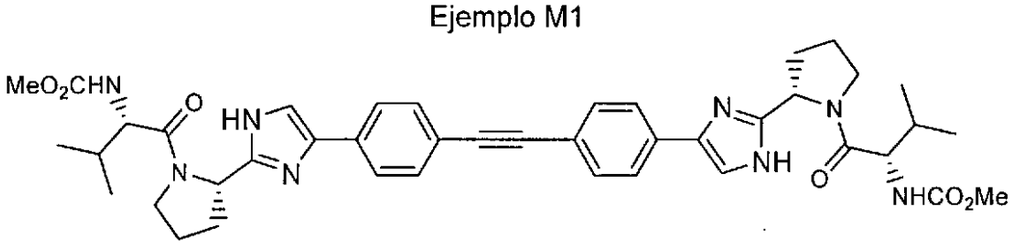
| | | |
|---|---|---|
| **D-3** |  **A partir de D-3h1 y Cap 51** | **$T_R$ = 1,80 min (Cond. 3); CL/EM: Anal. Calc para $C_{44}H_{53}N_8O_6$ $[M+H]^+$ 789,41; Encontrado: 789,27. RMN de $^1H$ (500 MHz, *MeOD*, falta el N-H del imidazol) δ ppm** |

| | | |
|---|---|---|
| | | 7,86 - 7,91 (1 H, m), 7,73 - 7,80 (2 H, m), 7,64 - 7,71 (2 H, m), 7,50 - 7,59 (3 H, m), 5,59 - 5,65 y 5,16 - 5,31 (2 H, 2m), 4,21 - 4,29 (2 H, m), 4,06 - 4,16 (2 H, m), 3,81 - 3,93 (2 H, m), 3,67 (6 H, s), 3,15 - 3,24 (2 H, m), 2,95 - 3,07 (2 H, m), 2,51 - 2,65 (2 H, m), 2,25 - 2,37 (2 H, m), 2,14 - 2,23 (4 H, m), 1,99 - 2,11 (2 H, m), 0,09 – 0,95 (12 H, m), 0,97 - 1,05 (2 H, m). |
| D-4 |  A partir de D-3h1 y Cap 4 | $T_R$ = 1,88 min (Cond. 3); CL/EM: Anal. Calc para $C_{50}H_{49}N_8O_6$ $[M+H]^+$ 857,38; Encontrado: 857,31. |
| D-5 | | $T_R$ = 1,94 min (Cond. 3); CL/EM: Anal. Calc |

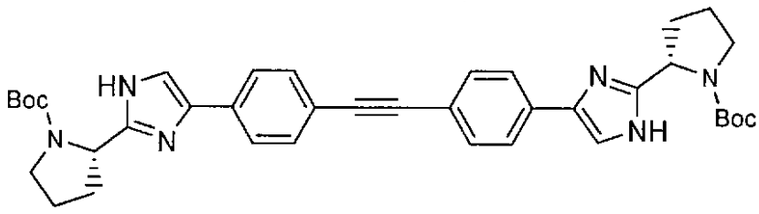
| | | |
|---|---|---|
| |  A partir de D-3h2 y Cap 4 | para $C_{50}H_{47}N_8O_6$ $[M+H]^+$ 855,36; Encontrado: 855,28. |
| D-6 |  A partir de D-3h2 y Cap 51 | $T_R$ = 1,88 min (Cond. 3); CL/EM: Anal. Calc para $C_{44}H_{51}N_8O_6$ $[M+H]^+$ 787,40; Encontrado: 787,30. |
| D-7 |  A partir de D-3h3 y Cap 51 | $T_R$ = 1,93 min (Cond. 3); CL/EM: Anal. Calc para $C_{46}H_{51}N_8O_6$ $[M+H]^+$ 811,40; Encontrado: 811,26. |
| D-8 |  A partir de D-3h3 y Cap 4 | $T_R$ = 2,01 min (Cond. 3); CL/EM: Anal. Calc para $C_{52}H_{47}N_8O_6$ $[M+H]^+$ 879,36; Encontrado: 879,25. |
| D-9 | | $T_R$ = 1,93 min (Cond. |

| | | |
|---|---|---|
| |  A partir de D-3h4 y Cap 51 | 3); CL/EM: Anal. Calc para $C_{48}H_{55}N_8O_6$ $[M+H]^+$ 839,43; Encontrado: 839,26. |
| D-10 |  A partir de D-3h5 y Cap 51 | $T_R$ = 2,07 min (Cond. 3); CL/EM: Anal. Calc para $C_{48}H_{51}N_8O_6$ $[M+H]^+$ 835,40; Encontrado: 835,26. |
| D-11 |  A partir de D-3h6 y Cap 170 | $T_R$ = 1,99 min (Cond. 3); CL/EM: Anal. Calc para $C_{50}H_{53}N_8O_7$ $[M+H]^+$ 877,41; Encontrado: 877,63. |

Ejemplo M1

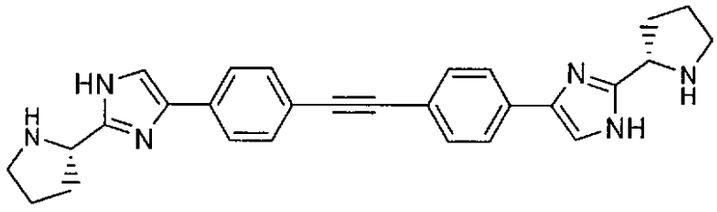


Ejemplo M1, Etapa a



Se añadió $Pd(Ph_3P)_4$ (0,078 g, 0,067 mmol) a una solución en DMF (5 ml) de 2-(5-(4-bromofenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo (D-1b) (0,675 g, 1,721 mmol) y 1,2-bis(trimetilstannil)etino (0,3134 g, 0,891 mmol) en un tubo a presión, la mezcla se purgó con nitrógeno durante 1 min y después se calentó a 90 °C durante 15 h. El componente volátil se eliminó a vacío y el residuo se sometió directamente a una purificación en Biotage® (110 g; EtOAc) proporcionando el alquino M1a en forma de una espuma naranja amarillenta que contenía una impureza no identificada y disolvente residual (430 mg). RMN de $^1H$ (DMSO, δ = 2,50 ppm, 400 MHz): 12,23/11,98/11,91 (tres br s, 2H), 7,80-7,35 (m, 10H), 4,84-4,76 (m, 2H), 3,54 (m, 2H), 3,39-3,33 (m, 2H), 2,28-1,78 (m, 8H), 1,40 (s ancho, 7,54H), 1,16 (s ancho, 10,46H). CL/EM: Anal. Calc. para $[M+H]^+$ $C_{38}H_{45}N_6O_4$: 649,35; encontrado 649,27.

Ejemplo M1, Etapa b



Se añadió HCl/dioxanos (4 N; 8 ml, 32,0 mmol), $CH_2Cl_2$ (1 ml) y MeOH (1,0 ml) a bis-carbamato M1a (0,427 g, 0,658 mmol), y la mezcla heterogénea se agitó durante 5 h. El componente volátil se eliminó a vacío, y el residuo se expuso a vacío

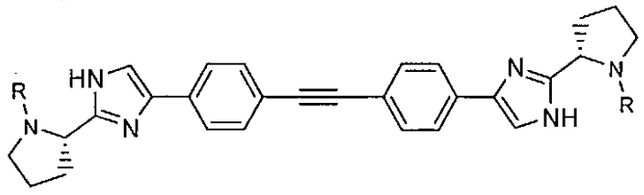
elevado proporcionando M1b (,4HCl) en forma de un sólido blanquecino (452 mg), que se sometió a la siguiente etapa tal cual. El análisis por RMN de $^1$H indica que la muestra puede contener dioxano residual (~1 equiv. molar). RMN de $^1$H (DMSO, δ = 2,50 ppm, 400 MHz): 10,29 (s ancho, 2H), 9,73 (s ancho, 2H), 8,11 (s, 2H), 7,96 (d, J = 8,3, 4H), 7,67 (d, J = 8,6, 4H), 4,97 (m ancho, 2H), 3,47-3,31 (m, 4H), 2,50-2,36 ('m' parcialmente superpuesto con la señal del disolvente, 4H), 2,23-2,14 (m, 2H), 2,07-1,95 (m, 2H). CL/EM: Anal. Calc. para $[M+H]^+$ $C_{28}H_{29}N_6$: 449,25; encontrado 49,23.

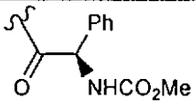
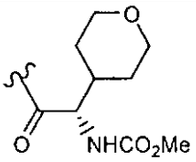
Ejemplo M1

Se añadió HATU (0,069 g, 0,181 mmol) a la solución en HATU (0,069 g, 0,181 mmol) de la pirrolidina M1b/4HCl (70,5 mg, 0,103 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (36,3 mg, 0,207 mmol) y DIEA (0,1 ml, 0,573 mmol) y se agitó a temperatura ambiente durante 70 min. El componente volátil se eliminó a vacío y el residuo se disolvió en MeOH y se sometió a una purificación por HPLC de fase inversa (MeOH/agua/TFA) proporcionando la sal TFA del Ejemplo M1 en forma de una espuma blanquecina (68,9 mg). CL (Cond. 9 y 10): >95% de índice de homogeneidad. CL/EM (Cond. 3): $T_r$ = 1,78 min. RMN de $^1$H (DMSO, δ = 2,50 ppm, 400 MHz): 8,10 (s ancho, 2H), 7,88-7,83 (m, 4H), 7,71 (d, J = 8,3, 3,91H), 7,34 (d, J = 8,5, 2H; $NHCO_2$), 6,92 (s ancho aparente, 0,09H), 5,52 (m ancho, 0,17H), 5,12 (t ap, 1,93H), 4,11 (t ap, 2H), 3,89-3,77 (m, 4H), 3,54 (s, 5,52H), 3,33 (s, 0,48H), 2,41-2,33 (m, 2H), 2,21-1,93 (m, 8H), 0,89 (t ap, 0,91H), 0,83/0,79 (dos d superpuestos, J = 6,8/6,8, 11,09 H). CL/EM: Anal. Calc. para $[M+H]^+$ $C_{42}H_{51}N_8O_6$: 763,39; encontrado 763,33.

Ejemplo M2 a M2.1

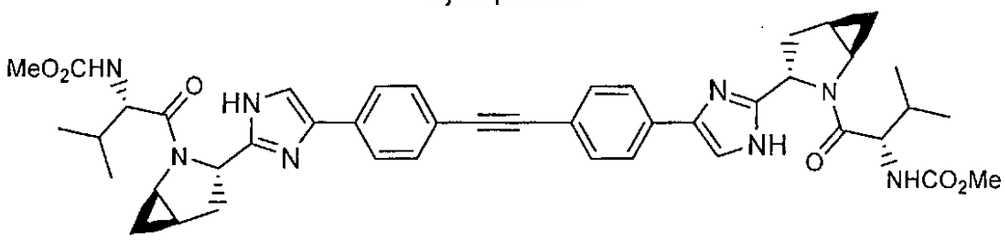
Los Ejemplos M2 a M2,1 se prepararon en forma de sales TFA a partir de la pirrolidina M1b y ácidos apropiados de acuerdo con el procedimiento descrito para la preparación del Ejemplo M1 con un protocolo de purificación modificado que se describe en la tabla siguiente.



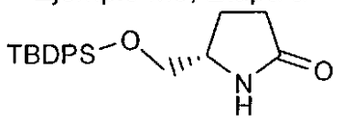
| Ejemplo | R | Datos analíticos |
|---|---|---|
| M2 |  | Se purificó usando dos condiciones de HPLC de fase inversa diferentes (Columna: Phenomenex Luna, 30x100 mm, S10; MeOH/agua/TFA) y (Waters Sunfire, 30x100 mm, S5; $CH_3CN$/agua/TFA). CL (Cond. 9 y 10): >95% de índice de homogeneidad. CL/EM (Cond. 3): $T_r$ = 2,04 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{48}H_{47}N_8O_6$: 831,36; encontrado 841,41. |
| M2.1 |  | Se purificó usando dos condiciones de HPLC de fase inversa diferentes (Columna: Xbridge, 19x100 mm, S5; MeOH/agua/TFA) y (Waters Sunfire, 30x100 mm, S5; $CH_3CN$/agua/TFA). CL (Cond. 9 y 10): 95% de índice de homogeneidad. CL/EM (Cond. 10d): $T_r$ = 2,82 |

| | | |
|---|---|---|
| | | min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{46}H_{55}N_8O_8$: 847,41; encontrado 847,25. |

Ejemplo M3

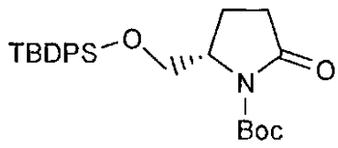



Ejemplo M3, Etapa a



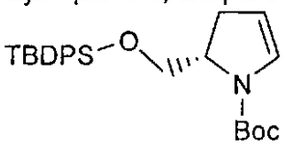

A una solución de (S)-5-(hidroximetil)pirrolidin-2-ona (10 g, 87 mmol) en $CH_2Cl_2$ (50 ml) se añadió terc-butilclorodifenilsilano (25,6 g, 93 mmol), $Et_3N$ (12,1 ml, 87 mmol) y DMAP (1,06 g, 8,7 mmol). La mezcla se agitó a temperatura ambiente hasta que la pirrolidinona inicial se consumió completamente, y después se diluyó con $CH_2Cl_2$ (50 ml) y se lavó con agua (50 ml). La fase orgánica se secó ($Na_2SO_4$), se filtró, y se evaporó a vacío, y el material en bruto se sometió a cromatografía ultrarrápida (gel de sílice; 30 a 100% de EtOAc/hexanos) proporcionando el éter M3a en forma de un aceite incoloro (22,7 g, 74% de rendimiento). RMN de $^1H$ (400 MHz, DMSO-$d_6$, $\delta$ = 2,5 ppm) 7,69 (s ancho, 1H), 7,64-7,61 (m, 4H), 7,50-7,42 (m, 6H), 3,67-3,62 (m, 1H), 3,58-3,51 (m, 2H), 2,24-2,04 (m, 3H), 1,87-1,81 (m, 1H), 1,00 (s, 9H). CL/EM $(M+H)^+$ = 354,58.

Ejemplo M3, Etapa b



Se añadió dicarbonato de di-terc-butilo (38,5 g, 177 mmol) en porciones en forma de un sólido durante 10 min a una solución en $CH_2Cl_2$ (200 ml) del sililéter M3a (31,2 g, 88,3 mmol), $Et_3N$ (8,93 g, 88 mmol), y DMAP (1,08 g, 8,83 mmol) y se agitó durante 18 h a 24 °C. La mayor parte del material volátil se eliminó a vacío y el material en bruto se tomó en 20% de EtOAc/Hex y se aplicó a un embudo de 2 l que contenía 1,3 l de gel de sílice y después se eluyó con 3 l de 20% de EtOAc/hex y 2 l de 50% de EtOAc). Tras la concentración de las fracciones deseadas en una rotoevaporadora, se formó una suspensión blanca de sólido que se filtró, se lavó con hexanos y se secó a vacío proporcionando el carbamato M3b en forma de un sólido blanco (32,65 g, 82% de rendimiento). RMN de $^1H$ (400 MHz, DMSO-$d_6$, $\delta$ = 2,5 ppm) 7,61-7,59 (m, 2H), 7,56-7,54 (m, 2H), 7,50-7,38 (m, 6H), 4,18 (m, 1H), 3,90 (dd, J = 10,4, 3,6, 1H), 3,68 (dd, J = 10,4, 2,1, 1H), 2,68-2,58 (m, 1H), 2,40-2,33 (m, 1H), 2,22-2,12 (m, 1H), 2,01-1,96 (m, 1H), 1,35 (s, 9H), 0,97 (s, 9H). CL/EM $(M-Boc+H)^+$ = 354,58.

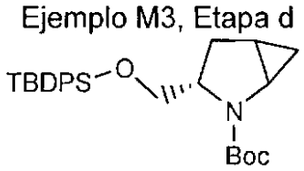
Ejemplo M3, Etapa c



Se cargó un matraz de tres bocas provisto de un termómetro y una admisión de nitrógeno con el carbamato M3b (10,05 g, 22,16 mmol) y tolueno (36 ml), y se introdujo en un baño refrigerante a -55 °C. Cuando la temperatura interna de la mezcla alcanzó -50 °C, se añadió trietilborohidruro de litio (23 ml de una solución 1,0 M/THF, 23,00 mmol) gota a gota durante 30 min y la mezcla se agitó durante 35 min

mientras se mantenía la temperatura interna entre -50 °C y -45 °C. Se añadió base de Hünig (16,5 ml, 94 mmol) gota a gota durante 10 min. Después, se añadió DMAP (34 mg, 0,278 mmol) en un lote, seguido de la adición de anhídrido trifluoroacético (3,6 ml, 25,5 mmol) durante 15 min, mientras la temperatura interna se mantenía entre -50 °C y -45 °C. Se extrajo del baño 10 min después, y la mezcla de reacción se agitó durante 14 h mientras se dejaba subir a temperatura ambiente. Se diluyó con tolueno (15 ml), se enfrió con un baño de agua y hielo, y se trató lentamente con agua (55 ml) durante 5 min. Las fases se separaron y la fase orgánica se lavó con agua (50 ml, 2x) y se concentró a vacío. El material en bruto se purificó por cromatografía ultrarrápida (gel de sílice; 5% de EtOAc/hexanos) proporcionando dihidropirrol M3c en forma de un aceite viscoso incoloro (7,947 g, 82% de rendimiento). CL/EM (Cond. 7): $T_r$ = 2,41 min. RMN de $^1$H (400 MHz, DMSO-$d_6$, δ = 2,5 ppm) 7,62-7,58 (m, 4H), 7,49-7,40 (m, 6H), 6,47 (s ancho, 1H), 5,07/5,01 (d ancho superpuesto, 1H), 4,18 (s ancho, 1H), 3,89 (s ancho, 0,49H), 3,69 (s ancho, 1,51H), 2,90-2,58 (m ancho, 2H), 1,40/1,26 (s ancho superpuesto, 9H), 0,98 (s, 9H). CL/EM: $[M+Na]^+$ = 460,19.

Ejemplo M3, Etapa d

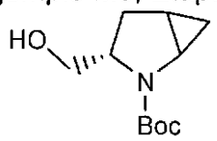



**M3d-1**: isómero trans
**M3d-2**: isómero cis

Se añadió dietilcinc (19 ml de ~1,1 M en tolueno, 20,9 mmol) gota a gota durante 15 min a una solución fría (-30 °C) en tolueno (27 ml) de dihidropirrol M3c

(3,94 g, 9,0 mmol). Se añadió cloroyodometano (estabilizado sobre cobre; 3,0 ml, 41,2 mmol) gota a gota durante 10 min, y se agitó mientras se mantenía la temperatura del baño a -25 °C durante 1 h y entre -25 °C y -21 °C durante 18,5 h. La mezcla de reacción se abrió al aire y se inactivó mediante la adición lenta de una solución saturada al 50% de $NaHCO_3$ (40 ml), y después se retiró del baño helado y se agitó a temperatura ambiente durante 20 min. Se filtró con papel de filtro y la torta blanca se lavó con 50 ml de tolueno. La fase orgánica del filtrado se separó y se lavó con agua (40 ml, 2x), se secó ($MgSO_4$) y se concentró a vacío. El material en bruto se purificó usando un sistema BIOTAGE® (350 g de gel de sílice; la muestra se cargó con 7% de EtOAc/hexanos; se eluyó con 7-20% de EtOAc/hexanos) proporcionando una mezcla de metanopirrolidinas M3d-1 y M3d-2 en forma de un aceite viscoso incoloro (3,69 g, 90,7%). [Nota: en este punto no se determinó la proporción exacta entre isómeros cis/trans]. CL/EM (Cond. 7): $T_r$ = 2,39 min RMN de $^1H$ (400 MHz, DMSO-$d_6$, δ = 2,5 ppm) 7,62-7,60 (m, 4H), 7,49-7,40 (m, 6H), 3,77/3,67 (s ancho superpuesto, 3H), 3,11-3,07 (m, 1H), 2,23 (s ancho aparente, 1H), 2,05-2,00 (m, 1H), 1,56-1,50 (m, 1H), 1,33 (s muy ancho, 9H), 1,00 (s, 9H), 0,80 (m, 1H), 0,30 (m, 1H). CL/EM: $[M+Na]^+$ = 474,14.

Ejemplo M3, Etapa e

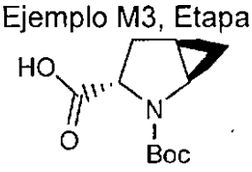



**M3e-1**: isómero trans
**M3e-2**: isómero cis

Se añadió TBAF (7,27 ml de 1,0 M en THF, 7,27 mmol) gota a gota durante 5 min a una solución en THF (30 ml) de sililéter M3d-1/-2 (3,13 g, 6,93 mmol) y la

mezcla se agitó a temperatura ambiente durante 4,75 h. Después de la adición de solución saturada de $NH_4Cl$ (5 ml), la mayor parte del material volátil se eliminó a vacío y el residuo se fraccionó entre $CH_2Cl_2$ (70 ml) y solución saturada al 50% de $NH_4Cl$ (30 ml). La fase acuosa se extrajo con $CH_2Cl_2$ (30 ml), y la fase orgánica combinada se secó ($MgSO_4$), se filtró, se concentró a vacío y después se expuso a vacío elevado toda la noche. El material en bruto se purificó usando un BIOTAGE® (gel de sílice; 40-50% de EtOAc/hexanos) proporcionando una mezcla de los alcoholes M3e-1 y M3e-2, contaminados con trazas de un punto con menor $R_f$, en forma de un aceite incoloro (1,39 g, ~94% de rendimiento). [Nota: en este punto no se determinó la proporción exacta entre isómeros cis/trans.] RMN de $^1H$ (400 MHz, DMSO-$d_6$, δ = 2,5 ppm) 4,70 (t, J = 5,7, 1H), 3,62-3,56 (m, 1H), 3,49-3,44 (m, 1H), 3,33-3,27 (m, 1H), 3,08-3,04 (m, 1H), 2,07 (m ancho, 1H), 1,93-1,87 (m, 1H), 1,51-1,44 (m, 1H), 1,40 (s, 9H), 0,76-0,71 (m, 1H), 0,26 (m, 1H). CL/EM $(M+Na)^+$ = 236,20.

Ejemplo M3, Etapa f



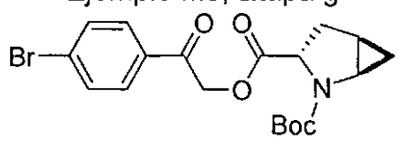

**M3f-1**: isómero trans
**M3f-2**: isómero cis

Se añadió una semisolución de $NaIO_4$ (6,46 g, 30,2 mmol) en $H_2O$ (31 ml) a una solución del alcohol M3e-1/-2 (2,15 g, 10,08 mmol) en $CH_3CN$ (20 ml) y $CCl_4$ (20

ml). Inmediatamente se añadió $RuCl_3$ (0,044 g, 0,212 mmol) y la mezcla de reacción heterogénea se agitó vigorosamente durante 75 min. La mezcla de reacción se diluyó con $H_2O$ (60 ml) y se extrajo con $CH_2Cl_2$ (50 ml, 3x). La fase orgánica combinada se trató con 1 ml de MeOH, se dejó reposar durante aproximadamente 5 min, y después se filtró a través de una capa de tierra de diatomeas (CELITE®). El CELITE® se lavó con $CH_2Cl_2$ (50 ml), y el filtrado se concentró a vacío proporcionando un sólido de color carbón claro. El análisis por RMN de $^1H$ de este material en bruto indicó una proporción molar de 1,00:0,04:0,18 entre el ácido M3f-1 trans:ácido M3f-2 cis:presunto subproducto, 3-oxo-2-azabiciclo[3.1.0]hexano-2-carboxilato de terc-butilo. El material en bruto se disolvió en EtOAc (~10 ml) con calor y se dejó reposar a temperatura ambiente con siembra. Aproximadamente 15 min después de empezar la fase de enfriamiento, se observó una rápida formación de cristales. Aproximadamente 1 h después, se añadió hexanos (~6 ml) y la mezcla se refrigeró toda la noche (no pareció que precipitara más material). La mezcla se filtró y se lavó con hexanos refrigerados con hielo y agua/EtOAc (proporción 2:1; 20 ml) y se secó a vacío elevado proporcionando la primera cosecha del ácido M3f-1 (cristales blanquecinos, 1,222 g). El licor madre se concentró a vacío, y el residuo se disolvió en ~3 ml de EtOAc calentando, se dejó reposar a temperatura ambiente durante 1 h, y después se añadieron 3 ml de hexanos y se almacenaron en un frigorífico durante ~15 h. Se obtuvo una segunda cosecha del ácido M3f-1 de forma similar (cristales grises, 0,133 g), para un rendimiento combinado de 59%. Ácido M3f-1: $T_r$ = 1,48 min en las siguientes condiciones de HPLC: Gradiente de disolventes de 100% de A : 0% de B a 0% de A : 100% de B (A = 0,1% de TFA en 1:9 de MeOH/$H_2O$; B = 0,1% de TFA en 9:1 de MeOH/$H_2O$) durante 3 min; detección a 220 nm; COLUMNA PHENOMENEX®-Luna

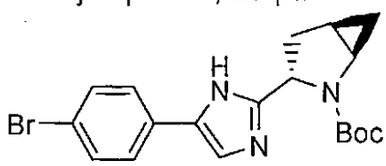
3,0X50 mm S10. PF (dec.) para la primera cosecha = 147,5-149,5 °C. RMN de $^1$H (400 MHz, DMSO-$d_6$, δ = 2,5 ppm) 12,46 (s, 1H), 3,88 (s ancho aparente, 1H), 3,27 (s ancho aparente, 1H; superpuesto a la señal del agua), 2,28 (m ancho, 1H), 2,07 (s ancho aparente, 1H), 1,56 (s ap, 1H), 1,40/1,34 (dos s superpuestos, 9H), 0,71 (m, 1H), 0,45 (m, 1H). RMN de $^{13}$C (100,6 MHz, DMSO-$d_6$, δ = 39,21 ppm) 172,96, 172,60, 154,45, 153,68, 78,74, 59,88, 59,58, 36,91, 31,97, 31,17, 27,77, 27,52, 14,86, 14,53, 13,69. CL/EM $[M+Na]^+$ = 250,22. Anal. Calc. para $C_{11}H_{17}NO_4$: C, 58,13; H, 7,54; N, 6,16. Hallada (para la primera cosecha): C, 58,24; H, 7,84; N, 6,07. Rotación óptica (10 mg/ml en $CHCl_3$): $[\alpha]_D$ = -216 y -212 para las cosechas primera y segunda, respectivamente.

Ejemplo M3, Etapa g



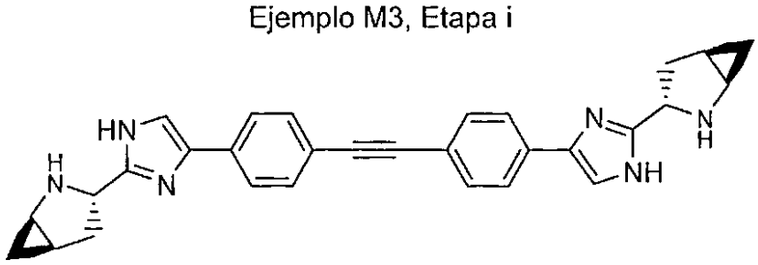

Se añadió DIEA (1,3 ml, 7,44 mmol) gota a gota durante 2 min a una mezcla semiheterogénea del ácido M3f-1 (1,697 g, 7,47 mmol) y 2-bromo-1-(4-bromofenil)etanona (2,01 g, 7,23 mmol) en $CH_3CN$ (30 ml) y se agitó a temperatura ambiente durante 8 h. El componente volátil se eliminó a vacío y el residuo se tomó en $CH_2Cl_2$ (100 ml), se lavó con agua (30 ml), se secó ($MgSO_4$) y se concentró a vacío proporcionando el cetoéster M3g en forma de un aceite semisespumoso viscoso blanquecino (3,076 g). RMN de $^1$H (400 MHz, DMSO-$d_6$, δ = 2,5 ppm): 7,92 (d, J = 8,3, 2H), 7,78 (d, J = 8,5, 2H), 5,61-5,42 (m, 2H), 4,16 (m, 1H), 3,34 ('m' parcialmente superpuesto a la señal del agua, 1H), 2,40 (m, 2H), 1,63 (m, 1H), 1,41/1,35 (dos 's' superpuestos, 9H), 0,74 (m, 1H), 0,53 (m, 1H). CL/EM: Anal. Calc. para $[M+Na]^+$ $C_{19}H_{22}{}^{79}BrNNaO_5$: 446,06; encontrado 446,06.

Ejemplo M3, Etapa h



Un tubo a presión de 350 ml se cargó con el cetoéster M3g (3,07g, 7,24 mmol), acetato de amonio (5,48 g, 71,1 mmol) y xileno (70 ml), se tapó y se calentó con un baño de aceite (140 °C) durante 4,5 h. La mezcla de reacción se dejó enfriar a temperatura ambiente y el componente volátil se eliminó a vacío. Se añadió $CH_2Cl_2$ (100 ml) y solución saturada al 50% de $NaHCO_3$ (30 ml) al residuo, se agitó vigorosamente hasta que dejó de desprender gas, y las fases se separaron. La fase orgánica se secó ($MgSO_4$), se concentró a vacío, y se purificó con a BIOTAGE® (240 g de gel de sílice; la muestra se cargó con $CH_2Cl_2$; 40-80% de EtOAc/hexanos) proporcionando el imidazol M3h en forma de una espuma amarillo oscuro (2,40 g). RMN de $^1H$ (400 MHz, DMSO-$d_6$, δ = 2,5 ppm): 12,21 (s, 0,11H), 1,93 (s, 0,89H), 7,69 (d, J = 8,8, 1,8H), 7,62-7,55 (m, 0,4H), 7,53 (d ancho, J = 2, 0,87H), 7,49 (d, J = 8,5, 1,8H), 7,29 (d ancho, J = 1,6, 0,13H), 4,59 (m, 1H), 3,41 (m, 1H), 2,37-2,17 (m ancho, 2H), 1,62 (m, 1H), 1,21 (muy ancho 's', 9H), 0,75 (m, 1H), 0,54 (m, 1H). CL/EM: Anal. Calc. para $[M+H]^+$ $C_{19}H_{23}{}^{81}BrN_3O_2$: 406,10; encontrado , 406,14.

Ejemplo M3, Etapa i

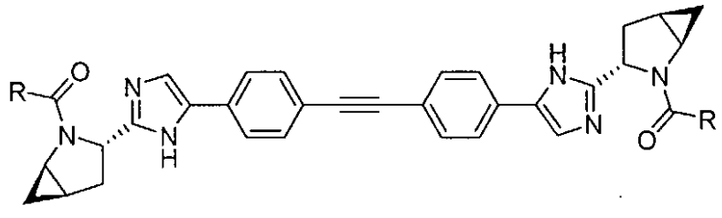


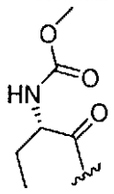
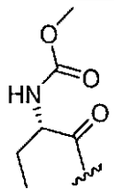
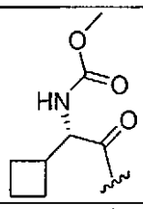
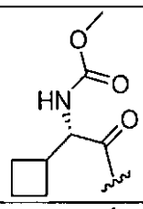
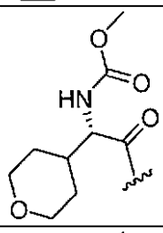
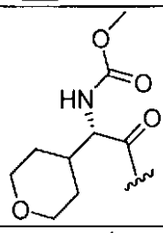
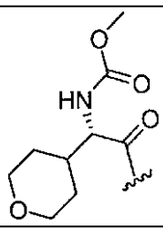
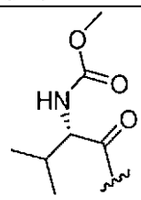
La pirrolidina M3i (4HCl) se preparó a partir del bromuro M3h de acuerdo con

el procedimiento descrito para la síntesis de pirrolidina M1b (,4HCl) a partir del bromuro D-1b. RMN de $^1$H (400 MHz, DMSO-$d_6$, δ = 2,5 ppm): 10,51 (s ancho aparente, 4H), 8,08 (s, 2H), 7,92 (d, J= 7,8, 4H), 7,66 (d, J = 8,5, 4H), 4,78 (m, 2H), 3,42 (m, 2H), 2,65 (m, 2H), ~2,53 ('m' parcialmente superpuesto con la señal del disolvente, 2H), 1,94 (m, 2H), 1,10 (m, 2H), 0,86 (m, 2H). CL/EM: Anal. Calc. para $[M+H]^+$ $C_{30}H_{29}N_6$: 473,25; encontrado 473,21.

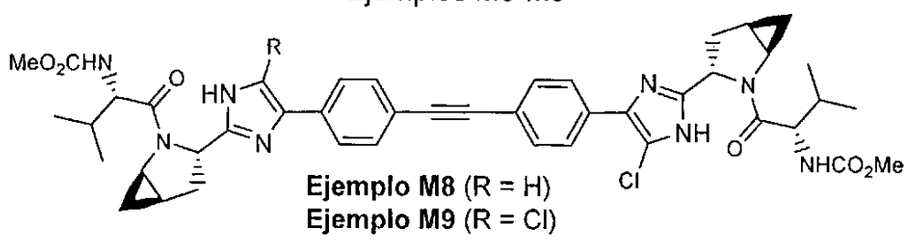
Ejemplo M3 (y Ejemplos M4-M7)

El Ejemplo M3, junto con sus análogos de los Ejemplos M4-M7 destacados en la tabla siguiente, se prepararon en forma de sales TFA a partir de pirrolidina M3i (,4HCl) empleando el procedimiento descrito para la síntesis del Ejemplo M1 y los ácidos apropiados. En el caso del Ejemplo M7 un se empleó una mezcla equimolar de ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético para la etapa de acoplamiento y la mezcla de productos estadística resultante se separó mediante la técnica de HPLC descrita para el Ejemplo M1. Ejemplo M3: CL (Cond. 9 y 10): >95% de índice de homogeneidad. CL/EM (Cond. 3): $T_r$ = 1,89 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{44}H_{51}N_8O_6$: 787,39; encontrado 787,40.



| Ejemplo |  |  | $T_r$ (Cond. 3); % de índice de homogeneidad (Cond. 9 y 10); CL/Datos de EM |
|---|---|---|---|
| M4 |  |  | 1,74 min; >95%; CL/EM: Anal. Calc. para $[M+H]^+$ $C_{42}H_{47}N_8O_6$: 759,36; encontrado 759,35 |
| M5 |  |  | 1,98 min; >95%; CL/EM: Anal. Calc. para $[M+H]^+$ $C_{46}H_{51}N_8O_6$: 811,39; encontrado 811,37 |
| M6 |  |  | 1,67 min; >95%; CL/EM: Anal. Calc. para $[M+H]^+$ $C_{48}H_{55}N_8O_8$: 871,41; encontrado 871,20 |
| M7 |  |  | 1,78 min; >95%; CL/EM: Anal. Calc. para $[M+H]^+$ $C_{46}H_{53}N_8O_7$: 829,40; encontrado 829,53 |

Ejemplos M8-M9

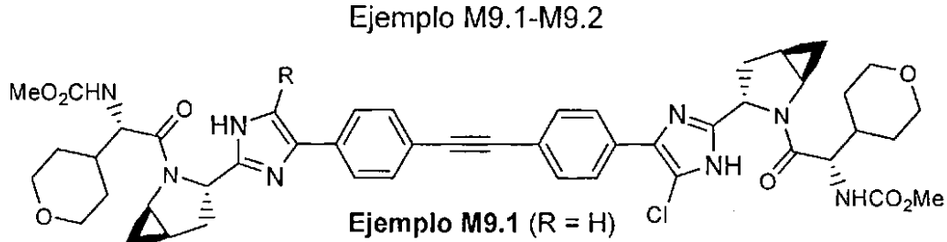


**Ejemplo M8** (R = H)
**Ejemplo M9** (R = Cl)

Se añadió NCS (0,0195 g, 0,143 mmol) a una solución en DMF (2 ml) de la forma de base libre del Ejemplo M3 (obtenida a partir de la sal TFA mediante un protocolo estándar de desbasificación con MCX; 0,109 g, 0,139 mmol), y se agitó a temperatura ambiente durante 16 h y a 50°C durante 25 h. La mayor parte del disolvente se eliminó a vacío, y el residuo se disolvió en MeOH y se sometió a una purificación por HPLC de fase inversa (MeOH/agua/TFA) proporcionando la sal TFA del Ejemplo M8 (50 mg) y el Ejemplo M9 (17,5 mg).

| Ejemplo | $T_r$ (Cond. 3); % de índice de homogeneidad (Cond. 9a y 10a); CL/Datos de EM |
|---|---|
| M8 | 2,42 min; >95%; CL/EM: Anal. Calc. para $[M+H]^+$ $C_{44}H_{50}ClN_8O_6$: 821,35; encontrado 821,31 |
| M9 | 2,95 min; >95%; CL/EM: Anal. Calc. para $[M+H]^+$ $C_{44}H_{49}Cl_2N_8O_6$: 855,32; encontrado 855,24 |

Ejemplo M9.1-M9.2

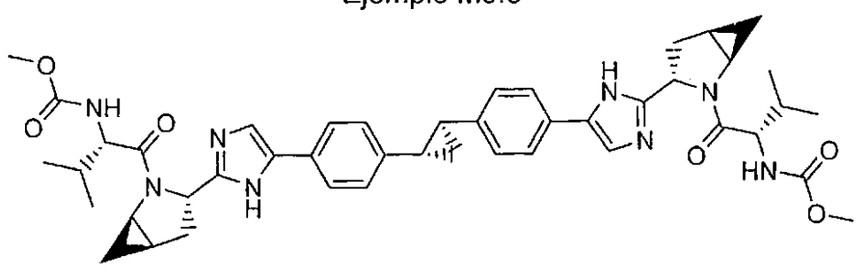


**Ejemplo M9.1** (R = H)
**Ejemplo M9.2** (R = Cl)

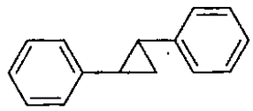
Se añadió NCS (0,021 g, 0,158 mmol) a una solución en DMF (1,5 ml) de la forma de base libre del Ejemplo M6 (obtenido a partir de la sal TFA mediante mediante un protocolo estándar de desbasificación con MCX; 0,1059 g, 0,122 mmol), y se agitó a 50°C durante 24 h. La mezcla de reacción se diluyó con MeOH (2,5 ml) y se sometió a una condición de purificación por HPLC de fase inversa (XTERRA, 30X100 mm, S5; MeOH/agua/TFA). La muestra resultante se volvió a purificar con una condición diferente de HPLC de fase inversa (Waters-Sunfire, 30X100 mm, S5; acetonitrilo/agua/TFA) proporcionando el Ejemplo M9.1 (38,8 mg) y el Ejemplo M9.2 (32,6 mg) en forma de sales TFA.

| Ejemplo | $T_r$ (Cond. 3); % de índice de homogeneidad (Cond. 9a y 10a); CL/Datos de EM |
|---|---|
| M9.1 | 2,26 min; >95%; CL/EM: Anal. Calc. para $[M+H]^+$ $C_{48}H_{54}ClN_8O_8$: 905,38; encontrado 905,44 |
| M9.2 | 2,78 min; >95%; CL/EM: Anal. Calc. para $[M+H]^+$ $C_{44}H_{53}Cl_2N_8O_8$: 939,34; encontrado 939,40 |

Ejemplo M9.3

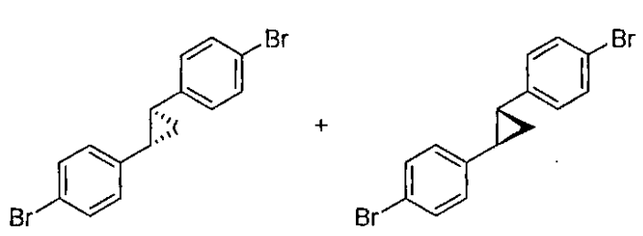


Ejemplo M9.3, etapa a



A $CH_2Cl_2$ (22 ml) frío (0°C) se añadió dietilcinc (1M en hexanos, 60,5 ml, 60,5 mmol) en atmósfera de nitrógeno seguido de la adición gota a gota de ácido trifluoroacético (5,1 ml, 66,2 mmol) en 10 ml de $CH_2Cl_2$ durante 15 min. La reacción se agitó durante 15 min, y después se añadió diyodometano (5,4 ml, 66,9 mmol) en 10 ml $CH_2Cl_2$ gota a gota a la reacción. La reacción se siguió agitando a 0 °C durante 1 h, y después se añadió (E)-1,2-difenileteno (2 g, 11,10 mmol) en 10 ml $CH_2Cl_2$. La mezcla se sacó del baño frío y se agitó a ~25 °C en atmósfera de nitrógeno durante 20 h. La reacción se inactivó con HCl 0,1 N (50 ml), las fases se separaron, y la fase acuosa se extrajo con hexanos (2 x 100 ml). La fase orgánica combinada se lavó con $NaHCO_3$ saturado (acuoso) (50 ml) y salmuera (50 ml), se secó sobre $MgSO_4$, se filtró, y se concentró a vacío. El residuo se sometió a cromatografía ultrarrápida sobre gel de sílice (hexanos) proporcionando el bifenilo M9.3a en forma de un aceite incoloro (1,6 g). RMN de $^1H$ (400 MHz, $CDCl_3$) δ ppm 7,34-7,31 (m, 4H), 7,24-7,17 (m, 6H), 2,22-2,18 (m, 2H), 1,51-1,47 (m, 2H).

Ejemplo M9.3, etapa b

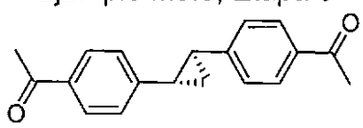



M9.3b1 M9.3b2

A una solución del bifenilo M9.3a (3,3 g, 16,99 mmol) en 1,2-dimetoxietano (197 ml) y agua (82 ml) se añadió NBS (12,09 g, 67,9 mmol). El matraz de reacción

se cubrió con papel de aluminio y se agitó a temperatura ambiente durante 51 h. La reacción se fraccionó entre dietil éter y agua, y la fase orgánica se lavó con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró a vacío. El residuo se sometió a una cromatografía ultrarrápida (la muestra se cargó con cloroformo; se eluyó con hexanos) proporcionando una mezcla estereoisomérica de producto dibromado en forma de un sólido blanco (3,1 g). La mezcla estereoisomérica se separó mediante SFC quiral (columna Chiral pak AD-H, 30X250 mm, 5 µm; 80% de $CO_2$-20% de EtOH; 35 °C; 150 bar; 70 ml/min durante 20 min; 220 nm) para aislar dos enantiómeros: M9.3b1 (sólido blanco, 1,1 g); RMN de $^1H$ (400 MHz, $CDCl_3$) δ ppm 7,43 (d, J = 8,6 Hz, 4H), 7,02 (d, J = 8,6 Hz, 4H), 2,12-2,09 (m, 2H), 1,47-1,43 (m, 2H); OR: +361,79, 3,15 mg en 1 ml de $CHCl_3$, δ = 589 nm, cubeta de 50 mm. M9.3b2 (sólido blanco, 1,2 g); RMN de $^1H$ (400 MHz, $CDCl_3$) δ ppm 7,43 (d, J = 8,6 Hz, 4H), 7,02 (d, J = 8,6 Hz, 4H), 2,12-2,09 (m, 2H), 1,47-1,43 (m, 2H); OR: -376,70, 3,03 mg en 1 ml de $CHCl_3$, δ = 589 nm, cubeta de 50 mm.

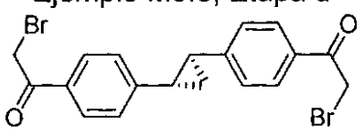
Ejemplo M9.3, Etapa c



A una solución del dibromuro M9.3b1 (0,8806 g, 2,501 mmol) y tributil(1-etoxivinil)stannano (2,71 g, 7,50 mmol) en 1,4-dioxano (17 ml) se añadió diclorobis(trifenilfosfina)-paladio(II) (0,105 g, 0,150 mmol). La reacción se purgó cuidadosamente con nitrógeno, se selló y se calentó a 80 °C durante 16 h. La reacción se retiró del calor, se añadió HCl 1 N (ac) (17 ml) y la mezcla se agitó durante 4 h. La mezcla se diluyó con agua (20 ml) y se extrajo con EtOAc (3 x 50 ml). La fase orgánica combinada se secó sobre $MgSO_4$, se filtró, y se concentró a

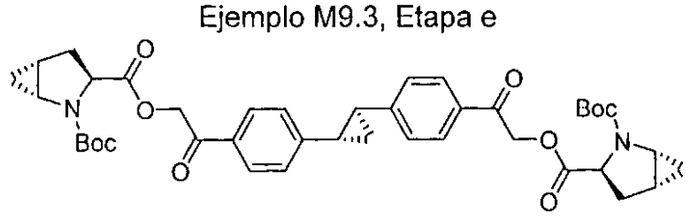
vacío. El residuo se purificó por cromatografía ultrarrápida (35% de acetato de etilo/hexanos), y la muestra obtenida se trituró con hexanos (3 x 50 ml) proporcionando la cetona M9.3c en forma de un sólido blanquecino (412,5 mg). RMN de $^1$H (400 MHz, $CDCl_3$) δ ppm 7,92 (d, J = 8,5 Hz, 4H), 7,23 (d, J = 8,6 Hz, 4H), 2,61 (s, 6H), 2,32-2,28 (m, 2H), 1,67-1,63 (m, 2H). CL/EM: Anal. Calc. para $[M+H]^+$ $C_{19}H_{19}O_2$: 279,14; encontrado 279,13.

Ejemplo M9.3, Etapa d




A una solución de la cetona M9.3c (0,4072 g, 1,463 mmol) en THF (7 ml) se añadió tribromuro de feniltrimetilamonio (1,10 g, 2,93 mmol), y la mezcla de reacción se agitó a ~25 °C durante 15 h. El componente volátil se eliminó a vacío, y el residuo se fraccionó entre agua (25 ml) y $CH_2Cl_2$ (100 ml). La fase orgánica se secó sobre $MgSO_4$, se filtró, y se concentró a vacío proporcionando el dibromuro M9.3d, que se usó sin purificación adicional. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{19}H_{17}$ $^{79}Br_2O_2$: 434,96; encontrado 434,98.

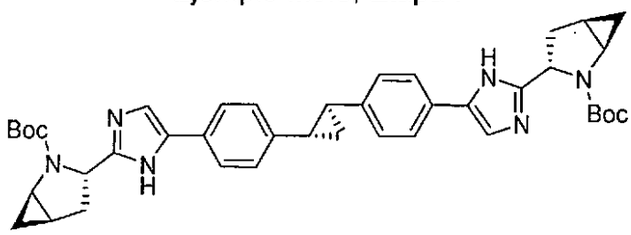
Ejemplo M9.3, Etapa e




A una solución del dibromuro M9.3d (~1,463 mmol) y el ácido M3f1 (0,698 g, 3,07 mmol) en acetonitrilo (10 ml) se añadió N,N-diisopropiletilamina (0,537 ml, 3,07 mmol), y la reacción se agitó a ~25 °C durante 5h. El componente volátil se eliminó

a vacío, y el residuo se tomó en cloroformo (4 ml) y se cargó en una columna de gel de sílice y se eluyó con 8% de acetato de etilo/cloruro de metileno en 1296 ml de disolventes proporcionando el dicetoéster M9.3e en forma de una espuma amarillo claro que contenía impurezas sin identificar (0,723 g). RMN de $^1H$ (400 MHz, DMSO-$d_6$) δ ppm 7,90 (d, J = 8,0 Hz, 4H), 7,37 (d, J = 8,3 Hz, 4H), 5,59-5,40 (m, 3H), 4,24-4,09 (m, 2H), 3,37-3,25 (m, 2H), 2,47-2,36 (m, 5H), 1,87-1,80 (m, 2H), 1,72-1,68 (m, 2H), 1,57-1,49 (m, 2H), 1,41 (s, 7H), 1,35 (s, 11H), 0,80-0,67 (m, 2H), 0,58-0,48 (m, 2H). CL/EM: Anal. Calc. para $[M+H]^+$ $C_{41}H_{48}N_2NaO_{10}$: 751,32; encontrado 751,55.

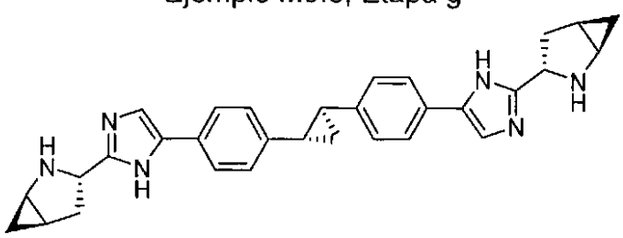
Ejemplo M9.3, Etapa f




Una mezcla del dicetoéster M9.3e (0,723 g, 0,992 mmol) y acetato de amonio (1,529 g, 19,84 mmol) en xileno (10 ml) en un recipiente de reacción sellado se calentó a 140 °C durante 2,5 h. Después de dejar enfriar la reacción en condiciones ambientales, el componente volátil se eliminó a vacío. El residuo se tomó en 20% de MeOH/$CHCl_3$ (50 ml) y se trató con $NaHCO_3$ saturado (acuoso) (20 ml), se agitó y las fases se separaron. La fase acuosa se extrajo además con 20% de MeOH/$CHCl_3$ (2 x 50 ml), y la fase orgánica combinada se secó sobre $MgSO_4$, se filtró, y se concentró a vacío. El residuo se tomó en $CHCl_3$ (4 ml), se cargó en una columna de gel de sílice y se eluyó con 45% de acetato de etilo/cloruro de metileno en 1296 ml proporcionando el imidazol M9.3f en forma de un sólido naranja (261,7

mg). RMN de $^1$H (400 MHz, DMSO-$d_6$) δ ppm 12,08 (s, 0,5H), 11,81 (s, 1,5H), 7,64 (d, J = 8,3 Hz, 3H), 7,55 (d, J = 8,3 Hz, 1H), 7,41 (d, J = 1,7 Hz, 1,7H), 7,19-1,17 (m, 1,3H), 7,11 (d, J = 8,3 Hz, 3H), 4,59 (s ancho aparente, 2H), 3,41 (s ancho aparente, 2H), 2,37-2,14 (m, 6H), 1,68-1,57 (m, 2H), 1,48-1,40 (m, 2H), 1,40-0,95 (s ancho, 18H), 0,79-0,69 (m, 2H), 0,59-0,48 (m, 2H). CL/EM: Anal. Calc. para $[M+H]^+$ $C_{41}H_{49}N_6O_4$: 689,38; encontrado 689,43.

Ejemplo M9.3, Etapa g



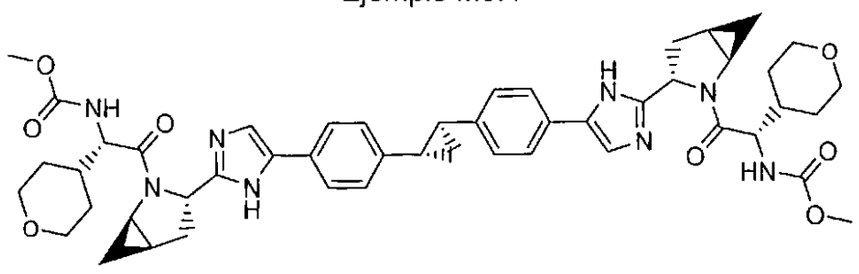
Se agitó una solución del carbamato M9.3f (0,2391 g, 0,347 mmol) en 25% de TFA/$CH_2Cl_2$ (1,7 ml) a ~25 °C durante 1h. El componente volátil se eliminó a vacío proporcionando la sal TFA de la pirrolidina M9.3g en forma de una espuma tostada (328 mg). RMN de $^1$H (400 MHz, DMSO-$d_6$) δ ppm 10,01 (s ancho, 2H), 7,70-7,68 (m, 6H), 7,20 (d, J = 8,6 Hz, 4H), 4,63-4,58 (m, 2H), 3,37-3,33 (m, 2H), 2,51-2,42 (m, 6H), 2,24-2,20 (m, 2H), 1,93-1,86 (m, 2H), 1,51-1,47 (m, 2H), 1,16-1,09 (m, 2H), 0,084-0,78 (m, 2H). CL/EM: Anal. Calc. para $[M+H]^+$ $C_{31}H_{33}N_6$: 489,28; encontrado 489,26.

Ejemplo M9.3

A una solución de la pirrolidina M9.3g/sal TFA (0,0834 g, 0,088 mmol), ácido

(S)-2-(metoxicarbonilamino)-3-metilbutanoico (0,034 g, 0,194 mmol), y N,N-diisopropiletilamina (0,123 ml, 0,706 mmol) en DMF (1,5 ml) se añadió HATU (0,070 g, 0,185 mmol), y la mezcla se agitó a 25 °C durante 4h. La mezcla de reacción se diluyó con MeOH (2,5 ml) y se sometió a una purificación por HPLC de fase inversa (XTERRA, 30X100 mm, S5; MeOH/$H_2O$/TFA) proporcionando el Ejemplo M9.3 en forma de una espuma blanquecina (58 mg). RMN de $^1H$ (400 MHz, DMSO-$d_6$) δ ppm 14,90-14,20 (bs, 3H), 8,00 (s ancho, 2H), 7,68 (d, J = 8,3 Hz, 4H), 7,34 (d, J = 8,6 Hz, 4H), 7,25 (d, J = 8,6 Hz, 2H), 5,00-4,96 (m, 2H), 4,42-4,39 (m, 2H), 3,79-3,69 (m, 2H), 3,54 (s, 6H), 2,38-2,31 (m, 5H), 2,16-2,07 (m, 2H), 1,95-1,88 (m, 2H), 1,61-1,58 (m, 2H), 0,97-0,90 (m, 8H), 0,80 (d, J = 6,5 Hz, 8H). $T_r$ = 1,96 min (Cond. 3); >95% de índice de homogeneidad (Cond. 9 y 10); CL/EM: Anal. Calc. para $[M+H]^+$ $C_{45}H_{55}N_8O_6$: 803,42; encontrado 803,43.

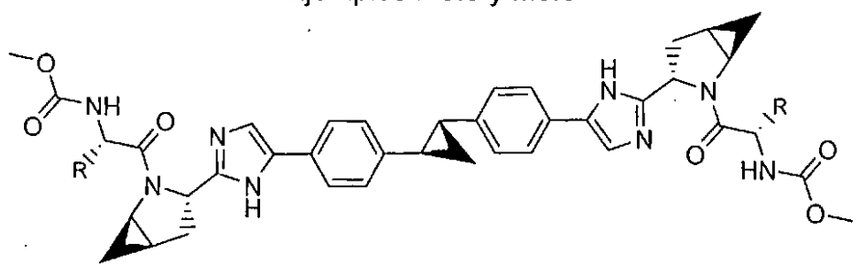
Ejemplo M9.4



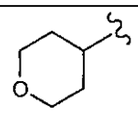
El Ejemplo M9.4 se preparó a partir de la pirrolidina M9.3g/sal TFA y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético de acuerdo con el mismo procedimiento que se usó para la preparación del Ejemplo M9.3. RMN de $^1H$ (400 MHz, DMSO-$d_6$) δ ppm 15-14 (bs, 6H), 7,98 (s ancho, 2H), 7,66 (d, J = 8,3 Hz, 4H), 7,34-7,32 (m, 5H), 4,98-4,94 (m, 2H), 4,50-4,46 (m, 2H), 3,84-3,78 (m, 6H), 3,54 (s, 6H), 3,32-3,18 (m, 4H), 2,39-2,29 (m, 4H), 2,11-1,97 (m, 2H), 1,97-1,88 (m, 2H), 1,60-1,57 (m, 2H), 1,51-1,26 (m, 8H), 0,99-0,87 (m, 2H), 0,84-0,72 (m, 2H). $T_r$

= 1,77 min (Cond. 3); >95% de índice de homogeneidad (Cond. 9 y 10); CL/EM: Anal. Calc. para $[M+H]^+$ $C_{49}H_{59}N_8O_8$: 887,45; encontrado 887,50.

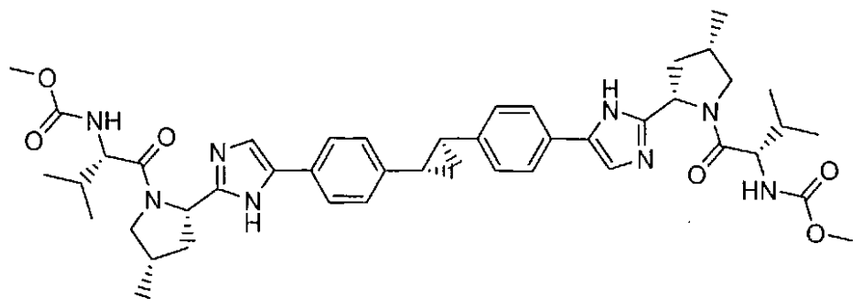
Ejemplos M9.5 y M9.6



Los Ejemplos M9.5 y M9.6 se prepararon en forma de sales TFA comenzando a partir del dibromuro M9.3b2 de acuerdo con los procedimientos que se describen para la preparación de los Ejemplos M9.3 y M9.4 a partir del estereoisómero del dibromuro M9.3b1 correspondiente.

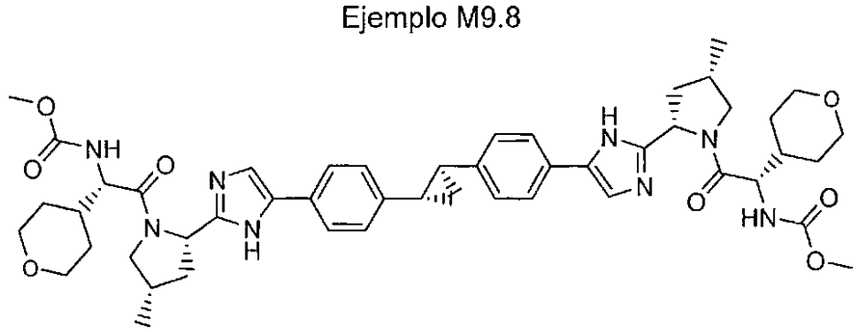
| Ejemplo | R | $T_r$ (Cond. 3); índice de homogeneidad (Cond. 9 y 10); CL/Datos de EM |
|---|---|---|
| M9.5 |  | 1,98 min; >95%; CL/EM: Anal. Calc. para $[M+H]^+$ $C_{45}H_{55}N_8O_6$: 803,42; encontrado 803,43 |
| M9.6 |  | 1,77 min; >95%; CL/EM: Anal. Calc. para $[M+H]^+$ $C_{49}H_{59}N_8O_8$: 887,45; encontrado 887,60 |

Ejemplo M9.7



El Ejemplo M9.7 (sal TFA) se preparó a partir del dibromuro M9.3d y el ácido M12.2c de acuerdo con los procedimientos que se describen para la preparación de los Ejemplos M9.3. RMN de $^1$H (400 MHz, DMSO-$d_6$) δ ppm 14,90-14,42 (s ancho, 4H), 8,02 (s ancho, 2H), 7,70 (d, J = 8,5 Hz, 4H), 7,36 (d, J = 8,6 Hz, 4H), 7,25 (d, J = 8,3 Hz, 2H), 5,07 (dd, J = 10,7 Hz/7,1 Hz, 2H), 4,18-4,13 (t ap, 2H), 4,12-4,08 (t ap, 2H), 3,55 (s, 6H), 3,42-3,37 (t ap, 2H), 2,49-2,39 (m, 2H), 2,37-2,31 (t ap, 2H), 2,02-1,93 (m, 2H), 1,87-1,78 (ap q, 2H), 1,62-1,59 (t ap, 2H), 1,14 (d, J = 6,3 Hz, 6H), 0,82 (d, J = 6,5 Hz, 6H), 0,77 (d, J = 6,8 Hz, 6H). $T_r$ = 3,12 min (Cond. 10d); >95% de índice de homogeneidad (Cond. 9 y 10); CL/EM: Anal. Calc. para $[M+H]^+$ $C_{45}H_{59}N_8O_6$: 807,46; encontrado 807,45.

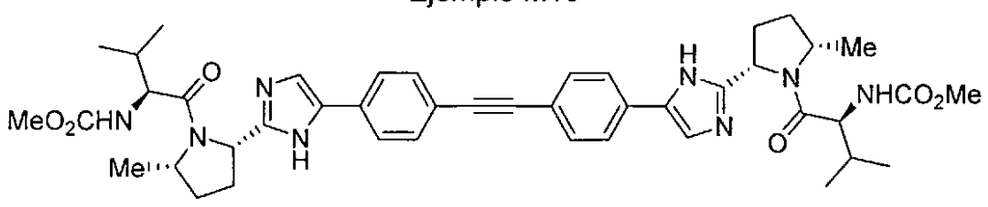
Ejemplo M9.8



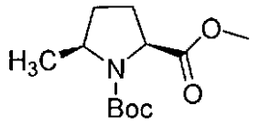
El Ejemplo M9.7 (sal TFA) se preparó a partir del dibromuro M9.3d y el ácido M12.2c de acuerdo con los procedimientos que se describen para la preparación de los Ejemplos M9.4. $T_r$ = 3,01 min (Cond. 10d); >95% de índice de homogeneidad

(Cond. 9 y 10); CL/EM: Anal. Calc. para $[M+H]^+$ $C_{49}H_{63}N_8O_8$: 891,48; encontrado 891,52.

Ejemplo M10

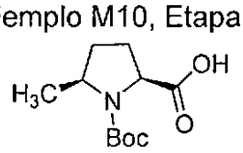


Ejemplo M10, Etapa a



El compuesto del título, que contenía una impureza diastereomérica, se preparó en 5 etapas a partir del 5 –oxopirrolidin-2-carboxilato de (S)-metilo empleando el procedimiento descrito en J. Med. Chem., 49:3520-3535 (2006) para la síntesis de sus análogo de éster etílico. RMN de $^1H$ ($CDCl_3$, 400 MHz): 4,35 (m, 0,5H), 4,25 (m, 0,5H), 4,05 (m, 0,5H), 3,90 (m, 0,5H), 3,73 (s, 3H), 2,20 (m, 1H), 2,00 (m, 2H), 1,65 (m, 1H), 1,50/1,40 (dos superpuestos br s, 9H), 1,31 (d, J = 6,0, 3H).

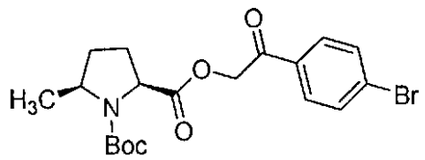
Ejemplo M10, Etapa b



Se añadió una solución de hidróxido de litio (0,23g, 9,62 mmol) en agua (5 ml) gota a gota a una solución del éster M10a (1,8g, 7,4 mmol) en etanol (10 ml), y se agitó a temperatura ambiente durante 17 h. La mayor parte del disolvente se

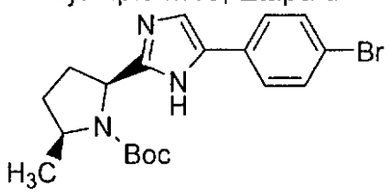
evaporó, y el residuo se diluyó con agua, se añadió HCl 1 N gota a gota para llevarlo a pH 3. Se extrajo con acetato de etilo (20 ml, 4x), se secó ($Na_2SO_4$) y se evaporó a vacío proporcionando un aceite incoloro, que proporcionó cristales cuando se disolvió en un sistema de disolventes de EtOAc/hexanos y se dejó reposar a temperatura ambiente. El sólido blanco se filtró y se secó a vacío (1,42 g). RMN de $^1H$ ($CDCl_3$, 400 MHz, d = 7,24 ppm): 4,35 (m, 1H), 3,95 (m, 1H), 2,35 (m, 1H), 2,05 (m, 2H), 1,70 (m, 1H), 1,50 (s ancho, 9H), 1,25 (d, J = 7,1, 3H).

Ejemplo M10, Etapa c



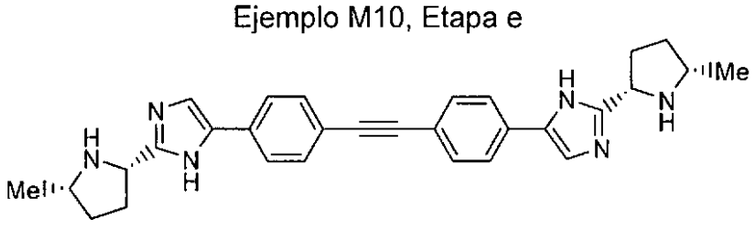

A una solución del ácido M10b (2,16 g, 9,42 mmol) y 2-bromo-1-(4-bromofenil)etanona (2,62 g, 9,42 mmol) en acetonitrilo (50 ml) se añadió lentamente diisopropiletilamina (1,645 ml, 9,42 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 5 h. El disolvente se eliminó a vacío, y el residuo se fraccionó entre acetato de etilo y agua (1:1, 100 ml). La fase orgánica se lavó con $NaHCO_3$ saturado, se secó ($Na_2SO_4$) y se concentró a vacío proporcionando el cetoéster M10c en forma de un sólido blanco (3,9 g), que se usó en la siguiente etapa sin purificación adicional. RMN de $^1H$ (400 MHz , DMSO-$d_6$, $\delta$ = 2,5 ppm): 7,92 (d, J = 8,3, 2H), 7,78 (d, J = 8,5, 2H), 5,6-5,4 (m, 2H), 4,35 (m, 1H), 3,85 (m, 1H), 2,25 (m, 1H), 2,05 (m, 2H), 1,60 (m, 1H), 1,5/1,4 (dos br s superpuestos, 9H), 1,18 (d, J = 6,6, 3H). CL/EM: Anal. Calc. para $[M+Na]^+$ $C_{19}H_{24}{}^{81}BrNaNO_5$: 450,07; Encontrado: 450,00.

Ejemplo M10, Etapa d



A una solución del cetoéster M10c (3,9 g, 9,15 mmol) en xileno (60 ml) en un tubo de 500 ml a presión, se añadió acetato de amonio (7,05 g, 91 mmol). El recipiente de reacción se selló y se calentó a 140 °C durante 5 h. El disolvente se eliminó a vacío, y el residuo se fraccionó entre $CH_2Cl_2$ (100 ml) y agua (100 ml). La fase orgánica se lavó ($NaHCO_3$ sat.), se secó ($Na_2SO_4$), y se evaporó a vacío. El material en bruto resultante se purificó por cromatografía ultrarrápida (30-100% de EtOAc/hexano) proporcionando el bromuro M10d en forma de una espuma marrón (3,0 g, rendimiento de 81%). RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): 11,77 (s, 1H), 7,70 (d, J = 8,5, 2H), 7,52 (s ancho, 1H), 7,50 (d, J = 8,5, 2H), 4,80 (m, 1H), 3,85 (m, 1H), 2,10 (m, 3H), 2,70 (m, 1H), 1,5/1,3 (s ancho superpuesto, 9H), 1,20 (m, 3H). CL/EM: Anal. Calc. para $[M+H]^+$ $C_{19}H_{25}{}^{79}BrN_3O_2$: 406,11; Encontrado: 406,18.

Ejemplo M10, Etapa e



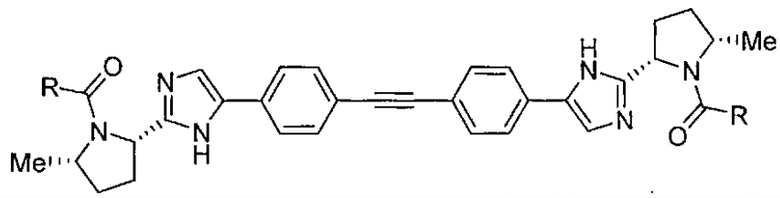
La pirrolidina M10e (sal HCl) se preparó a partir del bromuro M10d de acuerdo con el procedimiento descrito para la síntesis de la pirrolidina M1b (sal HCl) a partir del bromuro D1b.

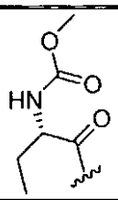
Ejemplo M10

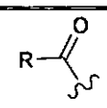
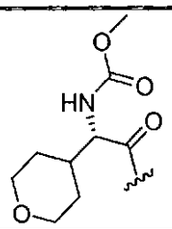
El Ejemplo M10 (sal TFA) se preparó a partir del bromuro de la pirrolidina M10e (sal HCl) de acuerdo con el procedimiento descrito para la síntesis del Ejemplo M1 a partir de la pirrolidina M3i (sal HCl). RMN de $^1$H (DMSO-$d_6$, δ = 2,5 ppm, 400 MHz): 8,05 (s, 2H), 7,85 (d, J = 8,1, 4H), 7,69 (d, J = 7,6, 4H), 7,56 (d, J = 8,0, 2H), 5,5 (m, 0,4H), 5,0 (m, 1,6H), 4,75 (1,6H), 4,10 (m, 0,4H), 3,95 (m, 2H), 3,50 (s, 6H), 2,50-2,30 (m, 4H), 2,10 (m, 2H), 1,85 (m, 4H), 1,46 (d, J = 6,6, 5H), 1,20 (d, J = 6,8, 1H), 0,9-0,9 (m, 7,2H), 0,74 (d, J = 6,8, 4,8H). CL (Cond. 9 y 10): >95% de índice de homogeneidad. CL/EM (Cond. 3): $T_r$ = 2,03 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{44}H_{55}N_8O_6$: 791,42; Encontrado: 791,39.

Ejemplos M11-M12

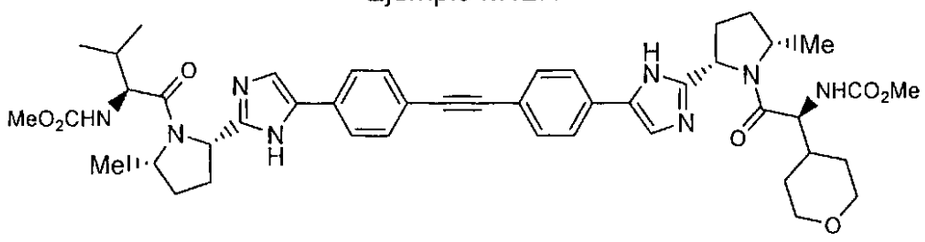
Las sales TFA de los Ejemplos M11-M12 se prepararon de acuerdo con el procedimiento descrito para el Ejemplo M10 y empleando ácidos apropiados.




| Ejemplo |  | $T_r$ (Cond. 3); % de índice de homogeneidad (Cond. 9 y 10); CL/Datos de EM |
|---|---|---|
| M11 |  | 1,89 min.; >98%; CL/EM: Anal. Calc. para $[M+H]^+$ $C_{42}H_{51}N_8O_6$: 763,39; encontrado 763,40. |

| Ejemplo |  | $T_r$ (Cond. 3); % de índice de homogeneidad (Cond. 9 y 10); CL/Datos de EM |
|---|---|---|
| M12 |  | 1,82 min.; >98%; CL/EM: Anal. Calc. para $[M+H]^+$ $C_{48}H_{59}N_8O_8$: 875,45; encontrado 875,42. |

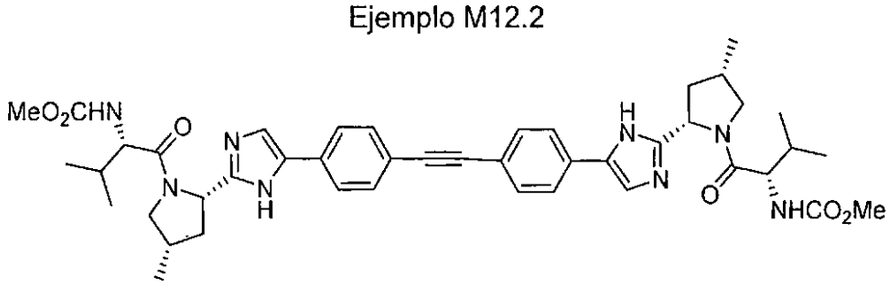
Ejemplo M12.1



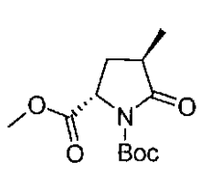
A una solución de la pirrolidina M10e/sal HCl (119 mg, 0,191 mmol), ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (49,0 mg, 0,226 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (40,9 mg, 0,233 mmol) en DMF (5 ml) se añadió DIEA (0,200 ml, 1,147 mmol) y HATU (148 mg, 0,390 mmol), y la mezcla se agitó a temperatura ambiente durante 1 h. El disolvente se eliminó a vacío y el residuo se disolvió en metanol y se purificó con una HPLC de fase inversa (MeOH/TFA/agua) para separar la mezcla estadística de productos, uno de que was Ejemplo M12.1 (sal TFA; espuma amarillo claro; 55 mg). RMN de $^1H$ (DMSO-$d_6$, δ = 2,5 ppm, 400 MHz): 8,09-7,82 (m, 6H), 7,68-7,55 (m, 6H), 5,00 (m, 2H), 4,64 (t ap, 2H), 4,21-3,75 (m, 6H), 3,53 (m, 6H), 3,17 (m, 2H), 2,33-2,21 (m, 6H), 1,85 (m, 3H), 1,62-1,17 (overlay de 'd' y 'm', J durante 'd' = 6,6 Hz, 9H), 0,88 (m, 3,6H), 0,74 (d, J = 6,8 Hz, 2,4H). CL (Cond. 9 y 10): >95% de índice de homogeneidad. CL/EM (Cond. 10h): $T_r$ = 1,92 min. CL/EM: Anal. Calc. para $[M+H]^+$

$C_{46}H_{57}N_8O_7$: 833,44; Encontrado: 833,40.

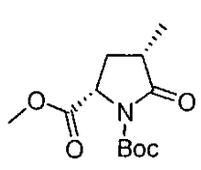
Ejemplo M12.2



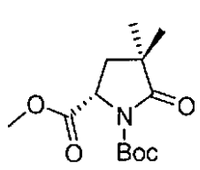

Ejemplo M12.2, Etapa a




M12.2a-1



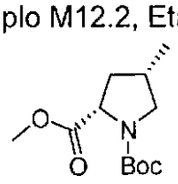

M12.2a-2




M12.2a-3

Los tres ésteres anteriores se prepararon a partir de 5-oxopirrolidin-1,2-dicarboxilato de (S)-1-terc-butil 2-metilo de acuerdo con el procedimiento descrito en Tetrahedon Letters, 2003, 3203-3205.

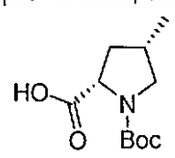
Ejemplo M12.2, Etapa b




Se añadió complejo de borano y sulfuro de metilo (5,44 ml, 10,88 mmol) a una solución del éster M12.2a-2 (1,4 g, 5,44 mmol) en THF (25 ml), y la mezcla de reacción se calentó a 40 °C durante 7 h. El componente volátil se eliminó a vacío y el residuo se fraccionó entre EtOAc y agua (50 ml cada uno). La fase acuosa se

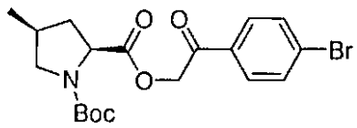
extrajo con EtOAc (30 ml), y la fase orgánica combinada se secó con $Na_2SO_4$, y se concentró a vacío. El aceite incoloro resultante se purificó con una cromatografía ultrarrápida (0-50% de EtOAc/hexano) proporcionando el éster M12.2b en forma de un aceite incoloro (0,77 g). RMN de $^1H$ ($CDCl_3$, δ = 7,24 ppm, 400 MHz): 4,29-4,18 (m, 1H), 3,78-3,66 (m, 4H), 2,99 (t ap, J = 10,1, 1H), 2,43-2,97 (m, 1H), 2,43-2,37 (m, 1H), 2,30-2,18 (m, 1H), 1,60-1,52 (m, 1H), 1,47/1,42 (dos 's', 9H), 1,08-1,05 (m, 3H).

Ejemplo M12.2, Etapa c



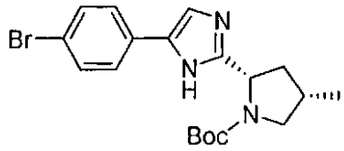

A una solución del éster M12.2b (1,69 g, 6,95 mmol) en etanol (10 ml) se añadió solución de LiOH (0,250 g, 10,42 mmol) en agua (5,00 ml), y la mezcla de reacción se agitó a temperatura ambiente durante 5 h. El disolvente orgánico se evaporó a vacío y el residuo se diluyó con agua (10 ml) y se lavó con éter (10 ml). Se enfrió en un baño de agua y hielo, y se acidificó a un intervalo de pH de ~2 con HCl 1 N. Después se se extrajo con EtOAc (20 ml, 3x). La fase orgánica se secó con $Na_2SO_4$ y se concentró a vacío proporcionando el ácido M12.2c en forma de un aceite incoloro, que se convirtió en un sólido blanco tras la exposición prolongada a vacío elevado (1,38 g). RMN de $^1H$ ($CDCl_3$, δ = 7,24 ppm, 400 MHz): 4,39-4,22 (m, 1H), 3,80-3,69 (m, 0,91H), 3,59-3,35 (m, 0,18H), 3,03-2,89 (m, 0,91H), 2,51-2,22 (m, 2H), 1,98-1,91 (m, 0,71H), 1,68-1,60 (0,29H), 1,50/1,44 (dos 's', 9H), 1,09 (ap m, 3H).

Ejemplo M12.2, etapa d



A una solución de M12.2c (1,38 g, 6,02 mmol) y 2-bromo-1-(4-bromofenil)etanona (1,673 g, 6,02 mmol) en acetonitrilo (35 ml) se añadió DIEA (1,051 ml, 6,02 mmol). Se agitó a temperatura ambiente durante 5 h. El disolvente se evaporó a vacío y se añadió agua (50 ml) y EtOAc (70 ml), la fase orgánica se separó y se lavó con $NaHCO_3$ sat. (30 ml), se secó con $Na_2SO_4$, se evaporó a vacío proporcionando M12.2d en bruto en forma de un aceite rojo (2,71 g), que se usó en la siguiente etapa sin purificación adicional. RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): 7,91 (m, 2H), 7,78 (d, J = 8,5 Hz, 2H), 5,60-4,90 (m, 2H), 4,29 (t ap, 1H), 3,61 (m, 1H), 2,85 (m, 1H), 2,35-1,80 (m, 2H), 1,65 (m, 1H), 1,40-1,32 (dos s, 9H), 1,02 (d, J = 6,5 Hz, 3H). CL/EM: Anal. Calc. para $[M+Na]^+$ $C_{19}H_{24}$ $^{81}BrNNaO_5$: 450,07; Encontrado: 450,11.

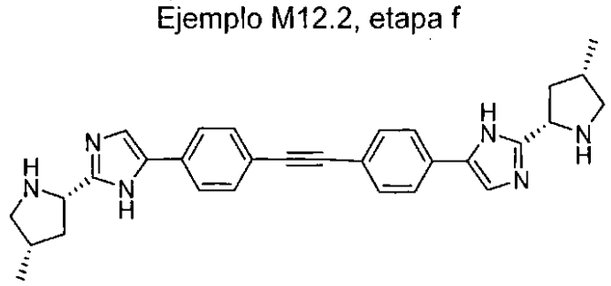
Ejemplo M12.2, etapa e



A un tubo a presión que contenía una solución del cetoéster M12.2d (2,57 g, 6,03 mmol) en xileno (50 ml) se añadió acetato de amonio (4,65 g, 60,3 mmol). El recipiente se tapó y se calentó a 140 $^0C$ durante 5 h. El componente volátil se eliminó a vacío y el residuo se fraccionó entre DCM (50 ml) y agua (40 ml). La fase orgánica se secó con $Na_2SO_4$, y se concentró a vacío. La mezcla en bruto resultante se purificó con cromatografía ultrarrápida (30-100% de EtOAc/hexano)

proporcionando el imidazol M12.2.e en forma de un sólido marrón (1,24g). RMN de $^1$H (DMSO-$d_6$, δ = 2,5 ppm, 400 MHz): 7,69 (d, J = 8,5 Hz, 2H), 7,58-7,48 (m, 3H), 4,70 (m, 1H), 3,65 (m, 1H), 3,02(m, 1H), 2,37 (m, 1H), 2,22 (m, 1H), 1,74-1,54 (m, 1H), 1,37-1,08 (dos s, 9H), 1,03 (d, J = 6,3 Hz, 3H). CL/EM: Anal. Calc. para $[M+H]^+$ $C_{19}H_{25}{}^{79}BrN_3O_2$: 406,11; Encontrado: 406,18.

Ejemplo M12.2, etapa f



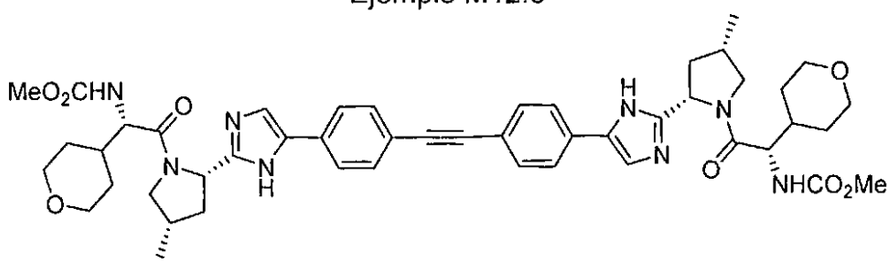
Se preparó la pirrolidina M12.2f (sal HCl) a partir del bromuro M12.2e de acuerdo con el procedimiento descrito para la síntesis de la pirrolidina M1b (sal HCl) a partir del bromuro D1b.

Ejemplo M12.2

A una mezcla de la pirrolidina M12.2f /sal HCl (200 mg, 0,321 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (124 mg, 0,707 mmol) en DMF (5 ml) se añadió DIEA (0,337 ml, 1,928 mmol) y HATU (250 mg, 0,659 mmol), y la mezcla se agitó a temperatura ambiente durante 2 h. El componente volátil se eliminó a vacío y el residuo se purificó con una HPLC de fase inversa (Phenomenex-Luna 30X100mm, S10 Axia, MeOH/TFA/agua). La muestra resultante se volvió a purificar con una HPLC de fase inversa diferente (agua-Sunfire 30X100mm S5, ACN/TFA/agua) proporcionando la sal TFA del Ejemplo M12.2 en forma de una espuma amarillo claro (77,1 mg). RMN de $^1$H (Metanol-$d_4$, δ = 3,29 ppm, 400 MHz):

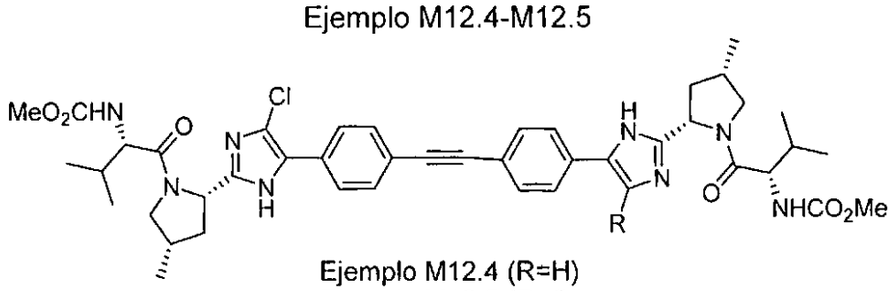
7,90 (s, 2H), 7,74 (d, J = 8,6 Hz, 4H), 7,67 (d, J = 8,5 Hz, 4H), 5,18 (m, 2H), 4,30 (t ap, 2H), 4,18 (d, J= 7,3 Hz, 2H), 3,63 (s, 6H), 3,38 (m, 2H), 2,63 (m, 2H), 2,51 (m, 2H), 1,98 (m, 2H), 1,81 (m, 2H), 1,21 (d, J = 6,3 Hz, 6H), 0,83-0,90 (m, 12H). CL (Cond. 9 y 10): >95% de índice de homogeneidad. CL/EM (Cond. 10h): $T_r$ = 2,01 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{44}H_{55}N_8O_6$: 791,42; Encontrado: 791,46.

Ejemplo M12.3




El Ejemplo M12.3 (sal TFA) se preparó a partir de la pirrolidina M12.2f /HCl y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético de acuerdo con el procedimiento descrito para la preparación del Ejemplo M12.2. TR: CL (Cond. 9 y 10): >95% de índice de homogeneidad. CL/EM (Cond. 10h): $T_r$ = 1,89 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{48}H_{59}N_8O_8$: 875,45; encontrado 875,42.

Ejemplo M12.4-M12.5

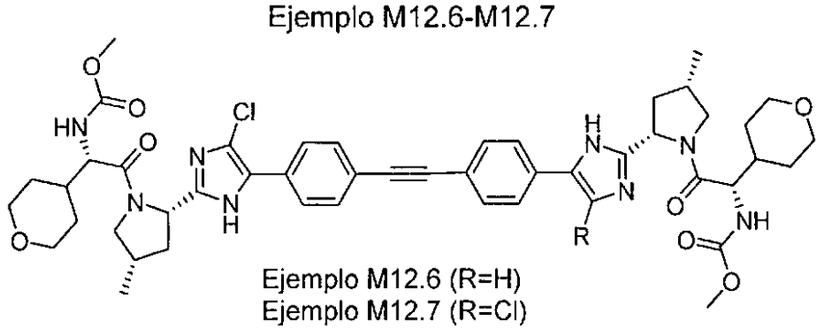



Ejemplo M12.4 (R=H)
Ejemplo M12.5 (R=Cl)

A una solución del Ejemplo M12.2 (desbasificado usando una columna MCX

y $NH_3$ 2 N/MeOH) (80 mg, 0,101 mmol) en DMF (5 ml) se añadió NCS (17,56 mg, 0,131 mmol), y se calentó a 50 °C durante 3 h. Se añadió más NCS (5 mg, 0,037 mmol) a la mezcla y se continuó agitando durante 5 horas más. El componente volátil se eliminó a vacío y el residuo se disolvió en MeOH y se sometió a una condición de HPLC de fase inversa (MeOH/TFA/agua) proporcionando el Ejemplo M12.4/sal TFA (espuma amarillo claro, 24 mg) y el Ejemplo M12.5/sal TFA (espuma amarillo claro, 28 mg). Ejemplo M12.4/sal TFA: RMN de $^1H$ (DMSO-$d_6$, δ = 2,5 ppm, 400 MHz): 8,17(s, 1H), 7,83-7,73 (m, 6H), 7,66 (d, J = 8,6 Hz, 2H), 7,30 (d, J = 8,3 Hz, 1H), 7,22 (d, J = 8,3 Hz, 1H), 5,05 (m, 1H), 4,85 (m, 1H), 4,16-4,02 (m, 4H), 3,52 (s, 6H), 3,37 (m, 1H), 3,23 (m, 1H), 2,54-2,24 (m, 4H), 1,87-1,63 (m, 4H), 1,13-1,08 (m, 6H), 0,85-0,74 (m, 12H). CL (Cond. 9a,1 y 10a,1): >95% de índice de homogeneidad. CL/EM (Cond. 11): $T_r$ = 4,26 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{44}H_{54}ClN_8O_8$: 825,39; Encontrado: 825,50. Ejemplo M12.5/sal TFA: (DMSO-$d_6$, δ = 2,5 ppm, 400 MHz): 7,79 (d, J = 8,4 Hz, 4H), 7,66 (d, J = 8,4 Hz, 4H), 7,22 (d, J = 8,3 Hz, 2H), 4,85 (m, 2H), 4,13 (t ap, 2H), 4,04 (t ap, 2H), 3,53 (s, 6H), 3,24 (t ap, 2H), 2,39 (m, 2H), 2,26 (m, 2H), 1,90 (m, 2H), 1,66 (m, 2H), 1,09 (d, J = 6,5 Hz, 6H), 0,85 (d, J = 6,8 Hz, 6H), 0,80 (d, J = 6,5 Hz, 6H). CL (Cond. 9a y 10a,1): >95% de índice de homogeneidad. CL/EM (Cond. 11): $T_r$ = 4,44 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{44}H_{53}Cl_2N_8O_6$: 859,35; Encontrado: 859,30.

Ejemplo M12.6-M12.7

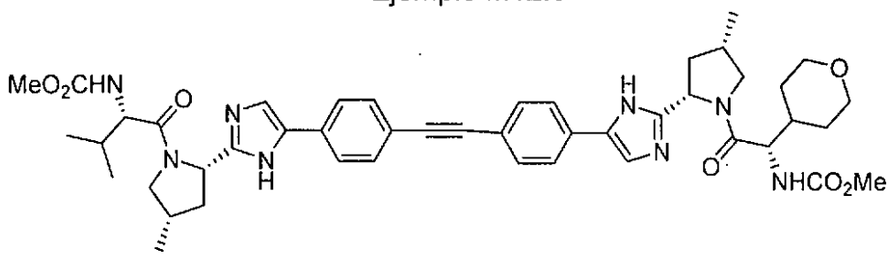


Ejemplo M12.6 (R=H)
Ejemplo M12.7 (R=Cl)

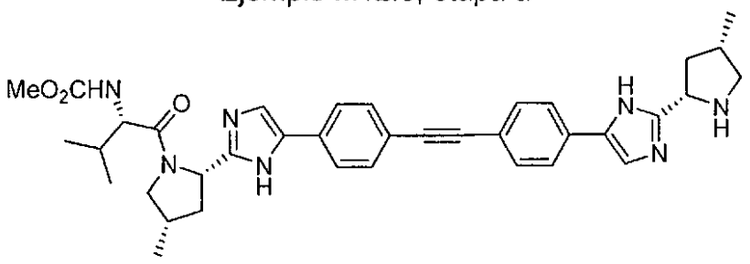
Los Ejemplos 12.6 - 12.7 se prepararon en forma de sales TFA a partir del Ejemplo M12.3 de acuerdo con el procedimiento descrito para la preparación del Ejemplo 12.4 - 12.5.

| Ejemplo | **TR (Cond. 12); % de índice de homogeneidad (Cond. 12); Datos de EM** |
|---|---|
| **M12.6** | 13,68 min.; >95%; CL/EM: Anal. Calc. para $[M+H]^+$ $C_{48}H_{58}ClN_8O_8$: 909,41; encontrado 909,8 |
| **M12.7** | 17,12 min; >95%; CL/EM: Anal. Calc. para $[M+H]^+$ $C_{48}H_{57}Cl_2N_8O_8$: 943,37; encontrado 943,7 |

Ejemplo M12.8



Ejemplo M12.8, etapa a



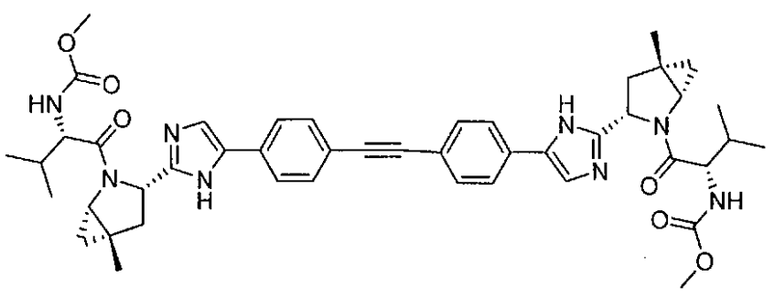
A una mezcla de la pirrolidina M12.2f/sal HCl (120 mg, 0,193 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (35,1 mg, 0,200 mmol) en DMF (2 ml), se añadió DIEA (0,168 ml, 0,964 mmol) seguido de HATU (70,4 mg, 0,185 mmol), y la mezcla se agitó a temperatura ambiente durante 1 h. El componente volátil se

eliminó a vacío y el residuo se disolvió en MeOH y se sometió a una condición de HPLC de fase inversa (MeOH/TFA/agua) para aislar la sal TFA de pirrolidina M12.8a en forma de un sólido amarillo (36 mg). La muestra se desbasificó (columna MCX; lavada con MeOH; elución con $NH_3$ 2 N/MeOH) proporcionando un sólido amarillo (22,3 mg). CL/EM: Anal. Calc. para $[M+H]^+$ $C_{37}H_{44}N_7O_3$: 634,35; Encontrado: 634,35.

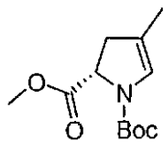
Ejemplo M12.8

A una solución de la pirrolidina M12.8a (22,3 mg, 0,035 mmol) y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (12,99 mg, 0,060 mmol) en DMF (2 ml) se añadió DIEA (0,018 ml, 0,106 mmol) y HATU (13,65 mg, 0,036 mmol), y la mezcla se agitó a temperatura ambiente durante 2 h. El componente volátil se eliminó a vacío y el residuo se disolvió en MeOH y se sometió a una condición de HPLC de fase inversa (Columna: Phenomenex-Luna 30X100mm, S10 Axia; MeOH/TFA/agua). La muestra resultante se volvió a purificar con una segunda HPLC de fase inversa (Columna: agua-Sunfire 30X100mm S5; ACN/TFA/agua) proporcionando la sal TFA del Ejemplo M12.8 en forma de una espuma amarillo claro (16 mg). RMN de $^1H$ (Metanol-$d_4$, $\delta$ = 3,29 ppm, 400 MHz): 7,92 (d, J = 5,0 Hz, 2H), 7,77 (d, J = 8,5 Hz, 4H), 7,72-7,69 (m, 4H), 5,21 (m, 2H), 4,39-4,22 (m, 4H), 3,92 (m, 2H), 3,67 (s, 6H), 3,47-3,28 (m, 4H), 2,68 (m, 2H), 2,54 (m, 2H), 2,06-1,85 (m, 4H), 1,25 (d, J = 6,5 Hz, 6H), 0,93 (d, J = 6,7 Hz, 3H), 0,91 (d, J = 7,3 Hz, 6H). CL (Cond. 9 y 10): >95% de índice de homogeneidad. CL/EM (Cond. 10d): $T_r$ = 3,10 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{46}H_{57}N_8O_7$: 833,44; Encontrado: 833,47.

Ejemplo M12.9

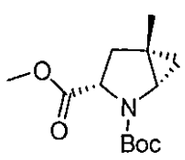


Ejemplo M12.9, Etapa a

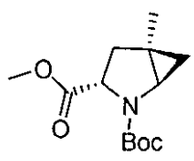


A una solución de una mezcla de M12.2a-1 y M12.2a-2 (4,75 g, 18,46 mmol) se añadió Superhidruro (19,20 ml, 19,20 mmol) gota a gota a -50 °C en un baño de hielo carbónico/acetona durante 10 min. Se añadió base de Hünig (13,58 ml, 78 mmol) y se agitó durante 10 min, y se añadió DMAP (0,122 g, 0,997 mmol) en forma sólida, se agitó durante 15 min, y se añadió anhídrido trifluoroacético (2,98 ml, 21,08 mmol) gota a gota durante 15 min. Después se retiró del baño de hielo carbónico/acetona y la mezcla de reacción se agitó durante 4 h mientras se dejaba descongelar a temperatura ambiente. La mezcla de reacción se lavó con agua (50 ml), NaCl sat. (30 ml), y se concentró a vacío. El material en bruto resultante se purificó con cromatografía ultrarrápida (8-60% de EtOAc/hexano) proporcionando el éster M12.9a en forma de un aceite amarillo (2,85 g). RMN de $^1$H ($CDCl_3$, 400 MHz): 6,36 (s, 0,5H), 6,25 (s, 0,5H), 4,70-4,57 (m, 1H), 3,78 (s, 3H), 2,96 (m, 1H), 2,54 (m, 1H), 1,70 (s, 3H), 1,50 (s, 4,5H), 1,44 (s, 4,5H).

Ejemplo M12.9, Etapa b



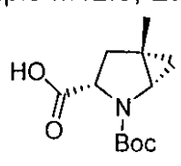

M12.9b-1




M12.9b-2

Se añadió dietilcinc (1,1 M en tolueno, 59,1 ml, 65,0 mmol) gota a gota durante 20 min a una solución fría (-23 °C) en tolueno (60 ml) del éster M12.9a (5,23 g, 21,68 mmol), y se agitó durante 10 min. Se añadió cloroyodometano (9,44 ml, 130 mmol) gota a gota durante 10 min, y la mezcla de reacción se agitó a -21 °C durante 16 h. Se añadió $NaHCO_3$ sat. (60 ml) a la mezcla de reacción, se extrajo del baño helado y la mezcla se agitó durante 10 min. Después se filtró, y la torta de filtrado se lavó con tolueno (50 ml). El filtrado se fraccionó, y la fase orgánica se secó con $Na_2SO_4$, y se concentró a vacío. El material en bruto resultante se purificó con cromatografía ultrarrápida (2-10% de EtOAc/hexano) proporcionando el éster M12.9b-1 (primero en eluir; aceite incoloro; 2,88 g) y el éster M12.9b-2 (segundo en eluir; aceite incoloro; 1,01g). La asignación de las estereoquímicas relativas se realizó basándose en estudios NOE. Ester M12.9b-1: RMN de $^1H$ ($CDCl_3$, 400 MHz): 4,65-4,52 (m, 1H), 3,72 (s, 3H), 3,28-3,17 (m, 1H), 2,44-2,32 (m, 1H), 2,16-2,10 (m, 1H), 1,51-1,42 (dos s, 9H), 1,24 (s, 3H), 1,07 (m, 1H), 0,69-0,60 (m, 1H).

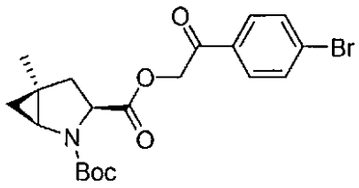
Ejemplo M12.9, Etapa c




A una solución de M12.9b-1 (2,88 g, 11,28 mmol) en etanol (20 ml) se añadió una solución de LiOH (0,324 g, 13,54 mmol) en agua (10,00 ml), y la mezcla se agitó a temperatura ambiente durante 6 h. La mayor parte del componente volátil se

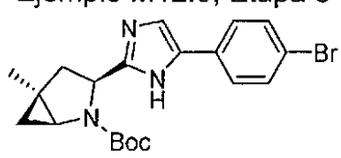
eliminó a vacío, y el residuo se fraccionó entre agua (20 ml) y éter (20 ml). La fase acuosa se enfrió en un baño de agua y hielo, se acidificó con HCl 1 N a una región de pH de 2, y se extrajo con EtOAc (30 ml, 4x). La fase orgánica combinada se secó con $Na_2SO_4$, se evaporó a vacío proporcionando el ácido M12.9c en forma de un sólido pegajoso (2,55 g). RMN de $^1H$ ($CDCl_3$, 400 MHz): 4,64 (m, 1H), 3,25 (s ap, 1H), 2,70-2,40 (m, 1H), 2,14 (m, 1H), 1,54-1,44 (m, 9H), 1,27 (s, 3H), 1,10-0,80 (m, 1H), 0,67 (m, 1H).

Ejemplo M12.9, Etapa d



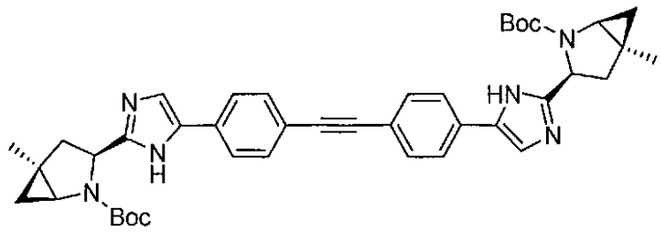

A una solución del ácido M12.9c (2,05 g, 8,50 mmol) en acetonitrilo (50 ml) se añadió 2-bromo-1-(4-bromofenil)etanona (2,361 g, 8,50 mmol) seguido de DIEA (1,484 ml, 8,50 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 16 h. La mayor parte del componente volátil se eliminó a vacío, y el residuo se fraccionó entre EtOAc (50 ml) y agua (50 ml). La fase orgánica se lavó con $NaHCO_3$ sat. (30 ml) y NaCl sat. (20 ml), se secó con $Na_2SO_4$, y se evaporó a vacío proporcionando el cetoéster M12.9d en forma de espuma blanca (3,5 g). CL/EM: Anal. Calc. para $[M+Na]^+$ $C_{20}H_{24}{}^{81}BrNNaO_5$: 462,07; Encontrado: 461,91.

Ejemplo M12.9, Etapa e



A una mezcla del cetoéster M12.9e (3,5 g, 7,99 mmol) y xileno (80 ml) en un tubo a presión se añadió acetato de amonio (6,16 g, 80 mmol), y la mezcla de reacción se tapó y se calentó a 140 °C durante 4,5 h. El componente volátil se eliminó a vacío y el residuo se fraccionó entre DCM (70 ml) y agua (70 ml). La fase orgánica se lavó con $NaHCO_3$ sat. (30 ml), y se concentró a vacío. El material en bruto resultante se purificó con cromatografía ultrarrápida (40-100% de EtOAc/hexano) proporcionando el imidazol M12.9e en forma de un sólido marrón (2,8 g). RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): 7,68 (m, 2H), 7,57-7,49 (m, 3H), 5,08 (m, 1H), 3,20 (m, 1H), 2,45-2,09 (M, 2H), 1,69-1,52 (m, 1H), 1,42-1,16 (m, 12H), 0,62 (m, 1H). CL/EM: Anal. Calc. para $[M+H]^+$ $C_{20}H_{25}{}^{81}BrN_3O_2$: 420,11; Encontrado: 420,02.

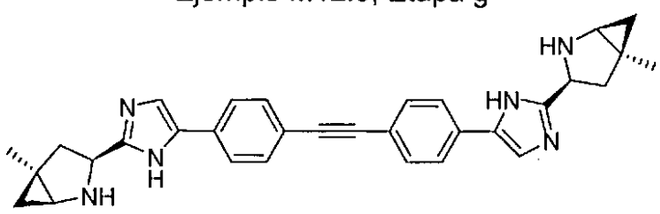
Ejemplo M12.9, Etapa f




A un tubo a presión que contenía una solución del bromuro M12.9e (0,354 g, 1,007 mmol) y 1,2-bis(trimetilstannil)etino (0,354 g, 1,007 mmol) en DMF (15 ml) se añadió Pd $(Ph_3P)_4$ (0,070 g, 0,060 mmol), y la mezcla de reacción se desgasificó durante 10 min y el recipiente de reacción se tapó y se calentó a 90 °C durante 14 h. La mayor parte del componente volátil se eliminó a vacío, y el residuo se fraccionó entre DCM (60 ml) y agua (40 ml). La fase orgánica se secó con $Na_2SO_4$, y se evaporó a vacío. El material en bruto resultante se purificó con cromatografía ultrarrápida (40-100% de EtOAc/hexanos) proporcionando el alquino M12.9f en

forma de un sólido rojo (0,3 g). CL/EM: Anal. Calc. para $[M+H]^+$ $C_{42}H_{49}N_6O_4$: 701,38; Encontrado: 701,43.

Ejemplo M12.9, Etapa g



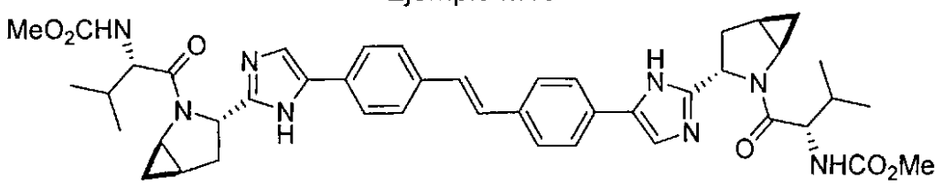

Se añadió HCl 4 N en dioxano (3,90 ml, 128 mmol) al carbamato M12.9f (0,3 g, 0,428 mmol), y la mezcla se agitó a temperatura ambiente durante 5 h. El componente volátil se eliminó a vacío y el residuo se secó a vacío elevado toda la noche proporcionando la sal HCl de pirrolidina M12.9g en forma de un sólido amarillo (0,27 g). CL/EM: Anal. Calc. para $[M+H]^+$ $C_{32}H_{33}N_6$: 501,28; Encontrado: 501,22.

Ejemplo M12.9

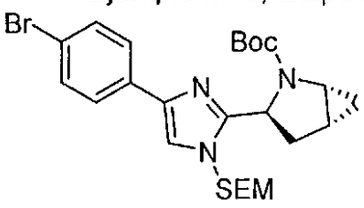
A una mezcla de M12.9g/sal HCl (60 mg, 0,093 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (35,8 mg, 0,204 mmol) en DMF (2 ml) se añadió DIEA (0,097 ml, 0,557 mmol) y HATU (72,7 mg, 0,191 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 2 h. El componente volátil se eliminó a vacío y el residuo se disolvió en MeOH y se sometió a una purificación por HPLC de fase inversa (Phenomenex-Luna 30X100mm, S10 Axia, MeOH/TFA/agua). La muestra resultante se volvió a purificar con una segunda HPLC de fase inversa (agua-Sunfire 30X150 mm OBD, ACN/TFA/agua) proporcionando la sal TFA del Ejemplo M12.9 en forma de espuma amarillo claro (37 mg). CL/EM (Cond. 10d): $T_r$

= 3,08 min. CL (Cond. 9 y 10): >95% de índice de homogeneidad. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{46}H_{55}N_8O_6$: 815,42; Encontrado: 815,46.

Ejemplo M13




Ejemplo M13, Etapa a

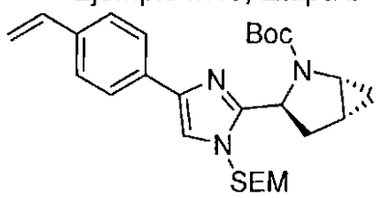



(No se determinó la regioquímica por MEB)

A una solución del bromuro M3h (1,0 g, 2,47 mmol) en DMF (25 ml) se añadió hidruro sódico (60%; 0,109 g, 2,72 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 20 min. Después se añadió (2-(clorometoxi)etil)trimetilsilano (0,482 ml, 2,72 mmol) gota a gota, y la reacción se agitó durante 21h. El componente volátil se eliminó a vacío, y el residuo se fraccionó entre acetato de etilo (25 ml) y agua (25 ml). La fase acuosa se extrajo con acetato de etilo (2 x 25 ml), y la fase orgánica combinada se lavó con salmuera (25 ml), se secó sobre $MgSO_4$, se filtró, y se concentró a vacío. El residuo se tomó en $CHCl_3$ (2 ml) y se cargó en un cartucho de gel de sílice Thomson eluyendo con 25% de acetato de etilo/hexanos proporcionando el bromuro M13a de estructura regioquímica desconocida en forma de espuma amarillo claro (1,171 g). RMN de $^1H$

(DMSO-$d_6$, δ = 2,5 ppm, 400 MHz): 7,71 (s, 1H), 7,69 (d, J = 8,6, 2H), 7,52 (d, J = 8,6, 2H), 5,62–5,31 (s ancho, 1H), 5,26 (d, J = 10,8, 1H), 4,84–4,66 (s ancho aparente, 1H), 3,57–3,36 (s ancho aparente, 1H), 3,50 (t, J = 8,1, 2H), 2,44–2,20 (s ancho aparente, 2H), 1,77–1,60 (s ancho aparente, 1H), 1,52–1,23 (s ancho, 4H), 1,23–0,96 (s ancho, 5H), 0,92–0,79 (m, 2H), 0,78–0,69 (m, 1H), 0,64– 0,55 (s ancho aparente, 1H), 0,00 (s, 9H). CL/EM: Anal. Calc. para $[M+H]^+$ $C_{25}H_{37}{}^{79}BrN_3O_3Si$: 534,18; Encontrado: 533,99.

Ejemplo M13, Etapa b

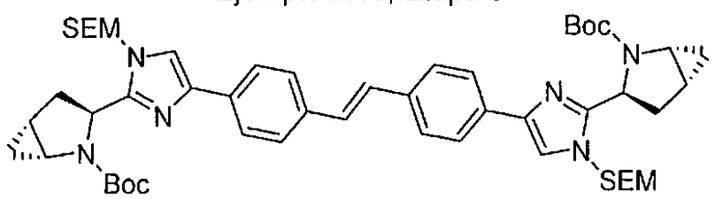



(No se determinó la regioquímica por MEB)

A una solución del bromuro M13a (0,5542 g, 1,037 mmol) y trietilamina (0,434 ml, 3,11 mmol) en 2-propanol (2,000 ml) y agua (1 ml) en un recipiente de reacción sellado se añadió viniltrifluoroborato potásico (0,181 g, 1,348 mmol) seguido de complejo de dicloruro de 1,1'-bis(difenilfosfino)ferroceno-paladio(II) y diclorometano (0,085 g, 0,104 mmol). La mezcla de reacción se purgó con nitrógeno, se tapó y se calentó a 100 °C durante 17h. El componente volátil se eliminó a vacío, y el residuo se fraccionó entre acetato de etilo (25 ml) y agua (25 ml), y la fase acuosa se extrajo con acetato de etilo (2 x 25 ml). La fase orgánica combinada se secó sobre $MgSO_4$, se filtró, y se concentró a vacío. El residuo se tomó en $CHCl_3$ (4 ml) y se cargó en un cartucho de gel de sílice Thomson eluyendo con 25% de acetato de etilo/hexanos proporcionando el alqueno M13b en forma de un aceite viscoso amarillo claro (345,4 mg). RMN de $^1H$ (DMSO-$d_6$, δ = 2,5 ppm, 400 MHz): 7,71 (d, J = 8,3, 2H), 7,67 (s,

1H), 7,45 (d, J = 8,3, 2H), 6,72 (dd, J = 17,6,11,1, 1H), 5,8 (dd, J = 0,8, 17,6, 1H), 5,60–5,29 (s ancho aparente, 1H), 5,26 (d, J = 10,8, 1H), 5,22 (d, J = 11,8, 1H), 4,83–4,67 (s ancho aparente, 1H), 3,59 – 3,35 (s ancho aparente, 1H), 3,51 (t, J = 8,1, 2H), 2,41–2,23 (s ancho aparente, 2H), 1,76–1,59 (s ancho aparente, 1H), 1,51–1,22 (s ancho aparente, 4H), 1,22–0,97 (s ancho aparente, 5H), 0,93-0,80 (m, 2H), 0,80–0,71 (m, 1H), 0,65–0,56 (s ancho aparente, 1H), 0,00 (s, 9H). CL/EM: Anal. Calc. para $[M+H]^+$ $C_{27}H_{40}N_3O_3Si$: 482,28; Encontrado: 482,24.

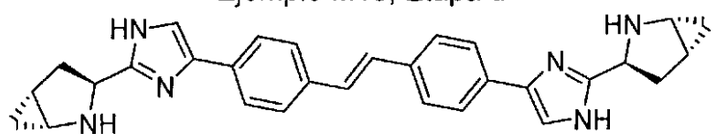
Ejemplo M13, Etapa c




(No se determinó la regioquímica por MEB)

A una solución del alqueno M13b (0,748 g, 1,552 mmol) en $CH_2Cl_2$ (2 ml) se añadió Catalizador de 2ª Generación Grubbs (0,132 g, 0,155 mmol), y se agitó a temperatura ambiente en atmósfera de nitrógeno durante 18 h. La reacción se cargó en un cartucho de gel de sílice Thomson eluyendo con 30% de acetato de etilo/hexanos proporcionando M13c en forma de una espuma tostada (0,50 g). RMN de $^1H$ (DMSO-$d_6$, δ = 2,5 ppm, 400 MHz): 7,74 (d, J = 8,4, 4H), 7,68 (s, 2H), 7,58 (d, J = 8,3, 4H), 7,22 (s, 2H), 5,72-5,34 (bs, 3H), 5,34-5,21 (m, 2H), 4,94-4,63 (s ancho aparente, 3H), 3,52 (t, J = 7,8, 4H), 2,45-2,20 (s ancho aparente, 4H), 1,88-1,57 (s ancho aparente, 2H), 1,57-1,26 (s ancho, 8H), 1,26-0,98 (s ancho, 10H), 0,93-0,80 (m, 4H), 0,80-0,69 (m, 2H), 0,69 -0,51 (ap bs, 2H), 0,00 (s, 18H).

Ejemplo M13, Etapa d



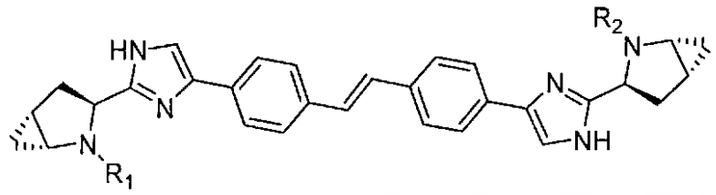
Se añadió cuidadosamente HCl 4 N/dioxano (13 ml) a un matraz que contenía M13c (0,4799 g, 0,513 mmol) que se enfrió con un baño de hielo/agua. Se añadió una mezcla de agua (4 ml) y HCl 12 N (2 ml) a la mezcla anterior y el baño helado se eliminó y se continuó agitando la mezcla de reacción durante 24 h. Se añadió MeOH (2 ml) a la reacción, y se siguió agitando durante 17 h. Todos los disolventes se eliminaron a vacío proporcionando la pirrolidina M13d (0,4 HCl) en forma de un sólido amarillo/tostado (317 mg). RMN de $^1$H (DMSO-$d_6$, δ = 2,5 ppm, 400 MHz): 10,78-9,87 (muy br s, ~3H), 8,01 (s, 2H), 7,87 (d, J = 8,4, 4H), 7,71 (d, J = 8,6, 4H), 7,35 (s, 2H), 4,76 (t ap, J = 8,8, 2H), 3,43 (t ap, J = 5,1, 2H), 2,64 (m, 2H), 2,55-2,52 (m, 2H), 1,95 (m, 2H), 1,16-1,05 (m, 2H), 0,86 (m, 2H). CL/EM: Anal. Calc. para $[M+H]^+$ $C_{30}H_{31}N_6$: 475,26; Encontrado: 475,26.

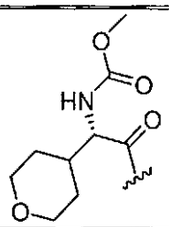
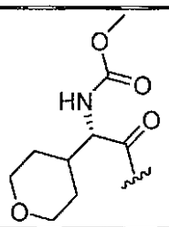
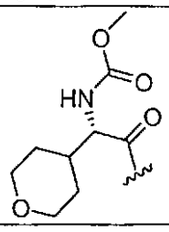
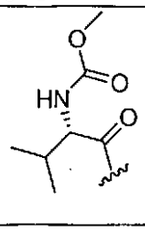
Ejemplo M13

La sal TFA del Ejemplo M13 se preparó a partir de la pirrolidina M13d (0,4 HCl) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico de acuerdo con el procedimiento descrito para la preparación del Ejemplo M1. RMN de $^1$H (DMSO-$d_6$, δ = 2,5 ppm, 400 MHz): 8,14-7,95 (s ancho, 2H), 7,80-7,74 (m, 8H), 7,40 (s, 2H), 7,25 (d, J = 8,3, 2H), 5,0 (t ap, J = 7,3, 2H), 4,41 (t ap, J = 7,6, 2H), 3,81-3,67 (m, 2H), 3,54 (s, 6H), 2,57-2,46 (superpuesto a DMSO-$_{d6}$) (m, 2H), 2,44-2,31 (m, 2H), 2,19-2,05 (m, 2H), 1,98-1,87 (m, 2H), 1,02-0,89 (m, 7,5H), 0,89-0,70 (m, 8,5H). CL (Cond. 3): $T_r$ = 1,92 min; CL/EM: Anal. Calc. para $[M+H]^+$ $C_{44}H_{53}N_8O_6$: 789,41; Encontrado: 789,46.

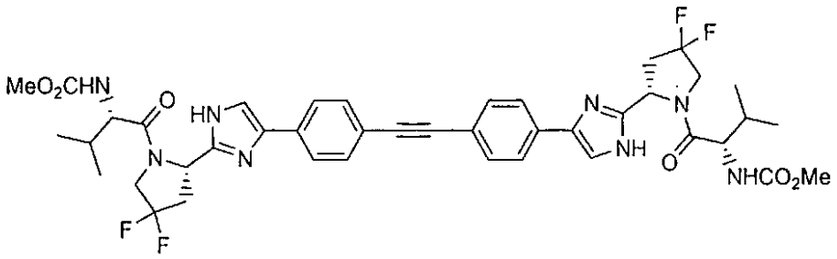
Ejemplos M14-M15

El Ejemplo M14 (sal TFA) se preparó a partir de la pirrolidina M13d y del ácido apropiado empleando el procedimiento descrito para la síntesis del Ejemplo M1. En el caso del Ejemplo M15 un se empleó una mezcla equimolar de ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético para la etapa de acoplamiento y la mezcla de productos estadística resultante se separó mediante la técnica de HPLC descrita para el Ejemplo M1.

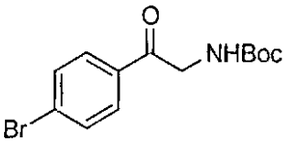


| Ejemplo | $R_1$ | $R_2$ | $T_r$ (Cond. 3); % de índice de homogeneidad (Cond. 9 y 10); CL/Datos de EM |
|---|---|---|---|
| M14 |  |  | 1,72 min.; >98%; CL/EM: Anal. Calc. para $[M+H]^+$ $C_{48}H_{57}N_8O_8$: 873,43; encontrado 873,48 |
| M15 |  |  | 1,82 min.; >98%; CL/EM: Anal. Calc. para $[M+H]^+$ $C_{46}H_{55}N_8O_7$: 831,42; encontrado 831,47 |

Ejemplo N1

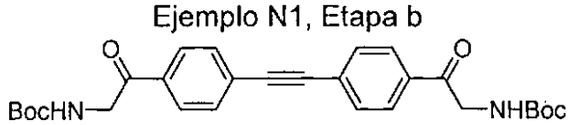


Ejemplo N1, Etapa a



A una suspensión de 2-amino-1-(4-bromofenil)etanona, HCl (4,0 g, 15,97 mmol) en DCM (50,0 ml) se añadió bicarbonato sódico (4,02 g, 47,9 mmol). Después se añadió anhídrido de Boc (3,89 ml, 16,77 mmol) a la solución y la mezcla de reacción se calentó a temperatura ambiente y se agitó durante 18 h. Después se añadió DIEA (3 ml, 17,18 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 2 h, la CLEM mostró que se había completado la reacción. La mezcla de reacción se diluyó con EtOAc y agua, la fase orgánica se lavó con ácido cítrico al 5%, agua y NaCl sat., se secó sobre $Na_2SO_4$ anhidro, se filtró y se concentró proporcionando el bromuro N1A (5,0 g) en forma de un sólido amarillo, que se usó en la siguiente etapa sin purificación adicional. RMN de $^1H$ (400 MHz, MeOD) ppm 7,89 (2 H, m), 7,68 (2 H, m, *J*=8,53 Hz), 4,52 (2 H, s), 1,38 - 1,51 (9 H, m). CL/EM (Cond. 10d): $T_r$ = 3,56 min. CL/EM: Anal. Calc. para $[M+Na]^+$ $C_{13}H_{16}BrNaNO_3$: 336,03; Encontrado: 335,97.

Ejemplo N1, Etapa b



A una solución del carbamato N1a (2,0 g, 6,37 mmol) en DMF (5 ml) se

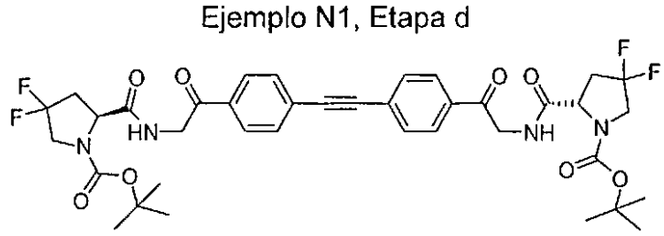
añadió 1,2-bis(trimetilstannil)etina (1,119 g, 3,18 mmol). La mezcla de reacción se desgasificó, se añadió tetrakis(trifenilfosfina)paladio(0) (0,184 g, 0,159 mmol) y la mezcla se calentó a 90 °C durante 4 h. La mezcla de reacción en bruto se cargó en un cartucho de gel de sílice de 90 g que se eluyó con un gradiente de 20 min de 0-60% de EtOAc en hexano. El alquino N1b (0,83 g) se recolectó en forma de un sólido amarillo. CL/EM (Cond. 10d): $T_r$ = 4,1 min. CL/EM: Anal. Calc. para $[M+Na]^+$ $C_{28}H_{32}NaN_2O_6$: 515,23; Encontrado: 515,10.

Ejemplo N1, Etapa c



A una solución del alquino N1b (1,13 g, 2,294 mmol) en 1,4-dioxano (5 ml) se añadió HCl 4 M en dioxano (4 ml, 16,00 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se concentró a sequedad proporcionando un sólido amarillo. El sólido se lavó con hexano y EtOAc, después se secó proporcionando la aminocetona N1c, 2 HCl (0,508 g). RMN de $^1H$ (400 MHz, MeOD) ppm 8,10 (4 H, d, *J*=8,53 Hz), 7,78 (4 H, d, *J*=8,53 Hz), 4,64 (4 H, s). CL/EM (Cond. 10d): $T_r$ = 1,94 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{18}H_{17}N_2O_2$: 293,12; Encontrado: 293,07.

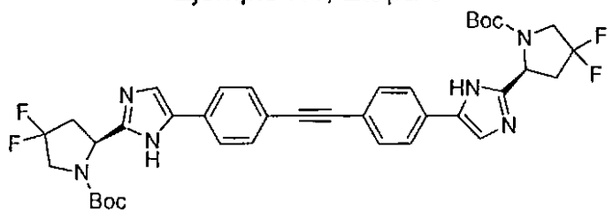
Ejemplo N1, Etapa d



A una mezcla del ácido (S)-1-(terc-butoxicarbonil)-4,4-difluoropirrolidin-2-

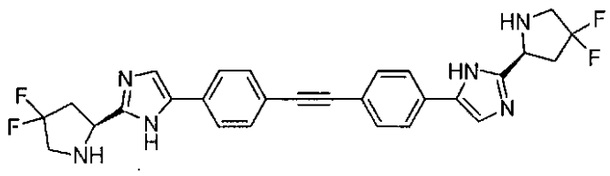
carboxílico (0,25 g, 0,995 mmol), la aminocetona N1c, 2 HCl (0,182 g, 0,498 mmol), HATU (0,189 g, 0,498 mmol) en DMF (2 ml) se añadió DIEA (0,521 ml, 2,99 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se cargó en un cartucho de gel de sílice de 80 g que se eluyó con un gradiente durante 20 min de 0-100% de EtOAc en hexano. La cetoamida N1d (0,12 g) se recolectó en forma de un sólido amarillo. CL/EM (Cond. 10d): $T_r$ = 4,08 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{38}H_{43}F_4N_4O_8$ : 759,29; Encontrado: 759,03.

Ejemplo N1, Etapa e



En un tubo sellado, una mezcla de cetoamida N1d (0,12 g, 0,158 mmol) y acetato de amonio (0,122 g, 1,582 mmol) en xileno (2 ml) se calentó a 140 °C durante 4 h. La mezcla de reacción se fraccionó entre EtOAc y agua, la fase orgánica se lavó con $NaHCO_3$ sat. y NaCl sat., se secó sobre $Na_2SO_4$ anhidro, se filtró y se concentró. El residuo se disolvió en una cantidad pequeña de cloruro de metileno y se cargó en un cartucho de 40 g de gel de sílice que se eluyó con un gradiente durante 20 min de 0-100% de EtOAc en hexano. El imidazol N1e (0,054 g) se recolectó en forma de un sólido amarillo. CL/EM (Cond. 10d): $T_r$ = 3,3 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{38}H_{41}F_4N_6O_4$: 721,3; Encontrado: 721,10.

Ejemplo N1, Etapa f

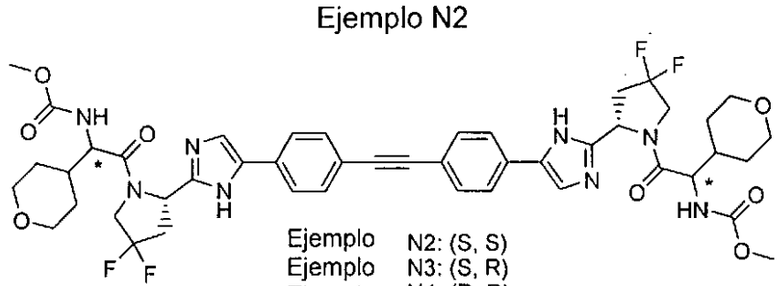


A una solución del imidazol N1e (0,054 g, 0,075 mmol) en 1,4-dioxano se añadió HCl 4 M en dioxano (0,5 ml, 2,0 mmol) más unas pocas gotas de MeOH. La mezcla de reacción se agitó a temperatura ambiente durante 4 h, y se concentró proporcionando la pirrolidina N1f, 4 HCl (0,055 g) en forma de un sólido amarillo claro. CL/EM (Cond. 10d): $T_r$ = 2,94 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{28}H_{25}F_4N_6$: 520,2; Encontrado: 521,10.

Ejemplo N1

A una mezcla de ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (0,014 g, 0,079 mmol), la pirrolidina N1f, 4 HCl (0,025 g, 0,038 mmol), HATU (0,030 g, 0,079 mmol) en DMF (2 ml) se añadió DIEA (0,039 ml, 0,225 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 18 h, se diluyó con MeOH, se filtró y se purificó mediante HPLC de fase inversa proporcionando la sal TFA del Ejemplo N1 (0,026 g) en forma de un sólido blanco. CL (Cond. 10b y 10c): >95% de índice de homogeneidad. CL/EM (Cond. 10d): $T_r$ = 3,11 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{42}H_{47}F_4N_8O_6$: 835,35; Encontrado: 835,16.

Ejemplo N2



Ejemplo N2: (S, S)
Ejemplo N3: (S, R)
Ejemplo N4: (R, R)

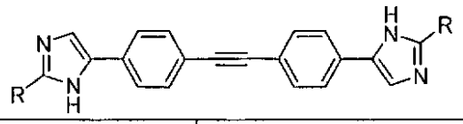
La pirrolidina N1f se acopló con ácido 2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético empleando el procedimiento descrito para la síntesis del Ejemplo N1. Los tres diaestereómeros resultantes (sales TFA) se separaron empleando las siguientes condiciones: Columna = Waters-Sunfire 30 X 100 mm S5; % inicial de B = 0; % final de B = 32; Tiempo de gradiente = 25 min; Tiempo de terminación = 25 min; Caudal = 40 ml/min; Longitud de onda = 220 nm; Disolvente A = 0,1 % de TFA en 10% de MeCN/90% de agua; Disolvente B = 0,1 % de TFA en 90% de MeCN/10% de agua.

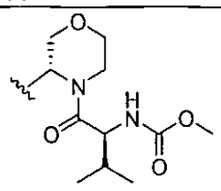
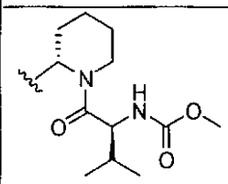
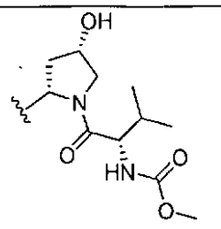
| Ejemplo | Condiciones analíticas |
|---|---|
| N2 | CL (Cond. 10b y 10c): >95% de índice de homogeneidad. CL/EM (Cond. 10d): $T_r$ = 2,90 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{46}H_{51}F_4N_8O_8$: 919,37; Encontrado: 919,41. |
| N3 | CL (Cond. 10b y 10c): >95% de índice de homogeneidad. CL/EM (Cond. 10d): $T_r$ = 2,96 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{46}H_{51}F_4N_8O_8$: 919,37; Encontrado: 919,41. |
| N4 | CL (Cond. 10b y 10c): >95% de índice de homogeneidad. CL/EM (Cond. 10d): $T_r$ = 3,00 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{46}H_{51}F_4N_8O_8$: 919,37; Encontrado: 919,41. |

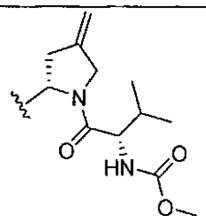
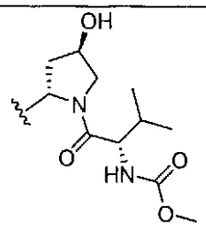
Ejemplos N5-N7

Los Ejemplos N5-N7 (sal TFA) se prepararon comenzando a partir de la

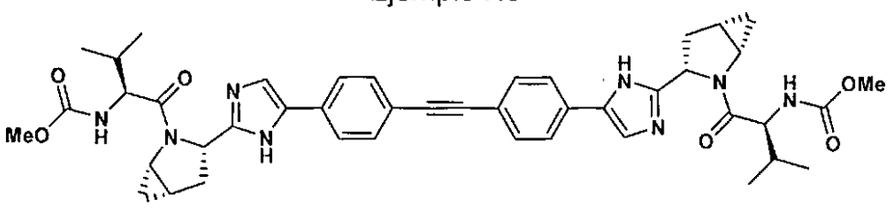
aminocetona N1c y materiales iniciales apropiados, obtenidos de fuentes comerciales, empleando los procedimientos que se describen para la síntesis del Ejemplo N1.



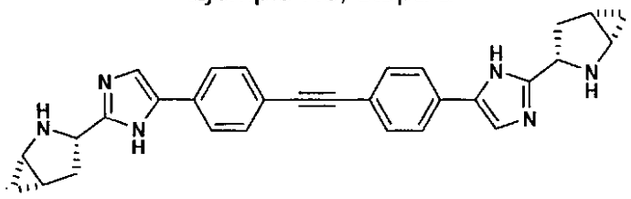
| Ejemplo | R | Condiciones analíticas |
|---|---|---|
| N5 |  | CL (Cond. 10b y 10c): >95% de índice de homogeneidad. CL/EM (Cond. 10d): $T_r$ = 3,05 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{42}H_{51}N_8O_8$: 795,38; Encontrado: 795,23. |
| N6 |  | CL (Cond. 10b y 10c): >95% de índice de homogeneidad. CL/EM (Cond. 10d): $T_r$ = 3,23 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{44}H_{55}N_8O_6$: 791,42; Encontrado: 791,54. |
| N7 |  | CL (Cond. 10b y 10c): 93% de índice de homogeneidad. CL/EM (Cond. 10d): $T_r$ = 3,06 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{42}H_{51}N_8O_8$: 795,38; Encontrado: 795,4. |

| | | |
|---|---|---|
| N7.1 |  | CL (Cond. 10b y 10c): 97% de índice de homogeneidad. CL/EM (Cond. 10d): $T_r$ = 3,056 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{44}H_{51}N_8O_6$: 787,39; Encontrado: 787,4. |
| N7.2 |  | CL (Cond. 10b y 10c): 98% de índice de homogeneidad. CL/EM (Cond. 10d): $T_r$ = 2,878 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{42}H_{51}N_8O_8$: 795,38; Encontrado: 795,41. |

Ejemplo N8



Ejemplo N8, etapa a



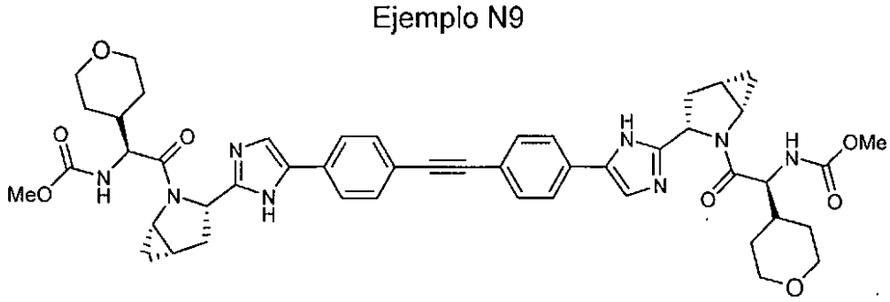
La pirrolidina N8a (sal HCl) se preparó a partir de la aminocetona N1c y ácido (1S,3S,5S)-2-(terc-butoxicarbonil)-2-azabiciclo[3.1.0]hexano-3-carboxílico (para el

procedimiento de preparación, véase el documento WO2004/052850) de acuerdo con los procedimientos que se describen para la preparación de la pirrolidina N1f. RMN de $^1$H (MeOD, δ = 3,33 ppm, 400 MHz): 7,98 (s, 2H ), 7,87 (d, J = 8,4, 4H), 7,69 (d, J = 8,4, 4H), 5,59 (dd, J = 10,2, 5,4, 2H), 3,61-3,56 (m, 2H), 3,05-2,98 (m, 2H), 2,67 (dd, J = 14,2, 5,4, 2H), 2,20-2,14 (m, 2H), 1,28-1,22 (m, 2H), 1,19-1,13 (m, 2H). CL/EM: Anal. Calc. para $[M+H]^+$ $C_{30}H_{29}N_6$: 473,24; encontrado 473,2.

Ejemplo N8

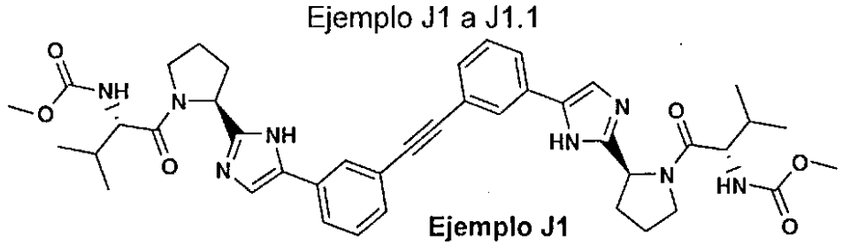
El Ejemplo N8 se preparó a partir de pirrolidina N8a de acuerdo con el procedimiento descrito para la preparación del Ejemplo N1 a excepción de que la purificación se realizó con unas condiciones de HPLC de fase inversa modificadas (ACN/agua/$NH_4OAc$). El Ejemplo N8 se recuperó en forma de un sólido amarillo claro. CL (Cond. 10e): >99% de índice de homogeneidad. CL/EM (Cond. 10f): $T_r$ = 2,21 min. RMN de $^1$H (DMSO, δ = 2,50 ppm, 400 MHz): 12,33 (s, 0,28H), 11,86 (s, 1,72H), 7,74 (d, J = 8,4, 3,42H), 7,65 (d, J = 8,4, 0,58H), 7,55 (d, J = 8,4, 0,58H), 7,51 (s, 2H), 7,49 (d, J = 8,4, 3.,42H), 7,31 (d, J = 8,8, 2H), 5,39 (d ap, 0,15H), 3,34 (dd, J = 10,8, 2,4, 3,85H), 4,29 (t ap, 2H), 3,90 (m ancho, 2H), 3,55 (s, 6H), 2,64-2,56 (m, 2H), 2,17 (d ap, 2H), 2,08-1,98 (m, 2H), 1,79-1,74 (m, 4H), 0,92-0,83 (m, 14H). CL/EM: Anal. Calc. para $[M+H]^+$ $C_{44}H_{51}N_8O_6$: 787,39; encontrado 787,8.

Ejemplo N9

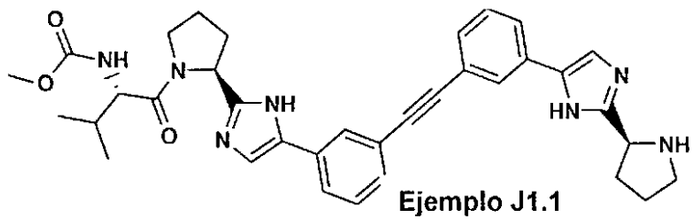


El compuesto N9 (sal TFA) se preparó a partir de la pirrolidina N8a y ácido (*S*)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético de acuerdo con el procedimiento descrito para la preparación del Ejemplo N1 a excepción de que se empleó el sistema de disolventes ACN/agua/TFA en su purificación. CL (Cond. 10e): >97% de índice de homogeneidad. CL/EM (Cond. 10g): $T_r$ = 1,82 min. CL/EM: Anal. Calc. para $[M+H]^+$ $C_{48}H_{55}N_8O_8$: 871,41; encontrado 871,6.

Ejemplo J1 a J1.1

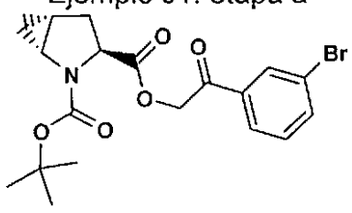


**Ejemplo J1**



**Ejemplo J1.1**

Ejemplo J1. etapa a

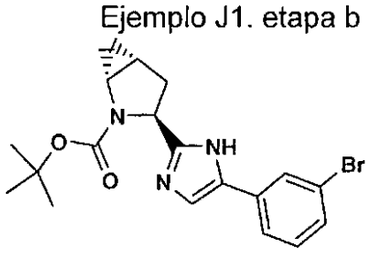


Se añadió DIPEA (2,8 ml, 16 mmol) a una suspensión del ácido M3f (2,00 g, 8,80 mmol) y 2-bromo-1-(3-bromofenil)etanona (2,22 g, 8,00 mmol) en acetonitrilo (25 ml) y la mezcla de reacción se agitó toda la noche a temperatura ambiente. La mezcla de reacción se concentró y se purificó con un Biotage Horizon (80g $SiO_2$, 10-25% de EtOAc/hexanos) proporcionando el cetoéster J1a (3,37 g) en forma de un

aceite amarillo claro viscoso.

Tiempo de retención en la CL-EM 1,853 min; m/z 423 y 425,98 (1:1) (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu CL-10AS equipado con una columna Waters Xterra MS de 7u C18 3,0x50 mm usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nM. Las condiciones de elución emplearon un caudal de 4 ml/minuto, un gradiente de 100% de disolvente A / 0% de disolvente B a 0% de disolvente A / 100% de disolvente B, un tiempo para el gradiente de 2 minutos, un tiempo de retención de 1 minuto, y un tiempo de análisis de 3 minutos donde el disolvente A era 5% de MeOH/ 95% de $H_2O$ / acetato de amonio 10 mM y el disolvente B era 5% de $H_2O$ / 95% de MeOH/ acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma Micromass para CL en modo de electropulverización. RMN de $^1H$ (400 MHz, $CDCl_3$) δ ppm 8,04 (t, *J*=1,8 Hz, 1H), 7,83 (d, *J*=7,8 Hz, 1H), 7,75 (d, *J*=8,0 Hz, 1H), 7,38 (t, *J*=7,9 Hz, 1H), 5,33 - 5,59 (m, 1H), 5,13 - 5,32 (m, 1H), 4,22 (s ancho, 1H), 3,40 - 3,63 (m, 1H), 2,52 - 2,63 (m, 1H), 2,46 (dd, *J*=13,1, 9,3 Hz, 1H), 1,63 - 1,73 (m, 1H), 1,47 (s ancho, 9H), 0,86 (s ancho, 1H), 0,51 (s ancho, 1H).

Ejemplo J1. etapa b



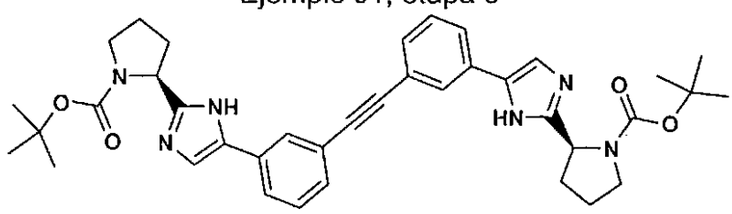

Una solución del cetoéster J1a (3,33 g, 7,85 mmol) en xileno (75 ml) se añadió a acetato de amonio (5,94 g, 77 mmol) en un recipiente a presión y la mezcla de reacción se agitó en atmósfera de nitrógeno durante 5 min. El recipiente de

reacción se selló y después se introdujo en un baño de aceite que se había precalentado a 140 °C y la reacción se mantuvo a esa temperatura durante 6 h. La reacción se enfrió a temperatura ambiente, se agitó toda la noche y se volvió a calentar a 140 °C durante 5 h. Se añadió más acetato de amonio (3,0 g) y la reacción se agitó a 145 ºC durante 8 h, se enfrió a temperatura ambiente y se concentró a vacío elevado dando un aceite marrón. El aceite se fraccionó entre DCM (~ 200 ml) y 1/2 bicarbonato sódico sat. (~200 ml). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró. La espuma naranja solidificada en bruto se purificó en un Biotage Horizon (20-50% de EtOAc/hexanos, 160 g $SiO_2$) proporcionando el imidazol J1b (2,03 g) en forma de una espuma amarilla solidificada.

Tiempo de retención en la CL-EM 2,450 min; m/z 404 y 406,06 (1:1) (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu CL-10AS equipado con una columna Phenomenex-Luna 10u C18 3,0x50 mm usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nM. Las condiciones de elución emplearon un caudal de 4 ml/minuto, un gradiente de 100% de disolvente A / 0% de disolvente B a 0% de disolvente A / 100% de disolvente B, un tiempo para el gradiente de 3 minutos, un tiempo de retención de 1 minuto, y un tiempo de análisis de 4 minutos donde el disolvente A era 5% de MeOH/ 95% de $H_2O$ / acetato de amonio 10 mM y el disolvente B era 5% de $H_2O$ / 95% de MeOH/ acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma Micromass para CL en modo de electropulverización. RMN de $^1H$ (400 MHz, MeOD) δ ppm 7,89 (s ancho, 1H), 7,65 (d, *J*=6,5 Hz, 1H), 7,32 - 7,44 (m, 2H), 7,26 (t, *J*=7,8 Hz, 1H), 4,66 (s ancho, 1H), 3,52 - 3,63 (m, 1H), 2,51 (dd, *J*=13,1, 8,8 Hz, 1H), 2,25 - 2,37 (m, 1H), 1,66 - 1,75 (m, 1H), 1,29 (s ancho, 9H), 0,84 (ddd,

*J*=8,2, 6,0, 5,8 Hz, 1H), 0,56 - 0,63 (m, 1H).

Ejemplo J1, etapa c

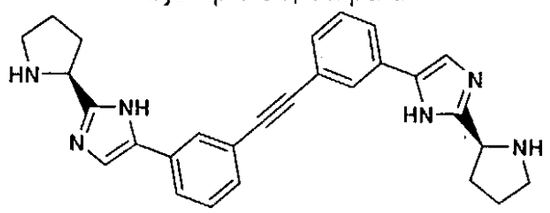


Se burbujeó nitrógeno a través de una solución en agitación del bromuro J1b (854 mg, 2,18 mmol) y 1,2-bis(trimetilstannil)etino (403 mg, 1,15 mmol) en DMF (10 ml) durante 10 minutos. Después se añadió $Pd(PPh_3)_4$ (79 mg, 0,069 mmol), se burbujeó nitrógeno a través de la reacción durante 1 min y después la reacción se calentó a 90 °C en atmósfera de nitrógeno durante 17 h. La mezcla de reacción se enfrió a temperatura ambiente, se concentró a un aceite viscoso y se purificó en un Biotage Horizon (40 g $SiO_2$, 70-100% de EtOAc/hexanos, cargado con DCM)) proporcionando el alquino J1c (500 mg) en forma de una espuma amarilla solidificada.

Tiempo de retención en la CL-EM 2,876 min; m/z 649,51 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu CL-10AS equipado con una columna Phenomenex-Luna 10u C18 3,0x50 mm usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nM. Las condiciones de elución emplearon un caudal de 4 ml/minuto, un gradiente de 100% de disolvente A / 0% de disolvente B a 0% de disolvente A / 100% de disolvente B, un tiempo para el gradiente de 3 minutos, un tiempo de retención de 1 minuto, y un tiempo de análisis de 4 minutos donde el disolvente A era 5% de MeOH/ 95% de $H_2O$ / acetato de amonio 10 mM y el disolvente B era 5% de $H_2O$ / 95% de MeOH/ acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma Micromass para

CL en modo de electropulverización. RMN de $^1$H (400 MHz, MeOD) δ ppm 7,89 (s, 2H), 7,67 - 7,74 (m, 2H), 7,35 - 7,44 (m, 6H), 4,85 - 5,04 (m, 2H), 3,64 - 3,74 (m, 2H), 3,47 - 3,56 (m, 2H), 2,29 - 2,45 (m, 2H), 1,90 - 2,13 (m, 6H), 1,48 (s ancho, 6H), 1,26 (s ancho, 12H).

Ejemplo J1, etapa d




Se añadió TFA (3 ml, 38,9 mmol) a una solución en agitación del carbamato J1c (238 mg, 0,367 mmol) en DCE (7 ml) y la reacción se agitó a temperatura ambiente durante 1h. La mezcla de reacción se concentró a vacío proporcionando una sal TFA de la pirrolidina J1d (260 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 2,505 min; m/z 449,22 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu CL-10AS equipado con una columna Phenomenex-Luna 10u C18 3,0x50 mm usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nM. Las condiciones de elución emplearon un caudal de 4 ml/minuto, un gradiente de 100% de disolvente A / 0% de disolvente B a 0% de disolvente A / 100% de disolvente B, un tiempo para el gradiente de 3 minutos, un tiempo de retención de 1 minuto, y un tiempo de análisis de 4 minutos donde el disolvente A era 5% de MeOH/ 95% de $H_2O$ / acetato de amonio 10 mM y el disolvente B era 5% de $H_2O$ / 95% de MeOH/ acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma Micromass para CL en modo de electropulverización. RMN de $^1$H (400 MHz, MeOD) δ ppm 7,96 - 8,00 (m, 2H), 7,79 (dt, *J*=6,6, 2,1 Hz, 2H), 7,65 (s, 2H), 7,41 - 7,48 (m, 4H), 4,91 (t,

*J*=7,8 Hz, 2H), 3,44 - 3,61 (m, 4H), 2,51 - 2,62 (m, 2H), 2,27 - 2,45 (m, 4H), 2,16 - 2,24 (m, 2H).

Ejemplo J1 a J1.1

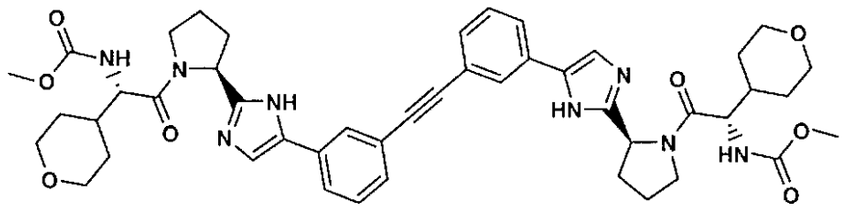
Se añadió HATU (61,8 mg, 0,162 mmol) a una solución en agitación de una sal TFA de la pirrolidina J1d (110 mg, 0,12 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (28,5 mg, 0,162 mmol) en DMF (0,7 ml) y base de Hünig (0,10 ml, 0,54 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 3 horas y después se concentró en un chorro de nitrógeno. La reacción se purificó en dos inyecciones mediante HPLC preparativa (MeOH/agua /acetato de amonio 10 mM) proporcionando el Ejemplo J1 (31,5 mg) en forma de un sólido amarillo claro y el Ejemplo J1.1 (41,1 mg) en forma de un a sólido amarillo claro.

Ejemplo J1: Tiempo de retención en la CL-EM 2,605 min; m/z 763,36 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu CL-10AS equipado con una columna Phenomenex-Luna 10u C18 3,0x50 mm usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nM. Las condiciones de elución emplearon un caudal de 4 ml/minuto, un gradiente de 100% de disolvente A / 0% de disolvente B a 0% de disolvente A / 100% de disolvente B, un tiempo para el gradiente de 3 minutos, un tiempo de retención de 1 minuto, y un tiempo de análisis de 4 minutos donde el disolvente A era 5% de MeOH/ 95% de $H_2O$ / acetato de amonio 10 mM y el disolvente B era 5% de $H_2O$ / 95% de MeOH/ acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma Micromass para CL en modo de electropulverización. La RMN de $^1H$ presenta una mezcla 4 :1 de rotámeros. El rotámero principal es: RMN de $^1H$ (400

MHz, MeOD) δ ppm 7,86 (s, 2H), 7,64 - 7,70 (m, 2H), 7,36 - 7,43 (m, 4H), 7,34 (s, 2H), 5,17 (dd, *J*=7,8, 5,3 Hz, 2H), 4,24 (d, *J*=7,3 Hz, 2H), 3,95 - 4,04 (m, 2H), 3,84 - 3,92 (m, 2H), 3,66 (s, 6H), 2,17 - 2,42 (m, 6H), 2,00 - 2,13 (m, 4H), 0,96 (d, *J*=6,8 Hz, 6H), 0,91 (d, *J*=6,8 Hz, 6H).

Ejemplo J1.1: Tiempo de retención en la CL-EM 2,620 min; m/z 606,23 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu CL-10AS equipado con una columna Phenomenex-Luna 10u C18 3,0x50 mm usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nM. Las condiciones de elución emplearon un caudal de 4 ml/minuto, un gradiente de 100% de disolvente A / 0% de disolvente B a 0% de disolvente A / 100% de disolvente B, un tiempo para el gradiente de 3 minutos, un tiempo de retención de 1 minuto, y un tiempo de análisis de 4 minutos donde el disolvente A era 5% de MeOH/ 95% de $H_2O$ / acetato de amonio 10 mM y el disolvente B era 5% de $H_2O$ / 95% de MeOH/ acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma Micromass para CL en modo de electropulverización. La RMN de $^1H$ presenta una mezcla 3 :1 de rotámeros. RMN de $^1H$ (400 MHz, MeOD) δ ppm 7,94 (s, 1H), 7,87 (s, 1H), 7,74 (ddd, *J*=5,6, 3,4, 1,8 Hz, 1H), 7,65 - 7,70 (m, 1H), 7,51 (s, 1H), 7,36 - 7,44 (m, 6H), 7,35 (s, 1H), 5,18 (dd, *J*=7,7, 5,4 Hz, 1H), 4,68 (t, *J*=7,8 Hz, 1H), 4,24 (d, *J*=7,5 Hz, 1H), 3,95 - 4,06 (m, 1H), 3,85 - 3,92 (m, 1H), 3,66 (s, 3H), 3,35 - 3,52 (m, 2H), 2,01 - 2,50 (m, 9H), 0,96 (d, *J*=6,8 Hz, 3H), 0,91 (d, *J*=6,8 Hz, 3H).

Ejemplo J2

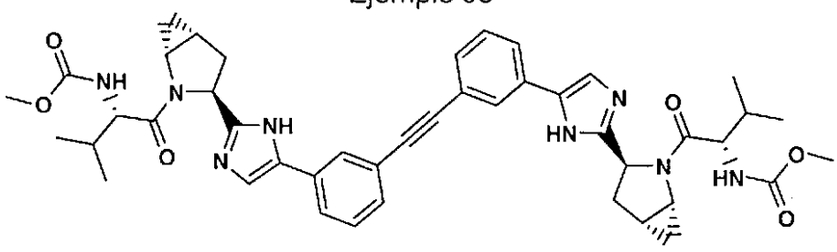


Se añadió HATU (118 mg, 0,310 mmol) a una solución en agitación de una sal TFA de la pirrolidina J1d (93,4 mg, 0,103 mmol) y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (67,3 mg, 0,310 mmol) en DIPEA (0,18 ml, 1,0 mmol) y DMF (1 ml) y la reacción se agitó a temperatura ambiente durante 2 h. La reacción se concentró en un chorro de nitrógeno, se disolvió en MeOH y se purificó mediante HPLC preparativa (MeOH/agua acetato de amonio 10 mM) proporcionando el Ejemplo J2 (18,1 mg) en forma de un sólido rosa pálido.

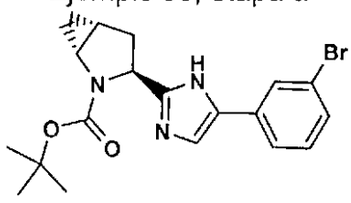
Tiempo de retención en la CL-EM 2,428 min; m/z 847,39 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu CL-10AS equipado con una columna Phenomenex-Luna 10u C18 3,0x50 mm usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nM. Las condiciones de elución emplearon un caudal de 4 ml/minuto, un gradiente de 100% de disolvente A / 0% de disolvente B a 0% de disolvente A / 100% de disolvente B, un tiempo para el gradiente de 3 minutos, un tiempo de retención de 1 minuto, y un tiempo de análisis de 4 minutos donde el disolvente A era 5% de MeOH/ 95% de $H_2O$ / acetato de amonio 10 mM y el disolvente B era 5% de $H_2O$ / 95% de MeOH/ acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma Micromass para CL en modo de electropulverización. La RMN de $^1H$ presenta una mezcla 4 :1 de rotámeros. El rotámero principal es : RMN de $^1H$ (400 MHz, MeOD) δ ppm 7,83 (s, 2H), 7,62 - 7,67 (m, 2H), 7,33 - 7,42 (m, 6H), 5,15 (dd, *J*=7,5, 5,5 Hz, 2H), 4,32 (d, *J*=8,3 Hz, 2H), 3,89 - 4,08 (m, 6H), 3,66 (s, 6H), 3,33 - 3,50 (m, 6H), 2,23 - 2,40 (m,

4H), 2,13 - 2,22 (m, 2H), 1,92 - 2,10 (m, 4H), 1,61 - 1,71 (m, 4H), 1,32 - 1,56 (m, 4H).

Ejemplo J3

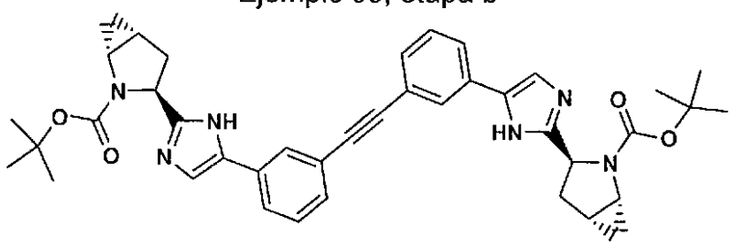


Ejemplo J3, etapa a



Se preparó el bromuro J3a a partir del ácido M3f de acuerdo con el procedimiento descrito para el bromuro J1b.

Ejemplo J3, etapa b

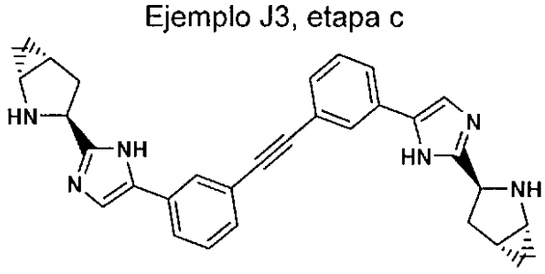


Se burbujeó nitrógeno a través de una solución en agitación del bromuro J3a (825 mg, 2,041 mmol) y 1,2-bis(trimetilstannil)etino (378 mg, 1,074 mmol) en DMF (10 ml) durante 10 minutos. Después se añadió $Pd(PPh_3)_4$ (74,5 mg, 0,064 mmol) a la mezcla de reacción, se burbujeó nitrógeno a través de la reacción durante 1 min y

después la reacción se calentó a 90 °C en atmósfera de nitrógeno durante 17 h. La mezcla de reacción se enfrió a temperatura ambiente, se concentró a un aceite negro espeso, se diluyó con DCM y se purificó en un Biotage Horizon (40 g $SiO_2$, 60-100% de EtOAc/hexanos) proporcionando el alquino J3b (312 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 2,800 min; m/z 671,53 (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu CL-10AS equipado con una columna Phenomenex-Luna 10u C18 3,0x50 mm usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nM. Las condiciones de elución emplearon un caudal de 4 ml/minuto, un gradiente de 100% de disolvente A / 0% de disolvente B a 0% de disolvente A / 100% de disolvente B, un tiempo para el gradiente de 3 minutos, un tiempo de retención de 1 minuto, y un tiempo de análisis de 4 minutos donde el disolvente A era 5% de MeOH/ 95% de $H_2O$ / acetato de amonio 10 mM y el disolvente B era 5% de $H_2O$ / 95% de MeOH/ acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma Micromass para CL en modo de electropulverización. RMN de $^1H$ (400 MHz, MeOD) δ ppm 7,89 (s, 2H), 7,70 (ddd, *J*=5,6, 3,3, 1,9 Hz, 2H), 7,38 - 7,43 (m, 6H), 4,69 (s ancho, 2H), 3,59 (s ancho, 2H), 2,53 (dd, *J*=13,2, 8,9 Hz, 2H), 2,28 - 2,39 (m, 2H), 1,68 - 1,77 (m, 2H), 1,29 - 1,31 (m, 18H), 0,85 (dt, *J*=8,5, 5,8 Hz, 2H), 0,58 - 0,64 (m, 2H).

Ejemplo J3, etapa c



Se añadió TFA (3 ml, 38,9 mmol) a una solución en agitación del carbamato J3b (316 mg, 0,470 mmol) en DCE (7 ml) y la reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se concentró a vacío proporcionando una sal TFA de la pirrolidina J3c (360 mg) en forma de un sólido amarillo.

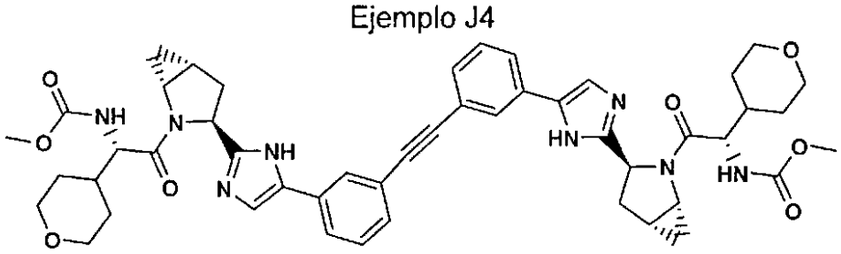
Tiempo de retención en la CL-EM 2,711min; m/z 473,24 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu CL-10AS equipado con una columna Phenomenex-Luna 10u C18 3,0x50 mm usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nM. Las condiciones de elución emplearon un caudal de 4 ml/minuto, un gradiente de 100% de disolvente A / 0% de disolvente B a 0% de disolvente A / 100% de disolvente B, un tiempo para el gradiente de 3 minutos, un tiempo de retención de 1 minuto, y un tiempo de análisis de 4 minutos donde el disolvente A era 5% de MeOH/ 95% de $H_2O$ / acetato de amonio 10 mM y el disolvente B era 5% de $H_2O$ / 95% de MeOH/ acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma Micromass para CL en modo de electropulverización.

Ejemplo J3

Se añadió HATU (69,6 mg, 0,183 mmol) a una solución en agitación de una sal TFA de la pirrolidina J3c (56,7 mg, 0,061 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (32,1 mg, 0,183 mmol) en DMF (0,7 ml) y base de Hünig (0,11 ml, 0,61 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 3 h. La reacción se concentró en un chorro de nitrógeno, se disolvió en MeOH y se purificó en dos inyecciones mediante HPLC preparativa (MeOH/agua acetato de amonio 10 mM) proporcionando el Ejemplo J3 (31,8 mg) en forma de un sólido amarillo claro.

Tiempo de retención en la CL-EM 2,605 min; m/z 787,36 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu CL-10AS equipado con una columna Phenomenex-Luna 10u C18 3,0x50 mm usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nM. Las condiciones de elución emplearon un caudal de 4 ml/minuto, un gradiente de 100% de disolvente A / 0% de disolvente B a 0% de disolvente A / 100% de disolvente B, un tiempo para el gradiente de 3 minutos, un tiempo de retención de 1 minuto, y un tiempo de análisis de 4 minutos donde el disolvente A era 5% de MeOH/ 95% de $H_2O$ / acetato de amonio 10 mM y el disolvente B era 5% de $H_2O$ / 95% de MeOH/ acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma Micromass para CL en modo de electropulverización. RMN de $^1H$ (400 MHz, MeOD) δ ppm 7,87 (s, 2H), 7,65 - 7,71 (m, 2H), 7,37 - 7,43 (m, 4H), 7,36 (s, 2H), 5,16 (dd, *J*=8,8, 4,8 Hz, 2H), 4,59 (d, *J*=6,5 Hz, 2H), 3,67 (s, 6H), 3,63 - 3,68 (m, 2H), 2,49 - 2,58 (m, 2H), 2,37 - 2,45 (m, 2H), 2,10 - 2,21 (m, 2H), 1,98 - 2,07 (m, 2H), 1,12 (ddd, *J*=8,7, 5,6, 5,5 Hz, 2H), 1,01 (d, *J*=6,8 Hz, 6H), 0,93 (d, *J*=6,8 Hz, 6H), 0,78 (s ancho, 2H).

Ejemplo J4

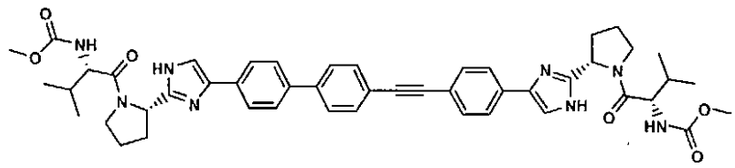


Se añadió HATU (120 mg, 0,317 mmol) a una solución en agitación de una sal TFA de la pirrolidina J3c (98 mg, 0,106 mmol) y ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (68,8 mg, 0,317 mmol) en

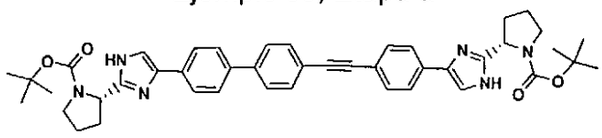
DIPEA (0,18 ml, 1,1 mmol) y DMF (1 ml) y la reacción se agitó a temperatura ambiente durante 3 h. La reacción se concentró en un chorro de nitrógeno, se disolvió en MeOH y se purificó mediante HPLC preparativa (MeOH/agua acetato de amonio 10 mM) y después se volvió a purificar mediante HPLC prep (MeOH/agua 0,1% de TFA) proporcionando una sal TFA del Ejemplo J4 (18 mg) en forma de un sólido blanco.

Tiempo de retención en la CL-EM 2,463 min; m/z 869,40 (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu CL-10AS equipado con una columna Phenomenex-Luna 10u C18 3,0x50 mm usando un detector UV-Vis SPD-10AV a una longitud de onda del detector de 220 nM. Las condiciones de elución emplearon un caudal de 4 ml/minuto, un gradiente de 100% de disolvente A / 0% de disolvente B a 0% de disolvente A / 100% de disolvente B, un tiempo para el gradiente de 3 minutos, un tiempo de retención de 1 minuto, y un tiempo de análisis de 4 minutos donde el disolvente A era 5% de MeOH/ 95% de $H_2O$ / acetato de amonio 10 mM y el disolvente B era 5% de $H_2O$ / 95% de MeOH/ acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma Micromass para CL en modo de electropulverización. RMN de $^1H$ (400 MHz, MeOD) δ ppm 7,89 - 7,92 (m, 2H), 7,87 (s, 2H), 7,74 (dt, *J*=7,8, 1,5 Hz, 2H), 7,61 - 7,66 (m, 2H), 7,54 - 7,60 (m, 2H), 5,11 (dd, *J*=9,0, 7,0 Hz, 2H), 4,59 (d, *J*=7,5 Hz, 2H), 3,91 - 3,99 (m, 4H), 3,83 (t, *J*=4,8 Hz, 2H), 3,67 (s, 6H), 3,33 - 3,45 (m, 4H), 2,67 (dd, *J*=13,7, 9,4 Hz, 2H), 2,43 - 2,52 (m, 2H), 2,02 - 2,14 (m, 4H), 1,39 - 1,63 (m, 8H), 1,03 - 1,11 (m, 2H), 0,83 - 0,90 (m, 2H).

Ejemplo J5



Ejemplo J5, Etapa a

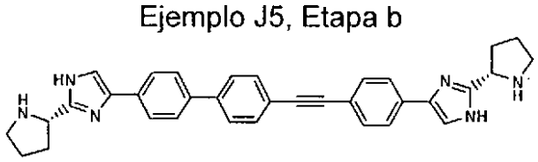


Se burbujeó nitrógeno a través de una solución en agitación de 2-(4-(4-bromofenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-terc-butilo (bromuro D-1b) (400 mg, 1,02 mmol), ácido 4-etinilfenilborónico (149 mg, 1,02 mmol) y bicarbonato sódico (214 mg, 2,55 mmol) en DME (8 ml) y agua (2 ml) durante 15 min. Después se añadió $Pd(PPh_3)_4$ (58,9 mg, 0,051 mmol) y se continuó burbujeando el nitrógeno durante 5 min. antes de sellar el recipiente de reacción y calentar a 90 °C toda la noche. La reacción se enfrió, se diluyó con THF, se lavó con salmuera y se concentró a sequedad. El residuo se purificó mediante Biotage Horizon (60-90% de EtOAc/hexanos) proporcionando el carbamato J5a (85 mg) en forma de un sólido amarillo.

Tiempo de retención en la CL-EM 2,911 min; m/z 723,64 (MH-). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Phenomenex-Luna, de 10 u, C18, de 3,0 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución emplearon un caudal de 4 ml/minuto, un gradiente de 100% de disolvente A / 0% de disolvente B a 0% de disolvente A / 100% de disolvente B, un tiempo para el gradiente de 3 minutos, un tiempo de retención de 1 minuto, y un tiempo de análisis de 4 minutos donde el disolvente A era 5% de MeOH/ 95% de

$H_2O$ / acetato de amonio 10 mM y el disolvente B era 5% de $H_2O$ / 95% de MeOH/ acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma Micromass para CL en modo de electropulverización. RMN de $^1H$ (400 MHz, MeOD) δ ppm 7,78 (d, *J*=8,0 Hz, 2H), 7,72 (d, *J*=8,0 Hz, 2H), 7,64 - 7,69 (m, 4H), 7,58 (d, *J*=8,3 Hz, 2H), 7,52 (d, *J*=8,3 Hz, 2H), 7,31 - 7,41 (m, 2H), 4,86 - 5,03 (m, 2H), 3,68 (s ancho, 2H), 3,46 - 3,57 (m, 2H), 2,37 (s ancho, 2H), 1,89 - 2,13 (m, 6H), 1,47 (s ancho, 6H), 1,25 (s ancho, 12H).

Ejemplo J5, Etapa b



Se añadió TFA (250 µl, 3,24 mmol) a una solución del carbamato J5a en DCE (1 ml) y la reacción se agitó a temperatura ambiente durante 1,5 h. La reacción se concentró en un chorro de nitrógeno proporcionando una sal TFA de la pirrolidina J5b (45 mg).

Tiempo de retención en la CL-EM 2,928 min; m/z 525,32 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Phenomenex-Luna, de 10 u, C18, de 3,0 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución emplearon un caudal de 4 ml/minuto, un gradiente de 100% de disolvente A / 0% de disolvente B a 0% de disolvente A / 100% de disolvente B, un tiempo para el gradiente de 4 minutos, un tiempo de retención de 1 minuto, y un tiempo de análisis de 5 minutos donde el disolvente A era 5% de MeOH/ 95% de $H_2O$ / acetato de amonio 10 mM y el disolvente B era 5% de $H_2O$ / 95% de MeOH/ acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma Micromass para CL en modo de electropulverización.

Ejemplo J5

Se añadió HATU (53 mg, 0,14 mmol) a una solución de UNa sal TFA de J5b (45 mg, 0,046 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (24,2 mg, 0,138 mmol) en DMF (0,7 ml) y TEA (0,038 ml, 0,28 mmol) y la reacción se agitó durante 30 min. La reacción se diluyó con MeOH, se filtró y se purificó mediante HPLC prep (MeOH/agua con acetato de amonio 10 mM) proporcionando Ejemplo J5 (14,7 mg) en forma de un sólido amarillo claro. Tiempo de retención en la CL-EM 2,728 min; m/z 839,57 (MH+). Los datos de CL se registraron en un cromatógrafo de líquidos Shimadzu LC-10AS equipado con una columna Phenomenex-Luna, de 10 u, C18, de 3,0 x 50 mm usando un detector SPD-10AV UV-Vis con una longitud de onda del detector de 220 nM. Las condiciones de elución emplearon un caudal de 4 ml/minuto, un gradiente de 100% de disolvente A / 0% de disolvente B a 0% de disolvente A / 100% de disolvente B, un tiempo para el gradiente de 4 minutos, un tiempo de retención de 1 minuto, y un tiempo de análisis de 5 minutos donde el disolvente A era 5% de MeOH/ 95% de $H_2O$ / acetato de amonio 10 mM y el disolvente B era 5% de $H_2O$ / 95% de MeOH/ acetato de amonio 10 mM. Los datos de EM se determinaron usando una plataforma Micromass para CL en modo de electropulverización. RMN de $^1H$ (400 MHz, MeOD) δ ppm 7,73 - 7,78 (m, 2H), 7,65 - 7,71 (m, 6H), 7,57 - 7,62 (m, 2H), 7,52 (d, *J*=8,5 Hz, 2H), 7,33 - 7,36 (m, 2H), 5,18 (dt, *J*=7,6, 5,2 Hz, 2H), 4,21 - 4,27 (m, 2H), 3,96 - 4,05 (m, 2H), 3,84 - 3,92 (m, 2H), 3,66 (s, 6H), 2,17 - 2,42 (m, 6H), 2,00 - 2,13 (m, 4H), 0,95 (dd, *J*=6,8, 1,3 Hz, 6H), 0,91 (dd, *J*=6,8, 1,0 Hz, 6H).

*Síntesis de Caps comunes*

*Condiciones de ensayo de los compuestos*

La valoración de la pureza y el análisis de masas de baja resolución se llevaron a cabo en un sistema de CL Shimadzu CL acoplado con un sistema de EM Waters Micromass ZQ. Se apreciará que los tiempos de retención pueden variar ligeramente entre máquinas. Condiciones adicionales de CL aplicables a la presente sección, a no ser que se indique de otro modo.

*Condiciones de EM-W1*

Columna = XTERRA 3,0 X 50 mm S7

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 2 min

Tiempo de terminación = 3 min

Caudal = 5 ml/min

Longitud de onda = 220 nm

Disolvente A = 0,1% de TFA en 10% de metanol/90% de $H_2O$

Disolvente B = 0,1% de TFA en 90% de metanol/10% de $H_2O$

*Condiciones de EM-W2*

Columna = XTERRA 3,0 X 50 mm S7

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 3 min

Tiempo de terminación = 4 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = 0,1% de TFA en 10% de metanol/90% de $H_2O$

Disolvente B = 0,1% de TFA en 90% de metanol/10% de $H_2O$

*Condiciones de EM-W5*

Columna = XTERRA 3,0 X 50 mm S7

% Inicial de B = 0

% Final de B = 30

Tiempo de gradiente = 2 min

Tiempo de terminación = 3 min

Caudal = 5 ml/min

Longitud de onda = 220 nm

Disolvente A = 0,1% de TFA en 10% de metanol/90% de $H_2O$

Disolvente B = 0,1% de TFA en 90% de metanol/10% de $H_2O$

*Condiciones-D1*

Columna = XTERRA C18 3,0 X 50 mm S7

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 3 min

Tiempo de terminación = 4 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = 0,1% de TFA en 10% de metanol/90% de $H_2O$

Disolvente B = 0,1% de TFA en 90% de metanol/10% de $H_2O$

*Condiciones-D2*

Columna = Phenomenex-Luna 4,6 X 50 mm S10

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 3 min

Tiempo de terminación = 4 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = 0,1% de TFA en 10% de metanol/90% de $H_2O$

Disolvente B = 0,1% de TFA en 90% de metanol/10% de $H_2O$

Condiciones-MD1

Columna = XTERRA 4.6 X 50 mm S5

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 3 min

Tiempo de terminación = 4 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = 0,1% de TFA en 10% de metanol/90% de $H_2O$

Disolvente B = 0,1% de TFA en 90% de metanol/10% de $H_2O$

*Condiciones-M3*

Columna = XTERRA C18 3,0 X 50 mm S7

% Inicial de B = 0

% Final de B = 40

Tiempo de gradiente = 2 min

Tiempo de terminación = 3 min

Caudal = 5 ml/min

Longitud de onda = 220 nm

Disolvente A = 0,1% de TFA en 10% de metanol/90% de $H_2O$

Disolvente B = 0,1% de TFA en 90% de metanol/10% de $H_2O$

Condiciones-OL1

Columna = Phenomenex-Luna 3,0 x 50 mm S10

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 4 min

Tiempo de terminación = 5 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = 0,1% de TFA en 10% de metanol/90% de $H_2O$

Disolvente B = 0,1% de TFA en 90% de metanol/10% de $H_2O$

Condiciones-OL2

Columna = Phenomenex-Luna 50 x 2 mm 3 u

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 4 min

Tiempo de terminación = 5 min

Caudal = 0,8 ml/min

Temperatura del horno = 40ºC

Longitud de onda = 220 nm

Disolvente A = 0,1% de TFA en acetonitrilo al 10%/90% de $H_2O$

Disolvente B = 0,1% de TFA en acetonitrilo al 90%/10% de $H_2O$

*Condición I*

Columna = Phenomenex-Luna 3,0X 50 mm S10

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 2 min

Tiempo de terminación = 3 min

Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = 0,1% de TFA en 10% de metanol/90% de $H_2O$

Disolvente B = 0,1% de TFA en 90% de metanol/10% de $H_2O$

*Condición II*

Columna = Phenomenex-Luna 4,6X50 mm S10

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 2 min

Tiempo de terminación = 3 min

Caudal = 5 ml/min

Longitud de onda = 220 nm

Disolvente A = 0,1% de TFA en 10% de metanol/90% de $H_2O$

Disolvente B = 0,1% de TFA en 90% de metanol/10% de $H_2O$

*Condición III*

Columna = HPLC XTERRA C18 3,0 x 50mm S7

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 3 min

Tiempo de terminación = 4 min

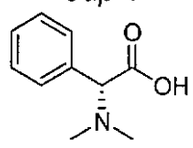
Caudal = 4 ml/min

Longitud de onda = 220 nm

Disolvente A = 0,1% de TFA en 10% de metanol/90% de $H_2O$

Disolvente B = 0,1% de TFA en 90% de metanol/10% de $H_2O$

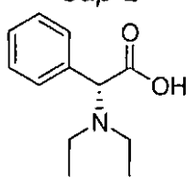
*Cap-1*




Se añadió una suspensión de Pd al 10%/C (2,0 g) en metanol (10 ml) a una mezcla de (R)-2-fenilglicina (10 g, 66,2 mmol), formaldehído (33 ml de 37% en peso en agua), HCl 1N (30 ml) y metanol (30 ml) y se expuso a $H_2$ (413,57 kPa) durante 3 horas. La mezcla de reacción se filtró a través de tierra de diatomeas (Celite®) y el filtrado se concentró a vacío. El material bruto resultante se recristalizó en isopropanol proporcionando la sal HCl de *Cap*-1 como agujas blancas (4,0 g). Rotación óptica: -117,1° [c = 9,95 mg/ml en $H_2O$; $\lambda$ = 589 nm]. RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 500 MHz): $\delta$ 7,43-7,34 (m, 5H), 4,14 (s, 1H), 2,43 (s, 6H); CL (Cond. I): $T_R$ = 0,25; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{10}H_{14}NO_2$ 180,10; encontrado

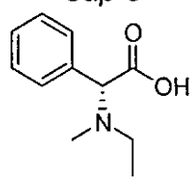
180,17; EMAR: Anal. Calculado para $[M+H]^+$ $C_{10}H_{14}NO_2$ 180,1025; encontrado 180,1017.

*Cap-2*



Se añadió $NaBH_3CN$ (6,22 g, 94 mmol) en porciones durante unos pocos minutos a una mezcla enfriada (hielo/agua) de (R)-2-fenilglicina (6,02 g, 39,8 mmol) y MeOH (100 ml), y se agitó durante 5 min. Se añadió acetaldehído (10 ml) gota a gota durante 10 minutos y se continuó agitando a la misma temperatura fría durante 45 minutos y a temperatura ambiente durante ~6,5 horas. La mezcla de reacción se volvió a enfriar con baño de hielo-agua, se trató con agua (3 ml) y luego se inactivó con una adición gota a gota de HCl concentrado durante ~ 45 min hasta que el pH de la mezcla fue ~ 1,5 – 2,0. El baño de enfriamiento se retiró y se continuó agitando mientras se añadía HCl concentrado con el fin de mantener el pH de la mezcla aproximadamente a 1,5-2,0. La mezcla de reacción se agitó durante una noche, se filtró para separar la suspensión blanca y el filtrado se concentró a vacío. El material bruto se recristalizó en etanol proporcionando la sal HCl de *Cap*-2 como un sólido blanco brillante en dos tandas (tanda-1: 4,16 g; tanda-2: 2,19 g). RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): 10,44 (1,00, s ancho, 1H), 7,66 (m, 2H), 7,51 (m, 3H), 5,30 (s, 1H), 3,15 (m ancho, 2H), 2,98 (m ancho, 2H), 1,20 (s ancho aparente, 6H). Tanda-1: $[\alpha]^{25}$ -102,21° (c = 0,357, $H_2O$); canda-2: $[\alpha]^{25}$ -99,7° (c = 0,357, $H_2O$). CL (Cond. I): $T_R$ = 0,43 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{18}NO_2$: 208,13; encontrado 208,26

*Cap-3*

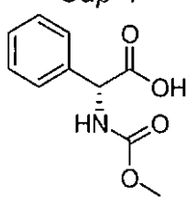


Se añadió secuencialmente acetaldehído (5,0 ml, 89,1 mmol) y una suspensión de Pd al 10%/C (720 mg) en metanol/$H_2O$ (4 ml/1 ml) a una mezcla enfriada (~ 15 °C) de (R)-2-fenilglicina (3,096g, 20,48 mmol), HCl 1N (30 ml) y metanol (40 ml). Se retiró el baño de enfriamiento y la mezcla de reacción se agitó bajo un globo de $H_2$ durante 17 horas. Se añadió más acetaldehído (10 ml, 178,2 mmol) y se continuó agitando en atmósfera de $H_2$ durante 24 horas [Nota: el suministro de $H_2$ se reponía cuando era necesario a través de la reacción]. La mezcla de reacción se filtró a través de tierra de diatomeas (Celite®) y el filtrado se concentró a vacío. El material bruto resultante se recristalizó en isopropanol proporcionando la sal HCl de ácido (R)-2-(etilamino)-2-fenilacético como un sólido blanco brillante (2,846 g). RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): $\delta$ 14,15 (s ancho, 1H), 9,55 (s ancho, 2H), 7,55-7,48 (m, 5H), 2,88 (m ancho, 1H), 2,73 (m ancho, 1H), 1,20 (t aparente, $J$ = 7,2, 3H). CL (Cond. I): $T_R$ = 0,39 min; >95% de índice de homogeneidad; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{10}H_{14}NO_2$: 180,10; encontrado 180,18.

Se añadió una suspensión de Pd al 10%/C (536 mg) en metanol/$H_2O$ (3 ml/1 ml) a una mezcla de ácido (R)-2-(etilamino)-2-fenilacético/HCl (1,492 g, 6,918 mmol), formaldehído (20 ml de 37% en peso en agua), HCl 1N (20 ml) y metanol (23 ml). La mezcla de reacción se agitó bajo un globo de $H_2$ durante ~72 horas, en el que se el suministro de $H_2$ se reanudaba según se necesitaba. La mezcla de

reacción se filtró a través de tierra de diatomeas (Celite®) y el filtrado se concentró a vacío. El material bruto resultante se recristalizó en isopropanol (50 ml) proporcionando la sal HCl de *Cap*-3 como un sólido blanco (985 mg). RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): $\delta$ 10,48 (s ancho, 1H), 7,59-7,51 (m, 5H), 5,26 (s, 1H), 3,08 (s ancho aparente, 2H), 2,65 (s ancho, 3H), 1,24 (m ancho, 3H). CL (Cond. I): $T_R$ = 0,39 min; >95% de índice de homogeneidad; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{11}H_{16}NO_2$: 194,12; encontrado 194,18; EMAR: Anal. Calculado para $[M+H]^+$ $C_{11}H_{16}NO_2$: 194,1180; encontrado 194,1181.

*Cap-4*

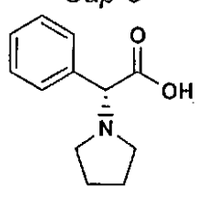



Se añadió $ClCO_2Me$ (3,2 ml, 41,4 mmol) gota a gota a una semisolución en THF enfriada (hielo/agua) (410 ml) de 2-amino-2-fenilacetato de (R)-terc-butilo/HCl (9,877 g, 40,52 mmol) y diisopropiletilamina (14,2 ml, 81,52 mmol) durante 6 min, y se agitó a una temperatura similar durante 5,5 horas. El componente volátil se eliminó a vacío, y el residuo se repartió entre agua (100 ml) y acetato de etilo (200 ml). La fase orgánica se lavó con HCl 1N (25 ml) y solución saturada de $NaHCO_3$ (30 ml), se secó ($MgSO_4$), se filtró y se concentró a vacío. El aceite resultante incoloro se trituró en hexanos, se filtró y se lavó con hexanos (100 ml) proporcionando 2-(metoxicarbonilamino)-2-fenilacetato de (R)-terc-butilo como un sólido blanco (7,7 g). RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): 7,98 (d, *J* = 8,0, 1H), 7,37-7,29 (m, 5H), 5,09 (d, *J* = 8, 1H), 3,56 (s, 3H), 1,33 (s, 9H). CL (Cond. I): $T_R$ = 1,53 min; índice de homogeneidad ~90 %; CL/EM: Anal. Calculado para

$[M+Na]^+$ $C_{14}H_{19}NNaO_4$: 288,12; encontrado 288,15.

Se añadió TFA (16 ml) gota a gota a una solución enfriada (hielo/agua) en $CH_2Cl_2$ (160 ml) del producto anterior durante 7 minutos y se retiró el baño de enfriamiento y la mezcla de reacción se agitó durante 20 horas. Puesto que la desprotección todavía no fue completa, se añadió más TFA (1,0 ml) y se continuó agitando durante otras 2 horas más. El componente volátil se eliminó a vacío, y el residuo oleoso resultante se trató con éter dietílico (15 ml) y hexanos (12 ml) proporcionando un precipitado. El precipitado se filtró y se lavó con éter dietílico/hexanos (relación ~1:3; 30 ml) y se secó a vacío proporcionando *Cap*-4 como un sólido blanco apelusado (5,57 g). Rotación óptica: -176,9° [c = 3,7 mg/ml en $H_2O$; $\lambda$ = 589 nm]. RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): $\delta$ 12,84 (s ancho, 1H), 7,96 (d, *J* = 8,3, 1H), 7,41-7,29 (m, 5H), 5,14 (d, *J* = 8,3, 1H), 3,55 (s, 3H). CL (Cond. I): $T_R$ = 1,01 min; >95% de índice de homogeneidad; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{10}H_{12}NO_4$ 210,08; encontrado 210,17; EMAR: Anal. Calculado para $[M+H]^+$ $C_{10}H_{12}NO_4$ 210,0766; encontrado 210,0756.

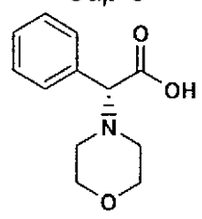
*Cap-5*




Se calentó a 100°C durante 21 horas una mezcla de (R)- 2-fenilglicina (1,0 g, 6,62 mmol), 1,4-dibromobutano (1,57 g, 7,27 mmol) y $Na_2CO_3$ (2,10 g, 19,8 mmol) en etanol (40 ml). La mezcla de reacción se enfrió hasta temperatura ambiente y se filtró, y el filtrado se concentró a vacío. El residuo se disolvió en etanol y se acidificó con HCl 1N hasta pH 3-4, y el componente volátil se eliminó a vacío. El material

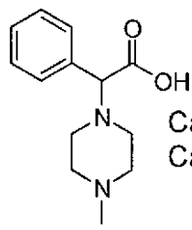
bruto resultante se purificó por una HPLC de fase inversa (agua/metanol/TFA) proporcionando la sal TFA de *Cap*-5 como una espuma blanca semiviscosa (1,0 g). RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5, 500 MHz) $\delta$ 10,68 (s ancho, 1H), 7,51 (m, 5H), 5,23 (s, 1H), 3,34 (s ancho aparente, 2H), 3,05 (s ancho aparente, 2H), 1,95 (s ancho aparente, 4H); $T_R$ = 0,30 min (Cond. I); >98% de índice de homogeneidad; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{16}NO_2$: 206,12; encontrado 206,25.

*Cap-6*




La sal TFA de *Cap*-6 se sintetizó a partir de (R)-2-fenilglicina y 1-bromo-2-(2-bromoetoxi)etano usando el procedimiento de preparación de *Cap*-5. RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5, 500 MHz) $\delta$ 12,20 (s ancho, 1H), 7,50 (m, 5H), 4,92 (s, 1H), 3,78 (s ancho aparente, 4H), 3,08 (s ancho aparente, 2H), 2,81 (s ancho aparente, 2H); $T_R$ = 0,32 min (Cond. I); >98%; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{16}NO_3$: 222,11; encontrado 222,20; EMAR: Anal. Calculado para $[M+H]^+$ $C_{12}H_{16}NO_3$: 222,1130; encontrado 222,1121.

*Cap-7*




Cap-7a: enantiómero-1
Cap-7b: enantiómero-2

Se añadió gota a gota una solución en $CH_2Cl_2$ (200 ml) de cloruro de p-

toluenosulfonilo (8,65 g, 45,4 mmol) a una solución (-5 °C) en $CH_2Cl_2$ (200 ml) de 2-hidroxi-2-fenilacetato de (S)-bencilo (10,0 g, 41,3 mmol), trietilamina (5,75 ml, 41,3 mmol) y 4-dimetilaminopiridina (0,504 g, 4,13 mmol), mientras se mantenía la temperatura de -5 °C a 0 °C. La reacción se agitó a 0 °C durante 9 horas, y luego se almacenó en un congelador (-25 °C) durante 14 horas. Se dejó descongelar hasta temperatura ambiente y se lavó con agua (200 ml), HCl 1N (100 ml) y salmuera (100 ml), se secó ($MgSO_4$), se filtró y se concentró a vacío proporcionando 2-fenil-2-(tosiloxi)acetato de bencilo como un aceite viscoso que solidificó en reposo (16,5 g). La integridad quiral del producto no se verificó y dicho producto se usó en la etapa siguiente sin purificación adicional. RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5, 500 MHz) $\delta$ 7,78 (d, *J* = 8,6, 2H), 7,43-7,29 (m, 10H), 7,20 (m, 2H), 6,12 (s, 1H), 5,16 (d, *J* = 12,5, 1H), 5,10 (d, *J* = 12,5, 1H), 2,39 (s, 3H). $T_R$ = 3,00 (Cond. III); >90% de índice de homogeneidad; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{22}H_{20}NaO_5S$: 419,09; encontrado 419,04.

Se calentó a 65°C durante 7 horas una solución en THF (75 ml) de 2-fenil-2-(tosiloxi)acetato de bencilo (6,0 g, 15,1 mmol), 1-metilpiperazina (3,36 ml, 30,3 mmol) y N,N-diisopropiletilamina (13,2 ml, 75,8 mmol). Se dejó enfriar la reacción hasta temperatura ambiente y el componente volátil se eliminó a vacío. El residuo se repartió entre acetato de etilo y agua, y la fase orgánica se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y se concentró a vacío. El material bruto resultante se purificó por cromatografía ultrarrápida (gel de sílice, etilo acetato) proporcionando 2-(4-metilpiperazin-1-il)-2-fenilacetato de bencilo como un aceite viscoso anaranjado-pardo (4,56 g). El análisis HPLC quiral (Chiralcel OD-H) indicó que la muestra es una mezcla de enantiómeros en una relación 38,2 a 58,7. La separación de los enantiómeros se realizó como sigue: se disolvió el producto en

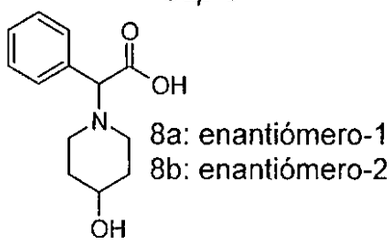
120 ml de etanol/heptano (1:1) y se inyectó (5 ml/inyección) en una columna HPLC quiral (Chiracel OJ, 5 cm ID x 50 cm L, 20 μm) eluyendo con 85:15 Heptano/etanol a 75 ml/min, y se controló a 220 nm. El enantiómero-1(1,474 g ) y el enantiómero-2 (2,2149 g) se recuperaron como aceite viscoso. RMN de $^1$H ($CDCl_3$, δ = 7,26, 500 MHz) 7,44-7,40 (m, 2H), 7,33-7,24 (m, 6H), 7,21-7,16 (m, 2H), 5,13 (d, *J* = 12,5, 1H), 5,08 (d, *J* = 12,5, 1H), 4,02 (s, 1H), 2,65-2,38 (s ancho aparente, 8H), 2,25 (s, 3H). $T_R$ = 2,10 (Cond. III); >98% de índice de homogeneidad; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{20}H_{25}N_2O_2$: 325,19; encontrado 325,20.

Se añadió una solución en metanol (10 ml) de cualquiera de los enantiómeros de 2-(4-metilpiperazin-1-il)-2-fenilacetato de bencilo (1,0 g, 3,1 mmol) a una suspensión de Pd al 10%/C (120 mg) en metanol (5,0 ml). La mezcla de reacción se expuso a un globo de hidrógeno con un control cuidadoso durante <50 min. Inmediatamente después de completarse la reacción, se filtró el catalizador a través de tierra de diatomeas (Celite®) y el filtrado se concentró a vacío proporcionando *Cap*-7, contaminado con ácido fenilacético como una espuma color castaño (867,6 mg; la masa es superior al rendimiento teórico). El producto se usó en la etapa siguiente sin purificación adicional. RMN de $^1$H (DMSO-$d_6$, δ = 2,5, 500 MHz) δ 7,44-7,37 (m, 2H), 7,37-7,24 (m, 3H), 3,92 (s, 1H), 2,63-2,48 (s ancho ap., 2H), 2,48-2,32 (m, 6H), 2,19 (s, 3H); $T_R$ = 0,31 (Cond. II); >90% de índice de homogeneidad; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235,14; encontrado 235,15; EMAR: Anal. Calculado para $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235,1447; encontrado 235,1440.

La síntesis de *Cap*-8 y *Cap*-9 se llevó a cabo de acuerdo con la síntesis de *Cap*-7 usando aminas apropiadas para la etapa de desplazamiento de $SN_2$ (es decir, 4-hidroxipiperidina para *Cap*-8 y (S)-3-fluoropirrolidina para *Cap*-9) y condiciones

modificadas para la separación de los intermedios estereoisoméricos respectivos, como se describe más adelante.

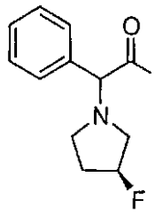
*Cap-8*




8a: enantiómero-1
8b: enantiómero-2

La separación enantiomérica del intermedio 2-(4-hidroxipiperidin-1-il)-2-fenil acetato de bencilo se efectuó empleando las siguientes condiciones: se disolvió el compuesto (500 mg) en etanol/heptano (5 ml/45 ml). La solución resultante se inyectó (5 ml/inyección) en una columna HPLC quiral (Chiracel OJ, 2 cm ID x 25 cm de longitud, 10 μm) eluyendo con 80:20 de heptano/etanol a 10 ml/min, controlada a 220 nm, proporcionando 186,3 mg de enantiómero-1 y 209,1 mg de enantiómero-2 como aceites viscosos amarillo claro. Estos ésteres bencílicos se sometieron a hidrogenación de acuerdo con la preparación de *Cap*-7 proporcionando *Cap*-8: RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5, 500 MHz) 7,40 (d, $J$ = 7, 2H), 7,28-7,20 (m, 3H), 3,78 (s 1H), 3,46 (m, 1H), 2,93 (m, 1H), 2,62 (m, 1H), 2,20 (m, 2H), 1,70 (m, 2H), 1,42 (m, 2H). $T_R$ = 0,28 (Cond. II); >98% de índice de homogeneidad; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{13}H_{18}NO_3$: 236,13; encontrado 236,07; EMAR: Calculado para $[M+H]^+$ $C_{13}H_{18}NO_3$: 236,1287; encontrado 236,1283.

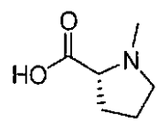
*Cap-9*



9a: diastereómero-1
9b: diastereómero-2

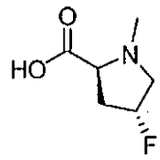
La separación enantiomérica del intermedio 2-((S)-3-fluoropirrolidin-1-il)-2-fenilacetato de bencilo se efectuó empleando las siguientes condiciones: se separó el éster (220 mg) en una columna HPLC quiral (Chiracel OJ-H, 0,46 cm ID x 25 cm L, 5 μm) eluyendo con 95% de $CO_2$ / 5% de metanol con 0,1% de TFA, a una presión de $10x10^5$ Pa, 70 ml/min de Caudal, y una temperatura de 35 °C. Se concentró el eluato de HPLC para los estereoisómeros respectivos y el residuo se disolvió en $CH_2Cl_2$ (20 ml) y se lavó con un medio acuoso (10 ml agua + 1 ml de solución saturada de $NaHCO_3$). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró a vacío proporcionando 92,5 mg de fracción-1 y 59,6 mg de fracción-2. Estos ésteres bencílicos se sometieron a hidrogenación de acuerdo con la preparación de *Cap*-7 para preparar Caps 9a y 9b. *Cap*-9a (diastereómero-1; la muestra es una sal TFA como resultado de la purificación en una HPLC de fase inversa usando $H_2O$/metanol/TFA como disolvente): RMN de $^1H$ (DMSO-$d_6$, δ = 2,5, 400 MHz) 7,55-7,48 (m, 5H), 5,38 (d de m, *J* = 53,7, 1H), 5,09 (s ancho, 1H), 3,84-2,82 (m ancho, 4H), 2,31-2,09 (m, 2H). $T_R$ = 0,42 (Cond. I); >95% de índice de homogeneidad; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224,11; encontrado 224,14; *Cap*-9b (diastereómero-2): RMN de $^1H$ (DMSO-$d_6$, δ = 2,5, 400 MHz) 7,43-7,21 (m, 5H), 5,19 (d de m, *J* = 55,9, 1H), 3,97 (s, 1H), 2,95-2,43 (m, 4H), 2,19-1,78 (m, 2H). $T_R$ = 0,44 (Cond. I); CL/EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224,11; encontrado 224,14.

*Cap-10*



A una solución de D-prolina (2,0 g, 17 mmol) y formaldehído (2,0 ml de 37% en peso en $H_2O$) en metanol (15 ml) se añadió una suspensión de Pd al 10%/C (500 mg) en metanol (5 ml). La mezcla se agitó bajo un globo de hidrógeno durante 23 horas. La mezcla de reacción se filtró a través de tierra de diatomeas (Celite®) y se concentró a vacío proporcionando *Cap*-10 como un sólido blanquecino (2,15 g). RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5, 500 MHz) 3,42 (m, 1H), 3,37 (dd, *J* = 9,4, 6,1, 1H), 2,85-2,78 (m, 1H), 2,66 (s, 3H), 2,21-2,13 (m, 1H), 1,93-1,84 (m, 2H), 1,75-1,66 (m, 1H). $T_R$ = 0,28 (Cond. II); >98% de índice de homogeneidad; CL/EM: Anal. Calculado para $[M+H]^+$ $C_6H_{12}NO_2$: 130,09; encontrado 129,96.

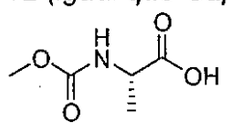
*Cap-11*



Una mezcla de ácido (2S,4R)-4-fluoropirrolidin-2-carboxílico (0,50 g, 3,8 mmol), formaldehído (0,5 ml de 37% en peso en $H_2O$), HCl 12 N (0,25 ml) y Pd al 10%/C (50 mg) en metanol (20 ml) se agitó bajo un globo de hidrógeno durante 19 horas. La mezcla de reacción se filtró a través de tierra de diatomeas (Celite®) y el filtrado se concentró a vacío. El residuo se recristalizó en isopropanol proporcionando la sal HCl de *Cap*-11 como un sólido blanco (337,7 mg). RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5, 500 MHz) 5,39 (d m, *J* = 53,7, 1H), 4,30 (m, 1H), 3,90 (ddd, *J* = 31,5, 13,5, 4,5, 1H), 3,33 (dd, *J* = 25,6, 13,4, 1H), 2,85 (s, 3H), 2,60-2,51 (m, 1H), 2,39-2,26 (m, 1H). $T_R$ = 0,28 (Cond. II); >98% de índice de homogeneidad; CL/EM:

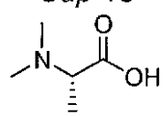
Anal. Calculado para $[M+H]^+$ $C_6H_{11}FNO_2$: 148,08; encontrado 148,06.

*Cap-12 (igual que Cap 52)*



Se disolvió L-alanina (2,0 g, 22,5 mmol) en solución acuosa al 10% de carbonato sódico (50 ml), y se añadió a la misma una solución en THF (50 ml) de cloroformiato de metilo (4,0 ml). La mezcla de reacción se agitó en condiciones ambientales durante 4,5 horas y se concentró a vacío. El sólido blanco resultante se disolvió en agua y se acidificó con HCl 1N hasta un pH ~ 2-3. Las soluciones resultantes se extrajeron con acetato de etilo (3 x 100 ml), y la fase orgánica reunida se secó ($Na_2SO_4$), se filtró y se concentró a vacío proporcionando un aceite incoloro (2,58 g). Se purificaron 500 mg de este material por una HPLC de fase inversa ($H_2O$/metanol/TFA) proporcionando 150 mg de *Cap*-12 como un aceite incoloro. RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5, 500 MHz) 7,44 (d, $J$ = 7,3, 0,8H), 7,10 (s ancho, 0,2H), 3,97 (m, 1H), 3,53 (s, 3H), 1,25 (d, $J$ = 7,3, 3H).

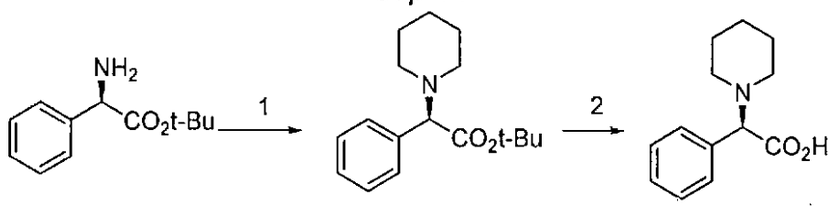
*Cap-13*



Se agitó una mezcla de L-alanina (2,5 g, 28 mmol), formaldehído (8,4 g, 37% en peso), HCl 1N (30 ml) y Pd al 10%/C (500 mg) en metanol (30 ml) en una atmósfera de hidrógeno (344,64 kPa) durante 5 horas. La mezcla de reacción se filtró a través de tierra de diatomeas (Celite®) y el filtrado se concentró a vacío proporcionando la sal HCl de *Cap*-13 como un aceite que solidificó en reposo a

vacío (4,4 g; la masa es superior al rendimiento teórico). El producto se usó sin purificación adicional. RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5, 500 MHz) $\delta$ 12,1 (s ancho, 1H), 4,06 (q, *J* = 7,4, 1H), 2,76 (s, 6H), 1,46 (d, *J* = 7,3, 3H).

*Cap-14*



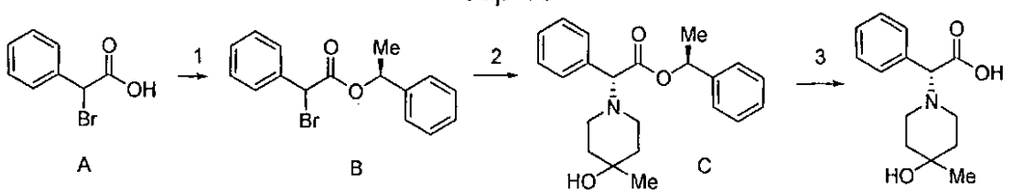

Cap-14

Etapa 1: Una mezcla éster terc-butílico de (R)-(-)-D-fenilglicina (3,00 g, 12,3 mmol), $NaBH_3CN$ (0,773 g, 12,3 mmol), KOH (0,690 g, 12,3 mmol) y ácido acético (0,352 ml, 6,15 mmol) se agitó en metanol a 0 °C. A esta mezcla se añadió dialdehído glutárico (2,23 ml, 12,3 mmol) gota a gota durante 5 minutos. La mezcla de reacción se agitó calentando hasta temperatura ambiente y se continuó agitando a la misma temperatura durante 16 horas. El disolvente se eliminó seguidamente y el residuo se repartió con NaOH acuoso al 10% y acetato de etilo. La fase orgánica se separó, se secó ($MgSO_4$), se filtró y se concentró hasta sequedad proporcionando un aceite transparente. Este material se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; $CH_3CN$-$H_2O$-0,1% de TFA) dando el éster intermedio (2,70 g, 56%) como un aceite transparente. RMN de $^1$H (400 MHz, $CDCl_3$) $\delta$ 7,53-7,44 (m, 3H), 7,40-7,37 (m, 2H), 3,87 (d, *J* = 10,9 Hz, 1H), 3,59 (d, *J* = 10,9 Hz, 1H), 2,99 (t, *J* = 11,2 Hz, 1H), 2,59 (t, *J* = 11,4 Hz, 1H), 2,07-2,02 (m, 2H), 1,82 (d, *J* = 1,82 Hz, 3H), 1,40 (s, 9H). CL/EM: Anal. Calculado para $C_{17}H_{25}NO_2$: 275; encontrado: 276 $(M+H)^+$.

Etapa 2: A una solución agitada del éster intermedio (1,12 g, 2,88 mmol) en

diclorometano (10 ml) se añadió TFA (3 ml). La mezcla de reacción se agitó a temperatura ambiente durante 4 horas y luego se concentró hasta sequedad dando un aceite amarillo claro. El aceite se purificó usando HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; $CH_3CN$-$H_2O$-0,1% de TFA). Las fracciones apropiadas se reunieron y se concentraron hasta sequedad a vacío. El residuo se disolvió entonces en una cantidad mínima de metanol y se aplicó en cartuchos de extracción MCX LP (2 x 6 g). Los cartuchos se aclararon con metanol (40 ml) y luego se eluyó el compuesto deseado usando amoníaco 2M en metanol (50 ml). Las fracciones que contenían producto se reunieron y concentraron y el residuo se suspendió en agua. La liofilización de esta solución proporcionó el compuesto del epígrafe (0,492 g, 78%) como un sólido amarillo claro. RMN de $^1H$ (DMSO-$d_6$) $\delta$ 7,50 (s, 5H), 5,13 (s, 1H), 3,09 (s ancho, 2H), 2,92-2,89 (m, 2H), 1,74 (m, 4H), 1,48 (s ancho, 2H). CL/EM: Anal. Calculado para $C_{13}H_{17}NO_2$: 219; encontrado: 220 $(M+H)^+$.

*Cap-15*



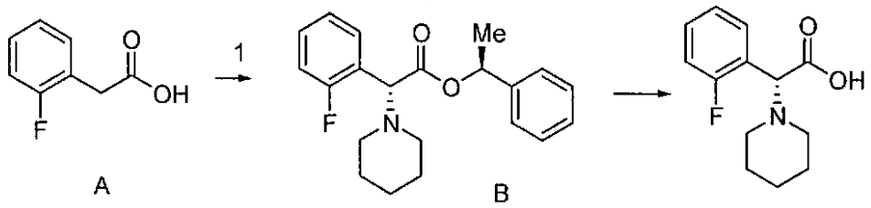

Etapa 1: 2-Bromo-2-fenilacetato de (S)-1-feniletilo: A una mezcla de ácido $\alpha$-bromofenilacético (10,75 g, 0,050 mol), (S)-(-)-1-feniletanol (7,94 g, 0,065 mol) y DMAP (0,61 g, 5,0 mmol) en diclorometano seco (100 ml) se añadió EDCI sólido (12,46 g, 0,065 mol) todo de una vez. La solución resultante se agitó a temperatura ambiente en Ar durante 18 horas y luego se diluyó con acetato de etilo, se lavó ($H_2O$ x 2, salmuera), se secó ($Na_2SO_4$), se filtró y se concentró dando un aceite amarillo pálido. La cromatografía ultrarrápida ($SiO_2$/ hexano-etilo acetato, 4:1) de este aceite

proporcionó el compuesto del epígrafe (11,64 g, 73%) como un sólido blanco. RMN de $^1$H (400 MHz, $CDCl_3$) δ 7,53-7,17 (m, 10H), 5,95 (q, *J* = 6,6 Hz, 0,5H), 5,94 (q, *J* = 6,6 Hz, 0,5H), 5,41 (s, 0,5H), 5,39 (s, 0,5H), 1,58 (d, *J* = 6,6 Hz, 1,5H), 1,51 (d, *J* = 6,6 Hz, 1,5H).

Etapa 2: (R)-2-(4-hidroxi-4-metilpiperidin-1-il)-2-fenilacetato de (S)-1-feniletilo: A una solución de 2-bromo-2-fenilacetato de (S)-1-feniletilo (0,464 g, 1,45 mmol) en THF (8 ml) se añadió trietilamina (0,61 ml, 4,35 mmol), seguido por yoduro de tetrabutilamonio (0,215 g, 0,58 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 5 minutos y luego se añadió una solución de 4-metil-4-hidroxipiperidina (0,251 g, 2,18 mmol) en THF (2 ml). La mezcla se agitó durante 1 hora a temperatura ambiente y luego se calentó a 55-60 °C (temperatura de baño de aceite) durante 4 horas. La mezcla de reacción enfriada se diluyó entonces con acetato de etilo (30 ml), se lavó ($H_2O$ x2, salmuera), se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó por cromatografía sobre gel de sílice (0-60% de etilo acetato-hexano) proporcionando primero el isómero (S,R) del compuesto del epígrafe (0,306 g, 60%) como un sólido blanco y luego el correspondiente isómero (S,S)(0,120 g, 23%), también como un sólido blanco. Isómero (S,R): RMN de $^1$H ($CD_3OD$) δ 7,51-7,45 (m, 2H), 7,41-7,25 (m, 8H), 5,85 (q, *J* = 6,6 Hz, 1H), 4,05 (s, 1H), 2,56-2,45 (m, 2H), 2,41-2,29 (m, 2H), 1,71-1,49 (m, 4H), 1,38 (d, *J* = 6,6 Hz, 3H), 1,18 (s, 3H). CLEM: Anal. Calculado para $C_{22}H_{27}NO_3$: 353; encontrado: 354 $(M+H)^+$. Isómero (S,S): RMN de $^1$H ($CD_3OD$) δ 7,41-7,30 (m, 5H), 7,20-7,14 (m, 3H), 7,06-7,00 (m, 2H), 5,85 (q, *J* = 6,6 Hz, 1H), 4,06 (s, 1H), 2,70-2,60 (m, 1H), 2,51 (dt, *J* = 6,6, 3,3 Hz, 1H), 2,44-2,31 (m, 2H), 1,75-1,65 (m, 1H), 1,65-1,54 (m, 3H), 1,50 (d, *J* = 6,8 Hz, 3H), 1,20 (s, 3H). CLEM: Anal. Calculado para $C_{22}H_{27}NO_3$: 353; encontrado: 354 $(M+H)^+$.

Etapa 3: ácido (R)-2-(4-hidroxi-4-metilpiperidin-1-il)-2-fenilacético: A una solución de (R)-2-(4-hidroxi-4-metilpiperidin-1-il)-2-fenilacetato de (S)-1-feniletilo (0,185 g, 0,52 mmol) en diclorometano (3 ml) se añadió ácido trifluoracético (1 ml) y la mezcla se agitó a temperatura ambiente durante 2 horas. Los volátiles se eliminaron seguidamente a vacío y el residuo se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 20 x 100mm; $CH_3CN$-$H_2O$-0,1% de TFA) dando el compuesto del epígrafe (como sal TFA) como un sólido azulado pálido (0,128 g, 98%). CLEM: Anal. Calculado para $C_{14}H_{19}NO_3$: 249; encontrado: 250 $(M+H)^+$.

*Cap-16*




A B *(R)*-Cap-16

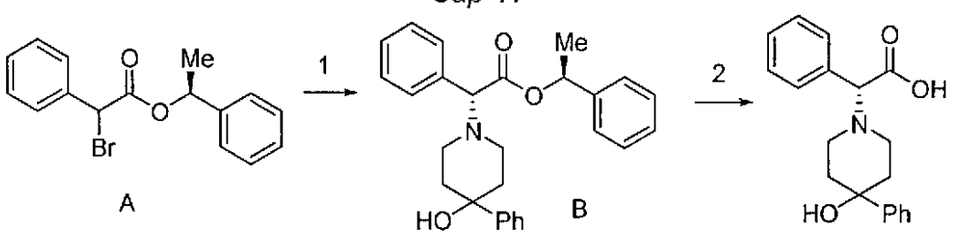
Etapa 1: 2-(2-fluorofenil)acetato de (S)-1-feniletilo: Una mezcla de ácido 2-fluorofenilacético (5,45 g, 35,4 mmol), (S)-1-feniletanol (5,62 g, 46,0 mmol), EDCI (8,82 g, 46,0 mmol) y DMAP (0,561 g, 4,60 mmol) en $CH_2Cl_2$ (100 ml) se agitó a temperatura ambiente durante 12 horas. El disolvente se concentró a continuación y el residuo se repartió con $H_2O$-acetato de etilo. Se separaron las fases y la fase acuosa se volvió a extraer con acetato de etilo (2x). Las fases orgánicas reunidas se lavaron ($H_2O$, salmuera), se secaron ($Na_2SO_4$), se filtraron y se concentraron a vacío. El residuo se purificó por cromatografía sobre gel de sílice (Biotage/ 0-20% de acetato de etilo-hexano) proporcionando el compuesto del epígrafe como un aceite incoloro (8,38 g, 92%). RMN de $^1H$ (400 MHz, $CD_3OD$) $\delta$ 7,32 - 7,23 (m, 7H), 7,10-7,04 (m, 2), 5,85 (q, $J$ = 6,5 Hz, 1H), 3,71 (s, 2H), 1,48 (d, $J$ = 6,5 Hz, 3H).

Etapa 2: 2-(2-Fluorofenil)-2-(piperidin-1-il)acetato de (R)-((S)-1-feniletilo): A una solución de 2-(2-fluorofenil)acetato de (S)-1-feniletilo (5,00 g, 19,4 mmol) en THF (1200 ml) a 0°C se añadió DBU (6,19 g, 40,7 mmol) y la solución se dejó calentar hasta temperatura ambiente mientras se agitaba durante 30 minutos. La solución se enfrió entonces hasta -78 °C y se añadió una solución de $CBr_4$ (13,5 g, 40,7 mmol) en THF (100 ml) y la mezcla se dejó calentar hasta -10 °C y se agitó a esta temperatura durante 2 horas. La mezcla de reacción se inactivó con $NH_4Cl$ acuoso saturado y se separaron las fases. La fase acuosa se volvió a extraer con acetato de etilo (2x) y las fases orgánicas reunidas se lavaron ($H_2O$, salmuera), se secaron ($Na_2SO_4$), se filtraron y se concentraron a vacío. Al residuo se añadió piperidina (5,73 ml, 58,1 mmol) y la solución se agitó a temperatura ambiente durante 24 horas. Los volátiles se concentraron entonces a vacío y el residuo se purificó por cromatografía sobre gel de sílice (Biotage/ 0-30% de éter dietílico-hexano) proporcionando una mezcla pura de diastereoisómeros (relación 2:1 por RMN de $^1H$) como un aceite amarillo (2,07 g, 31%), junto con material de partida sin reaccionar (2,53 g, 51%). Otra cromatografía de la mezcla diastereomérica (Biotage/ 0-10% éter dietílico-tolueno) proporcionó el compuesto del epígrafe como un aceite incoloro (0,737 g, 11%). RMN de $^1H$ (400 MHz, $CD_3OD$) $\delta$ 7,52 (ddd, $J$ = 9,4, 7,6, 1,8 Hz, 1H), 7,33 – 7,40 (m, 1), 7,23 – 7,23 (m, 4H), 7,02 – 7,23 (m, 4H), 5,86 (q, $J$ = 6,6 Hz, 1H), 4,45 (s, 1H), 2,39 – 2,45 (m, 4H), 1,52 – 1,58 (m, 4H), 1,40 – 1,42 (m, 1H), 1,38 (d, $J$ = 6,6 Hz, 3H). CLEM: Anal. Calculado para $C_{21}H_{24}FNO_2$: 341; encontrado: 342 $(M+H)^+$.

Etapa 3: ácido (R)-2-(2-fluorofenil)-2-(piperidin-1-il)acético: Una mezcla de 2-(2-fluorofenil)-2-(piperidin-1-il)acetato de (R)-((S)-1-feniletilo) (0,737 g, 2,16 mmol) y $Pd(OH)_2$ al 20%/C (0,070 g) en etanol (30 ml) se sometió a hidrogenación a

temperatura ambiente y presión atmosférica (globo de $H_2$) durante 2 horas. La solución se purgó entonces con Ar, se filtró a través de tierra de diatomeas (Celite®) y se concentró a vacío. Esto proporcionó el compuesto del epígrafe como un sólido incoloro (0,503 g, 98%). RMN de $^1$H (400 MHz, $CD_3OD$) $\delta$ 7,65 (ddd, $J$ = 9,1, 7,6, 1,5 Hz, 1H), 7,47-7,53 (m, 1H), 7,21-7,30 (m, 2H), 3,07-3,13 (m, 4H), 1,84 (s ancho, 4H), 1,62 (s ancho, 2H). CLEM: Anal. Calculado para $C_{13}H_{16}FNO_2$: 237; encontrado: 238 $(M+H)^+$.

*Cap-17*

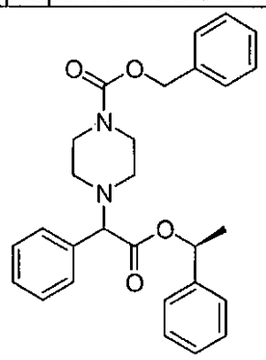


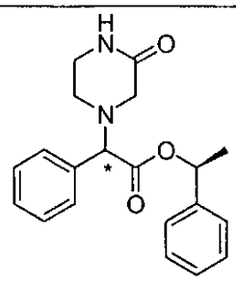

A B *(R)*-Cap-17

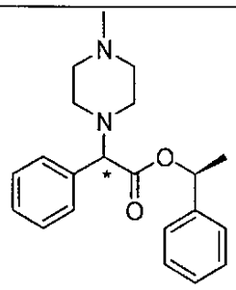
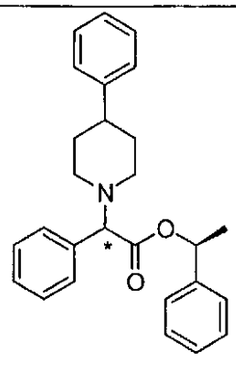
Etapa 1: (R)-2-(4-hidroxi-4-fenilpiperidin-1-il)-2-fenilacetato de (S)-1-feniletilo: A una solución de 2-bromo-2-fenilacetato de (S)-1-feniletilo (1,50 g, 4,70 mmol) en THF (25 ml) se añadió trietilamina (1,31 ml, 9,42 mmol), seguido por yoduro de tetrabutilamonio (0,347 g, 0,94 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 5 minutos y luego se añadió una solución de 4-fenil-4-hidroxipiperidina (1,00 g, 5,64 mmol) en THF (5 ml). La mezcla se agitó durante 16 horas y luego se diluyó con acetato de etilo (100 ml), se lavó ($H_2O$ x2, salmuera), se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó en una columna de gel de sílice (acetato de etilo 0-60%-hexano) proporcionando una mezcla aproximadamente 2:1 de diastereoisómeros, como se juzgó por RMN de $^1$H. La separación de esos isómeros se llevó a cabo usando cromatografía de fluido supercrítico (Chiralcel OJ-H, 30 x 250mm; 20% etanol en $CO_2$ a 35 °C), dando

primero el isómero (R) del compuesto del epígrafe (0,534 g, 27%) como un aceite amarillo y luego el isómero (S) correspondiente (0,271 g, 14%), también como un aceite amarillo. Isómero (S,R): RMN de $^1$H (400 MHz, $CD_3OD$) δ 7,55-7,47 (m, 4H), 7,44-7,25 (m, 10H), 7,25-7,17 (m, 1H), 5,88 (q, *J* = 6,6 Hz, 1H), 4,12 (s, 1H), 2,82-2,72 (m, 1H), 2,64 (dt, *J* = 11,1, 2,5 Hz, 1H), 2,58-2,52 (m, 1H), 2,40 (dt, *J* = 11,1, 2,5 Hz, 1H), 2,20 (dt, *J* = 12,1, 4,6 Hz, 1H), 2,10 (dt, *J* = 12,1, 4,6 Hz, 1H), 1,72-1,57 (m, 2H), 1,53 (d, *J* = 6,5 Hz, 3H). CLEM: Anal. Calculado para $C_{27}H_{29}NO_3$: 415; encontrado: 416 $(M+H)^+$; Isómero (S,S): RMN de $^1$H (400 MHz, $CD_3OD$) δ 7,55-7,48 (m, 2H), 7,45-7,39 (m, 2H), 7,38-7,30 (m, 5H), 7,25-7,13 (m, 4H), 7,08-7,00 (m, 2H), 5,88 (q, *J* = 6,6 Hz, 1H), 4,12 (s, 1H), 2,95-2,85 (m, 1H), 2,68 (dt, *J* = 11,1, 2,5 Hz, 1H); 2,57-2,52 (m, 1H), 2,42 (dt, *J* = 11,1, 2,5 Hz, 1H), 2,25 (dt, *J* = 12,1, 4,6 Hz, 1H), 2,12 (dt, *J* = 12,1, 4,6 Hz, 1H), 1,73 (dd, *J* = 13,6, 3,0 Hz, 1H), 1,64 (dd, *J* = 13,6, 3,0 Hz, 1H), 1,40 (d, *J* = 6,6 Hz, 3H). CLEM: Anal. Calculado para $C_{27}H_{29}NO_3$: 415; encontrado: 416 $(M+H)^+$.

Los ésteres siguientes se prepararon de una forma similar.

| | | |
|---|---|---|
| *Intermedio-17a* |  | Diastereómero 1: RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 1,36 (d, *J*=6,41 Hz, 3H) 2,23 - 2,51 (m, 4H) 3,35 (s, 4H) 4,25 (s, 1H) 5,05 (s, 2H) 5,82 (d, *J*=6,71 Hz, 1H) 7,15 - 7,52 (m, 15H). CLEM: Análisis calculado |

| | | |
|---|---|---|
| | | para: $C_{28}H_{30}N_2O_4$ 458,22; Encontrado: 459,44 $(M+H)^+$.<br><br>Diastereómero 2: RMN de $^1H$ (500 MHz, DMSO-$d_6$) $\delta$ ppm 1,45 (d, *J*=6,71 Hz, 3H) 2,27 - 2,44 (m, 4H) 3,39 (s, 4H) 4,23 (s, 1H) 5,06 (s, 2H) 5,83 (d, *J*=6,71 Hz, 1H) 7,12 (dd, *J*=6,41, 3,05 Hz, 2H) 7,19 - 7,27 (m, 3H) 7,27 - 7,44 (m, 10H).<br>CLEM: Análisis calculado para: $C_{28}H_{30}N_2O_4$ 458,22; Encontrado: 459,44 $(M+H)^+$. |
| *Intermedio -17b* |  | Diastereómero 1: $T_R$ = 11,76 min (Condición II); CLEM: Análisis calculado para: $C_{20}H_{22}N_2O_3$ 338,16 Encontrado: 339,39 $(M+H)^+$; Diastereómero 2: $T_R$ = 10,05 min |

| | | |
|---|---|---|
| | | (Condición II); CLEM: Análisis calculado para: $C_{20}H_{22}N_2O_3$ 338,16; Encontrado: 339,39 $(M+H)^+$. |
| *Intermedio -17c* |  | Diastereómero 1: $T_R$ = 4,55 min (Condición I); CLEM: Análisis calculado para: $C_{21}H_{26}N_2O_2$ 338,20 Encontrado: 339,45 $(M+H)^+$; Diastereómero 2: $T_R$ = 6,00 min (Condición I); CLEM: Análisis calculado para: $C_{21}H_{26}N_2O_2$ 338,20 Encontrado: 339,45 $(M+H)^+$. |
| *Intermedio -17d* |  | Diastereómero 1: $T_R$ = 7,19 min (Condición I); CLEM: Análisis calculado para: $C_{27}H_{29}NO_2$ 399,22 Encontrado: 400,48 $(M+H)^+$; Diastereómero 2: $T_R$ = 9,76 min (Condición I); CLEM: Análisis |

| | | |
|---|---|---|
| | | calculado para: $C_{27}H_{29}NO_2$ 399,22 Encontrado: 400,48 $(M+H)^+$. |

Condiciones de SFC quiral para determinar el tiempo de retención

Condición I

Columna: Columna Chiralpak AD-H, 4,62X250 mm, 5μm

Disolventes: 90% de $CO_2$ - 10% de metanol con DEA al 0,1%

Temp: 35 °C

Presión: 15 MPa

Caudal: 2,0 ml/min.

UV controlado a 220 nm

Inyección: 1,0 mg/3 ml de metanol

Condición II

Columna: Columna Chiralcel OD-H, 4,62X250 mm, 5μm

Disolventes: 90% de $CO_2$ - 10% de metanol con DEA al 0,1%

Temp: 35 °C

Presión: 15 MPa

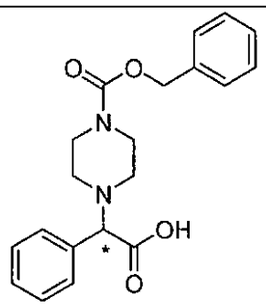
Caudal: 2,0 ml/min.

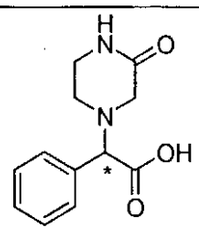
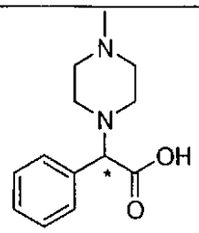
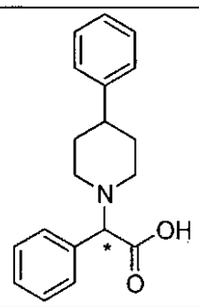
UV controlado a 220 nm

Inyección: 1,0 mg/ml de metanol

Cap-17, Etapa 2: ácido (R)-2-(4-hidroxi-4-fenilpiperidin-1-il)-2-fenilacético: A una solución de (R)-2-(4-hidroxi-4-fenilpiperidin-1-il)-2-fenilacetato de (S)-1-feniletilo (0,350 g, 0,84 mmol) en diclorometano (5 ml) se añadió ácido trifluoracético (1 ml) y la mezcla se agitó a temperatura ambiente durante 2 horas. Los volátiles se eliminaron seguidamente a vacío y el residuo se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 20 x 100mm; $CH_3CN$-$H_2O$-0,1% de TFA) dando el compuesto del epígrafe (como sal TFA) como un sólido blanco (0,230 g, 88%). CLEM: Anal. Calculado para $C_{19}H_{21}NO_3$: 311,15; encontrado: 312 $(M+H)^+$.

Los siguientes ácidos carboxílicos se prepararon en forma ópticamente pura de una forma similar:

| | | |
|---|---|---|
| *Cap-17a* |  | $T_R$ = 2,21 (Condición II); RMN de $^1H$ (500 MHz, DMSO-$d_6$) $\delta$ ppm 2,20 - 2,35 (m, 2H) 2,34 - 2,47 (m, 2H) 3,37 (s, 4H) 3,71 (s, 1H) 5,06 (s, 2H) 7,06 - 7,53 (m, 10H). CLEM: Análisis calculado para: $C_{20}H_{22}N_2O_4$ 354,16; Encontrado: 355,38 $(M+H)^+$. |

| | | |
|---|---|---|
| *Cap-17b* |  | $T_R$ = 0,27 (Condición III); CLEM: Análisis calculado para: $C_{12}H_{14}N_2O_3$ 234,10; Encontrado: 235,22 $(M+H)^+$. |
| *Cap-17c* |  | $T_R$ = 0,48 (Condición II); CLEM: Análisis calculado para: $C_{13}H_{18}N_2O_2$ 234,14; Encontrado: 235,31 $(M+H)^+$. |
| *Cap-17d* |  | $T_R$ = 2,21 (Condición I); CLEM: Análisis calculado para: $C_{19}H_{21}NO_2$ 295,16; Encontrado: 296,33 $(M+H)^+$. |

Condiciones de CLEM para determinar el tiempo de retención

Condición I

Columna: Phenomenex-Luna 4,6 X 50 mm S10

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 4 min

Caudal = 4 ml/min

Longitud de onda = 220

Disolvente A = 10% de metanol - 90% de $H_2O$ - 0,1% de TFA

Disolvente B = 90% de metanol - 10% de $H_2O$ - 0,1% de TFA

Condición II

Columna: Waters-Sunfire 4,6 X 50 mm S5

% Inicial de B = 0

% Final de B = 100

Tiempo de gradiente = 2 min

Caudal = 4 ml/min

Longitud de onda = 220

Disolvente A = 10% de metanol - 90% de $H_2O$ - 0,1% de TFA

Disolvente B = 90% de metanol - 10% de $H_2O$ - 0,1% de TFA

Condición III

Columna: Phenomenex 10μ 3,0 X 50 mm

% Inicial de B = 0

% Final de B = 100

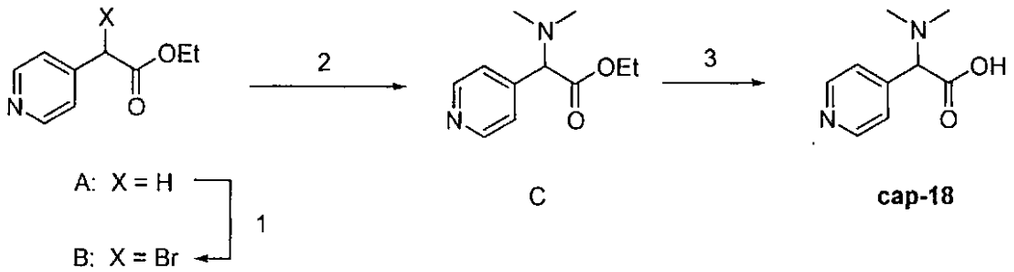
Tiempo de gradiente = 2 min

Caudal = 4 ml/min

Longitud de onda = 220

Disolvente A = 10% de metanol - 90% de $H_2O$ - 0,1% de TFA

Disolvente B = 90% de metanol - 10% de $H_2O$ - 0,1% de TFA



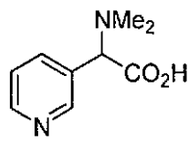
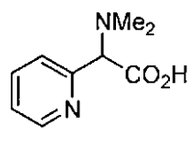
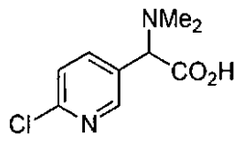

Etapa 1: 2-(4-piridil)-2-bromoacetato de (R,S)-etilo: A una solución de 4-piridilacetato de etilo (1,00 g, 6,05 mmol) en THF seco (150 ml) a 0 °C en argón se añadió DBU (0,99 ml, 6,66 mmol). La mezcla de reacción se dejó calentar hasta temperatura ambiente durante 30 minutos y luego se enfrió hasta -78 °C. A esta mezcla se añadió $CBr_4$ (2,21 g, 6,66 mmol) y se continuó agitando a -78 °C durante 2 horas. Seguidamente la mezcla de reacción se inactivó con $NH_4Cl$ acuoso saturado y se separaron las fases. La fase orgánica se lavó (salmuera), se secó ($Na_2SO_4$), se filtró y se concentró a vacío. El aceite amarillo resultante se purificó inmediatamente por cromatografía ultrarrápida ($SiO_2$/ hexano-acetato de etilo, 1:1) proporcionando el compuesto del epígrafe (1,40 g, 95%) como un aceite amarillo algo estable. RMN de $^1H$ (400 MHz, $CDCl_3$) $\delta$ 8,62 (dd, $J$ = 4,6, 1,8 Hz, 2H), 7,45 (dd, $J$ = 4,6, 1,8 Hz, 2H), 5,24 (s, 1H), 4,21-4,29 (m, 2H), 1,28 (t, $J$ = 7,1 Hz, 3H). CLEM: Anal. Calculado para $C_9H_{10}BrNO_2$: 242, 244; encontrado: 243, 245 $(M+H)^+$.

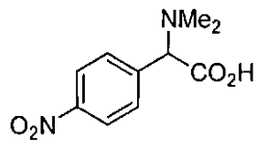
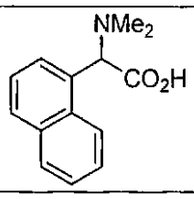
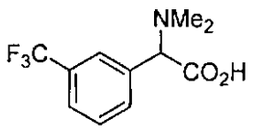
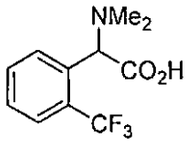
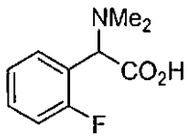
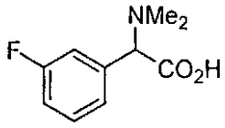
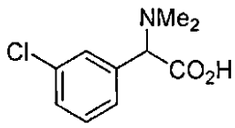
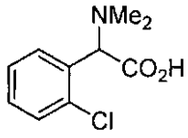
Etapa 2: 2-(4-piridil)-2-(N,N-dimetilamino)acetato de (R,S)-etilo: A una solución de 2-(4-piridil)-2-bromoacetato de (R,S)-etilo (1,40 g, 8,48 mmol) en DMF (10 ml) a temperatura ambiente se añadió dimetilamina (2M en THF, 8,5 ml, 17,0 mmol). Después de completarse la reacción (que se juzgó por cromatografía en capa fina) los volátiles se eliminaron a vacío y el residuo se purificó por cromatografía ultrarrápida (columna Biotage, 40+M $SiO_2$; 50%-100% de acetato de etilo-hexano) proporcionando el compuesto del epígrafe (0,539 g, 31%) como un aceite amarillo claro. RMN de $^1H$ (400 MHz, $CDCl_3$) $\delta$ 8,58 (d, $J$ = 6,0 Hz, 2H), 7,36

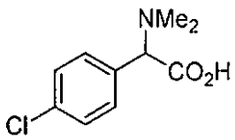
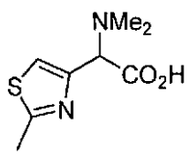
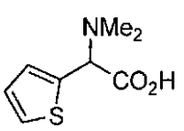
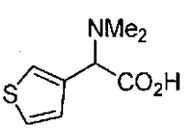
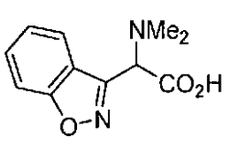
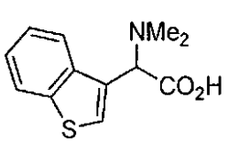
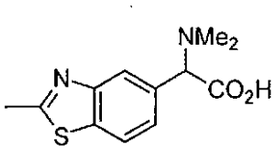
(d, $J$ = 6,0 Hz, 2H), 4,17 (m, 2H), 3,92 (s, 1H), 2,27 (s, 6H), 1,22 (t, $J$ = 7,0 Hz). CLEM: Anal. Calculado para $C_{11}H_{16}N_2O_2$: 208; encontrado: 209 $(M+H)^+$.

Etapa 3: ácido (R,S)-2-(4-piridil)-2-(N,N-dimetilamino)acético: A una solución de 2-(4-piridil)-2-(N,N-dimetilamino)acetato de (R,S)-etilo (0,200 g, 0,960 mmol) en una mezcla de THF-metanol-$H_2O$ (1:1:1, 6 ml) se añadió LiOH en polvo (0,120 g, 4,99 mmol) a temperatura ambiente. La solución se agitó durante 3 horas y luego se acidificó hasta pH 6 usando HCl 1N. La fase acuosa se lavó con acetato de etilo y luego se liofilizó dando el diclorhidrato del compuesto del epígrafe como un sólido amarillo (que contenía LiCl). El producto se usó como tal en las posteriores etapas. RMN de $^1$H (400 MHz, DMSO-$d_6$) $\delta$ 8,49 (d, $J$ = 5,7 Hz, 2H), 7,34 (d, $J$ = 5,7 Hz, 2H), 3,56 (s, 1H), 2,21 (s, 6H).

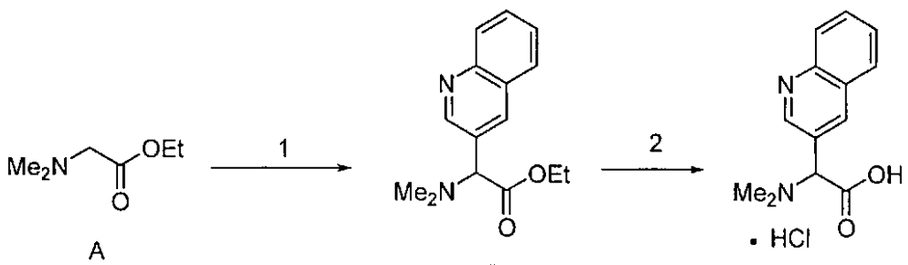
Los siguientes ejemplos se prepararon de una forma similar usando el procedimiento descrito antes;

| | | |
|---|---|---|
| *Cap-19* |  | CLEM: Anal. Calculado para $C_9H_{12}N_2O_2$: 180; encontrado: 181 $(M+H)^+$. |
| *Cap-20* |  | CLEM: sin ionización. RMN de $^1$H (400 MHz, $CD_3OD$) $\delta$ 8,55 (d, $J$ = 4,3 Hz, 1H), 7,84 (t aparente, $J$ = 5,3 Hz, 1H), 7,61 (d, $J$ = 7,8 Hz, 1H), 7,37 (t aparente, $J$ = 5,3 Hz, 1H), 4,35 (s, 1H), 2,60 (s, 6H). |
| *Cap-21* |  | CLEM: Anal. Calculado para $C_9H_{11}ClN_2O_2$: 214, 216; encontrado: 215, 217 $(M+H)^+$. |

| | | |
|---|---|---|
| *Cap-22* |  | CLEM: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$. |
| *Cap-23* |  | CLEM: Anal. Calculado para $C_{14}H_{15}NO_2$: 229; encontrado: 230 $(M+H)^+$. |
| *Cap-24* |  | CLEM: Anal. Calculado para $C_{11}H_{12}F_3NO_2$: 247; encontrado: 248 $(M+H)^+$. |
| *Cap-25* |  | CLEM: Anal. Calculado para $C_{11}H_{12}F_3NO_2$: 247; encontrado: 248 $(M+H)^+$. |
| *Cap-26* |  | CLEM: Anal. Calculado para $C_{10}H_{12}FNO_2$: 197; encontrado: 198 $(M+H)^+$. |
| *Cap-27* |  | CLEM: Anal. Calculado para $C_{10}H_{12}FNO_2$: 247; encontrado: 248 $(M+H)^+$. |
| *Cap-28* |  | CLEM: Anal. Calculado para $C_{10}H_{12}ClNO_2$: 213; encontrado: 214 $(M+H)^+$. |
| *Cap-29* |  | CLEM: Anal. Calculado para $C_{10}H_{12}ClNO_2$: 213; encontrado: 214 $(M+H)^+$. |

| | | |
|---|---|---|
| *Cap-30* |  | CLEM: Anal. Calculado para $C_{10}H_{12}ClNO_2$: 213; encontrado: 214 $(M+H)^+$. |
| *Cap-31* |  | CLEM: Anal. Calculado para $C_8H_{12}N_2O_2S$: 200; encontrado: 201 $(M+H)^+$. |
| *Cap-32* |  | CLEM: Anal. Calculado para $C_8H_{11}NO_2S$: 185; encontrado: 186 $(M+H)^+$. |
| *Cap-33* |  | CLEM: Anal. Calculado para $C_8H_{11}NO_2S$: 185; encontrado: 186 $(M+H)^+$. |
| *Cap-34* |  | CLEM: Anal. Calculado para $C_{11}H_{12}N_2O_3$: 220; encontrado: 221 $(M+H)^+$. |
| *Cap-35* |  | CLEM: Anal. Calculado para $C_{12}H_{13}NO_2S$: 235; encontrado: 236 $(M+H)^+$. |
| *Cap-36* |  | CLEM: Anal. Calculado para $C_{12}H_{14}N_2O_2S$: 250; encontrado: 251 $(M+H)^+$. |

*Cap-37*



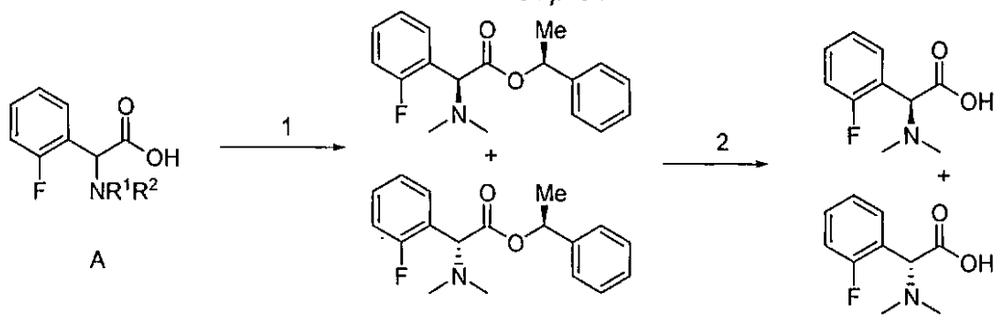

A B cap-37

*Etapa 1:* 2-(quinolin-3-il)-2-(N,N-dimetilamino)-acetato de (R,S)-etilo: Una mezcla de N,N-dimetilaminoacetato de etilo (0,462 g, 3,54 mmol), $K_3PO_4$ (1,90 g, 8,95 mmol), $Pd(t\text{-}Bu_3P)_2$ (0,090 g, 0,176 mmol) y tolueno (10 ml) se desgasificó con una corriente de burbujas de Ar durante 15 minutos. La mezcla de reacción se calentó entonces a 100 °C durante 12 horas, después de lo cual se enfrió hasta temperatura ambiente y se vertió en $H_2O$. La mezcla se extrajo con acetato de etilo (2x) y las fases orgánicas reunidas se lavaron ($H_2O$, salmuera), se secaron ($Na_2SO_4$), se filtraron y se concentraron a vacío. El residuo se purificó primero por HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; $CH_3CN$-$H_2O$-5 mM $NH_4OAc$) y luego por cromatografía ultrarrápida ($SiO_2$/ hexano-acetato de etilo, 1:1) proporcionando el compuesto del epígrafe (0,128 g, 17%) como un aceite naranja. RMN de $^1H$ (400 MHz, $CDCl_3$) $\delta$ 8,90 (d, $J$ = 2,0 Hz, 1H), 8,32 (d, $J$ = 2,0 Hz, 1H), 8,03-8,01 (m, 2H), 7,77 (ddd, $J$ = 8,3, 6,8, 1,5 Hz, 1H), 7,62 (ddd, $J$ = 8,3, 6,8, 1,5 Hz, 1H), 4,35 (s, 1H), 4,13 (m, 2H), 2,22 (s, 6H), 1,15 (t, $J$ = 7,0 Hz, 3H). CLEM: Anal. Calculado para $C_{15}H_{18}N_2O_2$: 258; encontrado: 259 $(M+H)^+$.

*Etapa 2:* Ácido (R,S) 2-(quinolin-3-il)-2-(N,N-dimetilamino)acético: Se calentó una mezcla de 2-(quinolin-3-il)-2-(N,N-dimetilamino)acetato de (R,S)-etilo (0,122 g, 0,472 mmol) y HCl 6M (3 ml) a 100 °C durante 12 horas. El disolvente se eliminó a vacío proporcionando el diclorhidrato del compuesto del epígrafe (0,169 g, >100%) como una espuma amarillo claro. El material sin purificar se usó en las etapas

siguientes sin purificación adicional. CLEM: Anal. Calculado para $C_{13}H_{14}N_2O_2$: 230; encontrado: 231 $(M+H)^+$.

*Cap-38*



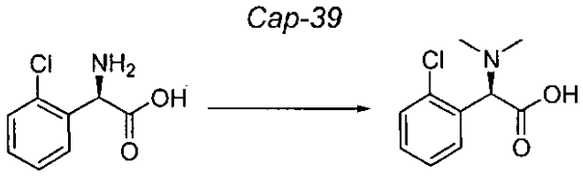

*Etapa 1:* 2-(dimetilamino)-2-(2-fluorofenil)acetato de (R)-((S)-1-feniletilo) y 2-(dimetilamino)-2-(2-fluorofenil)acetato de (S)-((S)-1-feniletil): A una mezcla de ácido (RS)-2-(dimetilamino)-2-(2-fluorofenil)acético (2,60 g, 13,19 mmol), DMAP (0,209 g, 1,71 mmol) y (S)-1-feniletanol (2,09 g, 17,15 mmol) en $CH_2Cl_2$ (40 ml) se añadió EDCI (3,29 g, 17,15 mmol) y la mezcla se dejó agitando a temperatura ambiente durante 12 horas. El disolvente se eliminó entonces a vacío y el residuo se repartió con acetato de etilo-$H_2O$. Se separaron las fases, la fase acuosa se volvió a extraer con acetato de etilo (2x) y las fases orgánicas reunidas se lavaron ($H_2O$, salmuera), se secaron ($Na_2SO_4$), se filtraron y se concentraron a vacío. El residuo se purificó por cromatografía sobre gel de sílice (Biotage/ 0-50% de éter dietílico-hexano). La mezcla diastereomérica pura resultante se separó entonces por HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; $CH_3CN$-$H_2O$-0,1% de TFA) dando primero (R)-2-(dimetilamino)-2-(2-fluorofenil)acetato de (S)-1-fenetilo (0,501 g, 13%) y luego (S)-2-(dimetilamino)-2-(2-fluorofenil)-acetato de (S)-1-fenetilo (0,727 g. 18%),

ambas como sus sales TFA. isómero (S,R): RMN de $^1$H (400 MHz, $CD_3OD$) δ 7,65 - 7,70 (m, 1H), 7,55-7,60 (ddd, *J* = 9,4, 8,1, 1,5 Hz, 1H), 7,36-7,41 (m, 2H), 7,28-7,34 (m, 5H), 6,04 (q, *J* = 6,5 Hz, 1H), 5,60 (s, 1H), 2,84 (s, 6H), 1,43 (d, *J* = 6,5 Hz, 3H). CLEM: Anal. Calculado para $C_{18}H_{20}FNO_2$: 301; encontrado: 302 $(M+H)^+$; isómero (S,S): RMN de $^1$H (400 MHz, $CD_3OD$) δ 7,58-7,63 (m, 1H), 7,18-7,31 (m, 6H), 7,00 (dd, *J* = 8,5, 1,5 Hz, 2H), 6,02 (q, *J* = 6,5 Hz, 1H), 5,60 (s, 1H), 2,88 (s, 6H), 1,54 (d, *J* = 6,5 Hz, 3H). CLEM: Anal. Calculado para $C_{18}H_{20}FNO_2$: 301; encontrado: 302 $(M+H)^+$.

Etapa 2: ácido (R)-2-(dimetilamino)-2-(2-fluorofenil)acético: Una mezcla de 2-(dimetilamino)-2-(2-fluorofenil)acetato de (R)-((S)-1-feniletilo), sal TFA (1,25 g, 3,01 mmol) y 20% de $Pd(OH)_2/C$ (0,125 g) en etanol (30 ml) se sometió a hidrogenación a temperatura ambiente y presión atmosférica (globo de $H_2$) durante 4 horas. La solución se purgó entonces con Ar, se filtró a través de tierra de diatomeas (Celite®) y se concentró a vacío. Esto dio el compuesto del epígrafe como un sólido incoloro (0,503 g, 98%). RMN de $^1$H (400 MHz, $CD_3OD$) δ 7,53-7,63 (m, 2H), 7,33-7,38 (m, 2H), 5,36 (s, 1H), 2,86 (s, 6H). CLEM: Anal. Calculado para $C_{10}H_{12}FNO_2$: 197; encontrado: 198 $(M+H)^+$.

El isómero S se podía obtener a partir de 2-(dimetilamino)-2-(2-fluorofenil)acetato de (S)-((S)-1-feniletilo), sal TFA de una forma similar.

*Cap-39*

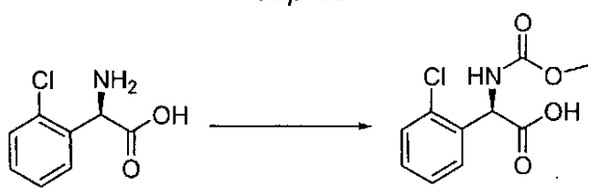



**cap-39**

Una mezcla de (R)-(2-clorofenil)glicina (0,300 g, 1,62 mmol), formaldehído

(solución acuosa al 35%, 0,80 ml, 3,23 mmol) y 20% de $Pd(OH)_2/C$ (0,050 g) se sometió a hidrogenación a temperatura ambiente y presión atmosférica (globo de $H_2$) durante 4 horas. La solución se purgó entonces con Ar, se filtró a través de tierra de diatomeas (Celite®) y se concentró a vacío. El residuo se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; $CH_3CN$-$H_2O$-0,1% de TFA) dando la sal TFA del compuesto del epígrafe ácido (R)-2-(dimetilamino)-2-(2-clorofenil)acético como un aceite incoloro (0,290 g, 55%). RMN de $^1H$ (400 MHz, $CD_3OD$) δ 7,59-7,65 (m, 2H), 7,45-7,53 (m, 2H), 5,40 (s, 1H), 2,87 (s, 6H). CLEM: Anal. Calculado para $C_{10}H_{12}ClNO_2$: 213; encontrado: 214 $(M+H)^+$.

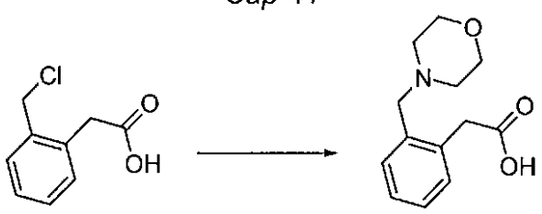
*Cap-40*




**cap-40**

A una solución enfriada en hielo de (R)-(2-clorofenil)glicina (1,00 g, 5,38 mmol) y NaOH (0,862 g, 21,6 mmol) en $H_2O$ (5,5 ml) se añadió cloroformiato de metilo (1,00 ml, 13,5 mmol) gota a gota. La mezcla se dejó agitando a 0 °C durante 1 hora y luego se acidificó mediante la adición de HCl concentrado (2,5 ml). La mezcla se extrajo con acetato de etilo (2x) y la fase orgánica reunida se lavó ($H_2O$, salmuera), se secó ($Na_2SO_4$), se filtró y se concentró a vacío dando el compuesto del epígrafe ácido (R)-2-(metoxicarbonilamino)-2-(2-clorofenil)acético como una espuma amarillo-naranja (1,31 g, 96%). RMN de $^1H$ (400 MHz, $CD_3OD$) δ 7,39 – 7,43 (m, 2H), 7,29 – 7,31 (m, 2H), 5,69 (s, 1H), 3,65 (s, 3H). CLEM: Anal. Calculado para $C_{10}H_{10}ClNO_4$: 243; encontrado: 244 $(M+H)^+$.

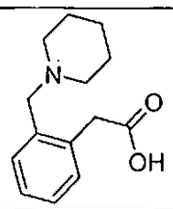
*Cap-41*

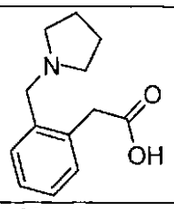
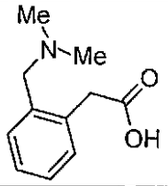
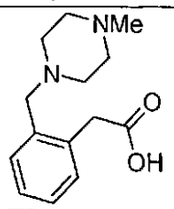



cap-41

A una suspensión de ácido 2-(2-(clorometil)fenil)acético (2,00 g, 10,8 mmol) en THF (20 ml) se añadió morfolina (1,89 g, 21,7 mmol) y la solución se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se diluyó entonces con acetato de etilo y se extrajo con $H_2O$ (2x). La fase acuosa se liofilizó y el residuo se purificó por cromatografía sobre gel de sílice (Biotage/ 0-10% de metanol-$CH_2Cl_2$) dando el compuesto del epígrafe ácido 2-(2-(morfolinometil)fenil)acético como un sólido incoloro (2,22 g, 87%). RMN de $^1H$ (400 MHz, $CD_3OD$) $\delta$ 7,37-7,44 (m, 3H), 7,29-7,33 (m, 1H), 4,24 (s, 2H), 3,83 (s ancho, 4H), 3,68 (s, 2H), 3,14 (s ancho, 4H). CLEM: Anal. Calculado para $C_{13}H_{17}NO_3$: 235; encontrado: 236 $(M+H)^+$.

Los siguientes ejemplos se prepararon de igual modo usando el procedimiento descrito para Cap-41:

| | | |
|---|---|---|
| *Cap-42* |   | CLEM: Anal. Calculado para $C_{14}H_{19}NO_2$: 233; encontrado: 234 $(M+H)^+$. |

| | | |
|---|---|---|
| *Cap-43* |  | CLEM: Anal. Calculado para $C_{13}H_{17}NO_2$: 219; encontrado: 220 $(M+H)^+$. |
| *Cap-44* |  | CLEM: Anal. Calculado para $C_{11}H_{15}NO_2$: 193; encontrado: 194 $(M+H)^+$. |
| *Cap-45* |  | CLEM: Anal. Calculado para $C_{14}H_{20}N_2O_2$: 248; encontrado: 249 $(M+H)^+$. |

*Cap-45a*



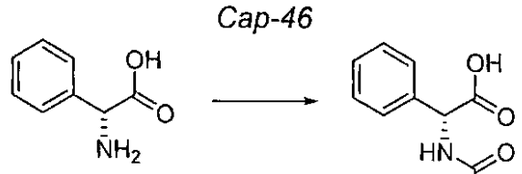
sal pTsOH

Cap-45a

Se añadió HMDS (1,85 ml, 8,77 mmol) a una suspensión de p-toluenosulfonato del ácido (R)-2-amino-2-fenilacético (2,83 g, 8,77 mmol) en $CH_2Cl_2$ (10 ml) y la mezcla se agitó a temperatura ambiente durante 30 minutos. Se añadió isocianato de metilo (0,5 g, 8,77 mmol) en una porción continuando la agitación durante 30 minutos. La reacción se inactivó mediante adición de $H_2O$ (5 ml) y se filtró el precipitado resultante, se lavó con $H_2O$ y n-hexanos, y se secó a vacío. Se recuperó ácido (R)-2-(3-metilureido)-2-fenilacético (1,5 g; 82 %) como un sólido blanco y se usó sin purificación adicional. RMN de $^1H$ (500 MHz, DMSO-$d_6$) $\delta$ ppm

2,54 (d, *J*=4,88 Hz, 3H) 5,17 (d, *J*=7,93 Hz, 1H) 5,95 (q, *J*=4,48 Hz, 1H) 6,66 (d, *J*=7,93 Hz, 1H) 7,26 - 7,38 (m, 5H) 12,67 (s, 1H). CLEM: Anal. Calculado para $C_{10}H_{12}N_2O_3$ 208,08 encontrado 209,121 $(M+H)^+$; HPLC Phenomenex C-18 3,0 × 46 mm, 0 a 100% de B durante 2 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0,1% de TFA, B = 10% de agua, 90% de metanol, 0,1% de TFA, $T_R$ = 1,38 min, índice de homogeneidad 90 %.

*Cap-46*



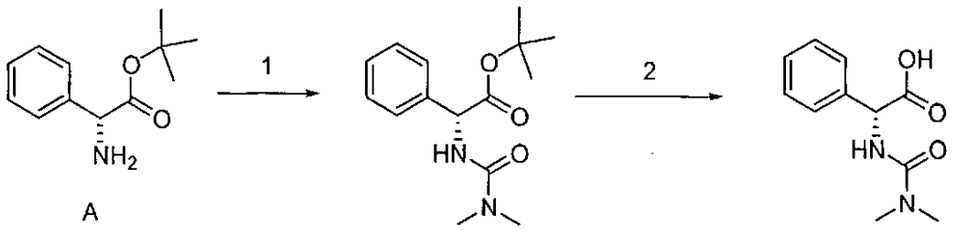

sal pTsOH

cap-46

El producto deseado se preparó de acuerdo con el procedimiento descrito para *Cap*-45a. RMN de $^1H$ (500 MHz, DMSO-$d_6$) δ ppm 0,96 (t, *J*=7,17 Hz, 3H) 2,94 - 3,05 (m, 2H) 5,17 (d, *J*=7,93 Hz, 1H) 6,05 (t, *J*=5,19 Hz, 1H) 6,60 (d, *J*=7,63 Hz, 1H) 7,26 - 7,38 (m, 5H) 12,68 (s, 1H). CLEM: Anal. Calculado para $C_{11}H_{14}N_2O_3$ 222,10 encontrado 223,15 $(M+H)^+$.

HPLC XTERRA C-18 3,0 × 506 mm, 0 a 100% de B durante 2 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0,2% de $H_3PO_4$, B = 10% de agua, 90% de metanol, 0,2% de $H_3PO_4$, $T_R$ = 0,87 min, índice de homogeneidad 90 %.

*Cap-47*



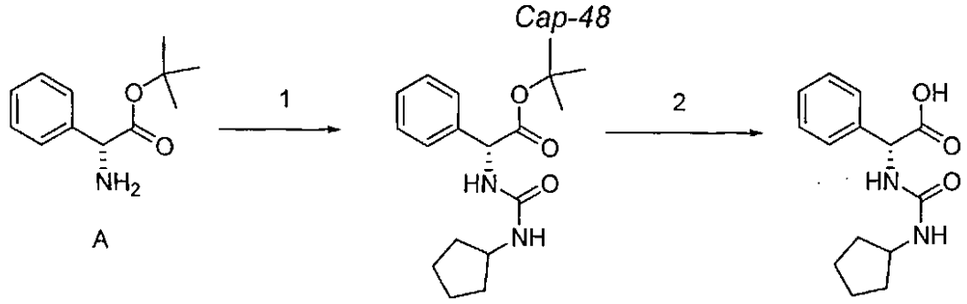

A B Cap-47

Etapa 1: 2-(3,3-dimetilureido)-2-fenilacetato de (R)-terc-butilo: A una solución agitada de (R)-terc–butil-2-amino-2-fenilacetato (1,0 g, 4,10 mmol) y base de Hunig (1,79 ml, 10,25 mmol) en DMF (40 ml) se añadió cloruro de dimetilcarbamoílo (0,38 ml, 4,18 mmol) gota a gota durante 10 minutos. Después de agitar a temperatura ambiente durante 3 horas, la reacción se concentró a presión reducida y el residuo resultante se disolvió en acetato de etilo. La fase orgánica se lavó con $H_2O$, HCl ac. 1N y salmuera, se secó ($MgSO_4$), se filtró y se concentró a presión reducida. Se obtuvo 2-(3,3-dimetilureido)-2-fenilacetato de (R)-terc-butilo como un sólido blanco ( 0,86 g; 75%) y se usó sin purificación posterior. RMN de $^1H$ (500 MHz, DMSO-$d_6$) δ ppm 1,33 (s, 9H) 2,82 (s, 6H) 5,17 (d, *J*=7,63 Hz, 1H) 6,55 (d, *J*=7,32 Hz, 1H) 7,24 - 7,41 (m, 5H). CLEM: Anal. Calculado para $C_{15}H_{22}N_2O_3$ 278,16 encontrado 279,23 $(M+H)^+$; HPLC Phenomenex LUNA C-18 4,6 × 50 mm, 0 a 100% de B durante 4 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0,1% de TFA, B = 10% de agua, 90% de metanol, 0,1% de TFA, $T_R$ = 2,26 min, índice de homogeneidad 97%.

Etapa 2: ácido (R)-2-(3,3-dimetilureido)-2-fenilacético: A una solución agitada de 2-(3,3-dimetilureido)-2-fenilacetato de ((R)-terc-butilo (0,86 g, 3,10 mmol) en $CH_2Cl_2$ (250 ml) se añadió TFA (15 ml) gota a gota y la solución resultante se agitó a ta durante 3 horas. El compuesto deseado precipitó entonces en solución con una mezcla de EtOAC:Hexanos (5:20), se separó por filtración y se secó a presión

reducida. Se aisló ácido (R)-2-(3,3-dimetilureido)-2-fenilacético como un sólido blanco (0,59g, 86%) y se usó sin purificación posterior. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 2,82 (s, 6H) 5,22 (d, *J*=7,32 Hz, 1H) 6,58 (d, *J*=7,32 Hz, 1H) 7,28 (t, *J*=7,17 Hz, 1H) 7,33 (t, *J*=7,32 Hz, 2H) 7,38 - 7,43 (m, 2H) 12,65 (s, 1H). CLEM: Anal. Calculado para $C_{11}H_{14}N_2O_3$: 222,24; encontrado: 223,21 $(M+H)^+$. HPLC XTERRA C-18 3,0 × 50 mm, 0 a 100% de B durante 2 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0,2% $H_3PO_4$, B = 10% de agua, 90% de metanol, 0,2% $H_3PO_4$, $T_R$ = 0,75 min, índice de homogeneidad 93%.

*Cap-48*



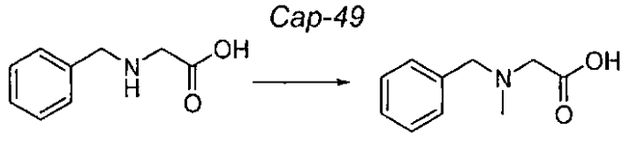

A B Cap-48

Etapa 1: 2-(3-ciclopentilureido)-2-fenilacetato de (R)-terc-butilo: A una solución agitada de clorhidrato del ácido (R)-2-amino-2-fenilacético (1,0 g, 4,10 mmol) y base de Hunig (1,0 ml, 6,15 mmol) en DMF (15 ml) se añadió isocianato de ciclopentilo (0,46 ml, 4,10 mmol) gota a gota y durante 10 minutos. Después de agitar a temperatura ambiente durante 3 horas, la reacción se concentró a presión reducida y el residuo resultante se suspendió en acetato de etilo. La fase orgánica se lavó con $H_2O$ y salmuera, se secó ($MgSO_4$), se filtró y se concentró a presión reducida. Se obtuvo 2-(3-ciclopentilureido)-2-fenilacetato de (R)-terc-butilo como un aceite opaco (1,32 g; 100 %) y se usó sin purificación posterior. RMN de $^1$H (500 MHz, $CD_3Cl$-D) δ ppm 1,50 - 1,57 (m, 2H) 1,58 - 1,66 (m, 2H) 1,87 - 1,97 (m, 2H)

3,89 - 3,98 (m, 1H) 5,37 (s, 1H) 7,26 - 7,38 (m, 5H). CLEM: Anal. Calculado para $C_{18}H_{26}N_2O_3$ 318,19 encontrado 319,21 $(M+H)^+$; HPLC XTERRA C-18 3,0 × 50 mm, 0 a 100% de B durante 4 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0,1% de TFA, B = 10% de agua, 90% de metanol, 0,1% de TFA, $T_R$ = 2,82 min, índice de homogeneidad 96%.

Etapa 2: Ácido (R)-2-(3-ciclopentilureido)-2-fenilacético: A una solución agitada de 2-(3-ciclopentilureido)-2-fenilacetato de (R)-terc-butilo (1,31 g, 4,10 mmol) en $CH_2Cl_2$ (25 ml) se añadió TFA (4 ml) y trietilsilano (1,64 ml; 10,3 mmol) gota a gota, y la solución resultante se agitó a temperatura ambiente durante 6 horas. Los componentes volátiles se eliminaron a presión reducida y el producto bruto se recristalizó en acetato de etilo/pentanos proporcionando ácido (R)-2-(3-ciclopentilureido)-2-fenilacético como un sólido blanco (0,69 g, 64%). RMN de $^1H$ (500 MHz, DMSO-$d_6$) δ ppm 1,17 - 1,35 (m, 2H) 1,42 - 1,52 (m, 2H) 1,53 - 1,64 (m, 2H) 1,67 - 1,80 (m, 2H) 3,75 - 3,89 (m, 1H) 5,17 (d, *J*=7,93 Hz, 1H) 6,12 (d, *J*=7,32 Hz, 1H) 6,48 (d, *J*=7,93 Hz, 1H) 7,24 - 7,40 (m, 5H) 12,73 (s, 1H). CLEM: Anal. Calculado para $C_{14}H_{18}N_2O_3$: 262,31; encontrado: 263,15 $(M+H)^+$. HPLC XTERRA C-18 3,0 × 50 mm, 0 a 100% de B durante 2 minutos, tiempo de mantenimiento 1 minuto, A = 90% de agua, 10% de metanol, 0,2% $H_3PO_4$, B = 10% de agua, 90% de metanol, 0,2% $H_3PO_4$, $T_R$ = 1,24 min, índice de homogeneidad 100%.

*Cap-49*

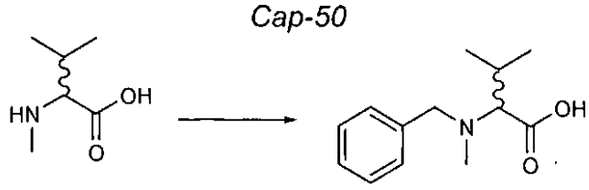


cap-49

A una solución agitada de ácido 2-(bencilamino)acético (2,0 g, 12,1 mmol) en ácido fórmico (91 ml) se añadió formaldehído (6,94 ml, 93,2 mmol). Después de

cinco horas a 70 °C, la mezcla de reacción se concentró a presión reducida hasta 20 ml y precipitó un sólido blanco. Después de filtrar, las aguas madres se recogieron y se concentró además a presión reducida proporcionando el producto bruto. La purificación por HPLC preparativa de fase inversa (Xterra 30 X 100 mm, detección a 220 nm, Caudal 35 ml/min, 0 a 35% de B durante 8 min; A = 90% de agua, 10 % de metanol, 0,1% de TFA, B = 10% de agua, 90 % de metanol, 0,1% de TFA) proporcionó el compuesto del epígrafe ácido 2-(bencil(metil)-amino)acético como su sal TFA (723 mg, 33%) como una cera incolora. RMN de $^1$H (300 MHz, DMSO-$d_6$) δ ppm 2,75 (s, 3H) 4,04 (s, 2H) 4,34 (s, 2H) 7,29 - 7,68 (m, 5H). CLEM: Análisis calculado para: $C_{10}H_{13}NO_2$ 179,09; Encontrado: 180,20 $(M+H)^+$.

*Cap-50*

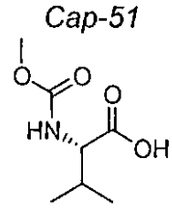



Cap-50

A una solución agitada de ácido 3-metil-2-(metilamino)butanoico(0,50 g, 3,81 mmol) en agua ( 30 ml) se añadió $K_2CO_3$ (2,63 g, 19,1 mmol) y cloruro de bencilo (1,32 g, 11,4 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se extrajo con acetato de etilo (30 ml x 2) y la fase acuosa se concentró a presión reducida proporcionando el producto bruto que se purificó por HPLC preparativa de fase inversa (Xterra 30 x 100mm, detección a 220 nm, Caudal 40 ml/min, 20 a 80% de B durante 6 min; A = 90% de agua, 10 % de metanol, 0,1% de TFA, B = 10% de agua, 90 % de metanol, 0,1% de TFA) proporcionando ácido 2-(bencil(metil)amino)-3-metilbutanoico, sal TFA (126 mg, 19%) como una cera incolora. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 0,98 (d, 3H)

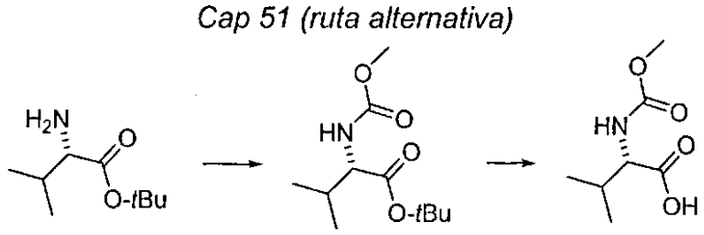
1,07 (d, 3H) 2,33 - 2,48 (m, 1H) 2,54 - 2,78 (m, 3H) 3,69 (s, 1H) 4,24 (s, 2H) 7,29 - 7,65 (m, 5H). CLEM: Análisis calculado para: $C_{13}H_{19}NO_2$ 221,14; Encontrado: 222,28 $(M+H)^+$.

*Cap-51*



Se añadió $Na_2CO_3$ (1,83g, 17,2 mmol) a una solución de NaOH (33 ml de 1M/$H_2O$, 33 mmol) de L-valina (3,9 g, 33,29 mmol) y la solución resultante se enfrió con baño de hielo-agua. Se añadió gota a gota durante 15 minutos cloroformiato de metilo (2,8 ml, 36,1 mmol), se retiró el baño de enfriamiento y la mezcla de reacción se agitó a temperatura ambiente durante 3,25 horas. La mezcla de reacción se lavó con éter (50 ml, 3x), y la fase acuosa se enfrió con un baño de hielo-agua y se acidificó con HCl concentrado hasta un pH de 1-2, y se extrajo con $CH_2Cl_2$ (50 ml, 3x). La fase orgánica se secó ($MgSO_4$) y se evaporó a vacío proporcionando *Cap*-51 como un sólido blanco (6 g). RMN de $^1H$ para el rotámero dominante (DMSO-$d_6$, $\delta$ = 2,5 ppm, 500 MHz): 12,54 (s, 1H), 7,33 (d, $J$ = 8,6, 1H), 3,84 (dd, $J$ = 8,4, 6,0, 1H), 3,54 (s, 3H), 2,03 (m, 1H), 0,87 (m, 6H). EMAR: Anal. Calculado para $[M+H]^+$ $C_7H_{14}NO_4$: 176,0923; encontrado 176,0922.

*Cap 51 (ruta alternativa)*



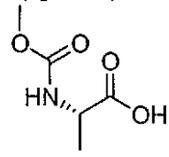
Se añadió DIEA (137,5 ml, 0,766 mol) a una suspensión de clorhidrato de 2-amino-3-metilbutanoato de (*S*)-*terc*-butilo (75,0 g, 0,357 mol) en THF (900 ml), y la mezcla se enfrió hasta 0 ºC (baño de hielo/agua). Se añadió gota a gota durante 45 minutos cloroformiato de metilo (29,0 ml, 0,375 mol), se retiró el baño de enfriamiento y la mezcla heterogénea se agitó a temperatura ambiente durante 3 h. El disolvente se eliminó a presión reducida y el residuo se repartió entre EtOAc y agua (1 litro de cada uno). La fase orgánica se lavó con $H_2O$ (1 l) y salmuera (1 l), se secó ($MgSO_4$), se filtró y se concentró a presión reducida. El material bruto se hizo pasar a través de un lecho corto de gel de sílice (1 kg), eluyendo con hexanos (4 l) y EtOAc:hexanos 15:85 (4 l) proporcionando 2-(metoxicarbonilamino)-3-metilbutanoato de (S)-terc-butilo como un aceite transparente (82,0 g, 99% de rendimiento). RMN de $^1$H (500 MHz, DMSO-$d_6$, $\delta$ = 2,5 ppm) 7,34 (d, *J* = 8,6, 1 H), 3,77 (dd, *J* = 8,6, 6,1, 1 H), 3,53 (s, 3 H), 1,94 - 2,05 (m, 1 H), 1,39 (s, 9 H), 0,83 - 0,92 (m, 6 H). RMN de $^{13}$C (126 MHz, DMSO-$d_6$, $\delta$ = 39,2 ppm) 170,92, 156,84, 80,38, 60,00, 51,34, 29,76, 27,62, 18,92, 17,95. CL/EM: $[M+Na]^+$ 254,17.

Se añadieron ácido trifluoroacético (343 ml, 4,62 mol) y $Et_3SiH$ (142 ml, 0,887 mol) secuencialmente a una solución de 2-(metoxicarbonilamino)-3-metilbutanoato de (S)-terc-butilo (82,0 g, 0,355 mol) en $CH_2Cl_2$ (675 ml), y la mezcla se agitó a temperatura ambiente durante 4 h. El componente volátil se eliminó a presión reducida y el aceite resultante se trituró con éter de petróleo (600 ml) proporcionando un sólido blanco, que se filtró y se lavó con hexanos (500 ml) y éter de petróleo (500 ml). La recristalización en EtOAc/éter de petróleo proporcionó *Cap-51* como cristales a modo de escamas blancos (54,8 g, 88 % de rendimiento). PF = 108,5-109,5 ºC. RMN de $^1$H (500 MHz, DMSO-$d_6$, $\delta$ = 2,5 ppm) 12,52 (s, 1 H), 7,31 (d, *J* = 8,6, 1 H), 3,83 (dd, *J* = 8,6, 6,1, 1 H), 3,53 (s, 3 H), 1,94 - 2,07 (m, 1 H), 0,86

(dd, $J$ = 8,9, 7,0, 6 H). RMN de $^{13}C$ (126 MHz, DMSO-$d_6$, $\delta$ = 39,2 ppm) 173,30, 156,94, 59,48, 51,37, 29,52, 19,15, 17,98. CL/EM: $[M+H]^+$ = 176,11. Análisis calculado para $C_7H_{13}NO_4$: C, 47,99; H, 7,48; N, 7,99. Encontrado: C, 48,17; H, 7,55; N, 7,99. Rotación óptica: $[\alpha]_D$ = -4,16 (12,02 mg/ml; MeOH). Pureza óptica: >99,5 % ee. Nota: la valoración de la pureza óptica se realizó en el derivado éster metílico de *Cap-51*, que se preparó según un protocolo de esterificación normalizado en $TMSCHN_2$ (benceno/MeOH). Condiciones del análisis de HPLC: columna, ChiralPak AD-H (4,6 x 250mm, 5µm); disolvente, heptano al 95% / IPA al 5% (isocrático); caudal, 1 ml/min; temperatura, 35 °C; UV controlado a 205 nm.

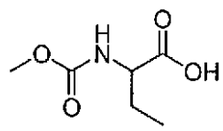
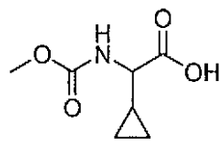
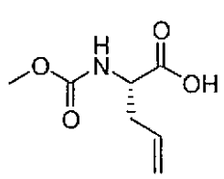
[Nota: Cap 51 también se podía adquirir de Flamm.]

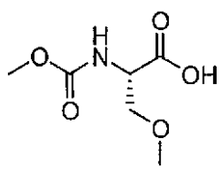
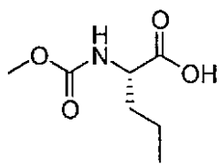
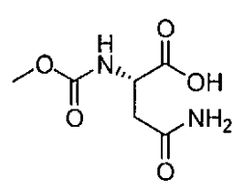
*Cap-52 (Igual que Cap-12)*

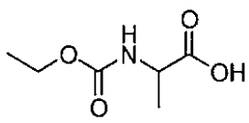
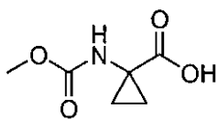
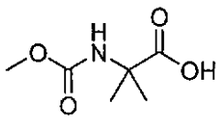
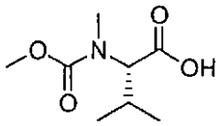


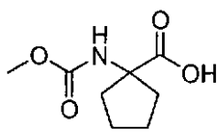
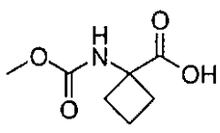
Se sintetizó *Cap*-52 a partir de L-alanina de acuerdo con el procedimiento descrito para la síntesis de *Cap*-51. Con fines caracterizadores, se purificó una porción del material bruto por una HPLC de fase inversa ($H_2O$/metanol/TFA) proporcionando *Cap*-52 como un aceite incoloro viscoso. RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 500 MHz): 12,49 (s ancho, 1H), 7,43 (d, $J$ = 7,3, 0,88H), 7,09 (s ancho aparente, 0,12H), 3,97 (m, 1H), 3,53 (s, 3H), 1,25 (d, $J$ = 7,3, 3H).

*Cap*-53 a -64 se prepararon a partir de materiales partida apropiados de acuerdo con el procedimiento descrito para la síntesis de *Cap*-51, con las modificaciones indicadas si las hubiera.

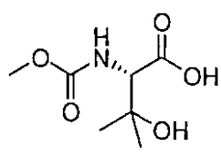
| Cap | Estructura | Datos |
|---|---|---|
| *Cap-53a*: (R)<br>*Cap-53b*: (S) |  | RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5 ppm, 500 MHz): $\delta$ 12,51 (s ancho, 1H), 7,4 (d, *J* = 7,9, 0,9H), 7,06 (s ap., 0,1H), 3,86-3,82 (m, 1H), 3,53 (s, 3H), 1,75-1,67 (m, 1H), 1,62-1,54 (m, 1H), 0,88 (d, *J* = 7,3, 3H). $T_R$ = 0,77 minutos (Cond. II); CL/EM: Anal. Calculado para $[M+Na]^+$ $C_6H_{11}NNaO_4$ : 184,06; encontrado 184,07. EMAR Calculado para $[M+Na]^+$ $C_6H_{11}NNaO_4$: 184,0586; encontrado 184,0592. |
| *Cap-54a*: (R)<br>*Cap-54b*: (S) |  | RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5 ppm, 500 MHz): $\delta$ 12,48 (s, 1H), 7,58 (d, *J* = 7,6, 0,9H), 7,25 (s ap., 0,1H), 3,52 (s, 3H), 3,36-3,33 (m, 1H), 1,10-1,01 (m, 1H), 0,54-0,49 (m, 1H), 0,46-0,40 (m, 1H), 0,39-0,35 (m, 1H), 0,31-0,21 (m, 1H). EMAR Calculado para $[M+H]^+$ $C_7H_{12}NO_4$: 174,0766; encontrado 174,0771 |
| *Cap-55* |  | RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5 ppm, 500 MHz): $\delta$ 12,62 (s, 1H), 7,42 (d, *J* = 8,2, 0,9H), 7,07 (s ap., 0,1H), 5,80-5,72 (m, 1H), 5,10 (d, *J* = 17,1, 1H), 5,04 (d, *J* = 10,4, 1H), 4,01-3,96 (m, 1H), 3,53 (s, 3H), 2,47- |

| | | |
|---|---|---|
| | | 2,42 (m, 1H), 2,35-2,29 (m, 1H). |
| *Cap-56* |  | RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5 ppm, 500 MHz): $\delta$ 12,75 (s, 1H), 7,38 (d, *J* = 8,3, 0,9H), 6,96 (s ap., 0,1H), 4,20-4,16 (m, 1H), 3,60-3,55 (m, 2H), 3,54 (s, 3H), 3,24 (s, 3H). |
| *Cap-57* |  | RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5 ppm, 500 MHz): $\delta$ 12,50 (s, 1H), 8,02 (d, *J* = 7,7, 0,08H), 7,40 (d, *J* = 7,9, 0,76H), 7,19 (d, *J* = 8,2, 0,07H), 7,07 (d, *J* = 6,7, 0,09H), 4,21-4,12 (m, 0,08H), 4,06-3,97 (m, 0,07H), 3,96-3,80 (m, 0,85H), 3,53 (s, 3H), 1,69-1,51 (m, 2H), 1,39-1,26 (m, 2H), 0,85 (t, *J* = 7,4, 3H). CL (Cond. II): $T_R$ = 1,39 CL/EM: Anal. Calculado para $[M+H]^+$ $C_7H_{14}NO_4$ : 176,09; encontrado 176,06. |
| *Cap-58* |  | RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5 ppm, 500 MHz): $\delta$ 12,63 (s ancho, 1H), 7,35 (s,1H), 7,31 ( d, *J* = 8,2, 1H), 6,92 (s, 1H), 4,33-4,29 (m, 1H), 3,54 (s, 3H), 2,54(dd, *J* = 15,5, 5,4, 1H), 2,43 (dd, *J* = 15,6, 8,0, 1H). $T_R$ = 0,16 min (Cond. II); CL/EM: Anal. Calculado para $[M+H]^+$ $C_6H_{11}N_2O_5$ : 191,07; encontrado 191,14. |

| | | |
|---|---|---|
| *Cap-59a*: (R)<br>*Cap-59b*: (S) |  | RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): $\delta$ 12,49 (s ancho, 1H), 7,40 (d, *J* = 7,3, 0,89H), 7,04 (s ancho, 0,11H), 4,00-3,95 (m, 3H), 1,24 (d, *J* = 7,3, 3H), 1,15 (t, *J* = 7,2, 3H). EMAR: Anal. Calculado para $[M+H]^+$ $C_6H_{12}NO_4$: 162,0766; encontrado 162,0771. |
| *Cap-60* |  | El material bruto se purificó con una HPLC de fase inversa ($H_2O$/MeOH/TFA) proporcionando un aceite viscoso incoloro que cristalizó en un sólido blanco al exponerse a alto vacío. RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): $\delta$ 12,38 (s ancho, 1H), 7,74 (s, 0,82H), 7,48 (s, 0,18H), 3,54/3,51 (dos s, 3H), 1,30 (m, 2H), 0,98 (m, 2H). EMAR: Anal. Calculado para $[M+H]^+$ $C_6H_{10}NO_4$: 160,0610; encontrado 160,0604. |
| *Cap-61* |  | RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): $\delta$ 12,27 (s ancho, 1H), 7,40 (s ancho, 1H), 3,50 (s, 3H), 1,32 (s, 6H). EMAR: Anal. Calculado para $[M+H]^+$ $C_6H_{12}NO_4$: 162,0766; encontrado 162,0765. |
| *Cap-62* |  | RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): $\delta$ 12,74 (s ancho, 1H), 4,21 (d, *J* = |

| | | |
|---|---|---|
| | | 10,3, 0,6H), 4,05 (d, *J* = 10,0, 0,4H), 3,62/3,60 (dos singletes, 3H), 3,0 (s, 3H), 2,14-2,05 (m, 1H), 0,95 (d, *J* = 6,3, 3H), 0,81 (d, *J* = 6,6, 3H). CL/EM: Anal. Calculado para $[M-H]^-$ $C_8H_{14}NO_4$: 188,09; encontrado 188,05. |
| *Cap-63* |  | [Nota: se dejó proceder la reacción durante más tiempo que el indicado para el procedimiento general.] RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): 12,21 (s ancho, 1H), 7,42 (s ancho, 1H), 3,50 (s, 3H), 2,02-1,85 (m, 4H), 1,66-1,58 (m, 4H). CL/EM: Anal. Calculado para $[M+H]^+$ $C_8H_{14}NO_4$: 188,09; encontrado 188,19. |
| *Cap-64* |  | [Nota: se dejó proceder la reacción durante más tiempo que el indicado para el procedimiento general.] RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): 12,35 (s ancho, 1H), 7,77 (s, 0,82H), 7,56/7,52 (s ancho solapante, 0,18H), 3,50 (s, 3H), 2,47-2,40 (m, 2H), 2,14-2,07 (m, 2H), 1,93-1,82 (m, 2H). |

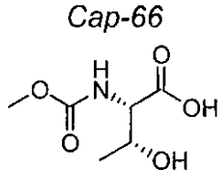
*Cap-65*



Se añadió cloroformiato de metilo (0,65 ml, 8,39 mmol) gota a gota durante 5 minutos a una mezcla enfriada (hielo-agua) de $Na_2CO_3$ (0,449 g, 4,23 mmol), NaOH (8,2 ml de 1M/$H_2O$, 8,2 mmol) y ácido (*S*)-2-amino-3-hidroxi-3-metilbutanoico (1,04 g, 7,81 mmol). La mezcla de reacción se agitó durante 45 min, y luego se retiró el baño de enfriamiento y se continuó agitando durante otras 3,75 horas. La mezcla de reacción se lavó con $CH_2Cl_2$, y la fase acuosa se enfrió con baño de hielo-agua y se acidificó con HCl concentrado hasta una región de pH de 1-2. El componente volátil se eliminó a vacío y el residuo se suspendió en una mezcla 2:1 de MeOH/$CH_2Cl_2$ (15 ml) y se filtró, y el filtrado se sometió a evaporación rotativa proporcionando *Cap*-65 como una espuma semiviscosa blanca (1,236 g). RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): $\delta$ 6,94 (d, *J* = 8,5, 0,9 H), 6,53 (s ancho, 0,1H), 3,89 (d, *J* = 8,8, 1H), 2,94 (s, 3H), 1,15 (s, 3H), 1,13 (s, 3H).

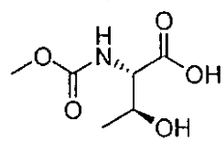
*Cap*-66 y -67 se prepararon a partir de materiales de partida disponibles comercialmente empleando el procedimiento descrito para la síntesis de *Cap*-65.

*Cap-66*



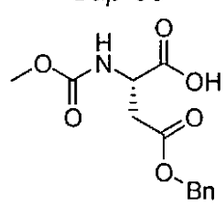
RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): $\delta$ 12,58 (s ancho, 1H), 7,07 (d, *J* = 8,3, 0,13H), 6,81 (d, *J* = 8,8, 0,67H), 4,10-4,02 (m, 1,15H), 3,91 (dd, *J* = 9,1, 3,5, 0,85H), 3,56 (s, 3H), 1,09 (d, *J* = 6,2, 3H). [Nota: solo se indican las señales dominantes de NH]

*Cap-67*



RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): 12,51 (s ancho, 1H), 7,25 (d, *J* = 8,4, 0,75H), 7,12 (d ancho, *J* = 0,4, 0,05H), 6,86 (s ancho, 0,08H), 3,95-3,85 (m, 2H), 3,54 (s, 3H), 1,08 (d, *J* = 6,3, 3H). [Nota: solo se indican las señales dominantes de NH]

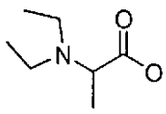
*Cap-68*



Se añadió cloroformiato de metilo (0,38 ml, 4,9 mmol) gota a gota a una mezcla de NaOH 1N (ac) (9,0 ml, 9,0 mmol), $NaHCO_3$ 1M (ac) (9,0 ml, 9,0 mol), éster β-bencílico del ácido L-aspártico (1,0 g, 4,5 mmol) y dioxano (9 ml). La mezcla de reacción se agitó en condiciones ambientales durante 3 horas, y luego se lavó con acetato de etilo (50 ml, 3x). La fase acuosa se acidificó con HCl 12N hasta un pH ~ 1-2, y se extrajo con acetato de etilo (3 x 50 ml). Las fases orgánicas reunidas se lavaron con salmuera, se secaron ($Na_2SO_4$), se filtraron y se concentraron a vacío proporcionando *Cap*-68 como un aceite amarillo claro (1,37g; la masa es superior al rendimiento teórico, y el producto se usó sin purificación adicional). RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5 ppm, 500 MHz): $\delta$ 12,88 (s ancho, 1H), 7,55 (d, *J* = 8,5, 1H), 7,40-7,32 (m, 5H), 5,13 (d, *J* = 12,8, 1H), 5,10 (d, *J* = 12,9, 1H), 4,42-4,38 (m, 1H), 3,55 (s, 3H), 2,87 (dd, *J* = 16,2, 5,5, 1H), 2,71 (dd, *J* =16,2, 8,3, 1H). CL (Cond.

II): $T_R$ = 1,90 min; CL/EM: Análisis calculado para $[M+H]^+$ $C_{13}H_{16}NO_6$: 282,10; encontrado 282,12.

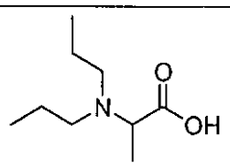
*Cap-69a y -69b*

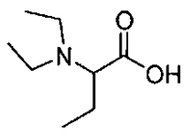
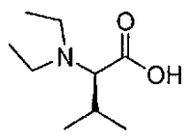
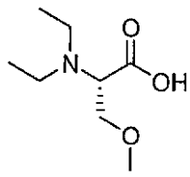
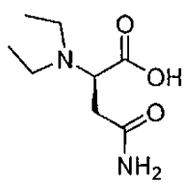


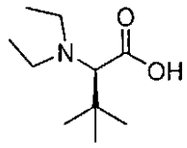
Cap-69a: enantiómero (*R*)
Cap-69b: enantiómero (*S*)

Se añadió $NaCNBH_3$ (2,416 g, 36,5 mmol) en lotes a una solución acuosa enfriada (~15°C) (17 ml)/MeOH (10 ml) de alanina (1,338 g, 15,0 mmol). Unos pocos minutos después se añadió gota a gota durante 4 minutos acetaldehído (4,0 ml, 71,3 mmol), se retiró entonces el baño de enfriamiento y la mezcla de reacción se agitó en condiciones ambientales durante 6 horas. Se añadió más acetaldehído (4,0 ml) y la reacción se agitó durante 2 horas. Se añadió HCl concentrado lentamente a la mezcla de reacción hasta que el pH alcanzó ~ 1,5, y la mezcla resultante se calentó durante 1 hora a 40°C. La mayoría del componente volátil se eliminó a vacío y el residuo se purificó con una resina de intercambio iónico Dowex ® 50WX8-100 (la columna se lavó con agua y el compuesto se eluyó con $NH_4OH$ diluido, preparado mezclando 18 ml de $NH_4OH$ y 282 ml de agua) proporcionando *Cap*-69 (2,0 g) como un sólido higroscópico blando blanquecino. RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): $\delta$ 3,44 (q, *J* = 7,1, 1H), 2,99-2,90 (m, 2H), 2,89-2,80 (m, 2H), 1,23 (d, *J* = 7,1, 3H), 1,13 (t, *J* = 7,3, 6H).

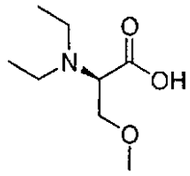
*Cap-70* a *-74x* se prepararon de acuerdo con el procedimiento descrito para la síntesis de *Cap*-69 empleando materiales de partida apropiados.

| | | |
|---|---|---|
| *Cap-70a*: (R)<br>*Cap-70b*: (S) |  | RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): $\delta$ 3,42 (q, *J* = 7,1, 1H), 2,68-2,60 (m, |

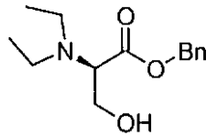
| | | |
|---|---|---|
| | | 4H), 1,53-1,44 (m, 4H), 1,19 (d, *J* = 7,3, 3H), 0,85 (t, *J* = 7,5, 6H). CL/EM: Anal. Calculado para $[M+H]^+$ $C_9H_{20}NO_2$: 174,15; encontrado 174,13. |
| *Cap-71a*: (R)<br>*Cap-71b*: (S) |  | RMN de $^1H$ (DMSO-$d_6$, δ = 2,5 ppm, 500 MHz): δ 3,18-3,14 (m, 1H), 2,84-2,77 (m, 2H), 2,76-2,68 (m, 2H), 1,69-1,54 (m, 2H), 1,05 (t, *J* = 7,2, 6H), 0,91 (t, *J* = 7,3, 3H). CL/EM: Anal. Calculado para $[M+H]^+$ $C_8H_{18}NO_2$: 160,13; encontrado 160,06. |
| *Cap-72* |  | RMN de $^1H$ (DMSO-$d_6$, δ = 2,5 ppm, 400 MHz): δ 2,77-2,66 (m, 3H), 2,39-2,31 (m, 2H), 1,94-1,85 (m, 1H), 0,98 (t, *J* = 7,1, 6H), 0,91 (d, *J* = 6,5, 3H), 0,85 (d, *J* = 6,5, 3H). CL/EM: Anal. Calculado para $[M+H]^+$ $C_9H_{20}NO_2$: 174,15; encontrado 174,15. |
| *Cap-73* |  | RMN de $^1H$ (DMSO-$d_6$, δ = 2,5 ppm, 500 MHz): δ 9,5 (s ancho, 1H), 3,77 (dd, *J* = 10,8, 4,1,1H), 3,69-3,61 ( m, 2H), 3,26 (s, 3H), 2,99-2,88 (m, 4H), 1,13 (t, *J* = 7,2, 6H). |
| *Cap-74* |  | RMN de $^1H$ (DMSO-$d_6$, δ = 2,5 ppm, 500 MHz): δ 7,54 (s, 1H), 6,89 (s, 1H), 3,81 (t, *J* = 6,6, k,1H), 2,82-2,71 (m, 4H), 2,63 (dd, *J* = 15,6, 7,0, 1H), 2,36 (dd, *J* = 15,4, 6,3, 1H), 1,09 (t, *J* = 7,2, 6H). $T_R$ = 0,125 |

| | | |
|---|---|---|
| | | minutos (Cond. II); CL/EM: Anal. Calculado para $[M+H]^+$ $C_8H_{17}N_2O_3$ : 189,12; encontrado 189,13. |
| *Cap-74x* |  | CL/EM: Anal. Calculado para $[M+H]^+$ $C_{10}H_{22}NO_2$ : 188,17; encontrado 188,21 |

*Cap-75*



*Cap-75, etapa a*



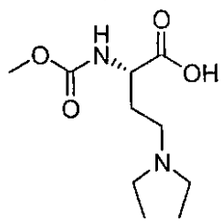
Se añadió $NaBH_3CN$ (1,6 g, 25,5 mmol) a una solución enfriada (baño de hielo/agua) en agua (25 ml)/metanol (15 ml) de H-D-Ser-OBzl HCl (2,0 g, 8,6 mmol). Se añadió acetaldehído (1,5 ml, 12,5 mmol) gota a gota durante 5 min, se retiró el baño de enfriamiento, y la mezcla de reacción se agitó en condiciones ambientales durante 2 horas. La reacción se inactivó cuidadosamente con HCl 12N y se concentró a vacío. El residuo se disolvió en agua y se purificó con una HPLC de fase inversa ($MeOH/H_2O$/TFA) proporcionando la sal TFA de 2-(dietilamino)-3-hidroxipropanoato de (R)-bencilo como un aceite incoloro viscoso (1,9 g). RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 500 MHz): $\delta$ 9,73 (s ancho, 1H), 7,52-7,36 (m, 5H), 5,32 (d, *J* = 12,2, 1H), 5,27 (d, *J* = 12,5, 1H), 4,54-4,32 (m, 1H), 4,05-3,97 (m, 2H), 3,43-3,21 (m, 4H), 1,23 (t, *J* = 7,2, 6H). CL/EM (Cond. II): $T_R$ = 1,38 min; CL/EM: Anal.

Calculado para $[M+H]^+$ $C_{14}H_{22}NO_3$: 252,16; encontrado 252,19.

*Cap-75*

Se añadió NaH (0,0727 g, 1,82 mmol, 60%) a una solución enfriada (hielo-agua) en THF (3,0 ml) de la sal TFA de 2-(dietilamino)-3-hidroxipropanoato de (R)-bencilo (0,3019 g, 0,8264 mmol) preparada antes, y la mezcla se agitó durante 15 min. Se añadió yoduro de metilo (56 µl, 0,90 mmol) y se continuó agitando durante 18 horas dejando que el baño se descongelara hasta condiciones ambiente. La reacción se inactivó con agua y se cargó en un cartucho MCX preacondicionado con MeOH (6 g) y se lavó con metanol seguido por elución del compuesto con $NH_3$ 2N/Metanol. La eliminación del componente volátil a vacío proporcionó *Cap*-75, contaminado con ácido (R)-2-(dietilamino)-3-hidroxipropanoico, como un semisólido amarillo (100 mg). El producto se usó como tal sin purificación adicional.

*Cap-76*

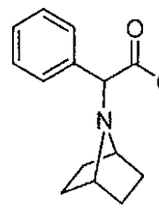


Se añadió $NaCNBH_3$ (1,60 g, 24,2 mmol) en cargas a una solución enfriada (~15 °C) en agua/MeOH (12 ml cada uno) de ácido (*S*)-4-amino-2-(terc-butoxicarbonilamino) butanoico (2,17 g, 9,94 mmol). Unos pocos minutos después se añadió acetaldehído (2,7 ml, 48,1 mmol) gota a gota durante 2 min, se retiró el baño de enfriamiento y la mezcla de reacción se agitó en condiciones ambientales durante 3,5 horas. Se añadió más acetaldehído (2,7 ml, 48,1 mmol) y la reacción se

agitó durante 20,5 horas. Se eliminó a vacío la mayoría del componente MeOH, y la mezcla restante se trató con HCl concentrado hasta que su pH llegó a ~ 1,0 y luego se calentó durante 2 horas a 40 °C. El componente volátil se eliminó a vacío, y el residuo se trató con HCl 4 M/dioxano (20 ml) y se agitó en condiciones ambientales durante 7,5 horas. El componente volátil se eliminó a vacío y el residuo se purificó con resina de intercambio iónico Dowex ® 50WX8-100 (la columna se lavó con agua y el compuesto se eluyó con $NH_4OH$ diluido, preparado a partir de 18 ml de $NH_4OH$ y 282 ml de agua) proporcionando el intermedio ácido (S)-2-amino-4-(dietilamino)butanoico como un sólido blanquecino (1,73 g).

Se añadió cloroformiato de metilo (0,36 ml, 4,65 mmol) gota a gota durante 11 min a una mezcla enfriada (hielo-agua) de $Na_2CO_3$ (0,243 g, 2,29 mmol), NaOH (4,6 ml de 1M/$H_2O$, 4,6 mmol) y el producto anterior (802,4 mg). La mezcla de reacción se agitó durante 55 min, y luego se retiró el baño de enfriamiento y se continuó agitando durante otras 5,25 horas. La mezcla de reacción se diluyó con un volumen igual de agua y se lavó con $CH_2Cl_2$ (30 ml, 2x), y la fase acuosa se enfrió con baño de hielo-agua y se acidificó con HCl concentrado hasta un pH en torno a 2. El componente volátil se eliminó a vacío y el material bruto se desbasificó con resina MCX (6,0g; la columna se lavó con agua, y la muestra se eluyó con $NH_3$ 2,0 M/MeOH) proporcionando *Cap*-76 impuro como un sólido blanquecino (704 mg). RMN de $^1H$ (MeOH-$d_4$, $\delta$ = 3,29 ppm, 400 MHz): $\delta$ 3,99 (dd, *J* = 7,5, 4,7, 1H), 3,62 (s, 3H), 3,25-3,06 (m, 6H), 2,18-2,09 (m, 1H), 2,04-1,96 (m, 1H), 1,28 (t, *J* = 7,3, 6H). CL/EM: Anal. Calculado para $[M+H]^+$ $C_{10}H_{21}N_2O_4$: 233,15; encontrado 233,24.

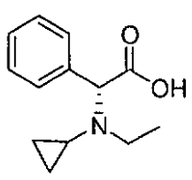
*Cap-77a y -77b*



Cap-77a: enantiómero 1
Cap-77b: enantiómero 2

La síntesis de *Cap*-77 se llevó a cabo de acuerdo con el procedimiento descrito para *Cap*-7 usando 7-azabiciclo[2.2.1]heptano para la etapa de desplazamiento $SN_2$, y efectuando la separación enantiomérica del intermedio 2-(7-azabiciclo[2.2.1]heptan-7-il)-2-fenilacetato de bencilo usando las siguientes condiciones: el intermedio (303,7 mg) se disolvió en etanol, y la solución resultante se inyectó en una columna HPLC quiral (columna Chiracel AD-H, 30 x 250 mm, 5 um) eluyendo con 90% de $CO_2$-10% de EtOH a 70 ml/min, y una temperatura de 35 °C proporcionando 124,5 mg de enantiómero-1 y 133,8 mg de enantiómero-2. Estos ésteres bencílicos se sometieron a hidrogenación de acuerdo con la preparación de *Cap*-7 proporcionando *Cap*-77: RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): $\delta$ 7,55 (m, 2H), 7,38-7,30 (m, 3H), 4,16 (s, 1H), 3,54 (s ancho aparente, 2H), 2,08-1,88 (m, 4 H), 1,57-1,46 (m, 4H). CL (Cond. I): $T_R$ = 0,67 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{14}H_{18}NO_2$: 232,13; encontrado 232,18. EMAR: Anal. Calculado para $[M+H]^+$ $C_{14}H_{18}NO_2$: 232,1338; encontrado 232,1340.

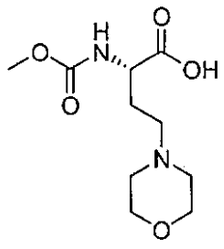
*Cap-78*



Se añadió $NaCNBH_3$ (0,5828 g, 9,27 mmol) a una mezcla de la sal HCl de ácido (*R*)-2-(etilamino)-2-fenilacético (un intermedio en la síntesis de *Cap*-3; 0,9923

mg, 4,60 mmol) y (1-etoxiciclopropoxi)trimetilsilano (1,640 g, 9,40 mmol) en MeOH (10 ml), y se calentó la mezcla semiheterogénea a 50 °C con un baño de aceite durante 20 horas. Se añadieron más (1-etoxiciclopropoxi)trimetilsilano (150 mg, 0,86 mmol) y $NaCNBH_3$ (52 mg, 0,827 mmol) y la mezcla de reacción se calentó otras 3,5 horas. Se dejó enfriar hasta temperatura ambiente y se acidificó ~ pH entorno a 2 con HCl concentrado, y la mezcla se filtró y el filtrado se evaporó en un evaporador rotatorio. El material bruto resultante se suspendió en *i*-PrOH (6 ml) y se calentó para efectuar la disolución y la parte no disuelta se separó por filtración y el filtrado se concentró a vacío. Se purificó aproximadamente 1/3 del material bruto resultante con una HPLC de fase inversa ($H_2O$/MeOH/TFA) proporcionando la sal TFA de *Cap*-78 como un aceite incoloro viscoso (353 mg). RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz; después de intercambio de $D_2O$): $\delta$ 7,56-7,49 (m, 5H), 5,35 (S, 1H), 3,35 (m, 1H), 3,06 (s ancho aparente, 1H), 2,66 (m, 1H), 1,26 (t, *J* = 7,3, 3H), 0,92 (m, 1H), 0,83-0,44 (m, 3H). CL (Cond. I): $T_R$ = 0,64 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{13}H_{18}NO_2$: 220,13; encontrado 220,21. EMAR: Anal. Calculado para $[M+H]^+$ $C_{13}H_{18}NO_2$: 220,1338; encontrado 220,1343.

*Cap-79*



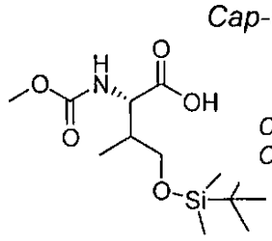
Se burbujeó ozono a través de una solución enfriada (-78 °C) en $CH_2Cl_2$ (5,0 ml) de *Cap*-55 (369 mg, 2,13 mmol) durante aproximadamente 50 min hasta que la mezcla de reacción alcanzó un tinte de color azul. Se añadió $Me_2S$ (10 gotas de

pipeta) y la mezcla de reacción se agitó durante 35 min. Se reemplazó el baño de -78 °C con un baño a -10 °C y se continuó agitando durante otros 30 min, y luego se eliminó el componente volátil a vacío proporcionando un aceite viscoso incoloro.

Se añadió $NaBH_3CN$ (149 mg, 2,25 mmol) a una solución en MeOH (5,0 ml) del material bruto anterior y morfolina (500 µl, 5,72 mmol) y la mezcla se agitó en condiciones ambientales durante 4 horas. Se enfrió hasta temperatura de hielo-agua y se trató con HCl concentrado para llevar el pH a ~2,0, y luego se agitó durante 2,5 horas. El componente volátil se eliminó a vacío, y el residuo se purificó con una combinación de resina MCX (lavado con MeOH; elución con $NH_3$ 2,0 N/MeOH) y una HPLC de fase inversa ($H_2O$/MeOH/TFA) proporcionando *Cap*-79 que contenía una cantidad desconocida de morfolina.

Con el fin de consumir la morfolina contaminante, se disolvió el material anterior en $CH_2Cl_2$ (1,5 ml) y se trató con $Et_3N$ (0,27 ml, 1,94 mmol) seguido por anhídrido acético (0,10 ml, 1,06 mmol) y se agitó en condiciones ambientales durante 18 horas. Se añadieron THF (1,0 ml) y $H_2O$ (0,5 ml) y se continuó agitando durante 1,5 horas. El componente volátil se eliminó a vacío, y el residuo resultante se hizo pasar a través de resina MCX (lavado con MeOH; elución con $NH_3$ 2,0 N/MeOH) proporcionando *Cap*-79 impuro como un aceite viscoso marrón, que se usó para la etapa siguiente sin purificación adicional.

*Cap-80a y -80b*



*Cap-80a: diastereómero S/S*
*Cap-80b: diastereómero S/R*

Se añadió $SOCl_2$ (6,60 ml, 90,5 mmol) gota a gota durante 15 min a una

mezcla enfriada (hielo-agua) de ácido (S)-3-amino-4-(benciloxi)-4-oxobutanoico (10,04g, 44,98 mmol) y MeOH (300 ml), se retiró el baño de enfriamiento y la mezcla de reacción se agitó en condiciones ambientales durante 29 horas. Se eliminó la mayor parte del componente volátil a vacío y el residuo se repartió cuidadosamente entre EtOAc (150 ml) y solución saturada de $NaHCO_3$. La fase acuosa se extrajo con EtOAc (150 ml, 2x), y la fase orgánica reunida se secó ($MgSO_4$), se filtró y se concentró a vacío proporcionando 4-metil-2-aminosuccinato de (S)-1-bencilo como un aceite incoloro (9,706g). RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): $\delta$ 7,40-7,32 (m, 5H), 5,11 (s, 2H), 3,72 (t aparente, *J* = 6,6, 1H), 3,55 (s, 3H), 2,68 (dd, *J* = 15,9, 6,3, 1H), 2,58 (dd, *J* = 15,9, 6,8, 1H), 1,96 (s, 2H). CL (Cond. I): $T_R$ = 0,90 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{12}H_{16}NO_4$: 238,11; encontrado 238,22.

Se añadió $Pb(NO_3)_2$ (6,06 g, 18,3 mmol) durante 1 minuto a una solución en $CH_2Cl_2$ (80 ml) de 4-metil-2-aminosuccinato de (S)-1-bencilo (4,50 g, 19,0 mmol), 9-bromo-9-fenil-9*H*-fluoreno (6,44 g, 20,0 mmol) y $Et_3N$ (3,0 ml, 21,5 mmol) y la mezcla heterogénea se agitó en condiciones ambientales durante 48 horas. La mezcla se filtró y el filtrado se trató con $MgSO_4$ y se filtró de nuevo y el filtrado final se concentró. El material bruto resultante se sometió a una purificación en Biotage (350 g gel de sílice, elución con $CH_2Cl_2$) proporcionando 4-metil 2-(9-fenil-9H-fluoren-9-ilamino)succinato de (S)-1-bencilo como aceite incoloro muy viscoso (7,93 g). RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): $\delta$ 7,82 (m, 2H), 7,39-7,13 (m, 16H), 4,71 (d, *J* = 12,4, 1H), 4,51 (d, *J* = 12,6, 1H), 3,78 (d, *J* = 9,1, NH), 3,50 (s, 3H), 2,99 (m, 1H), 2,50-2,41 (m, 2H, parcialmente solapado con disolvente). CL (Cond. I): $T_R$ = 2,16 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{31}H_{28}NO_4$: 478,20; encontrado 478,19.

Se añadió LiHMDS (9,2 ml de 1,0 M/THF, 9,2 mmol) gota a gota durante 10

min a una solución enfriada (-78 °C) THF (50 ml) de 4-metil 2-(9-fenil-9H-fluoren-9-ilamino)succinato de (S)-1-bencilo (3,907 g, 8,18 mmol) y se agitó durante ~1 horas. Se añadió MeI (0,57 ml, 9,2 mmol) gota a gota durante 8 min a la mezcla y se continuó agitando durante 16,5 horas dejando que el baño de enfriamiento se descongelara hasta temperatura ambiente. Después de inactivar con solución saturada de $NH_4Cl$ (5 ml), se eliminó a vacío la mayor parte del componente orgánico y el residuo se repartió entre $CH_2Cl_2$ (100 ml) y agua (40 ml). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró a vacío, y el material bruto resultante se purificó con un Biotage (350 g gel de sílice; 25% de EtOAc/hexanos) proporcionando 3,65 g de una mezcla de diastereoisómeros 2S/3S y 2S/3R de 4-metil 3-metil-2-(9-fenil-9H-fluoren-9-ilamino)succinato de 1-bencilo en una relación ~1,0:0,65 (RMN de $^1H$). La estereoquímica del isómero dominante no se determinó en este paso y la mezcla se sometió a la etapa siguiente sin separación. Datos parciales de RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): Diastereómero mayoritario, $\delta$ 4,39 (d, $J$ = 12,3, 1H de $CH_2$), 3,33 (s, 3H, solapado con señal de $H_2O$), 3,50 (d, $J$ = 10,9, NH), 1,13 (d, $J$ = 7,1, 3H); Diastereómero minoritario, $\delta$ 4,27 (d, $J$ =12,3, 1H de $CH_2$), 3,76 (d, $J$ = 10,9, NH), 3,64 (s, 3H), 0,77 (d, $J$ = 7,0, 3H). CL (Cond. I): $T_R$ = 2,19 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{32}H_{30}NO_4$: 492,22; encontrado 492,15.

Se añadió hidruro de diisobutilaluminio (20,57 ml de 1,0 M en hexanos, 20,57 mmol) gota a gota durante 10 min a una solución enfriada (-78 °C) en THF (120 ml) de 4-metil-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)succinato de (2S)-1-bencilo (3,37 g, 6,86 mmol) preparado antes y se agitó a -78 °C durante 20 horas. La mezcla de reacción se separó del baño de enfriamiento y se vertió rápidamente en $H_3PO_4$ ~1M/$H_2O$ (250 ml) con agitación y la mezcla se extrajo con éter (100 ml, 2x). La fase

orgánica reunida se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró a vacío. Se preparó una malla de gel de sílice del material bruto y se sometió a cromatografía (25% de EtOAc/hexanos; elución por gravedad) proporcionando 1,1 g de 4-hidroxi-3-metil-2-(9-fenil-9*H*-fluoren-9-ilamino)butanoato de (2S,3S)-bencilo, contaminado con alcohol bencílico, como un aceite incoloro viscoso y 4-hidroxi-3-metil-2-(9-fenil-9*H*-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo que contenía el estereoisómero (2S,3R) como una impureza. La muestra anterior se volvió a someter a las mismas condiciones de purificación de cromatografía en columna proporcionando 750 mg de material purificado como una espuma blanca. [Nota: el isómero (2S, 3S) se eluye antes que el isómero (2S,3R) en las condiciones anteriores]. Isómero (2S, 3S): RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): 7,81 (m, 2H), 7,39-7,08 (m, 16H), 4,67 (d, *J* = 12,3, 1H), 4,43 (d, *J* = 12,4, 1H), 4,21 (t aparente, *J* = 5,2, OH), 3,22 (d, *J* = 10,1, NH), 3,17 (m, 1H), 3,08 (m, 1H), ~2,5 (m, 1H, solapado con la señal del disolvente), 1,58 (m, 1H), 0,88 (d, *J* = 6,8, 3H). CL (Cond. I): $T_R$ = 2,00 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{31}H_{30}NO_3$: 464,45; encontrado 464,22. Isómero (2S, 3R): RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz): 7,81 (d, *J* = 7,5, 2H), 7,39-7,10 (m, 16H), 4,63 (d, *J*= 12,1, 1H), 4,50 (t aparente, *J* = 4,9, 1H), 4,32 (d, *J* = 12,1, 1H), 3,59-3,53 (m, 2H), 3,23 (m, 1H), 2,44 (dd, *J* = 9,0, 8,3, 1H), 1,70 (m, 1H), 0,57 (d, *J* = 6,8, 3H). CL (Cond. I): $T_R$ = 1,92 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{31}H_{30}NO_3$: 464,45; encontrado 464,52.

Las asignaciones estereoquímicas relativas de los productos de reducción con DIBAL se hicieron basándose en estudios NOE llevados a cabo en derivados lactona preparados a partir de cada isómero empleando el siguiente protocolo: Se añadió LiHMDS (50 µl de 1,0 M/THF, 0,05 mmol) a una solución enfriada (hielo-agua) en THF (2,0 ml) de 4-hidroxi-3-metil-2-(9-fenil-9*H*-fluoren-9-ilamino)butanoato

de (2S,3S)-bencilo (62,7 mg, 0,135 mmol), y la mezcla de reacción se agitó a temperatura similar durante ~2 horas. El componente volátil se eliminó a vacío y el residuo se repartió entre $CH_2Cl_2$ (30 ml), agua (20 ml) y solución acuosa saturada de $NH_4Cl$ (1 ml). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró a vacío, y el material bruto resultante se sometió a una purificación Biotage (40 g gel de sílice; 10-15% de EtOAc/hexanos) proporcionando (3S,4S)-4-metil-3-(9-fenil-9*H*-fluoren-9-ilamino)dihidrofuran-2(3*H*)-ona como una película incolora de sólido (28,1 mg). Se elaboró 4-hidroxi-3-metil-2-(9-fenil-9*H*-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo de forma similar a (3S,4R)-4-metil-3-(9-fenil-9*H*-fluoren-9-ilamino)dihidrofuran-2(3*H*)-ona. Isómero (3S,4S)-lactona: RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz), 7,83 (d, $J$ = 7,5, 2H), 7,46-7,17 (m, 11H), 4,14 (t aparente, $J$ = 8,3, 1H), 3,60 (d, $J$ = 5,8, NH), 3,45 (t aparente, $J$ = 9,2, 1H), ~2,47 (m, 1H, parcialmente solapado con la señal del disolvente), 2,16 (m, 1H), 0,27 (d, $J$ = 6,6, 3H). CL (Cond. I): $T_R$ = 1,98 min; CL/EM: Anal. Calculado para $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378,15; encontrado 378,42. Isómero (3S,4R)-lactona: RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz), 7,89 (d, $J$ = 7,6, 1H), 7,85 (d, $J$ = 7,3, 1H), 7,46-7,20 (m, 11H), 3,95 (dd, $J$ = 9,1, 4,8, 1H), 3,76 (d, $J$ = 8,8, 1H), 2,96 (d, $J$ = 3,0, NH), 2,92 (dd, $J$ = 6,8, 3, NCH), 1,55 (m, 1H), 0,97 (d, $J$ = 7,0, 3H). CL (Cond. I): $T_R$ = 2,03 min; CL/EM: Anal. Calculado para $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378,15; encontrado 378,49.

Se añadieron TBDEM-Cl (48 mg, 0,312 mmol) seguido por imidazol (28,8 mg, 0,423 mmol) a una solución en $CH_2Cl_2$ (3 ml) de 4-hidroxi-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3S)-bencilo (119,5 mg, 0,258 mmol), y la mezcla se agitó en condiciones ambientales durante 14,25 horas. La mezcla de reacción se diluyó entonces con $CH_2Cl_2$ (30 ml) y se lavó con agua (15 ml), y la fase orgánica se

secó ($MgSO_4$), se filtró y se concentró a vacío. El material bruto resultante se purificó con una Biotage (40 g gel de sílice; 5% de EtOAc/hexanos) proporcionando 4-(terc-butildimetilsililoxi)-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3S)-bencilo, contaminado con impurezas con base de TBDMS, como un aceite incoloro viscoso (124,4 mg). Se elaboró 4-hidroxi-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo de forma similar a 4-(terc-butildimetilsililoxi)-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo. Isómero (2S,3S)-silil éter: RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz), 7,82 (d, $J$ = 4,1, 1H), 7,80 (d, $J$ = 4,0, 1H), 7,38-7,07 (m, 16 H), 4,70 (d, $J$ = 12,4, 1H), 4,42 (d, $J$ = 12,3, 1H), 3,28-3,19 (m, 3H), 2,56 (dd, $J$ = 10,1, 5,5, 1H), 1,61 (m, 1H), 0,90 (d, $J$ = 6,8, 3H), 0,70 (s, 9H), -0,13 (s, 3H), -0,16 (s, 3H). CL (Cond. 1, donde el tiempo de ejecución de prolongó hasta 4 min): $T_R$ = 3,26 min; CL/EM: Anal. Calculado para $[M+H]^+$ $C_{37}H_{44}NO_3Si$: 578,31; encontrado 578,40. Isómero (2S,3R)-silil éter: RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz), 7,82 (d, $J$ = 3,0, 1H), 7,80 (d, $J$ = 3,1, 1H), 7,39-7,10 (m, 16H), 4,66 (d, $J$ = 12,4, 1H), 4,39 (d, $J$ = 12,4, 1H), 3,61 (dd, $J$ = 9,9, 5,6, 1H), 3,45 (d, $J$ = 9,5, 1H), 3,41 (dd, $J$ = 10, 6,2, 1H), 2,55 (dd, $J$ = 9,5, 7,3, 1H), 1,74 (m, 1H), 0,77 (s, 9H), 0,61 (d, $J$ = 7,1, 3H), -0,06 (s, 3H), -0,08 (s, 3H).

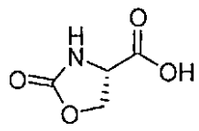
Se unió un globo de hidrógeno a una mezcla de 4-(terc-butildimetilsililoxi)-3-metil-2-(9-fenil-9*H*-fluoren-9-ilamino)butanoato de (2S,3S)-bencilo (836 mg, 1,447 mmol) y Pd al 10%/C (213 mg) en EtOAc (16 ml) y la mezcla se agitó a temperatura ambiente durante ~ 21 horas, recargándose el globo con $H_2$ cuando fue necesario. La mezcla de reacción se diluyó con $CH_2Cl_2$ y se filtró a través de un lecho de tierra de diatomeas (Celite-545®), y se lavó el lecho con EtOAc (200 ml), EtOAc/MeOH (mezcla 1:1, 200 ml) y MeOH (750 ml). La fase orgánica combinada se concentró y se preparó una malla de gel de sílice a partir del material bruto resultante y se

sometió a una cromatografía ultrarrápida (mezcla 8:2:1 de EtOAc/i-PrOH/$H_2O$) proporcionando ácido (2S,3S)-2-amino-4-(terc-butildimetilsililoxi)-3-metilbutanoico como un sólido apelusado blanco (325 mg). Se elaboró 4-(terc-butildimetilsililoxi)-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo de forma similar a ácido (2S,3R)-2-amino-4-(terc-butildimetilsililoxi)-3-metilbutanoico. (Isómero 2S,3S)-amino ácido: RMN de $^1H$ (Metanol-$d_4$, $\delta$ = 3,29 ppm, 400 MHz), 3,76 (dd, $J$ = 10,5, 5,2, 1H), 3,73 (d, $J$ = 3,0, 1H), 3,67 (dd, $J$ = 10,5, 7,0, 1H), 2,37 (m, 1H), 0,97 (d, $J$ = 7,0, 3H), 0,92 (s, 9H), 0,10 (s, 6H). CL/EM: Anal. Calculado para $[M+H]^+$ $C_{11}H_{26}NO_3Si$: 248,17; encontrado 248,44. Isómero (2S,3R)-amino ácido: RMN de $^1H$ (Metanol-$d_4$, $\delta$ = 3,29 ppm, 400 MHz), 3,76-3,75 (m, 2H), 3,60 (d, $J$ = 4,1, 1H), 2,16 (m, 1H), 1,06 (d, $J$ = 7,3, 3H), 0,91 (s, 9H), 0,09 (s, 6H). Anal. Calculado para $[M+H]^+$ $C_{11}H_{26}NO_3Si$: 248,17; encontrado 248,44.

Se añadieron agua (1 ml) y NaOH (0,18 ml de 1,0 M/$H_2O$, 0,18 mmol) a una mezcla de ácido (2S,3S)-2-amino-4-(terc-butildimetilsililoxi)-3-metilbutanoico (41,9 mg, 0,169 mmol) y $Na_2CO_3$ (11,9 mg, 0,112 mmol), y se sometió a ultrasonidos durante aproximadamente 1 minuto para efectuar la disolución de los reactivos. La mezcla se enfrió entonces con un baño de hielo-agua, se añadió cloroformiato de metilo (0,02 ml, 0,259 mmol) se durante 30 s y se continuó con agitación vigorosa a temperatura similar durante 40 minutos y luego a temperatura ambiente durante 2,7 horas. La mezcla de reacción se diluyó con agua (5 ml), se enfrió con baño de hielo-agua y se trató gota a gota con solución acuosa de HCl 1,0 N HCl (~0,23 ml). La mezcla se diluyó adicionalmente con agua (10 ml) y se extrajo con $CH_2Cl_2$ (15 ml, 2x). La fase orgánica reunida se secó ($MgSO_4$), se filtró y se concentró a vacío proporcionando *Cap*-80a como un sólido blanquecino. Se elaboró ácido (2S,3R)-2-amino-4-(terc-butildimetilsililoxi)-3-metilbutanoico de forma similar a *Cap*-80b. *Cap*-

80a: RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5 ppm, 400 MHz), 12,57 (s ancho, 1H), 7,64 (d, *J* = 8,3, 0,3H), 7,19 (d, *J* = 8,8, 0,7H), 4,44 (dd, *J* = 8,1, 4,6, 0,3H), 4,23 (dd, *J* = 8,7, 4,4, 0,7H), 3,56/3,53 (dos singletes, 3H), 3,48-3,40 (m, 2H), 2,22-2,10 (m, 1H), 0,85 (s, 9H), ~0,84 (d, 0,9H, solapado con la señal de t-Bu), 0,79 (d, *J* = 7, 2,1H), 0,02/0,01/0,00 (tres singletes solapados, 6H). CL/EM: Anal. Calculado para $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328,16; encontrado 328,46. *Cap*-80b: RMN de $^1$H ($CDCl_3$, $\delta$ = 7,24 ppm, 400 MHz), 6,00 (d ancho, *J* = 6,8, 1H), 4,36 (dd, *J* = 7,1, 3,1, 1H), 3,87 (dd, *J* = 10,5, 3,0, 1H), 3,67 (s, 3H), 3,58 (dd, *J* = 10,6, 4,8, 1H), 2,35 (m, 1H), 1,03 (d, *J* = 7,1, 3H), 0,90 (s, 9H), 0,08 (s, 6H). CL/EM: Anal. Calculado para $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328,16; encontrado 328,53. Los productos brutos se utilizaron sin purificación adicional.

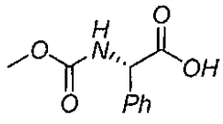
*Cap-81*



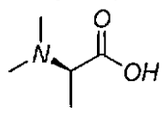
Se preparó de acuerdo con el protocolo descrito por Falb et al. *Synthetic Communications* 1993, *23*, 2839.

*Cap-82 a Cap-85*

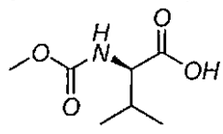
Se sintetizaron *Cap*-82 a *Cap*-85 a partir de los materiales de partida apropiados de acuerdo con el procedimiento descrito para *Cap*-51 o *Cap*-13. Las muestras presentaron perfiles espectrales similares a los de sus enantiómeros (es decir, *Cap*-4, *Cap*-13, *Cap*-51 y *Cap*-52, respectivamente).



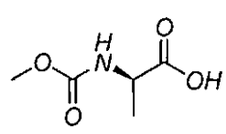
*Cap-82*



*Cap-83*

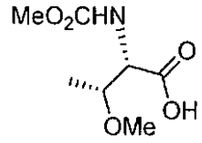


*Cap-84*



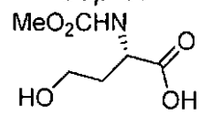
*Cap-85*

*Cap-86*



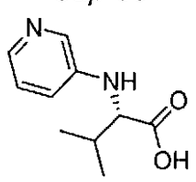
A una mezcla de O-metil-L-treonina (3,0 g, 22,55 mmol), NaOH (0,902 g, 22,55 mmol) en $H_2O$ (15 ml) se añadió $ClCO_2Me$ (1,74 ml, 22,55 mmol) gota a gota a 0°C. La mezcla se dejó agitando durante 12 h y se acidificó hasta pH 1 usando HCl 1N. La fase acuosa se extrajo con EtOAc y (2x250 ml) y MeOH al 10% en $CH_2Cl_2$ (250 ml) y las fases orgánicas reunidas se concentraron a vacío proporcionando un aceite incoloro (4,18 g, 97%) que era de pureza suficiente para usar en las etapas siguientes. RMN de $^1H$ (400 MHz, $CDCl_3$) δ 4,19 (s, 1H), 3,92-3,97 (m, 1H), 3,66 (s, 3H), 1,17 (d, *J* = 7,7 Hz, 3H). CLEM: Anal. Calculado para $C_7H_{13}NO_5$: 191; encontrado: 190 $(M-H)^-$.

*Cap-87*



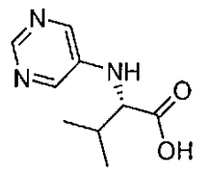
A una mezcla de L-homoserina (2,0 g, 9,79 mmol), $Na_2CO_3$ (2,08 g, 19,59 mmol) en $H_2O$ (15 ml) se añadió $ClCO_2Me$ (0,76 ml, 9,79 mmol) gota a gota a 0°C. La mezcla se dejó agitando durante 48 h y se acidificó hasta pH 1 usando HCl 1N. La fase acuosa se extrajo con EtOAc y (2X250 ml) y las fases orgánicas reunidas se concentraron a vacío proporcionando un sólido incoloro (0,719 g, 28%) que era de pureza suficiente para usar en las etapas siguientes. RMN de $^1H$ (400 MHz, $CDCl_3$) δ 4,23 (dd, *J* = 4,5, 9,1 Hz, 1H), 3,66 (s, 3H), 3,43-3,49 (m, 2H), 2,08 – 2,14 (m, 1H), 1,82 – 1,89 (m, 1H). CLEM: Anal. Calculado para $C_7H_{13}NO_5$: 191; encontrado: 192 $(M+H)^+$.

*Cap-88*



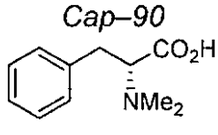
Se calentó una mezcla de L-valina (1,0 g, 8,54 mmol), 3-bromopiridina (1,8 ml, 18,7 mmol), $K_2CO_3$ (2,45 g, 17,7 mmol) y CuI (169 mg, 0,887 mmol) en DMSO (10 ml) a 100°C durante 12h. La mezcla de reacción se enfrió hasta ta, se vertió en $H_2O$ (aproximadamente 150 ml) y se lavó con EtOAc (x2). Las fases orgánicas se extrajeron con una pequeña cantidad de $H_2O$ y las fases acuosas reunidas se acidificaron hasta aproximadamente pH 2 con HCl 6N. El volumen se redujo hasta aproximadamente la tercera parte y se añadieron 20 g de resina de intercambio iónico (Strata). La suspensión se dejó reposar durante 20 min y se cargó en un lecho de resina de intercambio catiónico (Strata) (aproximadamente 25 g). Se lavó el lecho con $H_2O$ (200 ml), MeOH (200 ml) y luego $NH_3$ (3M en MeOH, 2X200 ml). Se concentraron las fracciones apropiadas a vacío y el residuo (aproximadamente 1,1 g) se disolvió en $H_2O$, se congeló y liofilizó. El compuesto del epígrafe se obtuvo como una espuma (1,02 g, 62%). RMN de $^1H$ (400 MHz, DMSO-$d_6$) $\delta$ 8,00 (s ancho, 1H), 7,68 – 7,71 (m, 1H), 7,01 (s ancho, 1H), 6,88 (d, $J$ = 7,5 Hz, 1H), 5,75 (s ancho, 1H), 3,54 (s, 1H), 2,04 – 2,06 (m, 1H), 0,95 (d, $J$ = 6,0 Hz, 3H), 0,91 (d, $J$ = 6,6 Hz, 3H). CLEM: Anal. Calculado para $C_{10}H_{14}N_2O_2$: 194; encontrado: 195 $(M+H)^+$.

*Cap-89*



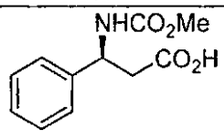
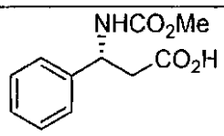
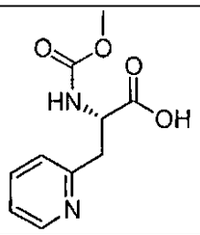
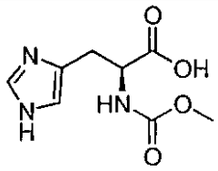
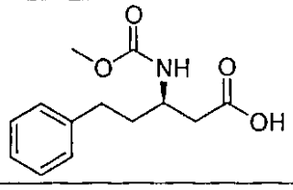
Se calentó a 100ºC durante 12 horas una mezcla de L-valina (1,0 g, 8,54 mmol), 5-bromopirimidina (4,03 g, 17,0 mmol), $K_2CO_3$ (2,40 g, 17,4 mmol) y CuI (179 mg, 0,94 mmol) en DMSO (10 ml). La mezcla de reacción se enfrió hasta TA, se vertió en $H_2O$ (aproximadamente 150 ml) y se lavó con EtOAc (x2). Las fases orgánicas se extrajeron con una pequeña cantidad de $H_2O$ y las fases acuosas reunidas se acidificaron hasta aproximadamente pH 2 con HCl 6N. El volumen se redujo hasta aproximadamente la tercera parte y se añadieron 20 g de resina de intercambio catiónico (Strata). La suspensión se dejó reposar durante 20 minutos y se cargó en un lecho de resina de intercambio catiónico (Strata) (aproximadamente 25g). El lecho se lavó con $H_2O$ (200 ml), MeOH (200 ml) y luego $NH_3$ (3M en MeOH, 2x200 ml). Se concentraron las fracciones apropiadas a vacío y se disolvió el residuo (aproximadamente 1,1 g) en $H_2O$, se congeló y liofilizó. El compuesto del epígrafe se obtuvo como una espuma (1,02 g, 62%). La RMN de $^1H$ (400 MHz, $CD_3OD$) mostró que la mezcla contenía valina y no se pudo estimar la pureza. El material se usó como tal en las posteriores reacciones. CLEM: Anal. Calculado para $C_9H_{13}N_3O_2$: 195; encontrado: 196 $(M+H)^+$.

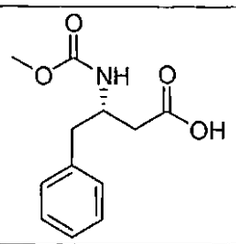
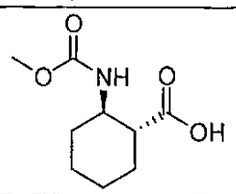
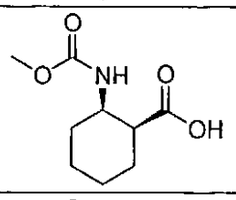
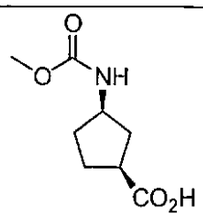
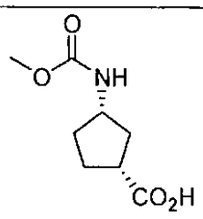
*Cap–90*

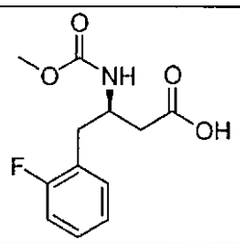
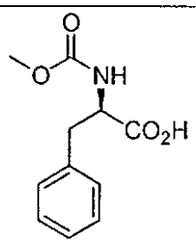
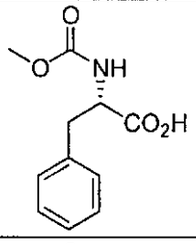
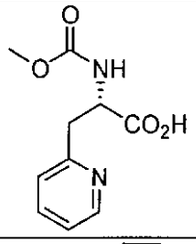
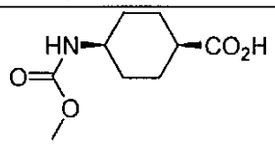
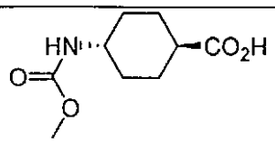


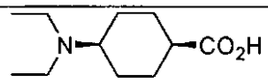
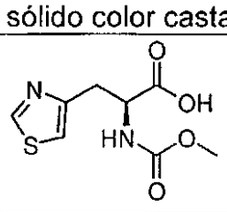
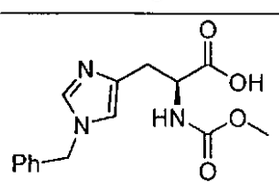
Se preparó *Cap*-90 de acuerdo con el procedimiento descrito para la preparación de *Cap*-1. El material bruto se usó como tal en las etapas posteriores. CLEM: Anal. Calculado para $C_{11}H_{15}NO_2$: 193; encontrado: 192 $(M-H)^-$.

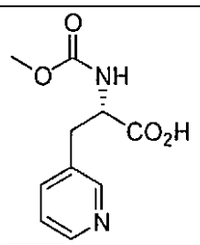
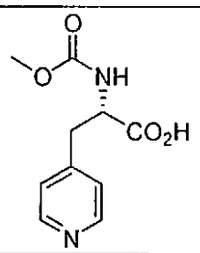
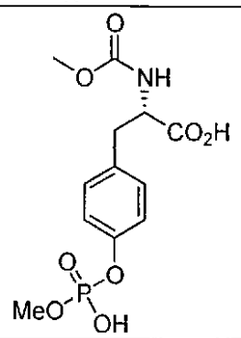
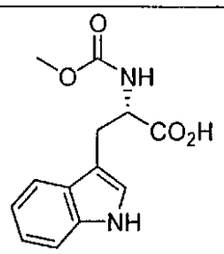
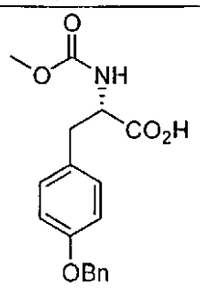
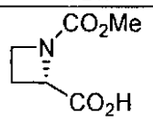
Los siguientes Caps se prepararon de acuerdo con el procedimiento del usado para la preparación del Cap 51, a menos que se indique de otro modo:

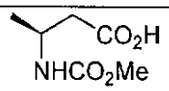
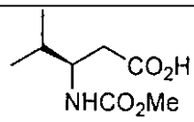
| Cap | Estructura | CLEM |
|---|---|---|
| *Cap-91* |  | CLEM: Anal. Calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$. |
| *Cap-92* |  | CLEM: Anal. Calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$. |
| *Cap-93* |  | CLEM: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$. |
| *Cap-94* |  | CLEM: Anal. Calculado para $C_8H_{11}N_3O_4$: 213; encontrado: 214 $(M+H)^+$. |
| *Cap-95* |  | CLEM: Anal. Calculado para $C_{13}H_{17}NO_4$: 251; encontrado: 250 $(M-H)^-$. |

| | | |
|---|---|---|
| *Cap-96* |  | CLEM: Anal. Calculado para $C_{12}H_{15}NO_4$: 237; encontrado: 236 $(M-H)^-$. |
| *Cap-97* |  | CLEM: Anal. Calculado para $C_9H_{15}NO_4$: 201; encontrado: 200 $(M-H)^-$. |
| *Cap-98* |  | CLEM: Anal. Calculado para $C_9H_{15}NO_4$: 201; encontrado: 202 $(M+H)^+$. |
| *Cap-99* |  | RMN de $^1H$ (400 MHz, $CD_3OD$) $\delta$ 3,88 – 3,94 (m, 1H), 3,60, 3,61 (s, 3H), 2,80 (m, 1H), 2,20 (m 1H), 1,82 – 1,94 (m, 3H), 1,45 – 1,71 (m, 2H). |
| *Cap-99a* |  | RMN de $^1H$ (400 MHz, $CD_3OD$) $\delta$ 3,88 – 3,94 (m, 1H), 3,60, 3,61 (s, 3H), 2,80 (m, 1H), 2,20 (m 1H), 1,82 – 1,94 (m, 3H), 1,45 – 1,71 (m, 2H). |

| | | |
|---|---|---|
| *Cap-100* |  | CLEM: Anal. Calculado para $C_{12}H_{14}NO_4F$: 255; encontrado: 256 $(M+H)^+$. |
| *Cap-101* |  | CLEM: Anal. Calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$. |
| *Cap-102* |  | CLEM: Anal. Calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$ |
| *Cap-103* |  | CLEM: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$. |
| *Cap-104* |  | RMN de $^1H$ (400 MHz, $CD_3OD$) $\delta$ 3,60 (s, 3H), 3,50 – 3,53 (m, 1H), 2,66 – 2,69 y 2,44 – 2,49 (m, 1H), 1,91 – 2,01 (m, 2H), 1,62 – 1,74 (m, 4H), 1,51 – 1,62 (m, 2H). |
| *Cap-105* |  | RMN de $^1H$ (400 MHz, $CD_3OD$) $\delta$ 3,60 (s, 3H), 3,33 – 3,35 (m, 1H, parcialmente oscurecido por disolvente), 2,37 – 2,41 y 2,16 – |

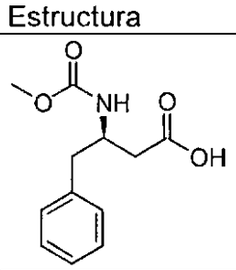
| | | |
|---|---|---|
| | | 2,23 (m, 1H), 1,94 – 2,01 (m, 4H), 1,43 – 1,53 (m, 2H), 1,17 – 1,29 (m, 2H). |
| *Cap-106* |  Se preparó a partir de ácido cis-4-aminociclohexanocarboxílico y acetaldehído empleando un procedimiento similar descrito para la síntesis de Cap-2. La sal HCl bruta se hizo pasar a través de MCX (lavado con $MeOH/H_2O/CH_2Cl_2$; elución con $NH_3$ 2N /MeOH) proporcionando un aceite que se disolvió en $CH_3CN/H_2O$ y se liofilizó proporcionando un sólido color castaño. | RMN de $^1H$ (400 MHz, $CD_3OD$) $\delta$ 3,16 (q, $J$ = 7,3 Hz, 4H), 2,38 - 2,41 (m, 1H), 2,28 – 2,31 (m, 2H), 1,79 – 1,89 (m, 2H), 1,74 (app, ddd $J$ = 3,5, 12,5, 15,9 Hz, 2H), 1,46 (dt aparente $J$ = 4,0, 12,9 Hz, 2H), 1,26 (t, $J$ = 7,3 Hz, 6H). |
| *Cap-107* |  | CLEM: Anal. Calculado para $C_8H_{10}N_2O_4S$: 230; encontrado: 231 $(M+H)^+$. |
| *Cap-108* |  | CLEM: Anal. Calculado para $C_{15}H_{17}N_3O_4$: 303; encontrado: 304 $(M+H)^+$. |

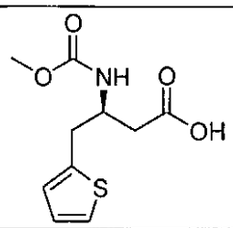
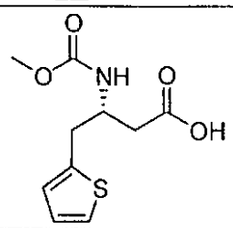
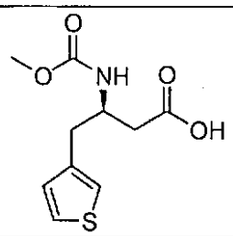
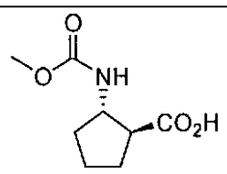
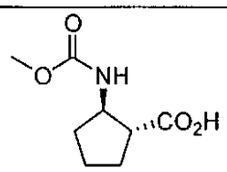
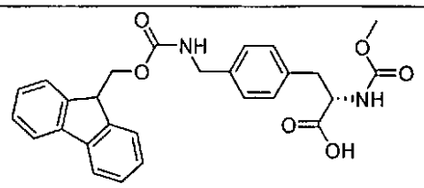
| | | |
|---|---|---|
| *Cap-109* |  | CLEM: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$. |
| *Cap-110* |  | CLEM: Anal. Calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$. |
| *Cap-111* |  | CLEM: Anal. Calculado para $C_{12}H_{16}NO_8P$: 333; encontrado: 334 $(M+H)^+$. |
| *Cap-112* |  | CLEM: Anal. Calculado para $C_{13}H_{14}N_2O_4$: 262; encontrado: 263 $(M+H)^+$. |
| *Cap-113* |  | CLEM: Anal. Calculado para $C_{18}H_{19}NO_5$: 329; encontrado: 330 $(M+H)^+$. |
| *Cap-114* |  | RMN de $^1H$ (400 MHz, $CDCl_3$) $\delta$ 4,82 – 4,84 (m, 1H), 4,00 – 4,05 (m, 2H), 3,77 (s, 3H), 2,56 (s |

| | | |
|---|---|---|
| | | ancho, 2H) |
| *Cap-115* |  | RMN de $^1$H (400 MHz, $CDCl_3$) δ 5,13 (s ancho, 1H), 4,13 (s ancho, 1H), 3,69 (s, 3H), 2,61 (d, *J* = 5,0 Hz, 2H), 1,28 (d, *J* = 9,1 Hz, 3H). |
| *Cap-116* |  | RMN de $^1$H (400 MHz, $CDCl_3$) δ 5,10 (d, *J* = 8,6 Hz, 1H), 3,74 – 3,83 (m, 1H), 3,69 (s, 3H), 2,54 – 2,61 (m, 2H), 1,88 (sept, *J* = 7,0 Hz, 1H), 0,95 (d, *J* = 7,0 Hz, 6H). |

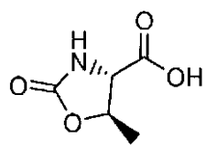
*Cap-117 a Cap-123*

Para la preparación de *Cap*-117 a *Cap*-123 los Boc aminoácidos se obtuvieron de suministradores comerciales y se desprotegieron por tratamiento con 25% de TFA en $CH_2Cl_2$. Después de completarse la reacción que se juzgó por CLEM se eliminaron los disolventes a vacío y se carbamoiló la sal TFA correspondiente del aminoácido con cloroformiato de metilo de acuerdo con el procedimiento descrito para el *Cap*-51.

| Cap | Estructura | CLEM |
|---|---|---|
| *Cap-117* |  | CLEM: Anal. Calculado para $C_{12}H_{15}NO_4S$: 237; encontrado: 238 $(M+H)^+$. |

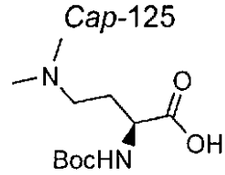
| | | |
|---|---|---|
| *Cap-118* |  | CLEM: Anal. Calculado para $C_{10}H_{13}NO_4S$: 243; encontrado: 244 $(M+H)^+$. |
| *Cap-119* |  | CLEM: Anal. Calculado para $C_{10}H_{13}NO_4S$: 243; encontrado: 244 $(M+H)^+$. |
| *Cap-120* |  | CLEM: Anal. Calculado para $C_{10}H_{13}NO_4S$: 243; encontrado: 244 $(M+H)^+$. |
| *Cap-121* |  | RMN de $^1H$ (400 MHz, $CDCl_3$) $\delta$ 4,06 – 4,16 (m, 1H), 3,63 (s, 3H), 3,43 (s, 1H), 2,82 y 2,66 (s ancho, 1H), 1,86 – 2,10 (m, 3H), 1,64 – 1,76 (m, 2H), 1,44 – 1,53 (m, 1H). |
| *Cap-122* |  | El perfil de RMN de $^1H$ es similar al de su enantiómero, Cap-121. |
| *Cap-123* |  | CLEM: Anal. Calculado para $C_{27}H_{26}N_2O_6$: 474; encontrado: 475 $(M+H)^+$. |

*Cap*-124



Se llevó a cabo la carbamoilación de la sal clorhidrato de éster terc-butílico de L-treonina de acuerdo con el procedimiento para *Cap*-51. La mezcla de reacción bruta se acidificó con HCl 1N hasta pH~1 y la mezcla se extrajo con EtOAc (2X50 ml). Las fases orgánicas reunidas se concentraron a vacío dando un aceite incoloro que solidificó en reposo. La capa acuosa se concentró a vacío y la mezcla resultante de producto y sales inorgánicas del producto y sales inorgánicas se trituró con EtOAc-$CH_2Cl_2$-MeOH (1:1:0,1) y luego se concentró la fase orgánica a vacío dando un aceite incoloro que por CLEM se mostró que era el producto deseado. Ambas tandas se reunieron dando 0,52 g de un sólido. RMN de $^1H$ (400 MHz, $CD_3OD$) $\delta$ 4,60 (m, 1H), 4,04 (d, $J$ = 5,0 Hz, 1H), 1,49 (d, $J$ = 6,3 Hz, 3H). CLEM: Anal. Calculado para $C_5H_7NO_4$: 145; encontrado: 146 $(M+H)^+$.

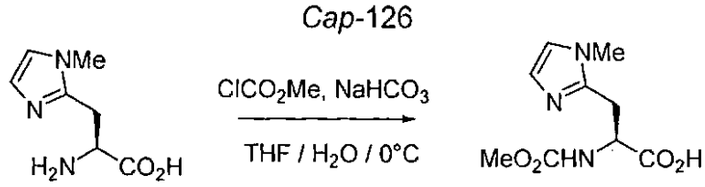
*Cap*-125



A una suspensión de $Pd(OH)_2$ (20%, 100 mg), formaldehído acuoso (37% en peso, 4 ml), ácido acético (0, 5 ml) en metanol (15 ml) se añadió ácido (S)-4-amino-2-(terc-butoxicarbonilamino)butanoico (1 g, 4,48 mmol). La reacción se purgó varias

veces con hidrógeno y se agitó durante la noche bajo un globo de hidrógeno a temperatura ambiente. La mezcla de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se eliminó el compuesto volátil a vacío. El material resultante bruto se usó como tal para la etapa siguiente. CLEM: Anal. Calculado para $C_{11}H_{22}N_2O_4$: 246; encontrado: 247 $(M+H)^+$.

*Cap*-126



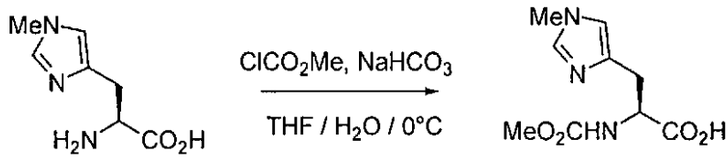

*cj-25* *cap-126*

Este procedimiento es una modificación del que se usó para preparar *Cap*-51. A una suspensión de 3-metil-L-histidina (0,80 g, 4,70 mmol) en THF (10mL) y $H_2O$ (10 ml) a 0°C se añadió $NaHCO_3$ (0,88 g, 10,5 mmol). La mezcla resultante se trató con $ClCO_2Me$ (0,40 ml, 5,20 mmol) y se dejó agitar la mezcla a 0°C. Después de agitar durante aproximadamente. 2h la CLEM no mostró material de partida. La reacción se acidificó hasta pH 2 con HCl 6 N.

Los disolventes se eliminaron a vacío y el residuo se suspendió en 20 ml de MeOH al 20% en $CH_2Cl_2$. La mezcla se filtró y se concentró dando una espuma amarillo claro (1,21 g,). La CLEM y RMN de $^1H$ mostraron que el material era una mezcla 9:1 del éster metílico y el producto deseado. Este material se suspendió en THF (10 ml) y $H_2O$ (10 ml), se enfrió hasta 0°C y se añadió LiOH (249,1 mg, 10,4 mmol). Después de agitar aproximadamente 1h la CLEM mostró que no quedaba éster. Seguidamente la mezcla se acidificó con HCl 6N y los disolventes se eliminaron a vacío. La CLEM y RMN de $^1H$ confirmaron la ausencia del éster. El compuesto del epígrafe se obtuvo como su sal HCl contaminada con sales

inorgánicas (1,91 g, >100%). El compuesto se usó como tal en posteriores etapas sin purificación adicional. RMN de $^1$H (400 MHz, $CD_3OD$) δ 8,84, (s, 1H), 7,35 (s, 1H), 4,52 (dd, *J* = 5,0, 9,1 Hz, 1H), 3,89 (s, 3H), 3,62 (s, 3H), 3,35 (dd, *J* = 4,5, 15,6 Hz, 1H, parcialmente oscurecido por disolvente), 3,12 (dd, *J* = 9,0, 15,6 Hz, 1H). CLEM: Análisis calculado para $C_9H_{13}N_3O_4$: 227,09; encontrado: 228,09 $(M+H)^+$.

*Cap*-127

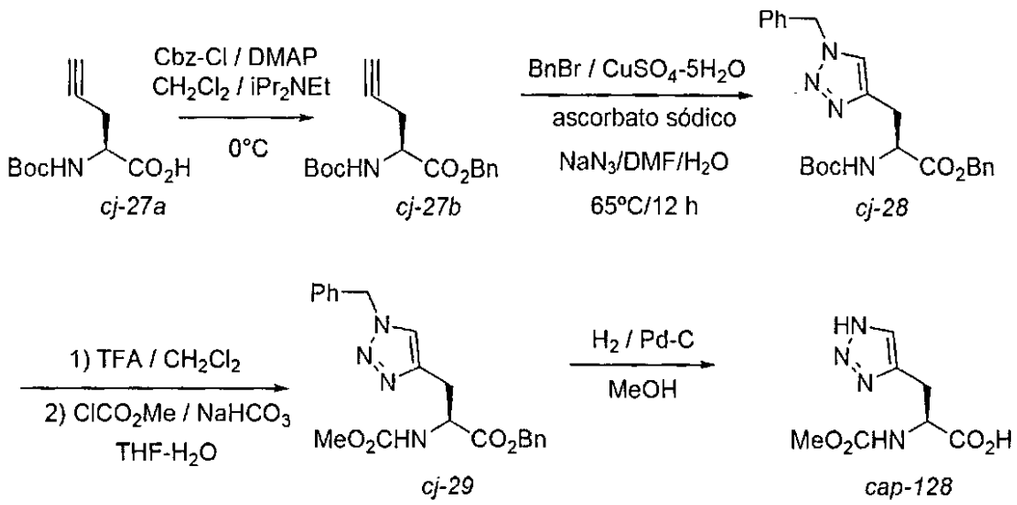



*cj-26* *cap-127*

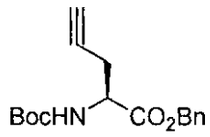
Se preparó *Cap*-127 de acuerdo con el procedimiento para *Cap*-126 anterior partiendo de ácido (S)-2-amino-3-(1-metil-1H-imidazol-4-il)propanoico (1,11 g, 6,56 mmol), $NaHCO_3$ (1,21 g, 14,4 mmol) y $ClCO_2Me$ (0,56 ml, 7,28 mmol). El compuesto del epígrafe se obtuvo como su sal HCl (1,79 g, >100%) contaminado con sales inorgánicas. La CLEM y RMN de $^1$H mostraron la presencia de aproximadamente 5% del éster metílico. La mezcla bruta se usó como tal sin purificación adicional. RMN de $^1$H (400 MHz, $CD_3OD$) δ 8,90 (s, 1H), 7,35 (s, 1H), 4,48 (dd, *J* = 5,0, 8,6 Hz, 1H), 3,89 (s, 3H), 3,62 (s, 3H), 3,35 (m, 1H), 3,08 (m, 1H).

CLEM: Anal. Calculado para $C_9H_{13}N_3O_4$: 227,09; encontrado: 228 $(M+H)^+$.

*Preparación de Cap*-128



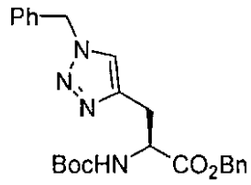

Etapa 1. Preparación de 2-(terc-butoxicarbonilamino)pent-4-inoato de (S)-bencilo (cj-27b).




*cj-27b*

A una solución de *cj-27a* (1,01 g, 4,74 mmol), DMAP (58 mg, 0,475 mmol) y $iPr_2NEt$ (1,7 ml, 9,8 mmol) en $CH_2Cl_2$ (100 ml) a 0°C se añadió Cbz-Cl (0,68 ml, 4,83 mmol). La solución se dejó agitando durante 4 h a 0°C, se lavó ($KHSO_4$ 1N, salmuera), se secó ($Na_2SO_4$), se filtró y se concentró a vacío. El residuo se purificó por cromatografía en columna ultrarrápida (TLC 6:1 hex:EtOAc) dando el compuesto del epígrafe (1,30 g, 91%) como un aceite incoloro. RMN de $^1H$ (400 MHz, $CDCl_3$) δ 7,35 (s, 5H), 5,35 (d ancho, *J* = 8,1 Hz, 1H), 5,23 (d, *J* = 12,2 Hz, 1H), 5,17 (d, *J* = 12,2 Hz, 1H), 4,48 – 4,53 (m, 1H), 2,68 – 2,81 (m, 2H), 2,00 (t, *J* = 2,5 Hz, 1H), 1,44 (s, 9H). CLEM: Anal. Calculado para $C_{17}H_{21}NO_4$: 303; encontrado: 304 $(M+H)^+$.

Etapa 2. Preparación de 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(terc-butoxicarbonilamino)propanoato de (S)-bencilo (cj-28).

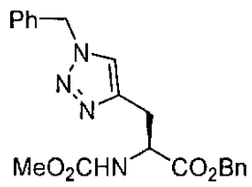



*cj-28*

A una mezcla de 2-(terc-butoxicarbonilamino)pent-4-inoato de (S)-bencilo (0,50 g, 1,65 mmol), ascorbato sódico (0,036 g, 0,18 mmol), $CuSO_4$-$5H_2O$ (0,022 g, 0,09 mmol) y $NaN_3$ (0,13 g, 2,1 mmol) en DMF-$H_2O$ (5 ml, 4:1) a ta se añadió BnBr (0,24 ml, 2,02 mmol) y la mezcla se calentó hasta 65°C. Después de 5 horas, la CLEM indicó baja conversión. Se añadió una porción adicional de $NaN_3$ (100 mg) y se continuó calentando durante 12 horas. La reacción se vertió en EtOAc y $H_2O$ y se agitó. Las fases se separaron y la fase acuosa se extrajo tres veces con EtOAc y las fases orgánicas reunidas se lavaron ($H_2O$ x3, salmuera), se secaron ($Na_2SO_4$), se filtraron y concentraron. El residuo se purificó por cromatografía ultrarrápida (Biotage, 40+M 0-5% de MeOH en $CH_2Cl_2$; TLC 3% de MeOH en $CH_2Cl_2$) proporcionando un aceite amarillo claro que solidificó en reposo (748,3 mg, 104%). La RMN fue consistente con el producto deseado pero sugirió la presencia de DMF. El material se usó como tal sin purificación adicional. RMN de $^1H$ (400 MHz, DMSO-$d_6$) $\delta$ 7,84 (s, 1H), 7,27 – 7,32 (m, 10H), 5,54 (s, 2H), 5,07 (s, 2H), 4,25 (m, 1H), 3,16 (dd, $J$ = 1,0, 5,3 Hz, 1H), 3,06 (dd, $J$ = 5,3, 14,7 Hz), 2,96 (dd, $J$ = 9,1, 14,7 Hz, 1H), 1,31 (s, 9H).

CLEM: Anal. Calculado para $C_{24}H_{28}N_4O_4$: 436; encontrado: 437 $(M+H)^+$.

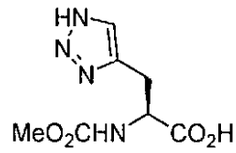
Etapa 3. Preparación de 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(metoxicarbonilamino)propanoato de (S)-bencilo (cj-29).




*cj-29*

Se añadió TFA (4 ml) a una solución de 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(terc-butoxicarbonilamino)propanoato de (S)-bencilo (0,52 g, 1,15 mmol) en $CH_2Cl_2$. La mezcla se dejó agitando a temperatura ambiente durante 2h. La mezcla se concentró a vacío dando un aceite incoloro que solidificó en reposo. Este material se disolvió en THF-$H_2O$ y se enfrió hasta 0°C. Se añadió $NaHCO_3$ sólido (0,25 g, 3,00 mmol) seguido por $ClCO_2Me$ (0,25 ml, 3,25 mmol). Después de agitar durante 1,5h la mezcla se acidificó hasta pH~2 con HCl 6N y luego se vertió en $H_2O$-EtOAc. Las capas orgánicas se separaron y se extrajo la capa acuosa 2x con EtOAc. Las capas orgánicas reunidas se lavaron ($H_2O$, salmuera), se secaron ($Na_2SO_4$), se filtraron y se concentraron a vacío dando un aceite incoloro (505,8 mg, 111%, la RMN sugirió la presencia de una impureza no identificada) que solidificó en reposo en la bomba. El material se usó como tal sin purificación posterior. RMN de $^1H$ (400 MHz, DMSO-$d_6$) $\delta$ 7,87 (s, 1H), 7,70 (d, $J$ = 8,1 Hz, 1H), 7,27 – 7,32 (m, 10H), 5,54 (s, 2H), 5,10 (d, $J$ = 12,7 Hz, 1H), 5,06 (d, $J$ = 12,7 Hz, 1H), 4,32 – 4,37 (m, 1H), 3,49 (s, 3H), 3,09 (dd, $J$ = 5,6, 14,7 Hz, 1H), 2,98 (dd, $J$ = 9,6, 14,7 Hz, 1H). CLEM: Anal. Calculado para $C_{21}H_{22}N_4O_4$: 394; encontrado: 395 $(M+H)^+$.

Etapa 4. Preparación de ácido (S)-2-(metoxicarbonilamino)-3-(1H-1,2,3-triazol-4-il)propanoico (*Cap*-128).

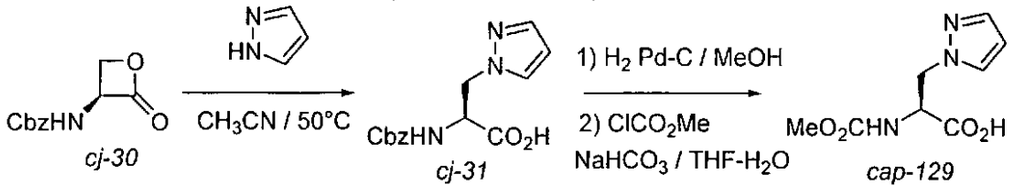


*Cap-128*

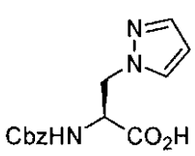
Se sometió 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(metoxicarbonilamino)-propanoato de (S)-bencilo (502 mg, 1,11 mmol) a hidrogenación en presencia de Pd-C (82 mg) en MeOH (5 ml) a presión atmosférica durante 12h. La mezcla se filtró a través de tierra de diatomeas (Celite®) y se concentró a vacío. Se obtuvo ácido (S)-2-(metoxicarbonilamino)-3-(1H-1,2,3-triazol-4-il)propanoico como una goma incolora (266 mg, 111%) que estaba contaminada con aproximadamente 10% del éster metílico. El material se usó sin purificación adicional.

RMN de $^1$H (400 MHz, DMSO-$d_6$) δ 12,78 (s ancho, 1H), 7,59 9s, 1H), 7,50 (d, *J* = 8,0 Hz, 1H), 4,19 – 4,24 (m, 1H), 3,49 (s, 3H), 3,12 (dd, *J* = 4,8 Hz, 14,9 Hz, 1H), 2,96 (dd, *J* = 9,9, 15,0 Hz, 1H). CLEM: Anal. Calculado para $C_7H_{10}N_4O_4$: 214; encontrado: 215 $(M+H)^+$.

*Preparación de Cap*-129




Etapa 1. Preparación de ácido (S)-2-(benciloxicarbonilamino)-3-(1H-pirazol-1-il)propanoico(cj-31).

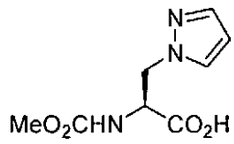


*cj-31*

Se calentó una suspensión de 2-oxooxetan-3-ilcarbamato de (S)-bencilo (0,67

g, 3,03 mmol) y pirazol (0,22 g, 3,29 mmol) en $CH_3CN$ (12 ml) a 50°C durante 24h. La mezcla se enfrió hasta TA durante la noche y el sólido se filtró proporcionando ácido (S)-2-(benciloxicarbonilamino)-3-(1H-pirazol-1-il)propanoico (330,1 mg). El filtrado se concentró a vacío y luego se trituró con una pequeña cantidad de $CH_3CN$ (aproximadamente 4 ml) proporcionando una segunda tanda (43,5 mg). Rendimiento total 370,4 mg (44%). P.f. 165,5 – 168°C. p.f. lit 168,5 – 169,5 Vederas et al. *J. Am. Chem. Soc.* 1985, *107*, 7105. RMN de $^1H$ (400 MHz, $CD_3OD$) $\delta$ 7,51 (d, $J$ = 2,0, 1H), 7,48 (s, $J$ = 1,5 Hz, 1H), 7,24 – 7,34 (m, 5H), 6,23 m, 1H), 5,05 (d, 12,7 H, 1H), 5,03 (d, $J$ = 12,7 Hz, 1H), 4,59 – 4,66 (m, 2H), 4,42 – 4,49 (m, 1H). CLEM: Anal. Calculado para $C_{14}H_{15}N_3O_4$: 289; encontrado: 290 $(M+H)^+$.

Etapa 2. Preparación de ácido (S)-2-(metoxicarbonilamino)-3-(1H-pirazol-1-il)propanoico (*Cap*-129).

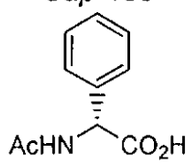



*cap-129*

Se sometió ácido (S)-2-(benciloxicarbonilamino)-3-(1H-pirazol-1-il)propanoico (0,20 g, 0,70 mmol) a hidrogenación en presencia de Pd-C (45 mg) en MeOH (5 ml) a presión atmosférica durante 2h. El producto parecía ser insoluble en MeOH, por tanto se diluyó la mezcla de reacción con 5 ml de $H_2O$ y unas pocas gotas de HCl 6N. La solución homogénea se filtró a través de tierra de diatomeas (Celite®), y el MeOH se eliminó a vacío. La solución restante se congeló y se liofilizó dando una espuma amarilla (188,9 mg). Este material se suspendió en THF-$H_2O$ (1:1, 10 ml) y luego se enfrió hasta 0°C. A la mezcla fría se añadió $NaHCO_3$ (146,0 mg, 1,74 mmol) cuidadosamente (generación de $CO_2$). Después de cesar la generación de

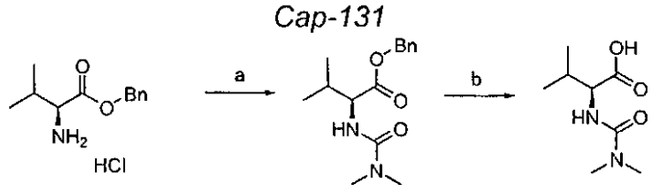
gas (aproximadamente 15 min) se añadió $ClCO_2Me$ (0,06 ml, 0,78 mmol) gota a gota. La mezcla se dejó agitando durante 2 horas y se acidificó hasta pH~2 con HCl 6N y se vertió en EtOAc. Las fases se separaron y la fase acuosa se extrajo con EtOAC (x5). Las fases orgánicas reunidas se lavaron (salmuera), se secaron ($Na_2SO_4$), se filtraron y concentraron dando el compuesto del epígrafe como un sólido incoloro (117,8 mg, 79%). RMN de $^1H$ (400 MHz, DMSO-$d_6$) $\delta$ 13,04 (s, 1H), 7,63 (d, $J$ = 2,6 Hz, 1H), 7,48 (d, $J$ = 8,1 Hz, 1H), 7,44 (d, $J$ = 1,5 Hz, 1H), 6,19 (t aparente, $J$ = 2,0 Hz, 1H), 4,47 (dd, $J$ = 3,0, 12,9 Hz, 1H), 4,29 – 4,41 (m, 2H), 3,48 (s, 3H). CLEM: Anal. Calculado para $C_8H_{11}N_3O_4$: 213; encontrado: 214 $(M+H)^+$.

*Cap*-130




Se preparó *Cap*-130 por acilación de (R)-fenilglicina disponible comercialmente de forma análoga al procedimiento dado en: Calmes, M.; Daunis, J.; Jacquier, R.; Verducci, J. *Tetrahedron*, 1987, *43*(10), 2285.

*Cap-131*

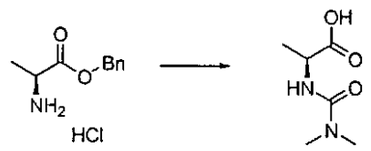



Etapa a: Se añadió cloruro de dimetilcarbamoilo (0,92 ml, 10 mmol) lentamente a una solución de clorhidrato de 2-amino-3-metilbutanoato de (S)-bencilo (2,44 g; 10 mmol) y base de Hunig (3,67 ml, 21 mmol) en THF (50 ml). La suspensión blanca resultante se agitó a temperatura ambiente durante la noche (16

horas) y se concentró a presión reducida. El residuo se repartió entre acetato de etilo y agua. La fase orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró a presión reducida. El aceite amarillo resultante se purificó por cromatografía ultrarrápida, eluyendo con acetato de etilo:hexanos (1:1). Las fracciones recogidas se concentraron a vacío proporcionando 2,35 g (85%) de aceite transparente. RMN de. $^1$H (300 MHz, DMSO-$d_6$) δ ppm 0,84 (d, *J*=6,95 Hz, 3H), 0,89 (d, *J*=6,59 Hz, 3H), 1,98-2,15 (m, 1H), 2,80 (s, 6H), 5,01-5,09 (m, *J*=12,44 Hz, 1H), 5,13 (d, *J*=12,44 Hz, 1H), 6,22 (d, *J*=8,05 Hz, 1H), 7,26-7,42 (m, 5H). CL (Cond. 1): $T_R$ = 1,76 min; EM: Análisis calculado para $[M+H]^+$ $C_{16}H_{22}N_2O_3$: 279,17; encontrado 279,03.

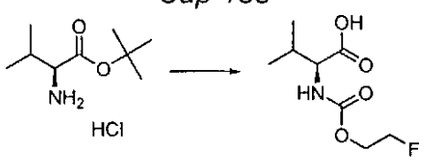
Etapa b: A una solución en MeOH (50 ml) del intermedio preparado antes (2,35 g; 8,45 mmol) se añadió Pd/C (10%; 200 mg) y la suspensión negra resultante se llenó con $N_2$ (3x) y se colocó en 10,13 kPa de $H_2$. La mezcla se agitó a temperatura ambiente durante la noche y se filtró a través de un filtro de microfibra para separar el catalizador. La solución transparente resultante se concentró entonces a presión reducida obteniendo 1,43 g (89%) de *Cap-131* como espuma blanca, que se usó sin purificación posterior. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 0,87 (d, *J*=4,27 Hz, 3H), 0,88 (d, *J*=3,97 Hz, 3H), 1,93-2,11 (m, 1H), 2,80 (s, 6H), 3,90 (dd, *J*=8,39, 6,87 Hz, 1H), 5,93 (d, *J*=8,54 Hz, 1H), 12,36 (s, 1H). CL (Cond. 1): $T_R$ = 0,33 min; EM: Análisis calculado para $[M+H]^+$ $C_8H_{17}N_2O_3$: 189,12; encontrado 189,04.

*Cap-132*



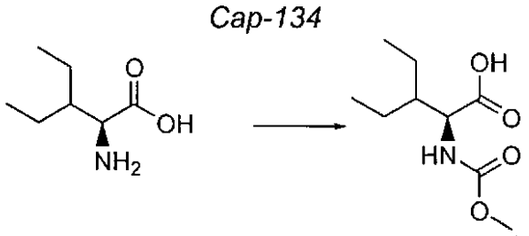
*Cap-132* se preparó a partir de clorhidrato de 2-aminopropanoato de (S)-bencilo de acuerdo con el procedimiento descrito para *Cap-131*. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 1,27 (d, *J*=7,32 Hz, 3H), 2,80 (s, 6H), 4,06 (ct, 1H), 6,36 (d, *J*=7,32 Hz, 1H), 12,27 (s, 1H). CL (Cond. 1): $T_R$ = 0,15 min; EM: Análisis calculado para $[M+H]^+$ $C_6H_{13}N_2O_3$: 161,09; encontrado 161,00.

*Cap-133*



*Cap-133* se preparó a partir de clorhidrato de 2-amino-3-metilbutanoato de (S)-terc-butilo y cloroformiato de 2-fluoroetilo de acuerdo con el procedimiento descrito para *Cap-47*. RMN de $^1$H (500 MHz, DMSO-$d_6$) δ ppm 0,87 (t, *J* = 6,71 Hz, 6H), 1,97-2,10 (m, 1H), 3,83 (dd, *J*=8,39, 5,95 Hz, 1H), 4,14-4,18 (m, 1H), 4,20-4,25 (m, 1H), 4,50-4,54 (m, 1H), 4,59-4,65 (m, 1H), 7,51 (d, *J* = 8,54 Hz, 1H), 12,54 (s, 1H).

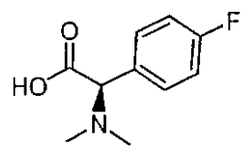
*Cap-134*



*Cap-134* se preparó a partir de (S)-dietil alanina y cloroformiato de metilo de acuerdo con el procedimiento descrito para *Cap-51*. RMN de $^1$H (500 MHz, DMSO-

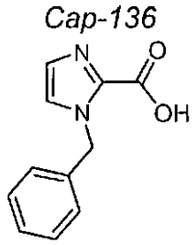
$d_6$) δ ppm 0,72-0,89 (m, 6H), 1,15-1,38 (m, 4H), 1,54-1,66 (m, 1H), 3,46-3,63 (m, 3H), 4,09 (dd, *J* = 8,85, 5,19 Hz, 1H), 7,24 (d, *J* = 8,85 Hz, 1H), 12,55 (s, 1H). CL (Cond. 2): $T_R$ = 0,66 min; CL/EM: Análisis calculado para $[M+H]^+$ $C_9H_{18}NO_4$: 204,12; encontrado 204,02.

*Cap-135*



Una solución de ácido D-2-amino-(4-fluorofenil)acético (338 mg, 2,00 mmol), HCl 1*N* en éter dietílico (2,0 ml, 2,0 mmol) y formalina (37%, 1 ml) en metanol (5 ml) se sometió a hidrogenación bajo un globo en paladio al 10% sobre carbón (60 mg) durante 16 h a 25°C. La mezcla se filtró a través de Celite proporcionando la sal HCl de *Cap-135* como una espuma blanca (316 mg, 80%). RMN de $^1$H (300 MHz, MeOH-$d_4$) δ 7,59 (dd, *J* = 8,80, 5,10 Hz, 2H), 7,29 (t, *J* = 8,6 Hz, 2H), 5,17 (s, 1H), 3,05 (s muy ancho, 3H), 2,63 (s muy ancho, 3H); $T_R$ = 0,19 min (Condiciones de EM-W5); índice de homogeneidad de 95%; EMBR: Análisis calculado para $[M+H]^+$ $C_{10}H_{13}FNO_2$: 198,09; encontrado: 198,10.

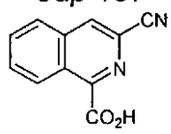
*Cap-136*



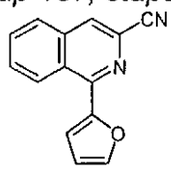
A una suspensión enfriada (-50 °C) de 1-bencil-1*H*-imidazol (1,58 g, 10,0

mmol) en éter dietílico anhidro (50 ml) en nitrógeno se añadió n-butil litio (2,5 M en hexanos, 4,0 ml, 10,0 mmol) gota a gota. Después de agitar durante 20 minutos a -50 °C, se hizo burbujear dióxido de carbono (pasado a través de Drierite) en la mezcla de reacción durante 10 minutos antes de dejar calentar hasta 25°C. El precipitado pesado que se formó al añadir dióxido de carbono a la mezcla de reacción se filtró proporcionando un sólido blanco higroscópico que se recogió en agua (7 ml), se acidificó hasta pH = 3, se enfrió y se indujo a cristalizar con raspado. La filtración de este precipitado dio un sólido blanco que se suspendió en metanol, se trató con HCl 1*N*/éter dietílico (4 ml) y se concentró a vacío. La liofilización del residuo en agua (5 ml) proporcionó la sal HCl de *Cap-136, (230 mg, 105%)* como un sólido blanco (40%). RMN de $^1$H (300 MHz, DMSO-$d_6$) $\delta$ 7,94 (d, $J$ = 1,5 Hz, 1H), 7,71 (d, $J$ = 1,5 Hz, 1H), 7,50-7,31 (m, 5H), 5,77 (s, 2H); $T_R$ = 0,51 min (Condiciones de EM-W5); índice de homogeneidad del 95%; EMBR: Análisis calculado para $[M+H]^+$ $C_{11}H_{12}N_2O_2$: 203,08; encontrado: 203,11.

*Cap-137*




*Cap-137, etapa a*




Una suspensión de 1-cloro-3-cianoisoquinolina (188 mg, 1,00 mmol; preparada de acuerdo con el procedimiento del documento WO 2003/ 099274) (188

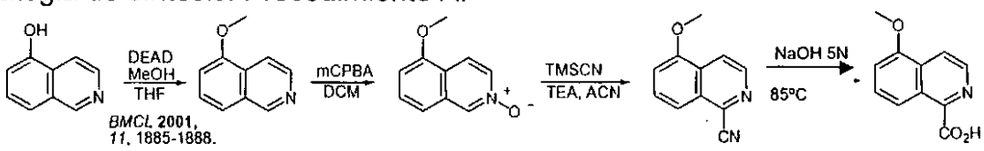
mg, 1,00 mmol), fluoruro de cesio (303,8 mg, 2,00 mmol), dicloruro de bis(tri-*terc*-butilfosfina)paladio (10 mg, 0,02 mmol) y 2-(tributilestannil)furano (378 µl, 1,20 mmol) en dioxano anhidro (10 ml) en nitrógeno se calentó a 80 °C durante 16 horas de enfriar hasta 25°C y se trató con solución acuosa saturada de fluoruro potásico con agitación vigorosa durante 1 h. La mezcla se repartió entre acetato de etilo y la fase orgánica se separó, se lavó con salmuera, se secó sobre $Na_2SO_4$, se filtró y se concentró. La purificación del residuo sobre gel de sílice (elución con acetato de etilo de 0% a 30%/hexanos) proporcionó *Cap-137, etapa a* (230 mg, 105%) como un sólido blanco que se usó directamente a continuación. $T_R$ = 1,95 min (Condiciones de EM-W2); índice de homogeneidad del 90%; EMBR: Análisis calculado para $[M+H]^+$ $C_{14}H_8N_2O$: 221,07; encontrado: 221,12.

*Cap-137*

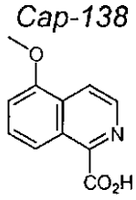
A una suspensión de *Cap 137, etapa a*, (110 mg, 0,50 mmol) y peryodato sódico (438 mg, 2,05 mmol) en tetracloruro de carbono (1 ml), acetonitrilo (1 ml) y agua (1,5 ml) se añadió tricloruro de rutenio hidratado (2 mg, 0,011 mmol). La mezcla se agitó a 25 °C durante 2 h y luego se repartió entre diclorometano y agua. La fase acuosa se separó, se extrajo dos veces más con diclorometano y se secaron los extractos reunidos sobre $Na_2SO_4$, se filtraron y concentraron. La trituración del residuo con hexanos proporcionó *Cap-137* (55 mg, 55%) como un sólido de color grisáceo. $T_R$ = 1,10 min (Condiciones de EM-W2); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_8N_2O_2$: 200,08; encontrado: 200,08.

*Caps 138 a 158*

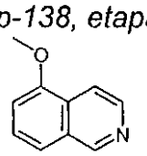
Estrategia de síntesis. Procedimiento A.




*Cap-138*

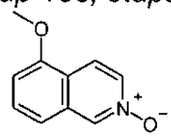



*Cap-138, etapa a*



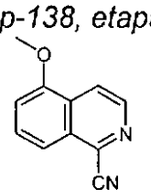
A una suspensión agitada de 5-hidroxiisoquinolina (preparada de acuerdo con el procedimiento del documento WO 2003/ 099274) (2,0 g, 13,8 mmol) y trifenilfosfina (4,3 g, 16,5 mmol) en tetrahidrofurano seco (20 ml) se añadió metanol seco (0,8 ml) y azodicarboxilato de dietilo (3,0 ml, 16,5 mmol) en varias porciones. La mezcla se agitó a temperatura ambiente durante 20 h antes de diluir con acetato de etilo y se lavó con salmuera, se secó sobre $Na_2SO_4$, se filtró y se concentró. El residuo se preabsorbió sobre gel de sílice y se sometió a cromatografía (elución con 40% de acetato de etilo/hexanos) proporcionando *Cap-138, etapa a* (1,00 g, 45%) como un sólido amarillo claro. RMN de $^1H$ ($CDCl_3$, 500 MHz) $\delta$ 9,19 (s, 1H), 8,51 (d, $J$ = 6,0 Hz, 1H), 7,99 (d, $J$ = 6,0 Hz, 1H), 7,52-7,50 (m, 2H), 7,00-6,99 (m, 1H), 4,01 (s, 3H); $T_R$ = 0,66 min (Cond. D2); índice de homogeneidad del 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_{10}NO$: 160,08; encontrado 160,1.

*Cap-138, etapa b*



A una solución agitada de *Cap 138, etapa a* (2,34 g, 14,7 mmol) en diclorometano anhidro (50 ml) a temperatura ambiente se añadió ácido *meta*-cloroperbenzoico (77%, 3,42 g, 19,8 mmol) en una porción. Después de agitar durante 20 horas, se añadió carbonato potásico en polvo (2,0 g) y la mezcla se agitó durante 1 hora a temperatura ambiente antes de que se filtrara y concentrara a vacío proporcionando *Cap-138, etapa b* (2,15 g, 83,3%) como un sólido amarillo pálido que era suficientemente puro para usarse posteriormente directamente. RMN de $^1$H ($CDCl_3$, 400 MHz) δ 8,73 (d, *J* = 1,5 Hz, 1H), 8,11 (dd, *J* = 7,3, 1,7 Hz, 1H), 8,04 (d, *J*=7,1 Hz, 1H), 7,52 (t, *J* = 8,1 Hz, 1H), 7,28 (d, *J* = 8,3 Hz, 1H), 6,91 (d, *J* = 7,8 Hz, 1H), 4,00 (s, 3H); $T_R$ = 0,92 min, (Condiciones-D1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_{10}NO_2$: 176,07; encontrado: 176,0.

*Cap-138, etapa c*



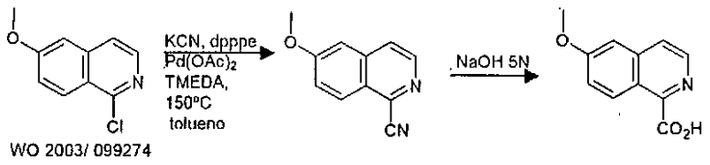
A una solución agitada de *Cap 138, etapa b* (0,70 g, 4,00 mmol) y trietilamina (1,1 ml, 8,00 mmol) en acetonitrilo seco (20 ml) a temperatura ambiente en nitrógeno se añadió cianuro de trimetilsililo (1,60 ml, 12,00 mmol). La mezcla se calentó a 75 ºC durante 20 h antes de enfriar hasta temperatura ambiente, se diluyó con acetato de etilo y se lavó con solución saturada de bicarbonato sódico y salmuera antes de secar sobre $Na_2SO_4$ y concentrar el disolvente. El residuo se

sometió a cromatografía ultrarrápida sobre gel de sílice (elución con gradiente de 5% de acetato de etilo/en hexanos) hasta 25% de acetato de etilo%/en hexanos) proporcionando *Cap-138, etapa c* (498,7 mg, 68%) como un sólido blanco cristalino junto con 223 mg (30%) de más *Cap-138, etapa c* recuperado del filtrado. RMN de $^1$H ($CDCl_3$, 500 MHz) δ 8,63 (d, *J* = 5,5 Hz, 1H), 8,26 (d, *J* = 5,5 Hz, 1H), 7,88 (d, *J* = 8,5 Hz, 1H), 7,69 (t, *J* = 8,0 Hz, 1H), 7,08 (d, *J* = 7,5 Hz, 1H), 4,04 (s, 3H); $T_R$ = 1,75 min, (Condiciones-D1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_9N_2O$: 185,07; encontrado: 185,10.

*Cap-138*

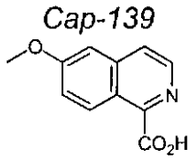
Se trató *Cap-138, etapa c* (0,45 g, 2,44 mmol) con solución de hidróxido sódico 5*N* (10 ml) y la suspensión resultante se calentó a 85°C durante 4 h, se enfrió hasta 25 °C, se diluyó con diclorometano y se acidificó con ácido clorhídrico 1*N*. La fase orgánica se separó, se lavó con salmuera, se secó sobre $Na_2SO_4$, se concentró hasta ¼ del volumen y se filtró proporcionando *Cap-138* (0,44 g, 88,9%) como un sólido amarillo. RMN de $^1$H (DMSO-$d_6$, 400 MHz) δ 13,6 (s ancho, 1H), 8,56 (d, *J* = 6,0 Hz, 1H), 8,16 (d, *J* = 6,0 Hz, 1H), 8,06 (d, *J* = 8,8 Hz, 1H), 7,71-7,67 (m, 1H), 7,30 (d, *J* = 8,0 Hz, 1H), 4,02 (s, 3H); $T_R$ = 0,70 min (Condiciones-D1); índice de homogeneidad del 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; encontrado: 204,05.

Estrategia de síntesis. Procedimiento B (derivado de *Tetrahedron Letters*, **2001**, *42*, 6707).

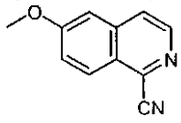



WO 2003/ 099274

*Cap-139*




*Cap-139, etapa a*



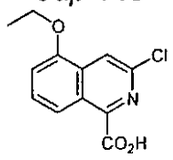

A un vial a rosca de pared gruesa que contenía una suspensión desgasificada en argón de 1-cloro-6-metoxiisoquinolina (1,2 g, 6,2 mmol; preparado de acuerdo con el procedimiento del documento WO 2003/ 099274), cianuro potásico (0,40 g, 6,2 mmol), 1,5-bis(difenilfosfino)pentano (0,27 g, 0,62 mmol) y acetato de paladio (II) (70 mg, 0,31 mmol) en tolueno anhidro (6 ml) se añadió *N,N,N',N'*-tetrametiletilendiamina (0,29 ml, 2,48 mmol). El vial se selló, se calentó hasta 150 °C durante 22 h y luego se dejó enfriar hasta 25 °C. La mezcla de reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre $Na_2SO_4$, se filtró y se concentró. El residuo se purificó sobre gel de sílice (elución con gradiente de 5% de acetato de etilo/hexanos hasta 25% de acetato de etilo%/hexanos proporcionando *Cap-139, etapa a* (669,7 mg, 59%) como un sólido blanco. RMN de $^1H$ ($CDCl_3$, 500 MHz) $\delta$ 8,54 (d, $J$ = 6,0 Hz, 1H), 8,22 (d, $J$ = 9,0 Hz, 1H), 7,76 (d, $J$ = 5,5 Hz, 1H), 7,41-7,39 (m, 1H), 7,13 (d, $J$ = 2,0 Hz, 1H), 3,98 (s, 3H); $T_R$ = 1,66 min (Condiciones-D1); índice de homogeneidad del 90%; CLEM:

Análisis calculado para $[M+H]^+$ $C_{11}H_9N_2O$: 185,07; encontrado: 185,2.

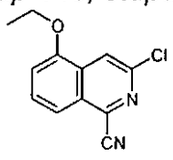
*Cap-139*

*Cap-139* se preparó a partir de la hidrólisis básica de *Cap-139, etapa a* con NaOH 5*N* de acuerdo con el procedimiento descrito para *Cap 138*. RMN de $^1H$ (400 MHz, DMSO-$d_6$) $\delta$ 13,63 s muy ancho, 1H), 8,60 (d, $J$ = 9,3 Hz, 1H), 8,45 (d, $J$ = 5,6 Hz, 1H), 7,95 (d, $J$ = 5,9 Hz, 1H), 7,49 (d, $J$ = 2,2 Hz, 1H), 7,44 (dd, $J$ = 9,3, 2,5 Hz, 1H), 3,95 (s, 3H); $T_R$ = 0,64 min (Condiciones-D1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; encontrado: 204,05.

*Cap-140*




*Cap-140, etapa a*



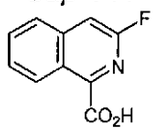

A una mezcla agitada vigorosamente de 1,3-dicloro-5-etoxiisoquinolina (482 mg, 2,00 mmol; preparada de acuerdo con el procedimiento del documento WO 2005/ 051410), acetato de paladio (II) (9 mg, 0,04 mmol), carbonato sódico (223 mg, 2,10 mmol) y 1,5-bis(difenilfosfino)pentano (35 mg, 0,08 mmol) en dimetilacetamida seca (2 ml) a 25 °C en nitrógeno se añadió N,N,N',N'-tetrametiletilendiamina (60 ml, 0,40 mmol). Después de 10 min, la mezcla se calentó hasta 150 °C, y luego se añadió una solución patrón de acetona cianohidrina (preparada a partir de 457 µl de

acetona cianohidrina en 4,34 ml de DMA) en porciones de 1 ml durante 18 h usando una bomba de jeringa. La mezcla se repartió entonces entre acetato de etilo y agua y se separó la fase orgánica, se lavó con salmuera, se secó sobre $Na_2SO_4$, se filtró y se concentró. El residuo se purificó sobre gel de sílice (elución con gradiente de 10% de acetato de etilo en hexanos hasta 40% de acetato de etilo en hexanos) proporcionando *Cap-140, etapa a* (160 mg, 34%) como un sólido amarillo. $T_R$ = 2,46 min (Condiciones de EM-W2); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{12}H_9ClN_2O$: 233,05; encontrado: 233,08.

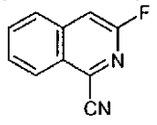
*Cap-140*

*Cap-140* se preparó por la hidrólisis ácida de *Cap-140, etapa a* con HCl 12*N* como se describe en el procedimiento para la preparación de *Cap 141*, descrito más adelante. $T_R$ = 2,24 min (Condiciones de EM-W2); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{12}H_{11}ClNO_3$: 252,04; encontrado: 252,02.

*Cap-141*




*Cap-141, etapa a*



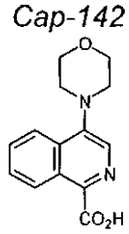

*Cap-141, etapa a* se preparó a partir de 1-bromo-3-fluoroisoquinolina (preparada a partir de 3-amino-1-bromoisoquinolina usando el procedimiento esbozado en *J. Med. Chem.* **1970**, *13*, 613) como se describe en el procedimiento

para la preparación de *Cap-140, etapa a* (*vide supra*). RMN de $^1$H (500 MHz, $CDCl_3$) δ 8,35 (d, *J* = 8,5 Hz, 1H), 7,93 (d, *J* = 8,5 Hz, 1H), 7,83 (t, *J* = 7,63 Hz, 1H), 7,77-7,73 (m, 1H), 7,55 (s, 1H); $T_R$ = 1,60 min (Condiciones-D1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_6FN_2$: 173,05; encontrado: 172,99.

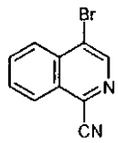
*Cap-141*

Se trató *Cap-141, etapa a* (83 mg, 0,48 mmol) con HCl 12*N* (3 ml) y la suspensión resultante se calentó a 80 °C durante 16 h antes de enfriar hasta temperatura ambiente y se diluyó con agua (3 ml). La mezcla se agitó durante 10 min y luego se filtró proporcionando *Cap-141* (44,1 mg, 48%) como un sólido blanquecino. El filtrado se diluyó con diclorometano y se lavó con salmuera, se secó sobre $Na_2SO_4$ y se concentró proporcionando más *Cap-141* (29,30 mg, 32%) que era suficientemente puro para usarlo posteriormente. RMN de $^1$H (DMSO-$d_6$, 500 MHz) δ 14,0 (s ancho, 1H), 8,59-8,57 (m, 1H), 8,10 (d, *J* = 8,5 Hz, 1H), 7,88-7,85 (m, 2H), 7,74-7,71 (m, 1H); $T_R$ = 1,33 min (Condiciones-D1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7FNO_2$: 192,05; encontrado: 191,97.

*Cap-142*

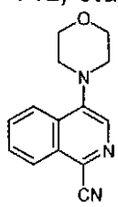



*Cap-142, etapa a*




*Cap-142, etapa a* se preparó a partir de N-óxido de 4-bromoisoquinolina como se describe en el procedimiento en dos etapas para la preparación de *Cap-138, etapas b y c*. $T_R$ = 1,45 min (Condiciones de EM-W1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_6BrN_2$: 232,97; encontrado: 233,00.

*Cap-142, etapa b*



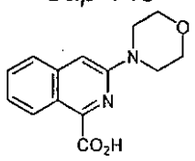

A una suspensión desgasificada en argón de *Cap-142, etapa a* (116 mg, 0,50 mmol), fosfato potásico tribásico (170 mg, 0,80 mmol), acetato de paladio (II) (3,4 mg, 0,015 mmol) y 2-(diciclohexilfosfino)bifenilo (11 mg, 0,03 mmol) en tolueno anhidro (1 ml) se añadió morfolina (61 µl, 0,70 mmol). La mezcla se calentó a 100 °C durante 16 h, se enfrió hasta 25 °C, se filtró a través de tierra de diatomeas (Celite®) y se concentró. La purificación del residuo sobre gel de sílice, (elución con gradiente de acetato de etilo del 10% a 70% en hexanos proporcionó *Cap-142, etapa b* (38 mg, 32%) como un sólido amarillo, que se llevó a etapas posteriores directamente. $T_R$ = 1,26 min (Condiciones de EM-W1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{14}H_{14}N_3O$: 240,11; encontrado: 240,13.

*Cap-142*

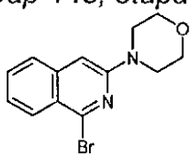
*Cap-142* se preparó a partir de *Cap-142, etapa b* con hidróxido sódico 5*N*

como se describe en el procedimiento para *Cap 138*. $T_R$ = 0,72 min (Condiciones de EM-W1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{14}H_{15}N_2O_3$: 259,11; encontrado: 259,08.

*Cap-143*



*Cap-143, etapa a*



A una solución agitada de 3-amino-1-bromoisoquinolina (444 mg, 2,00 mmol) en dimetilformamida anhidra (10 ml) se añadió hidruro sódico (60%, sin lavar, 96 mg, 2,4 mmol) en una porción. Esta mezcla se agitó a 25 °C durante 5 min antes de añadir éter 2-bromoetílico (90%, 250 µl, 2,00 mmol). La mezcla se agitó otra vez a 25 °C durante 5 h y a 75 °C durante 72 h antes de enfriar hasta 25 °C, se inactivó con solución saturada de cloruro amónico y se diluyó con acetato de etilo. La fase orgánica se separó, se lavó con agua y salmuera, se secó sobre $Na_2SO_4$, se filtró y se concentró. La purificación del residuo sobre gel de sílice (elución con gradiente de 0 a 70% de acetato de etilo en hexanos proporcionó *Cap-143, etapa a* (180 mg, 31%) como un sólido amarillo. $T_R$ = 1,75 min (Condiciones de EM-W1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{13}H_{14}BrN_2O$: 293,03; encontrado: 293,04.

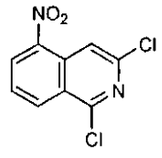
*Cap-143*

A una solución fria (-60 °C) de *Cap-143, etapa a* (154 mg, 0,527 mmol) en tetrahidrofurano anhidro (5 ml) se añadió una solución de *n*-butil litio en hexanos (2,5 M, 0,25 ml, 0,633 mmol). Después de 10 min, se burbujeó dióxido de carbono en la mezcla de reacción durante 10 minutos antes que se inactivara con HCl 1N y se dejó calentar hasta 25°C. La mezcla se extrajo entonces con diclorometano (3 x 30 ml) y los extractos orgánicos reunidos se concentraron a vacío. La purificación del residuo por una HPLC de fase inversa (MeOH/agua/TFA) proporcionó *Cap-143* (16 mg, 12%). $T_R$ = 1,10 min (Condiciones de EM-W1); índice de homogeneidad del 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{14}H_{15}N_2O_3$: 259,11; encontrado: 259,08.

*Cap-144*



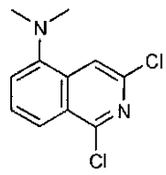

*Cap-144, etapa a*




Se añadió 1,3-dicloroisoquinolina (2,75 g, 13,89 mmol) en pequeñas porciones a una solución fría (0 °C) de ácido nítrico fumante (10 ml) y ácido sulfúrico concentrado (10 ml). La mezcla se agitó a 0°C durante 0,5 horas antes de que se calentara gradualmente hasta 25°C a la que se agitó durante 16 horas. La mezcla se vertió entonces en un vaso de precipitados que contenía hielo triturado y agua y la

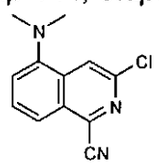
suspensión resultante se agitó durante 1 hora a 0ºC antes de que se filtrara proporcionando *Cap-144, etapa a* (2,73 g, 81%) como un sólido amarillo que se usó directamente. $T_R$ = 2,01 min. (Condiciones-D1); índice de homogeneidad del 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_9H_5Cl_2N_2O_2$: 242,97; encontrado: 242,92.

*Cap-144, etapa b*




Se suspendió *Cap-144, etapa a* (0,30 g, 1,23 mmol) en metanol (60 ml) y se trató con óxido de platino (30 mg) y la suspensión se sometió a hidrogenación de Parr a 48,26 kPa de $H_2$ durante 1,5 h. Antes se añadieron formalina (5 ml) y más óxido de platino (30 mg). La suspensión se volvió a someter a hidrogenación de Parr a 310,26 kPa de $H_2$ durante 13 h antes de someter a filtración por succión a través de tierra de diatomeas (Celite®) y se concentró hasta ¼ de su volumen. La filtración por succión del precipitado proporcionó el compuesto del epígrafe como un sólido amarillo que se sometió a cromatografía sobre gel de sílice (elución con gradiente de 5% de acetato de etilo en hexanos hasta 25% de acetato de etilo% en hexanos) proporcionando *Cap-144, etapa b* (231 mg, 78%) como un sólido amarillo pálido. $T_R$ = 2,36 min (Condiciones-D1); índice de homogeneidad del 95%; RMN de $^1H$ (400 MHz, $CDCl_3$) δ 8,02 (s, 1H), 7,95 (d, *J* = 8,6 Hz, 1H), 7,57-7,53 (m, 1H), 7,30 (d, *J* = 7,3 Hz, 1H), 2,88 (s, 6H); CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{11}Cl_2N_2$: 241,03; encontrado: 241,02. EMAR: Análisis calculado para $[M+H]^+$ $C_{11}H_{11}Cl_2N_2$: 241,0299; encontrado: 241,0296.

*Cap-144, etapa c*



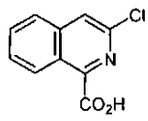
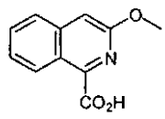
*Cap-144, etapa c* se preparó a partir de *Cap-144, etapa b* de acuerdo con el procedimiento descrito para la preparación de *Cap-139, etapa a*. $T_R$ = 2,19 min (Condiciones-D1); índice de homogeneidad del 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{12}H_{11}ClN_3$: 232,06; encontrado: 232,03. EMAR: Análisis calculado para $[M+H]^+$ $C_{12}H_{11}ClN_3$: 232,0642; encontrado: 232,0631.

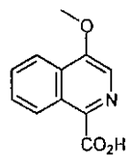
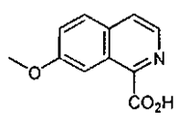
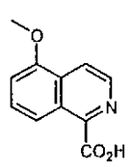
*Cap-144*

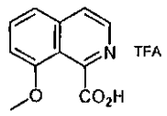
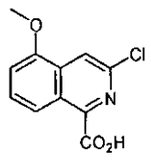
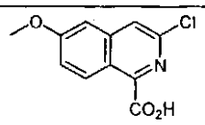
*Cap-144* se preparó de acuerdo con el procedimiento descrito para *Cap-141*. $T_R$ = 2,36 min (Condiciones-D1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{12}H_{12}ClN_2O_2$: 238,01; encontrado: 238,09.

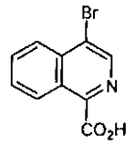
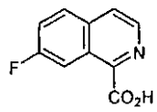
*Caps-145 a 162*

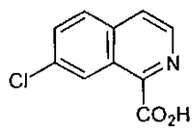
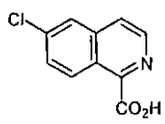
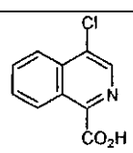
Se prepararon *Caps-145* a *162* a partir de las 1-cloroisoquinolinas apropiadas de acuerdo con el procedimiento descrito para la preparación de *Cap-138* (Procedimiento A) o *Cap-139* (Procedimiento B) a no ser que se describa de otro modo más adelante.

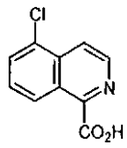
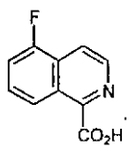
| *Cap nº* | Cap | Procedimiento | Hidrólisis | $T_r$ (Condición de CL); % de índice de homogeneidad; datos de EM |
|---|---|---|---|---|
| *Cap-145* |  Preparado a partir de 1,3-dicloroisoquinolina disponible comercialmente | B | 12*N* HCl | 1,14 min (Condiciones de EM-W1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7ClNO_2$: 208,02; encontrado: 208,00. |
| *Cap-146* |  Preparado a partir de 3-hidroxiisoquinolina disponible comercialmente | A | NaOH 5N | 1,40 min (Condiciones-D1); 95% ; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; encontrado: 204,06. |

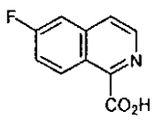
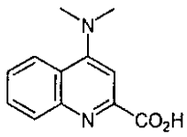
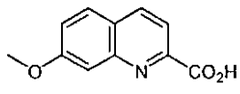
| | | | | |
|---|---|---|---|---|
| *Cap-147* |  Preparado a partir de 1-cloro-4-hidroxiisoquinolina disponible comercialmente | B | NaOH 5N | 0,87 min (Condiciones-D1); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; encontrado: 204,05. |
| *Cap-148* |  Preparado a partir de 7-hidroxiisoquinolina disponible comercialmente | A | NaOH 5N | 0,70 min (Condiciones-D1); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; encontrado: 204,05. |
| *Cap-149* |  Preparado a partir de 5-hidroxiisoquinolina disponible comercialmente | A | NaOH 5N | 0,70 min (Condiciones-D1); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; |

| | | | | |
|---|---|---|---|---|
| | | | | encontrado: 204,05. |
| *Cap-150* |  Preparado a partir de 8-metoxi-1-cloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/ 099274 | A | HCl 12N | 0,26 min (Condiciones-D1); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; encontrado: 204,04. |
| *Cap-151* |  Preparado a partir de 5-metoxi-1,3-dicloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2005 / 051410. | B | HCl 12N | 1,78 min (Condiciones-D1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_9ClNO_3$: 238,03; encontrado: 238,09. |
| *Cap-152* |  Preparado a partir de 6-metoxi-1,3- | B | HCl 12N | 1,65 min (Condiciones-D1); 95%; CLEM: Análisis |

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| | dicloroisoquinolina disponible comercialmente | | | calculado para $[M+H]^+$ $C_{11}H_9ClNO_3$: 238,00; encontrado: 238,09. |
| *Cap-153* |  Preparado a partir de 4-bromoisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/ 062241 | A | HCl 6N | 1,18 min (Condiciones de EM-W1); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7BrNO_2$: 251,97; encontrado: 251,95. |
| *Cap-154* |  Preparado a partir de 7-fluoro-1-cloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/ 099274 | B | NaOH 5N | 0,28 min (Condiciones de EM-W1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7FNO_2$: 192,05; encontrado: 192,03. |

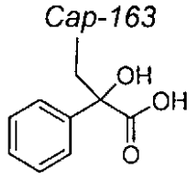
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| *Cap-155* |  Preparado a partir de 1,7-dicloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/099274 | B | NaOH 5N | 0,59 min (Condiciones de EM-W1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7ClNO_2$: 208,02; encontrado: 208,00. |
| *Cap-156* |  Preparado a partir de 1,6-dicloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/099274 | B | NaOH 5N | 0,60 min (Condiciones de EM-W1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7ClNO_2$: 208,02; encontrado: 208,03. |
| *Cap-157* |  Preparado a partir de 1,4-dicloroisoquinolina, que se puede sintetizar | B | HCl 12N | 1,49 min (Condiciones-D1); 95%; CLEM: Análisis calculado para |

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|---|---|---|---|---|
| | siguiendo el procedimiento del documento WO 2003/062241 | | | $[M+H]^+$ $C_{10}H_{17}ClNO$: 208,02; encontrado: 208,00. |
| *Cap-158* |  Preparado a partir de 1,5-dicloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/099274 | B | NaOH 5N | 0,69 min (Condiciones de EM-W1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7ClNO_2$: 208,02; encontrado: 208,01. |
| *Cap-159* |  Preparado a partir de 5-fluoro-1-cloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/099274 | B | NaOH 5N | 0,41 min (Condiciones de EM-W1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7FNO_2$: 192,05; encontrado: 192,03. |

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| *Cap-160* |  Preparado a partir de 6-fluoro-1-cloroisoquinolina, que se puede sintetizar siguiendo el procedimiento del documento WO 2003/099274 | B | NaOH 5N | 0,30 min (Condiciones de EM-W1); 90%; CLEM: Análisis calculado para $[M+H]^+$ $C_{10}H_7FNO_2$: 192,05; encontrado: 192,03. |
| *Cap-161* |  Preparado a partir de ácido 4-bromoquinolin-2-carboxílico y dimetilamina (DMSO, 100 °C) | -- | -- | 0,70 min (Cond. D1); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{12}H_{13}N_2O_2$: 217,10; encontrado: 217,06. |
| *Cap-162* |  Preparado a partir de *m*-anisidina siguiendo el procedimiento descrito en *J. Hetero. Chem.* **1993**, 17 y *Heterocycles*, **2003**, *60*, 953. | -- | -- | 0,65 min (Condiciones-M3); 95%; CLEM: Análisis calculado para $[M+H]^+$ $C_{11}H_{10}NO_3$: 204,07; |

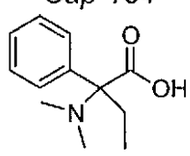
| | | | | |
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| | | | | encontrado: 203,94. |

*Cap-163*



A una solución de ácido 2-cetobutírico (1,0 g, 9,8 mmol) en éter dietílico (25 ml) se añadió gota a gota bromuro de fenilmagnesio (22 ml, 1M en THF). La reacción se agitó a ~25 °C en nitrógeno durante 17,5h. La reacción se acidificó con HCl 1N y el producto se extrajo con acetato de etilo (3 x 100 ml). La fase orgánica reunida se lavó con agua seguido por salmuera y se secó sobre $MgSO_4$. Después de concentrar a vacío se obtuvo un sólido blanco. El sólido se recristalizó en hexanos/acetato de etilo proporcionando *Cap-163* como agujas blancas (883,5 mg). RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 500 MHz): 12,71 (s ancho, 1 H), 7,54-7,52 (m, 2H), 7,34-7,31 (m, 2H), 7,26-7,23 (m, 1H), 5,52-5,39 (s ancho, 1H), 2,11 (m, 1H), 1,88 (m, 1H), 0,79 (t ap, J = 7,4 Hz, 3H).

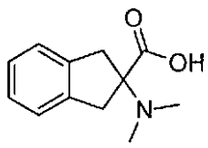
*Cap-164*



Se expuso a $H_2$ a 344,74 kPa en un frasco de Parr durante 42 horas una mezcla de ácido 2-amino-2-fenilbutírico (1,5 g, 8,4 mmol), formaldehído (14 ml, 37% en agua), HCl 1N (10 ml) y Pd al 10%/C (0,5 mg) en MeOH (40 ml). La reacción se filtró sobre Celite y se concentró a vacío, el residuo se suspendió en MeOH (36 ml) y

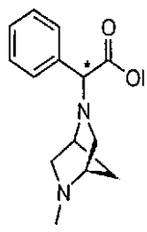
el producto se purificó con una HPLC de fase inversa ($MeOH/H_2O/TFA$) proporcionando la sal TFA de *Cap-164* como un sólido blanco (1,7 g). RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 500 MHz) 7,54-7,47 (m, 5H), 2,63 (m, 1H), 2,55 (s, 6H), 2,31 (m, 1H), 0,95 (t ap, J = 7,3 Hz, 3H).

*Cap-165*




A una mezcla de ácido 2-amino-2-indanocarboxílico (258,6 mg, 1,46 mmol) y ácido fórmico (0,6 ml, 15,9 mmol) en 1,2-dicloroetano (7 ml) se añadió formaldehído (0,6 ml, 37% en agua). La mezcla se agitó a ~25 °C durante 15 min luego se calentó a 70 °C durante 8h. El componente volátil se eliminó a vacío y el residuo se disolvió en DMF (14 ml) y se purificó por una HPLC de fase inversa ($MeOH/H_2O/TFA$) proporcionando la sal TFA de *Cap-165* como un aceite viscoso (120,2 mg). RMN de $^1H$ (DMSO-$d_6$, $\delta$ = 2,5 ppm, 500 MHz): 7,29-7,21 (m, 4 H), 3,61 (d, J = 17,4 Hz, 2H), 3,50 (d, J = 17,4 Hz, 2H), 2,75 (s, 6H). CL/EM: Análisis calculado para $[M+H]^+$ $C_{12}H_{16}NO_2$: 206,12; encontrado: 206,07.

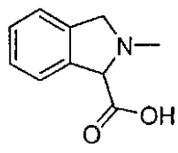
*Cap-166a y -166b*



*Cap*-166a: Diastereómero-1
*Cap*-166b: Diastereómero-2

*Caps-166a* y *-166b* se prepararon a partir de (1S, 4S)-(+)-2-metil-2,5-diazabiciclo[2.2.1]heptano (2HBr) de acuerdo con el procedimiento descrito para la síntesis de *Cap-7a y Cap-7b*, con la salvedad de que se separó el éster bencílico intermedio usando una columna semipreparativa Chiralcel OJ, 20 x 250 mm, 10 μm eluyendo con una mezcla 85:15 de heptano/etanol a 10 ml/min de caudal de elución durante 25 min. *Cap-166b*: RMN de $^1$H (DMSO-$d_6$, δ = 2,5 ppm, 500 MHz): 7,45 (d, J = 7,3 Hz, 2H), 7,27-7,19 (m, 3H), 4,09 (s, 1H), 3,34 (s ancho ap, 1H), 3,16 (s ancho ap, 1H), 2,83 (d, *J*=10,1 Hz, 1H), 2,71 (m, 2H), 2,46 (m, 1H), 2,27 (s, 3H), 1,77 (d, J = 9,8 Hz, 1H), 1,63 (d, J = 9,8 Hz, 1H). CL/EM: Análisis calculado para $[M+H]^+$ $C_{14}H_{19}N_2O_2$: 247,14; encontrado: 247,11.

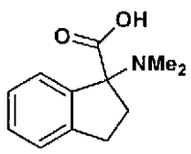
*Cap-167*



Se agitó una solución de ácido Boc-1,3-dihidro-2H-isoindol carboxílico racémico (1,0g, 3,8 mmol) en 20% de TFA/$CH_2Cl_2$ a ~25 °C durante 4h. Se eliminó todo el componente volátil a vacío. Se expuso una mezcla del material bruto resultante, formaldehído (15 ml, 37% en agua), HCl 1N (10 ml) y Pd al 10%/C (10

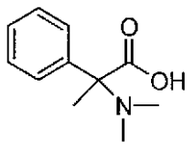
mg) en MeOH a $H_2$ (275,71 kPa) en un frasco de Parr durante 23 h. La mezcla de reacción se filtró sobre Celite y se concentró a vacío proporcionando *Cap-167* como una espuma amarilla (873,5 mg). RMN de $^1$H (DMSO-$d_6$, $\delta$ = 2,5 ppm, 500 MHz) 7,59-7,38 (m, 4H), 5,59 (s, 1H), 4,84 (d, J = 14 Hz, 1H), 4,50 (d, J = 14,1 Hz, 1H), 3,07 (s, 3H). CL/EM: Análisis calculado para $[M+H]^+$ $C_{10}H_{12}NO_2$: 178,09; encontrado: 178,65.

*Cap-168*




Se preparó *Cap-168* racémico a partir de ácido Boc-aminoindano-1-carboxílico racémico de acuerdo con el procedimiento descrito para la preparación de *Cap-167*. El producto bruto se empleó como tal.

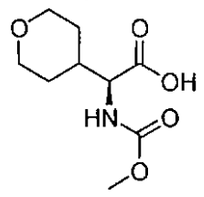
*Cap-169*




Se colocó una mezcla de clorhidrato de ácido 2-amino-2-fenilpropanoico (5,0 g, 2,5 mmol), formaldehído (15 ml, 37% en agua), HCl 1N (15 ml) y Pd al 10%/C (1,32 g) en MeOH (60 ml) en un frasco de Parr y se agitó en hidrógeno (379,11 kPa) durante 4 días. La mezcla de reacción se filtró a través de tierra de diatomeas (Celite®) y se concentró a vacío. El residuo se suspendió en MeOH y se purificó por

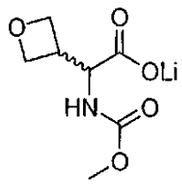
HPLC preparativa de fase inversa (MeOH/agua/TFA) proporcionando la sal TFA de *Cap-169* como un semisólido viscoso (2,1 g). RMN de $^1$H ($CDCl_3$, $\delta$ = 7,26 ppm, 500 MHz): 7,58-7,52 (m, 2 H), 7,39-7,33 (m, 3H), 2,86 (s ancho, 3H), 2,47 (s ancho, 3H), 1,93 (s, 3H). CL/EM: Análisis calculado para $[M+H]^+$ $C_{11}H_{16}NO_2$: 194,12; encontrado: 194,12.

*Cap-170*



A ácido (*S*)-2-amino-2-(tetrahidro-2*H*-piran-4-il)acético (505 mg; 3,18 mmol; obtenido de Astatech) en agua (15ml) se añadió carbonato sódico (673 mg; 6,35 mmol) y la mezcla resultante se enfrió hasta 0ºC momento en el que se añadió cloroformiato de metilo (0,26ml; 3,33mmol) gota a gota durante 5 minutos. Se dejó agitando la reacción durante 18 horas llegando lentamente a temperatura ambiente a medida que se fundía el baño de hielo. La mezcla de reacción se repartió entonces entre HCl 1N y acetato de etilo. La fase orgánica se separó y la fase acuosa se extrajo de nuevo con dos porciones más de acetato de etilo. Las fases orgánicas reunidas se lavaron con salmuera, se secaron sobre sulfato de magnesio, se filtraron y se concentraron a vacío dando *Cap-170* como un residuo incoloro. RMN de $^1$H (500 MHz, *DMSO-d*$_6$) $\delta$ ppm 12,65 (1 H, s ancho), 7,44 (1 H, d, *J*=8,24 Hz), 3,77 - 3,95 (3 H, m), 3,54 (3 H, s), 3,11 - 3,26 (2 H, m), 1,82 - 1,95 (1 H, m), 1,41 - 1,55 (2 H, m), 1,21 - 1,39 (2 H, m); CL/EM: Análisis calculado para $[M+H]^+$ $C_9H_{16}NO_5$: 218,1; encontrado 218,1.

*Cap-171*

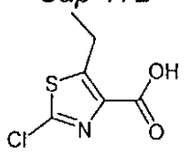


Una solución de 2-(benciloxicarbonilamino)-2-(oxetan-3-iliden)acetato de metilo (200 mg, 0,721 mmol; Il Farmaco (2001), 56, 609–613) en acetato de etilo (7 ml) y $CH_2Cl_2$ (4,00 ml) se desgasificó burbujeando nitrógeno durante 10min. Se añadieron entonces dicarbonato de dimetilo (0,116 ml, 1,082 mmol) y Pd/C (20 mg, 0,019 mmol), la mezcla de reacción se ajustó bajo un globo de hidrógeno y se dejó agitando a temperatura ambiente durante la noche momento en el que la TLC (95:5 $CH_2Cl_2$ / MeOH: visualizada con tinción realizada en 1g de $Ce(NH_4)_2SO_4$, 6g de molibdato amónico, 6 ml de ácido sulfúrico y 100 ml de agua) indicó la conversión completa. La reacción se filtró a través de Celite y se concentró. El residuo se purificó por Biotage® (cada con diclorometano en 25 de muestra; elución en columna 25S con diclorometano para 3CV luego 0 a 5% de MeOH / diclorometano sobre 250ml luego mantenido a 5% de MeOH / diclorometano para 250ml; fracciones de 9 ml). Las fracciones obtenidas que contenían material deseado y se concentraron hasta 120 mg (81%) de 2-(metoxicarbonilamino)-2-(oxetan-3-il)acetato de metilo como un aceite incoloro. RMN de $^1H$ (500 MHz, CLOROFORMO-D) $\delta$ ppm 3,29 - 3,40 (m, *J*=6,71 Hz, 1 H) 3,70 (s, 3 H) 3,74 (s, 3 H) 4,55 (t, *J*=6,41 Hz, 1 H) 4,58 - 4,68 (m, 2 H) 4,67 - 4,78 (m, 2 H) 5,31 (s ancho, 1 H). CL/EM: Análisis calculado para $[M+H]^+$ $C_8H_{14}NO_5$: 204,2; encontrado 204,0.

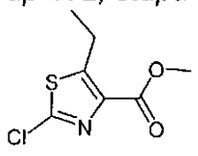
Se añadió a 2-(metoxicarbonilamino)-2-(oxetan-3-il)acetato de metilo (50 mg, 0,246 mmol) en THF (2 ml) y agua (0,5 ml) hidróxido de litio monohidratado (10,33 mg, 0,246 mmol). La solución resultante se dejó agitando durante la noche a

temperatura ambiente. La TLC (1:1 EA / Hex; tinción de Hanessian [1g de $Ce(NH_4)_2SO_4$, 6 g de molibdato amónico, 6 ml de ácido sulfúrico y 100 ml de agua]) indicó que quedaba ~10% de material de partida. Se añadieron otros 3 mg de LiOH y se dejó agitando durante la noche momento en el que la TLC mostró que no quedaba material de partida. Se concentró a vacío y se colocó en alto vacío durante la noche proporcionando 55 mg de 2-(metoxicarbonilamino)-2-(oxetan-3-il)acetato de litio como un sólido incoloro. RMN de $^1H$ (500 MHz, MeOD) δ ppm 3,39 - 3,47 (m, 1 H) 3,67 (s, 3 H) 4,28 (d, *J*=7,93 Hz, 1 H) 4,64 (t, *J*=6,26 Hz, 1 H) 4,68 (t, *J*=7,02 Hz, 1 H) 4,73 (d, *J*=7,63 Hz, 2 H).

*Cap-172*




*Cap-172, etapa a*



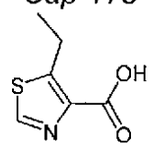

La siguiente etapa de diazotación se adaptó de Barton, A.; Breukelman, S. P.; Kaye, P. T.; Meakins, G. D.; Morgan, D. J. *J. C. S. Perkin Trans I* **1982**, 159-164: Se añadió una solución de $NaNO_2$ (166 mg, 2,4 mmol) en agua (0,6 ml) a una solución agitada, fría (0 °C) de 2-amino-5-etil-1,3-tiazol-4-carboxilato de metilo (186 mg, 1,0 mmol), $CuSO_4 \cdot 5H_2O$ (330 mg, 1,32 mmol), NaCl (260 mg, 4,45 mmol) y $H_2SO_4$ (5,5 ml) en agua (7,5 ml). La mezcla se agitó a 0 °C durante 45 min y se dejó calentar hasta temperatura ambiente donde se agitó durante otra 1 h antes de añadir CuCl

(118 mg). Esta mezcla se agitó de nuevo a temperatura ambiente durante 16 h antes de diluirse con salmuera y extraerse con éter dos veces. Las fases orgánicas se reunieron, se secaron sobre $MgSO_4$ y se concentraron dando 2-cloro-5-etiltiazol-4-carboxilato de metilo (es decir, *Cap-172, etapa a*) (175 mg, 85%) como un aceite naranja (80% de pureza) que se usó directamente en la siguiente reacción. $T_R$ = 1,99 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_7H_9ClNO_2S$: 206,01; encontrado: 206,05.

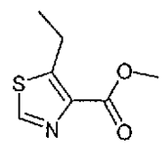
*Cap-172*

A una solución de 2-cloro-5-etiltiazol-4-carboxilato de metilo (175 mg) en THF/$H_2O$/MeOH (20 ml/ 3 ml/ 12 ml) se añadió LiOH (305 mg, 12,76 mmol). La mezcla se agitó a temperatura ambiente durante la noche antes de concentrar y neutralizar con HCl 1N en éter (25 ml). El residuo se extrajo dos veces con acetato de etilo y las fases orgánicas se reunieron, se secaron sobre $MgSO_4$ y se evaporaron proporcionando *Cap-172* (60 mg, 74%) como un sólido rojo que se usó sin purificación posterior. RMN de $^1H$ (300 MHz, DMSO-$d_6$) $\delta$ ppm 13,03-13,42 (1 H, m), 3,16 (2 H, q, $J$ = 7,4 Hz), 1,23 (3 H, t, $J$ = 7,5 Hz). $T_R$ = 1,78 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_6H_7ClNO_2S$: 191,99; encontrado: 191,99.

*Cap-173*




*Cap-173, etapa a*



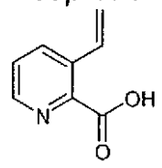
La siguiente etapa de diazotación se adaptó de Barton, A.; Breukelman, S. P.; Kaye, P. T.; Meakins, G. D.; Morgan, D. J. *J. C. S. Perkin Trans I* **1982**, 159-164: Se añadió una solución de $NaNO_2$ (150 mg, 2,17 mmol) en agua (1,0 ml) gota a gota a una solución agitada, fría (0 °C) de 2-amino-5-etil-1,3-tiazol-4-carboxilato de metilo (186 mg, 1,0 mmol) en $H_3PO_2$ al 50% (3,2 ml). La mezcla se agitó a 0 °C durante 1 h y se dejó calentar hasta temperatura ambiente donde se agitó durante otras 2h. Después de volver a enfriar hasta 0 °C, la mezcla se trató lentamente con una solución de NaOH (85 mg) en agua (10 ml). La mezcla se diluyó entonces con solución saturada de $NaHCO_3$ y se extrajo dos veces con éter. Las fases orgánicas se reunieron, se secaron sobre $MgSO_4$ y se concentraron dando 5-etiltiazol-4-carboxilato de metilo (es decir, *Cap-173, etapa a*) (134 mg, 78%) como un aceite naranja (85% de pureza) que se usó directamente en la siguiente reacción. $T_R$ = 1,58 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_7H_{10}NO_2S$: 172,05; encontrado: 172,05.

*Cap-173*

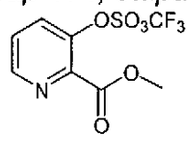
A una solución de 5-etiltiazol-4-carboxilato de metilo (134 mg) en THF/$H_2O$/MeOH (18 ml/ 2,7 ml/ 11 ml) se añadió LiOH (281 mg, 11,74 mmol). La mezcla se agitó a temperatura ambiente durante la noche antes de concentrar y neutralizar con HCl 1N en éter (25 ml). El residuo se extrajo dos veces con acetato de etilo y las fases orgánicas se reunieron, se secaron sobre $MgSO_4$ y se evaporaron proporcionando *Cap-173* (90 mg, 73%) como un sólido naranja que se usó sin purificación posterior. RMN de $^1H$ (300 MHz, DMSO-$d_6$) $\delta$ ppm 12,74-13,04

(1 H, m), 3,20 (2 H, q, *J* = 7,3 Hz), 1,25 (3 H, t, *J* = 7,5 Hz). $T_R$ = 1,27 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_6H_8NO_2S$: 158,03; encontrado: 158,04.

*Cap-174*



*Cap-174, etapa a*

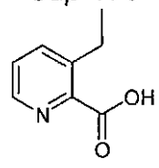


Se añadió anhídrido tríflico (5,0 g, 18,0 mmol) gota a gota a una solución fría (0 °C) de 3-hidroxipicolinato de metilo (2,5 g, 16,3 mmol) y TEA (2,5 ml, 18,0 mmol) en $CH_2Cl_2$ (80 ml). La mezcla se agitó a 0 °C durante 1h antes de dejar calentar hasta temperatura ambiente, momento en el que se agitó durante una hora más. La mezcla se inactivó entonces con solución saturada de $NaHCO_3$ (40 ml) y la fase orgánica se separó, se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró dando 3-(trifluorometilsulfoniloxi)picolinato de metilo (*es decir, Cap-174, etapa a*) (3,38 g, 73%) como un aceite marrón oscuro (>95% de pureza) que se usó directamente sin purificación posterior. RMN de $^1H$ (300 MHz, $CDCl_3$) $\delta$ ppm 8,72-8,79 (1 H, m), 7,71 (1 H, d, *J* = 1,5 Hz), 7,58-7,65 (1 H, m), 4,04 (3 H, s). $T_R$ = 1,93 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_8H_7F_3NO_5S$: 286,00; encontrado: 286,08.

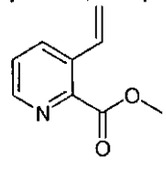
*Cap-174*

A una solución de 3-(trifluorometilsulfoniloxi)picolinato de metilo (570 mg, 2,0 mmol) en DMF (20 ml) se añadió LiCl (254 mg, 6,0 mmol), tributil(vinil)estannano (761 mg, 2,4 mmol) y dicloruro de bis(trifenilfosfina)paladio (42 mg, 0,06 mmol). La mezcla se calentó a 100 °C durante la noche antes d añadir una solución saturada de KF (20 ml) a la mezcla de reacción a temperatura ambiente. Esta mezcla se agitó durante 4 h antes de filtrar a través de tierra de diatomeas (Celite®) y el lecho corto se lavó con acetato de etilo. La fase acuosa del filtrado se separó entonces y se concentró a vacío. El residuo se trató con HCl 4*N* en dioxanos (5 ml) y la mezcla resultante se extrajo con metanol, se filtró y se evaporó proporcionando *Cap-174* (260 mg) como un sólido verde que estaba ligeramente contaminado con sales inorgánicas pero que se usó sin purificación posterior. RMN de $^1$H (300 MHz, DMSO-$d_6$) $\delta$ ppm 8,21 (1 H, d, *J* = 3,7 Hz), 7,81-7,90 (1 H, m), 7,09 (1 H, dd, *J* = 7,7, 4,8 Hz), 6,98 (1 H, dd, *J* = 17,9, 11,3 Hz), 5,74 (1 H, dd, *J* = 17,9, 1,5 Hz), 5,20 (1 H, d, *J* = 11,0 Hz). $T_R$ = 0,39 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_8H_8NO_2$: 150,06; encontrado: 150,07.

*Cap-175*

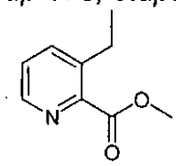



*Cap-175, etapa a*



A una solución de 3-(trifluorometilsulfoniloxi)picolinato de metilo (*es decir, Cap 173, etapa a*) (570 mg, 2,0 mmol), un intermedio en la preparación de *Cap-174*, en DMF (20 ml) se añadió LiCl (254 mg, 6,0 mmol), tributil(vinil)estannano (761 mg, 2,4 mmol) y dicloruro de bis(trifenilfosfina)paladio (42 mg, 0,06 mmol). La mezcla se calentó a 100 °C durante 4 h antes de eliminar el disolvente a vacío. El residuo se suspendió en acetonitrilo (50 ml) y hexanos (50 ml) y la mezcla resultante se lavó dos veces con hexanos. Se separó entonces la fase de acetonitrilo, se filtró a través de Celite y se evaporó. La purificación del residuo por cromatografía ultrarrápida en un aparato Horizon (elución con gradiente de 25% de acetato de etilo% en hexanos hasta 65% de acetato de etilo en hexanos) proporcionó 3-vinilpicolinato de metilo (es decir, *Cap-175, etapa a*) (130 mg, 40%) como un aceite amarillo. RMN de $^1$H (300 MHz, $CDCl_3$) δ ppm 8,60 (1 H, dd, *J* = 4,6, 1,7 Hz), 7,94 (1 H, d, *J* = 7,7 Hz), 7,33-7,51 (2 H, m), 5,72 (1 H, d, *J* = 17,2 Hz), 5,47 (1 H, d, *J* = 11,0 Hz), 3,99 (3 H, s). $T_R$ = 1,29 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_9H_{10}NO_2$: 164,07; encontrado: 164,06.

*Cap-175, etapa b*



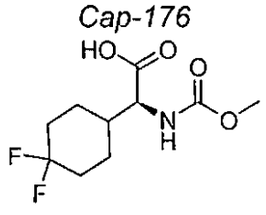

Se añadió paladio sobre carbón (10%, 25 mg) a una solución de 3-vinilpicolinato de metilo (120 mg, 0,74 mmol) en etanol (10 ml). La suspensión se agitó a temperatura ambiente en una atmósfera de hidrógeno durante 1 h antes de filtrar a través de Celite y se lavó el lecho de tierra de diatomeas (Celite®) con metanol. El filtrado se concentró hasta sequedad proporcionando 3-etilpicolinato de metilo (es decir, *Cap-175, etapa b*) que se llevó directamente a la siguiente reacción.

$T_R$ = 1,15 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_9H_{12}NO_2$: 166,09; encontrado: 166,09.

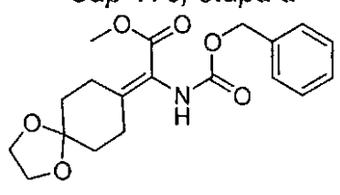
*Cap-175*

A una solución de 3-etilpicolinato de metilo en THF/$H_2O$/MeOH (5 ml/ 0,75 ml/ 3 ml) se añadió LiOH (35 mg, 1,47 mmol). La mezcla se agitó a temperatura ambiente durante 2 días antes de añadir más LiOH (80 mg). Después de otras 24 horas más a temperatura ambiente, la mezcla se filtró y el disolvente se eliminó a vacío. El residuo se trató entonces con HCl 4*N* en dioxanos (5 ml) y la suspensión resultante se concentró hasta sequedad proporcionando *Cap-175* como un sólido amarillo que se usó sin purificación posterior. RMN de $^1H$ (300 MHz, DMSO-$d_6$) $\delta$ ppm 8,47 (1 H, dd, *J* = 4,8, 1,5 Hz), 7,82-7,89 (1 H, m), 7,53 (1 H, dd, *J* = 7,7, 4,8 Hz), 2,82 (2 H, q, *J* = 7,3 Hz), 1,17 (3 H, t, *J* = 7,5 Hz). $T_R$ = 0,36 min (Condición-MD1); CL/EM: Análisis calculado para $[M+H]^+$ $C_8H_{10}NO_2$: 152,07; encontrado: 152,10.

*Cap-176*

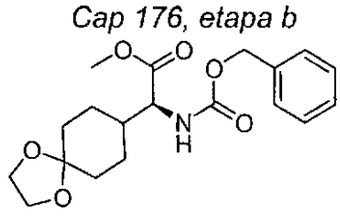


*Cap-176, etapa a*



Se añadió una solución de 1,4-dioxaspiro[4,5]decan-8-ona (15 g, 96 mmol) en EtOAc (150 ml) a una solución de 2-(benciloxicarbonilamino)-2-(dimetoxifosforil)acetato de metilo (21,21 g, 64,0 mmol) en 1,1,3,3-tetrametilguanidina (10,45 ml, 83 mmol) y EtOAc (150 ml). La solución resultante se agitó a temperatura ambiente durante 72 h y luego se diluyó con EtOAc (25 ml). La fase orgánica se lavó con HCl 1N (75 ml), $H_2O$ (100 ml) y salmuera (100 ml), se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó por Biotage (EtOAc al 5% hasta 25 %/Hexanos; 300g columna). Las fracciones reunidas que contenían el producto se concentraron entonces a vacío y el residuo se volvió a cristalizar en hexanos/EtOAc dando cristales blancos que corresponden a 2-(benciloxicarbonilamino)-2-(1,4-dioxaspiro[4,5]decan-8-iliden)acetato de metilo (6,2 g) RMN de $^1H$ (400 MHz, $CDCl_3$-*d*) $\delta$ ppm 7,30 - 7,44 (5 H, m), 6,02 (1 H, s ancho), 5,15 (2 H, s), 3,97 (4 H, s), 3,76 (3 H, s ancho), 2,84 - 2,92 (2 H, m), 2,47 (2 H, t, *J*=6,40 Hz), 1,74 - 1,83 (4 H, m). CL (Cond. OL1): $T_R$ = 2,89 min. CL/EM: Análisis calculado para $[M+Na]^+$ $C_{19}H_{23}NNaO_6$: 745,21; encontrado: 745,47.

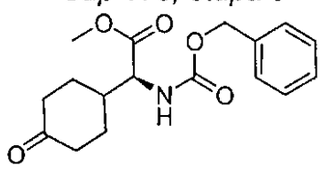
*Cap 176, etapa b*



Se preparó el éster *Cap 176, etapa b* a partir del alqueno *Cap 176, etapa a* de acuerdo con el procedimiento de Burk, M. J.; Gross, M. F. and Martinez J. P. (*J. Am. Chem. Soc.*, **1995**, *117*, 9375-9376 y referencias en el mismo): Se cargó una botella a alta presión de 500 ml con el alqueno *Cap 176, etapa a* (3,5 g, 9,68 mmol) en MeOH desgasificado (200 ml) en una capa de $N_2$. La solución se cargó entonces

con tetrafluoroborato de (-)-1,2-bis((2S,5S)-2,5-dimetilfosfolano)-etano(ciclooctadieno)rodio (I) (0,108 g, 0,194 mmol) y la mezcla resultante se cubrió con $N_2$ (3x) y se cargó con $H_2$ (3x). La solución se agitó vigorosamente a 482 kPa de $H_2$ a temperatura ambiente durante 72 h. El disolvente se eliminó a presión reducida y el residuo que quedó se suspendió en EtOAc. La solución pardusca se filtró entonces a través de un lecho de gel de sílice y se eluyó con EtOAc. El disolvente se concentró a vacío proporcionando un aceite transparente que correspondía al éster *Cap 176, etapa b* (3,4 g), RMN de $^1$H (500 MHz, $CDCl_3$-*d*) δ ppm 7,28 - 7,43 (5 H, m), 5,32 (1 H, d, *J*=9,16 Hz), 5,06 - 5,16 (2 H, m), 4,37 (1 H, dd, *J*=9,00, 5,04 Hz), 3,92 (4 H, t, *J*=3,05 Hz), 3,75 (3 H, s), 1,64 - 1,92 (4 H, m), 1,37 - 1,60 (5 H, m). CL (Cond. OL1): $T_R$ = 1,95 min. CL/EM: Análisis calculado para $[M+H]^+$ $C_{19}H_{26}NO_6$: 364,18; encontrado: 364,27.

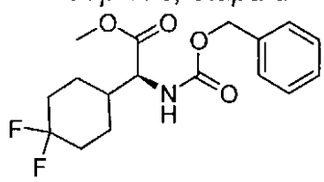
*Cap 176, etapa c*



Se disolvió el éster *Cap 176, etapa b* (4,78 g, 13,15 mmol) en THF (15 ml) seguido por la adición secuencial de agua (10 ml), ácido acético glacial (26,4 ml, 460 mmol) y ácido dicloroacético (5,44 ml, 65,8 mmol). La mezcla resultante se agitó durante 72 h a temperatura ambiente, y la reacción se inactivó mediante la adición lente de $Na_2CO_3$ sólido con agitación vigorosa hasta que no fue visible la generación de gas. El producto bruto se extrajo en 10% de acetato de etilo-diclorometano y las fases orgánicas se reunieron, se secaron ($MgSO_4$), se filtraron y concentraron. El residuo resultante se purificó por Biotage (EtOAc al 0 hasta 30%/Hex; 25 g de

columna) proporcionando la cetona *Cap 176, etapa c* (3,86g) como un aceite transparente. RMN de $^1$H (400 MHz, $CDCl_3$-*d*) δ ppm 7,28 - 7,41 (5 H, m), 5,55 (1 H, d, *J*=8,28 Hz), 5,09 (2 H, s), 4,46 (1 H, dd, *J*=8,16, 5,14 Hz), 3,74 (3 H, s), 2,18 - 2,46 (5 H, m), 1,96 - 2,06 (1 H, m), 1,90 (1 H, ddd, *J*=12,99, 5,96, 2,89 Hz), 1,44 - 1,68 (2 H, m, *J*=12,36, 12,36, 12,36, 12,36, 4,77 Hz). CL (Cond. OL1): $T_R$ = 1,66 min. CL/EM: Análisis calculado para $[M+Na]^+$ $C_{17}H_{21}NNaO_5$: 342,13; encontrado: 342,10.

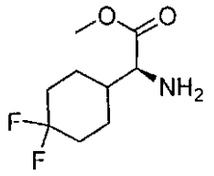
*Cap 176, etapa d*



Se añadió Deoxo-Fluor® (3,13 ml, 16,97 mmol) a una solución de la cetona *Cap 176, etapa c* (2,71 g, 8,49 mmol) en $CH_2Cl_2$ (50 ml) seguido por la adición de una cantidad catalítica de EtOH (0,149 ml, 2,55 mmol). La solución amarillenta resultante se agitó a ta durante la noche. La reacción se inactivó mediante la adición de $NaHCO_3$ acuoso saturado (25 ml) y la mezcla se extrajo con EtOAc (3X75 ml)). Las fases orgánicas reunidas se secaron ($MgSO_4$), se filtraron y se secaron dando un aceite amarillento. El residuo se purificó por cromatografía en Biotage (EtOAc al 2% hasta 15%/Hex; 90g de columna) y se recuperó un sólido blanco correspondiente al difluoruro de difluoro aminoácido *Cap 176, etapa d* (1,5 g). RMN de $^1$H (400 MHz, $CDCl_3$-*d*) δ ppm 7,29 - 7,46 (5 H, m), 5,34 (1 H, d, *J*=8,28 Hz), 5,12 (2 H, s), 4,41 (1 H, dd, *J*=8,66, 4,89 Hz), 3,77 (3 H, s), 2,06 - 2,20 (2 H, m), 1,83 - 1,98 (1 H, m), 1,60 - 1,81 (4 H, m), 1,38 - 1,55 (2 H, m). RMN de $^{19}$F (376 MHz, $CDCl_3$-*d*) δ ppm -92,15 (1 F, d, *J*=237,55 Hz), -102,44 (1 F, d, *J*=235,82 Hz). CL

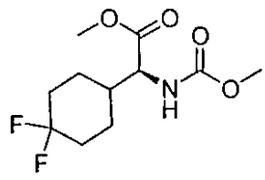
(Cond. OL1): $T_R$ = 1,66 min. CL/EM: Análisis calculado para $[2M+Na]^+$ $C_{34}H_{42}F_4N_2NaO_8$: 705,28; encontrado: 705,18.

*Cap 176, etapa e*



Se disolvió el difluoruro *Cap 176, etapa d* (4 g, 11,72 mmol) en MeOH (120 ml) y se cargó con Pd/C (1,247 g, 1,172 mmol). Se inyectó en la suspensión $N_2$ (3x) y la mezcla de reacción se colocó bajo una presión de 101 kPa de $H_2$ (globo). La mezcla se agitó a temperatura ambiente durante 48 h. La suspensión se filtró entonces a través de un lecho de Celite y se concentró a vacío dando un aceite que corresponde al aminoácido *Cap 176, etapa e* (2,04 g) y que se usó sin purificación posterior. RMN de $^1H$ (400 MHz, *DMSO-d*$_6$) δ ppm 3,62 (3 H, s), 3,20 (1 H, d, *J*=5,77 Hz), 1,91 - 2,09 (2 H, m), 1,50 - 1,88 (7 H, m), 1,20 - 1,45 (2 H, m). RMN de $^{19}F$ (376 MHz, *DMSO-d*$_6$) δ ppm -89,39 (1 F, d, *J*=232,35 Hz), -100,07 (1 F, d, *J*=232,35 Hz). RMN de $^{13}C$ (101 MHz, *DMSO-d*$_6$) δ ppm 175,51 (1 C, s), 124,10 (1 C, t, *J*=241,21, 238,90 Hz), 57,74 (1 C, s), 51,39 (1 C, s), 39,23 (1 C, s ancho), 32,02 - 33,83 (2 C, m), 25,36 (1 C, d, *J*=10,02 Hz), 23,74 (1 C, d, *J*=9,25 Hz). CL (Cond. OL2): $T_R$ = 0,95 min. CL/EM: Análisis calculado para $[2M+H]^+$ $C_{18}H_{31}F_4N_2O_2$: 415,22; encontrado: 415,40.

*Cap 176, etapa f*



Se añadió cloroformiato de metilo (1,495 ml, 19,30 mmol) a una solución de aminoácido *Cap 176, etapa e* (2 g, 9,65 mmol) y DIEA (6,74 ml, 38,6 mmol) en $CH_2Cl_2$ (100 ml). La solución resultante se agitó a ta durante 3 h y se eliminaron los volátiles a presión reducida. El residuo se purificó por Biotage (EtOAc al 0% hasta 20%/Hex; 90 g de columna). Se recuperó un aceite transparente que solidificó en reposo a vacío y que correspondía al carbamato *Cap-176, etapa f* (2,22 g). RMN de $^1$H (500 MHz, $CDCl_3$-*d*) δ ppm 5,27 (1 H, d, *J*=8,55 Hz), 4,39 (1 H, dd, *J*=8,85, 4,88 Hz), 3,77 (3 H, s), 3,70 (3 H, s), 2,07 - 2,20 (2 H, m), 1,84 - 1,96 (1 H, m), 1,64 - 1,82 (4 H, m), 1,39 - 1,51 (2 H, m). RMN de $^{19}$F (471 MHz, $CDCl_3$-*d*) δ ppm -92,55 (1 F, d, *J*=237,13 Hz), -102,93 (1 F, d, *J*=237,12 Hz). RMN de $^{13}$C (126 MHz, $CDCl_3$-*d*) δ ppm 171,97 (1 C, s), 156,69 (1 C, s), 119,77 - 125,59 (1 C, m), 57,24 (1 C, s ancho), 52,48 (1 C, s ancho), 52,43 (1 C, s), 39,15 (1 C, s), 32,50 - 33,48 (2 C, m), 25,30 (1 C, d, *J*=9,60 Hz), 24,03 (1 C, d, *J*=9,60 Hz). CL (Cond. OL1): $T_R$ = 1,49 min. CL/EM: Análisis calculado para $[M+Na]^+$ $C_{11}H_{17}F_2NNaO_4$: 288,10; encontrado: 288,03.

*Cap-176*

Se añadió una solución de LiOH (0,379 g, 15,83 mmol) en agua (25 ml) a una solución de carbamato *Cap-176, etapa f* (2,1 g, 7,92 mmol) en THF (75 ml) y la mezcla resultante se agitó a temperatura ambiente durante 4 h. Se eliminó el THF a vacío y la fase acuosa restante se acidificó con solución de HCl 1N (2 ml) y luego se extrajo con EtOAc (2 X 50 ml). Las fases orgánicas reunidas se secaron ($MgSO_4$), se filtraron y se concentraron dando una espuma que correspondía al *Cap-176* (1,92 g).

RMN de $^1$H (400 MHz, *DMSO-$d_6$*) δ ppm 12,73 (1 H, s), 7,50 (1 H, d, *J*=8,78 Hz), 3,97 (1 H, dd, *J*=8,53, 6,02 Hz), 3,54 (3 H, s), 1,92 - 2,08 (2 H, m), 1,57 - 1,90 (5 H, m), 1,34 - 1,48 (1 H, m), 1,27 (1 H, qd, *J*=12,72, 3,26 Hz). RMN de $^{19}$F (376 MHz, *DMSO-$d_6$*) δ ppm -89,62 (1 F, d, *J*=232,35 Hz), -99,93 (1 F, d, *J*=232,35 Hz). CL (Cond. OL2): $T_R$ = 0,76 min. CL/EM: Análisis calculado para $[M-H]^+$ $C_{10}H_{14}F_2NO_4$: 250,09; encontrado: 250,10.

## ACTIVIDAD BIOLÓGICA

Se utilizó un ensayo VHC Replicon en la presente divulgación, y se preparó, realizó y validó como se describe en la patente de propiedad conjunta PCT/US2006/022197 y en O'Boyle et. al. *Antimicrob Agents Chemother.* Abril de **2005**; 49(4):1346-53. También se usaron procedimientos de ensayo que incorporaban testigos de luciferasa como se ha descrito (Apath.com).

Se usaron células con el replicón VHC-neo y células con replicón que contenían mutaciones en la región NS5A para analizar la familia de compuestos descritos en este documento. Se determinó que los compuestos tenían una actividad de inhibición 10 veces menor en las células que contenían mutaciones que en las células de tipo silvestre. Por lo tanto, los compuestos de la presente divulgación pueden ser eficaces para inhibir la función de la proteína NS5A de VHC y se entiende que son tan eficaces en combinaciones como se ha descrito anteriormente en la solicitud de patente PCT/US2006/022197 y en la patente del solicitante WO/O4014852. Además, los compuestos de la presente divulgación pueden ser eficaces contra el genotipo VHC 1b. Debe entenderse además que los compuestos de la presente divulgación pueden inhibir múltiples genotipos de VHC. La Tabla 2 muestra los valores de $CE_{50}$ (concentración eficaz para una inhibición del

50%) de compuestos representativos de la presente divulgación contra el genotipo VHC 1b. En una realización, los compuestos de la presente divulgación son inhibidores de los genotipos 1a, 1b, 2a, 2b, 3a, 4a, y 5a. Los valores de $CE_{50}$ contra VHC 1b son los siguientes A (10-350 nM); B (1-9,9 nM); C (0,1-0,99 nM); D (0,002-0,099 nM).

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| OL-1 | | B | (1R)-2-((2S)-2-(4-(4-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenoxi) fenil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina |
| OL-2 | 9,1 | B | (1R)-2-((2S)-2-(4-(4-(4-(2-((2S)-1-((2R)-2-hidroxi-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenoxi)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletanol |
| OL-3 | | B | (oxibis(4,1-fenilen-1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil((1R)-2-oxo-1-fenil-2,1-etanodiil)))biscarbamato de dimetilo |
| OL-4 | 0,07 | D | (1R)-2-((2S)-2-(4-(3-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)fenoxi) fenil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina |

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| OL-5 | 80 | A | (1R)-2-((2S)-2-(4-(3-(4-(2-((2S)-1-((2R)-2-hidroxi-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)fenoxi)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletanol |
| OL-6 | | D | ((1R)-2-((2S)-2-(4-(3-(4-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)fenoxi)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo |
| OL-7 | | D | (1R)-2-((2S)-2-(4-(4-((4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)bencil)oxi) fenil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina |
| OL-8 | | D | ((1R)-2-((2S)-2-(4-(4-((4-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)bencil)oxi)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo |

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| OL-9 | | D | (1R)-2-((2S)-2-(4-(4-(2-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)etil) fenil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina |
| OL-10 | | D | (1R,1'R)-2,2'-(1,2-etanodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil))bis(2-oxo-1-feniletanol) |
| OL-11 | | D | (1,2-etanodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil ((1R)-2-oxo-1-fenil-2,1-etanodiil))) biscarbamato de dimetilo |
| OL-12 | | D | N',N'''-(1,2-etanodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil ((1R)-2-oxo-1-fenil-2,1-etanodiil)))bis(1-etilurea) |
| OL-13 | | D | 1-ciclopentil-3-((1R)-2-((2S)-2-(4-(4-(2-(4-(2-((2S)-1-((2R)-2-((ciclopentilcarbamoil) amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)etil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)urea |

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| OL-14 | | C | (1R)-2-((2S)-2-(4-(4-(((4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)bencil)oxi) metil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina |
| OL-15 | 1,1 | B | (1R)-2-((2S)-2-(4-(4-(((4-(2-((2S)-1-((2R)-2-hidroxi-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)bencil)oxi)metil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletanol |
| OL-16 | | D | (oxibis(metilen-4,1-fenilen-1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil ((1R)-2-oxo-1-fenil-2,1-etanodiil))) biscarbamato de dimetilo |
| OL-17 | | D | 1-metil-3-((1R)-2-((2S)-2-(4-(4-(((4-(2-((2S)-1-((2R)-2-((metilcarbamoil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)bencil)oxi)metil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)urea |

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| OL-18 | | D | 1-etil-3-((1R)-2-((2S)-2-(4-(4-(((4-(2-((2S)-1-((2R)-2-((etilcarbamoil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)bencil)oxi)metil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)urea |
| OL-19 | | B | 1-ciclopentil-3-((1R)-2-((2S)-2-(4-(4-(((4-(2-((2S)-1-((2R)-2-((ciclopentilcarbamoil) amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)bencil)oxi)metil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)urea |
| OL-20 | | C | (1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)bencil)oxi) metil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina |
| OL-21 | | C | (1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-hidroxi-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)bencil)oxi)metil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletanol |

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| OL-22 | | D | (((1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)bencil)oxi)metil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo |
| OL-23 | | C | 1-metil-3-((1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-((metilcarbamoil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)bencil)oxi)metil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)urea |
| OL-24 | | D | 1-etil-3-((1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-((etilcarbamoil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)bencil)oxi)metil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)urea |
| OL-25 | | D | 1-ciclopentil-3-((1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-((ciclopentilcarbamoil) amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)bencil)oxi)metil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)urea |

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| D-1 | | D | (1,1':4',1''-terfenil-4,4''-diilbis(1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil ((1R)-2-oxo-1-fenil-2,1-etanodiil))) biscarbamato de dimetilo |
| D-2 | | C | (1R)-2-((2S)-2-(4-(4''-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-1,1':4',1''-terfenil-4-il)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina |
| D-3 | 0,006 | D | ((1S)-1-(((2S)-2-(4-(4-((2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-4,5-dihidro-1H-nafto[1,2-d]imidazol-7-il)etinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo |
| D-4 | | D | ((1R)-2-((2S)-2-(4-(4-((2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-4,5-dihidro-1H-nafto[1,2-d]imidazol-7-il)etinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo |

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| D-5 | | D | ((1R)-2-((2S)-2-(7-((4-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)-1H-nafto[1,2-d]imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo |
| D-6 | | D | ((1S)-1-(((2S)-2-(4-(4-((2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-nafto[1,2-d]imidazol-7-il)etinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo |
| D-7 | | D | ((1S)-1-(((1R,3S,5R)-3-(4-(4-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-nafto[1,2-d]imidazol-7-il)etinil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo |

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| D-8 | 0,005 | D | ((1R)-2-((1R,3S,5R)-3-(7-((4-(2-((1R,3S,5R)-2-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)etinil)-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-feniletil)carbamato de metilo |
| D-9 | | D | ((1S)-1-(((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-4,5-dihidro-1H-nafto[1,2-d]imidazol-7-il)etinil)-4,5-dihidro-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo |
| D-10 | | D | ((1S)-1-(((1R,3S,5R)-3-(7-((2-((3S)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-nafto[1,2-d]imidazol-7-il)etinil)-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo |

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| D-11 | | D | ((1S)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-nafto[1,2-d]imidazol-7-il)etinil)-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo |
| M1 | | D | ((1S)-1-(((2S)-2-(4-(4-((4-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil) carbamato de metilo |
| M2 | 0,24 | C | (1,2-etinodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil ((1R)-2-oxo-1-fenil-2,1-etanodiil))) biscarbamato de dimetilo |
| M2.1 | | D | (1,2-etinodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo |

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| M3 | | D | ((1S)-1-(((1R,3S,5R)-3-(4-(4-((4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil) amino)-3-metilbutanoil)-2-azabiciclo[3.1.0] hex-3-il)-1H-imidazol-4-il)fenil)etinil) fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0] hex-2-il)carbonil)-2-metilpropil)carbamato de metilo |
| M4 | | D | (1,2-etinodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo [3.1.0]hexano-3,2-diil((2S)-1-oxo-1,2-butanodiil)))biscarbamato de dimetilo |
| M5 | | C | (1,2-etinodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo [3.1.0]hexano-3,2-diil((1S)-1-ciclobutil-2-oxo-2,1-etanodiil)))biscarbamato de dimetilo |
| M6 | 0,0033 | D | (1,2-etinodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo [3.1.0]hexano-3,2-diil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo |

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| M7 | | D | ((1S)-1-(((1R,3S,5R)-3-(4-(4-((4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo |
| M8 | | D | ((1S)-1-(((1R,3S,5R)-3-(4-cloro-5-(4-((4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo |
| M9 | | D | ((1S)-1-(((1R,3S,5R)-3-(4-cloro-5-(4-((4-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)fenil)etinil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo |

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| M9.1 | | D | ((1S)-2-((1R,3S,5R)-3-(4-(4-((4-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)fenil)etinil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo |
| M9.2 | | D | (1,2-etinodiilbis(4,1-fenileno(4-cloro-1H-imidazol-5,2-diil)(1R,3S,5R)-2-azabiciclo[3.1.0]hexano-3,2-diil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo |
| M9.3 | | D | ((1S)-1-(((1R,3S,5R)-3-(4-(4-((1S,2S)-2-(4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)ciclopropil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo |

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| M9.4 | | D | ((1S,2S)-1,2-ciclopropanodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0]hexano-3,2-diil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo |
| M9.5 | | D | ((1S)-1-(((1R,3S,5R)-3-(4-(4-((1R,2R)-2-(4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)ciclopropil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo |
| M9.6 | | D | ((1R,2R)-1,2-ciclopropanodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0]hexano-3,2-diil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo |
| M9.7 | | D | ((1S)-1-(((2S,4S)-2-(4-(4-((1S,2S)-2-(4-(2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)fenil)ciclopropil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo |

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| M9.8 | | D | ((1S,2S)-1,2-ciclopropanodiilbis(4,1-fenilen-1H-imidazol-4,2-diil((2S,4S)-4-metil-2,1-pirrolidinadiil)((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo |
| M10 | | D | ((1S)-1-(((2S,5S)-2-(4-(4-((4-(2-((2S,5S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil) carbonil)-2-metilpropil)carbamato de metilo |
| M11 | | D | (1,2-etinodiilbis(4,1-fenilen-1H-imidazol-4,2-diil((2S,5S)-5-metil-2,1-pirrolidinadiil)((2S)-1-oxo-1,2-butanodiil))) biscarbamato de dimetilo |
| M12 | | D | (1,2-etinodiilbis(4,1-fenilen-1H-imidazol-4,2-diil((2S,5S)-5-metil-2,1-pirrolidinadiil)((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo |

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| M12.1 | | D | ((1S)-1-(((2S,5S)-2-(4-(4-((4-(2-((2S,5S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo |
| M12.2 | | D | ((1S)-1-(((2S,4S)-2-(4-(4-((4-(2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo |
| M12.3 | 0,014 | D | (1,2-etinodiilbis(4,1-fenilen-1H-imidazol-4,2-diil((2S,4S)-4-metil-2,1-pirrolidinadiil)((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo |
| M12.4 | | D | ((1S)-1-(((2S,4S)-2-(4-(4-((4-(4-cloro-2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-5-il)fenil)etinil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo |

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| M12.5 | | D | ((1S)-1-(((2S,4S)-2-(4-cloro-5-(4-((4-(4-cloro-2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-5-il)fenil)etinil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo |
| M12.6 | | D | ((1S)-2-((2S,4S)-2-(4-(4-((4-(4-cloro-2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-4-metil-2-pirrolidinil)-1H-imidazol-5-il)fenil)etinil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo |
| M12.7 | 0,061 | D | (1,2-etinodiilbis(4,1-fenilen(4-cloro-1H-imidazol-5,2-diil)((2S,4S)-4-metil-2,1-pirrolidinadiil)((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo |

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| M12.8 | | D | ((1S)-2-((2S,4S)-2-(4-(4-((4-(2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo |
| M12.9 | | D | ((1S)-1-(((1S,3S,5S)-3-(4-(4-((4-(2-((1S,3S,5S)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-5-metil-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo |
| M13 | | D | ((1S)-1-(((1R,3S,5R)-3-(4-(4-((E)-2-(4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil) amino)-3-metilbutanoil)-2-azabiciclo[3.1.0] hex-3-il)-1H-imidazol-4-il)fenil)vinil) fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0] hex-2-il)carbonil)-2-metilpropil)carbamato de metilo |

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| M14 | 0,017 | D | ((E)-1,2-etenodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo [3.1.0]hexano-3,2-diil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil))) biscarbamato de dimetilo |
| M15 | | D | ((1S)-2-((1R,3S,5R)-3-(4-(4-((E)-2-(4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil) amino)-3-metilbutanoil)-2-azabiciclo[3.1.0] hex-3-il)-1H-imidazol-4-il)fenil)vinil) fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0] hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo |
| N1 | | D | ((1S)-1-(((2S)-2-(4-(4-((4-(2-((2S)-4,4-difluoro-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-4,4-difluoro-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo |
| N2 | | D | (etino-1,2-diilbis(4,1-fenilen-1H-imidazol-5,2-diil((2S)-4,4-difluoropirrolidin-2,1-diil)((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)etano-2,1-diil)))biscarbamato de dimetilo |

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| N3 | 0,25 | A | ((1R)-2-((2S)-2-(5-(4-((4-(2-((2S)-4,4-difluoro-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)pirrolidin-2-il)-1H-imidazol-5-il)fenil)etinil)fenil)-1H-imidazol-2-il)-4,4-difluoropirrolidin-1-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo |
| N4 | 0,18 | A | (etino-1,2-diilbis(4,1-fenilen-1H-imidazol-5,2-diil((2S)-4,4-difluoropirrolidin-2,1-diil)((1R)-2-oxo-1-(tetrahidro-2H-piran-4-il)etano-2,1-diil)))biscarbamato de dimetilo |
| N5 | | D | ((1S)-1-(((3S)-3-(4-(4-((4-(2-((3S)-4-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-3-morfolinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-4-morfolinil)carbonil)-2-metilpropil)carbamato de metilo |
| N6 | | A | ((1S)-1-(((2S)-2-(4-(4-((4-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-piperidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-1-piperidinil)carbonil)-2-metilpropil)carbamato de metilo |

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| N7 | | D | ((1S)-1-(((2S,4S)-4-hidroxi-2-(4-(4-((4-(2-((2S,4S)-4-hidroxi-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo |
| N7.1 | | | ((1S)-1-(((2S)-2-(4-(4-((4-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metilen-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-4-metilen-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo |
| N7.2 | | | ((1S)-1-(((2S,4R)-4-hidroxi-2-(4-(4-((4-(2-((2S,4R)-4-hidroxi-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo |

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| N8 | | A | ((1S)-1-(((1S,3S,5S)-3-(4-(4-((4-(2-((1S,3S,5S)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo |
| N9 | | D | (1,2-etinodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(1S,3S,5S)-2-azabiciclo[3.1.0]hexano-3,2-diil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo |
| J1 | | D | ((1S)-1-(((2S)-2-(4-(3-((3-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo |
| J1.1 | 338,8 | A | ((1S)-2-metil-1-(((2S)-2-(4-(3-((3-(2-((2S)-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo |

| Compuesto N.º | CE50 de 1b (nM) | Intervalo | Nombre |
|---|---|---|---|
| J2 | 0,12 | C | (1,2-etinodiilbis(3,1-fenilen-1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo |
| J3 | | D | ((1S)-1-(((1R,3S,5R)-3-(4-(3-((3-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo |
| J4 | | D | (1,2-etinodiilbis(3,1-fenilen-1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0]hexano-3,2-diil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo |
| J5 | | D | ((1S)-1-(((2S)-2-(4-(4'-((4-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo |

Los compuestos de la presente divulgación pueden inhibir VHC mediante

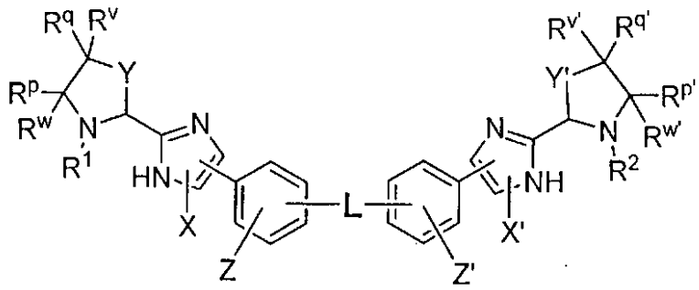
mecanismos además o distintos de la inhibición de NS5A. En una realización, los compuestos de la presente divulgación inhiben el replicón de VHC y en otra realización los compuestos de la presente divulgación inhiben NS5A.

Será evidente para un experto en la técnica que la presente divulgación no se limita a los anteriores ejemplos ilustrativos, y que puede realizarse en otras formas específicas sin separarse de sus atributos esenciales. Por lo tanto se desea que los ejemplos sean considerados en todos los respectos ilustrativos y no restrictivos, haciendo referencia a las reivindicaciones anexas, en lugar de a los ejemplos anteriores y, por lo tanto, se pretende que todos los cambios que entren dentro del significado y del alcance de equivalencia de las reivindicaciones estén incluidos en ellas.

Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes

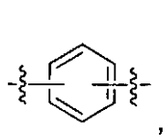
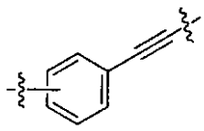
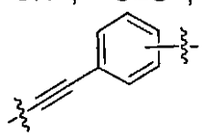
## REIVINDICACIONES

1. Un compuesto de la Fórmula (I):



(I),

o una sal farmacéuticamente aceptable del mismo, en la que:

L se selecciona a partir de –O–, $-CH_2CH_2-$, –CH=CH–, –C≡C–, $-OCH_2-$, $-CH_2O-$, $-CH_2OCH_2-$,  ,  ,  , y  ;

X es hidrógeno (H) o halógeno y Z es hidrógeno; o

X y Z, junto con los átomos de carbono a los que están unidos, forman un anillo condensado aromático o no aromático de cinco a ocho miembros que opcionalmente contiene uno o dos heteroátomos que se seleccionan independientemente a partir de nitrógeno, oxígeno, y azufre; en la que el anillo de cinco a ocho miembros está opcionalmente sustituido con uno, dos, o tres sustituyentes que se seleccionan independientemente a partir de alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, alquilsulfonilo, arilo, arilalquilo, arilsulfonilo, carboxi, formilo, halo, haloalcoxi, haloalquilo, hidroxi,

hidroxialquilo, $-NR^aR^b$, $(NR^aR^b)$alquilo, $(NR^aR^b)$carbonilo, oxo, y espirociclo;

X' es hidrógeno (H) o halógeno y Z' es hidrógeno; o

X' y Z', junto con los átomos de carbono a los que están unidos, forman un anillo condensado aromático o no aromático de cinco a ocho miembros que opcionalmente contiene uno o dos heteroátomos que se seleccionan independientemente a partir de nitrógeno, oxígeno, y azufre; en los que el anillo de cinco a ocho miembros está opcionalmente sustituido con uno, dos, o tres sustituyentes que se seleccionan independientemente a partir de alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, alquilsulfonilo, arilo, arilalquilo, arilsulfonilo, carboxi, formilo, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialquilo, $-NR^aR^b$, $(NR^aR^b)$alquilo, $(NR^aR^b)$carbonilo, oxo, y espirociclo;

Y y Y' son cada uno independientemente $-CH_2-$, $-CH_2CH_2-$, o $-CH_2O-$, en los que el $-CH_2O-$ se dibuja de tal forma que el átomo de oxígeno esté unido al átomo de carbono sustituido con $R^v$ y $R^q$ o $R^{v'}$ y $R^{q'}$;

$R^p$ es hidrógeno o alquilo $C_1$ a $C_4$;

$R^q$ es hidrógeno, alquilo, o halo; o

$R^p$ y $R^q$, junto con los átomos de carbono a los que están unidos, forman un anillo cicloalquilo;

$R^v$ se selecciona a partir de hidrógeno, alquilo, halo, e hidroxi; o

$R^v$ y $R^q$, junto con el átomo de carbono al que están unidos, forman un grupo etilenilo o un anillo cicloalquilo;

$R^{p'}$ es hidrógeno o alquilo $C_1$ a $C_4$;

$R^{q'}$ es hidrógeno, alquilo, o halo; o

$R^{p'}$ y $R^{q'}$, junto con los átomos de carbono a los que están unidos, forman un anillo cicloalquilo;

$R^{v'}$ se seleccionan independientemente a partir de hidrógeno, alquilo, halo, e hidroxi; o

$R^{v'}$ y $R^{q'}$, junto con el átomo de carbono al que están unidos, forman un grupo etilenilo o un anillo cicloalquilo;

$R^{w}$ y $R^{w'}$ se seleccionan independientemente a partir de hidrógeno y alquilo;

$R^1$ es hidrógeno o $-C(O)R^x$;

$R^2$ es hidrógeno o $-C(O)R^y$;

$R^x$ y $R^y$ se seleccionan independientemente a partir de cicloalquilo, heteroarilo, heterociclilo, alcoxi, y alquilo, estando dicho alquilo sustituido por uno o más sustituyentes que se seleccionan independientemente a partir de arilo, alquenilo, cicloalquilo, heterociclilo, heteroarilo, $-OR^3$, $-C(O)OR^4$, $-NR^aR^b$, y $-C(O)NR^cR^d$,

en los que cualquiera de dichos arilo y heteroarilo puede estar opcionalmente sustituido con uno o más sustituyentes que se seleccionan independientemente a partir de alquenilo, alquilo, haloalquilo, arilalquilo, heterociclilo, heterociclilalquilo, halógeno, ciano, nitro, $-C(O)OR^4$, $-OR^5$, $-NR^aR^b$, $(NR^aR^b)$alquilo, y (MeO)(HO)P(O)O-, y

en los que cualquiera de dichos cicloalquilo y heterociclilo puede opcionalmente estar condensado a un anillo aromático y puede estar opcionalmente sustituido con uno o más sustituyentes que se seleccionan independientemente a partir de alquilo, hidroxilo, halógeno, arilo, $-NR^aR^b$, oxo, y $-C(O)OR^4$;

$R^3$ es hidrógeno, alquilo, o arilalquilo;

$R^4$ es alquilo o arilalquilo;

$R^5$ es hidrógeno, alquilo, o arilalquilo;

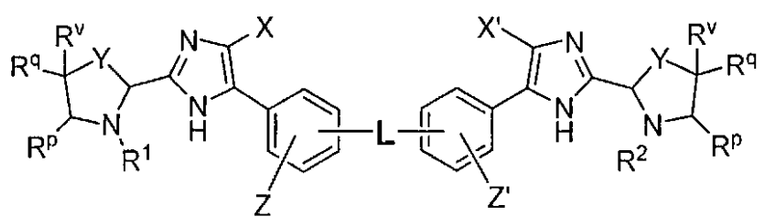
$R^a$ y $R^b$ se seleccionan independientemente a partir de hidrógeno, alquilo, cicloalquilo, arilalquilo, heteroarilo, $-C(O)R^6$, $-C(O)OR^7$, $-C(O)NR^cR^d$, y $(NR^cR^d)$alquilo, o de forma alternativa, $R^a$ y $R^b$, junto con el átomo de nitrógeno al que están unidos, forman un anillo de cinco o seis miembros o estructura anular bicíclica con puente, en la que dicho anillo de cinco o seis miembros o estructura anular bicíclica con puente opcionalmente pueden contener uno o dos heteroátomos adicionales que se seleccionan independientemente a partir de nitrógeno, oxígeno, y azufre y pueden contener uno, dos, o tres sustituyentes que se seleccionan independientemente a partir de alquilo $C_1$ a $C_6$, haloalquilo $C_1$ a $C_4$, arilo, hidroxilo, alcoxi $C_1$ a $C_6$, haloalcoxi $C_1$ a $C_4$, y halógeno;

$R^6$ es alquilo;

$R^7$ es alquilo, arilalquilo, cicloalquilo, o haloalquilo; y

$R^c$ y $R^d$ se seleccionan independientemente a partir de hidrógeno, alquilo, arilalquilo, y cicloalquilo.

2. El compuesto de la reivindicación 1, caracterizado además por la Fórmula (Ia):



(Ia),

o una sal o un tautómero farmacéuticamente aceptable del mismo, en la que:

X es hidrógeno o cloro (Cl) y Z es hidrógeno; o

X y Z, junto con los átomos de carbono a los que están unidos, forman un anillo condensado aromático o no aromático de seis miembros;

X' es hidrógeno o cloro (Cl) y Z' es hidrógeno; o

X' y Z', junto con los átomos de carbono a los que están unidos, forman un anillo condensado aromático o no aromático de seis miembros;

Y es $-CH_2-$, $-CH_2CH_2-$, o $-CH_2O-$, en los que el $-CH_2O-$ se dibuja de tal forma que el átomo de oxígeno esté unido al átomo de carbono sustituido con $R^v$ y $R^q$;

$R^p$ es hidrógeno o alquilo $C_1$ a $C_4$;

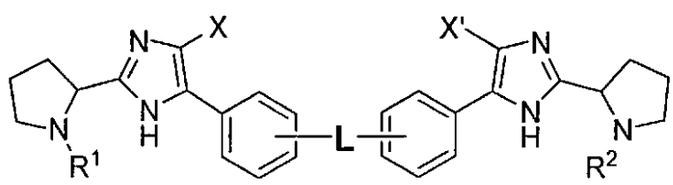
$R^q$ es hidrógeno, alquilo, o haloalquilo; o

$R^p$ y $R^q$, junto con los átomos de carbono a los que están unidos, forman un anillo cicloalquilo; y

$R^v$ se selecciona a partir de hidrógeno, alquilo, halo, e hidroxi; o

$R^v$ y $R^q$, junto con el átomo de carbono al que están unidos, forman un grupo etilenilo o un anillo cicloalquilo.

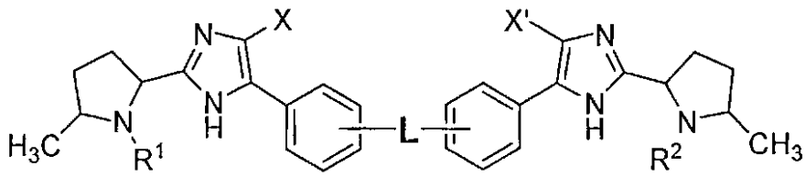
3. El compuesto de la reivindicación 2 caracterizado además por la Fórmula (Ib):




(Ib),

o una sal o un tautómero farmacéuticamente aceptable del mismo.

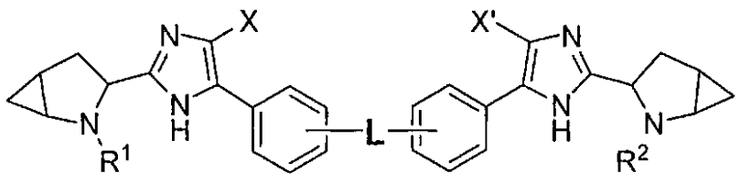
4. El compuesto de la reivindicación 2, caracterizado además por la Fórmula (Ic):



(Ic),

o una sal o un tautómero farmacéuticamente aceptable del mismo.

5. El compuesto de la reivindicación 2, caracterizado además por la Fórmula (Id):



(Id),

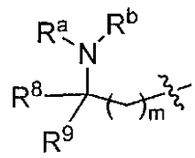
o una sal o un tautómero farmacéuticamente aceptable del mismo.

6. El compuesto de la reivindicación 2, o una sal o un tautómero farmacéuticamente aceptable del mismo, en el que:

$R^1$ es $-C(O)R^x$;

$R^2$ es $-C(O)R^y$;

$R^x$ y $R^y$ son independientemente alquilo sustituido por al menos un $-NR^aR^b$, caracterizado por la Fórmula (A):



(A),

en la que:

m es 0 ó 1;

$R^8$ es hidrógeno o alquilo;

$R^9$ se selecciona a partir de hidrógeno, cicloalquilo, arilo, heteroarilo, heterociclilo, y alquilo opcionalmente sustituido con un sustituyente que se selecciona a partir de arilo, alquenilo, cicloalquilo, heterociclilo, heteroarilo, heterobiciclilo, $-OR^3$, $-C(O)OR^4$, $-NR^aR^b$, y $-C(O)NR^cR^d$,

en el que cualquiera de dichos arilo y heteroarilo puede estar opcionalmente sustituido con uno o más sustituyentes que se seleccionan independientemente a partir de alquilo, haloalquilo, arilalquilo, heterociclilo, heterociclilalquilo, halógeno, ciano, nitro, $-C(O)OR^4$, $-OR^5$, $-NR^aR^b$, $(NR^aR^b)$alquilo, y (MeO)(HO)P(O)O-, y

en el que cualquiera de dichos cicloalquilo y heterociclilo puede opcionalmente estar condensado a un anillo aromático y puede estar opcionalmente sustituido con uno o más sustituyentes que se seleccionan independientemente a partir de alquilo, hidroxilo, halógeno, arilo, $-NR^aR^b$, oxo, y $-C(O)OR^4$; y

$R^3$, $R^4$, $R^5$, $R^a$, $R^b$, $R^c$, y $R^d$ se definen como en la reivindicación 1.

7. El compuesto de la reivindicación 6, o una sal o un tautómero farmacéuticamente aceptable del mismo, en el que:

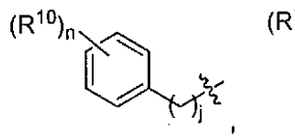
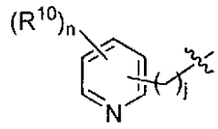
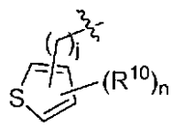
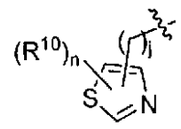
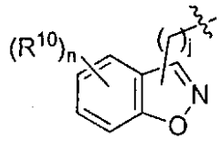
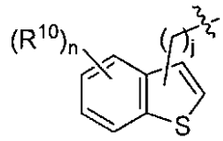
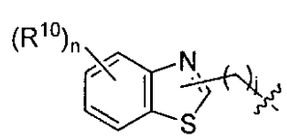
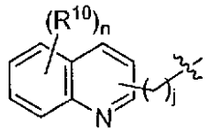
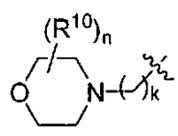
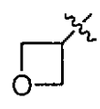
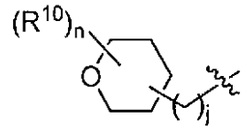
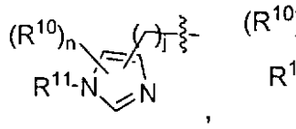
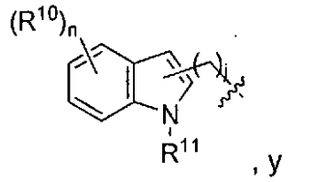
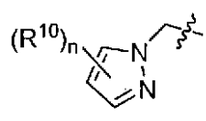
m es 0;

$R^8$ es hidrógeno o alquilo $C_1$ a $C_4$;

$R^9$ se selecciona a partir de hidrógeno, alquilo $C_1$ a $C_6$ opcionalmente

sustituido con

$-OR^{12}$, cicloalquilo $C_3$ a $C_6$, alilo, $-CH_2C(O)NR^cR^d$, $(NR^cR^d)$alquilo,

en las que j es 0 ó 1;

k es 1, 2 ó 3;

n es 0 o un número entero que se selecciona desde 1 hasta 4;

cada $R^{10}$ es independientemente hidrógeno, alquilo $C_1$ a $C_4$, haloalquilo $C_1$ a $C_4$, halógeno, nitro, -OBn, o (MeO)(OH)P(O)O-;

$R^{11}$ es hidrógeno, alquilo $C_1$ a $C_4$, o bencilo;

$R^{12}$ es hidrógeno, alquilo $C_1$ a $C_4$, o bencilo;

$R^a$ es hidrógeno o alquilo $C_1$ a $C_4$;

$R^b$ es alquilo $C_1$ a $C_4$, cicloalquilo $C_3$ a $C_6$, bencilo, 3-piridilo, pirimidin-5-ilo, acetilo, $-C(O)OR^7$, o $-C(O)NR^cR^d$;

$R^7$ es alquilo $C_1$ a $C_4$ o haloalquilo $C_1$ a $C_4$;

$R^c$ es hidrógeno o alquilo $C_1$ a $C_4$; y

$R^d$ es hidrógeno, alquilo $C_1$ a $C_4$, o cicloalquilo $C_3$ a $C_6$.

8. El compuesto de la reivindicación 6, o una sal o un tautómero farmacéuticamente aceptable del mismo, en el que:

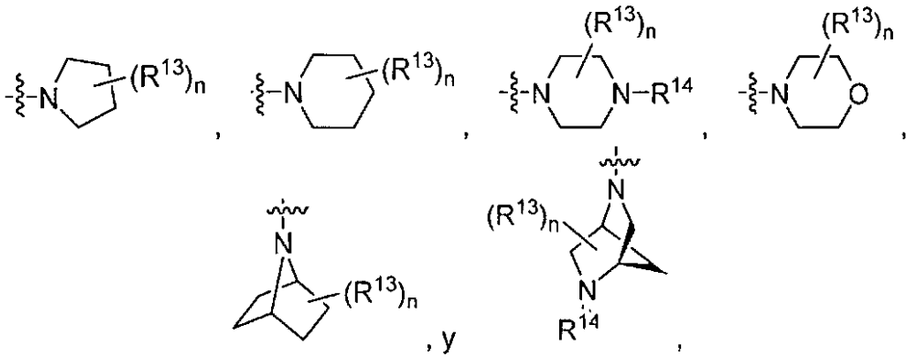
m es 0;

$R^8$ es hidrógeno;

$R^9$ es fenilo opcionalmente sustituido con de uno hasta cinco sustituyentes que se seleccionan independientemente a partir de alquilo $C_1$ a $C_6$, haloalquilo $C_1$ a $C_4$, halógeno,

alcoxi $C_1$ a $C_6$, hidroxilo, ciano, y nitro; y

$NR^aR^b$ es un grupo heterociclilo o heterobiciclilo que se selecciona a partir de:



en las que n es 0, 1 ó 2;

cada $R^{13}$ se selecciona independientemente a partir de alquilo $C_1$ a $C_6$, fenilo, trifluorometilo, halógeno, hidroxilo, metoxi, y oxo; y

$R^{14}$ es alquilo $C_1$ a $C_6$, fenilo, bencilo, o un grupo $-C(O)OR^{15}$, en el que $R^{15}$ es alquilo $C_1$ a $C_4$, fenilo, o bencilo.

9. El compuesto de la reivindicación 6, o una sal o un tautómero farmacéuticamente aceptable del mismo, en el que:

m es 1;

$R^8$ es hidrógeno;

$R^9$ es alquilo $C_1$ a $C_6$, arilalquilo, o heteroarilalquilo;

$R^a$ es hidrógeno; y

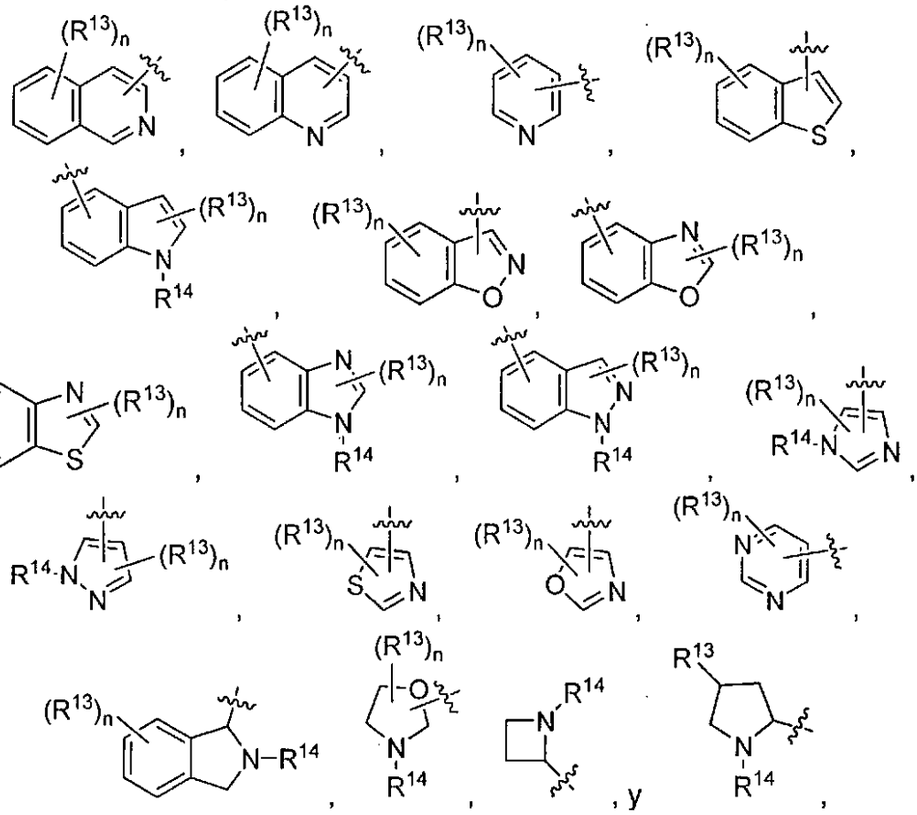
$R^b$ es $-C(O)OR^7$, en el que $R^7$ es alquilo $C_1$ a $C_6$.

10. El compuesto de la reivindicación 2, o una sal o un tautómero farmacéuticamente aceptable del mismo, en el que:

$R^1$ es $-C(O)R^x$;

$R^2$ es $-C(O)R^y$;

$R^x$ y $R^y$ son heteroarilo o heterociclilo que se selecciona independientemente a partir de:



en las que n es 0 o un número entero que se selecciona desde 1 hasta

4;

cada $R^{13}$ se selecciona independientemente a partir de hidrógeno, alquilo $C_1$ a $C_6$, haloalquilo $C_1$ a $C_4$, fenilo, bencilo, alcoxi $C_1$ a $C_6$, haloalcoxi $C_1$ a $C_4$, heterociclilo, halógeno, $NR^cR^d$, hidroxilo, ciano, y oxo, en el que $R^c$ y $R^d$ son independientemente hidrógeno o alquilo $C_1$ a $C_4$; y

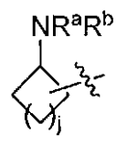
$R^{14}$ es hidrógeno (H), alquilo $C_1$ a $C_6$, bencilo, o $-C(O)OR^4$, en el que $R^4$ es alquilo $C_1$ a $C_6$.

11. El compuesto de la reivindicación 2, o una sal o un tautómero farmacéuticamente aceptable del mismo, en el que:

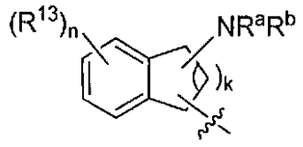
$R^1$ es $-C(O)R^x$;

$R^2$ es $-C(O)R^y$;

$R^x$ y $R^y$ son cicloalquilo que se selecciona independientemente a partir de:




y




,

en las que

j es 0, 1, 2 ó 3;

k es 0, 1 ó 2;

n es 0 o un número entero que se selecciona desde 1 hasta 4;

cada $R^{13}$ se selecciona independientemente a partir de hidrógeno, alquilo $C_1$ a $C_6$, haloalquilo $C_1$ a $C_4$, alcoxi $C_1$ a $C_6$, halógeno, hidroxilo, ciano, y nitro; y

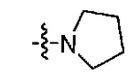
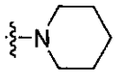
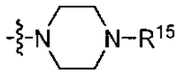
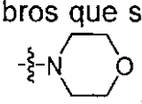
$R^a$ y $R^b$ son cada uno independientemente hidrógeno, alquilo $C_1$ a $C_6$, o $-C(O)OR^7$, en el que $R^7$ es alquilo $C_1$ a $C_6$.

12. El compuesto de la reivindicación 2, o una sal o un tautómero farmacéuticamente aceptable del mismo, en el que:

$R^1$ es $-C(O)R^x$;

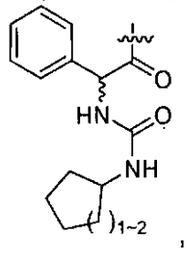
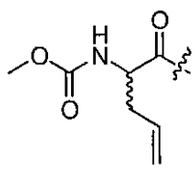
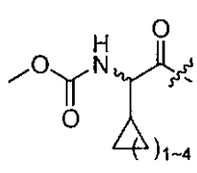
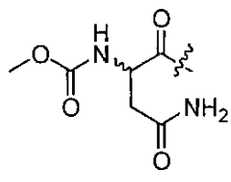
$R^2$ es $-C(O)R^y$;

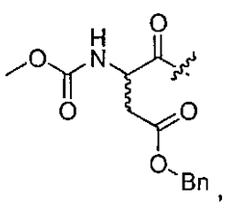
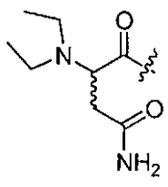
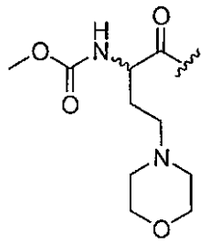
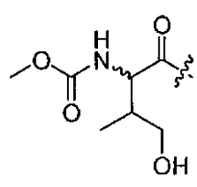
$R^x$ y $R^y$ son independientemente arilalquilo, en los que la parte arilo de dicho arilalquilo puede estar opcionalmente sustituida con $(NR^aR^b)$alquilo; y

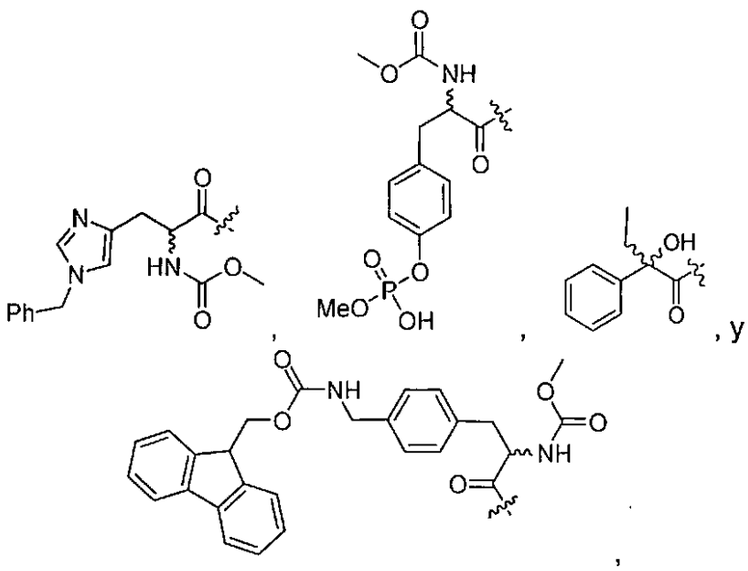
$R^a$ y $R^b$ son independientemente hidrógeno, alquilo $C_1$ a $C_6$, o bencilo, o de forma alternativa, $R^a$ y $R^b$, junto con el átomo de nitrógeno al que están unidos, forman un anillo de cinco o seis miembros que se selecciona a partir de  ,  ,  , y  , en la que $R^{15}$ es hidrógeno, alquilo $C_1$ a $C_6$, o bencilo.

13. El compuesto de la reivindicación 2, o una sal o un tautómero farmacéuticamente aceptable del mismo, en el que:

$R^1$ y $R^2$ son iguales y se seleccionan a partir del grupo constituido por:

 ,  ,  ,  ,

 ,  ,  ,  ,



en las que un enlace ondulado (〰) en la estructura indica que un centro estereógeno al que está unido el enlace puede tomar la configuración (R)- o (S)- siempre que no se incumplan los principios del enlace químico.

14. El compuesto de la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en el que:

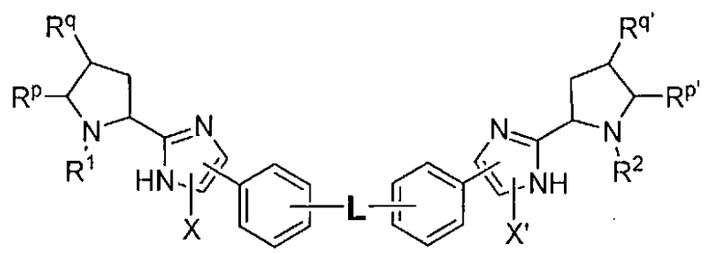
$R^1$ es $-C(O)R^x$;

$R^2$ es $-C(O)R^y$; y

$R^x$ y $R^y$ son ambos t-butoxi.

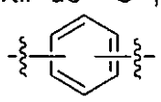
15. El compuesto de la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en el que $R^1$ y $R^2$ son ambos hidrógeno.

16. Un compuesto de la Fórmula (II):



(I),

o una sal farmacéuticamente aceptable del mismo, en la que:

L se selecciona a partir de –O–, $–CH_2CH_2–$, –CH=CH–, –C≡C–, $–OCH_2–$, $-CH_2O–$, $-CH_2OCH_2–$,  , y  ;

X y X' son independientemente hidrógeno (H) o halógeno;

$R^p$ es hidrógeno o alquilo $C_1$ a $C_4$, y $R^q$ es hidrógeno, o de forma alternativa, $R^p$ y $R^q$, junto con los átomos de carbono a los que están unidos, forman un anillo ciclopropilo;

$R^{p'}$ es hidrógeno o alquilo $C_1$ a $C_4$, y $R^{q'}$ es hidrógeno, o de forma alternativa, $R^{p'}$ y $R^{q'}$, junto con los átomos de carbono a los que están unidos, forman un anillo ciclopropilo;

$R^1$ es hidrógeno o $–C(O)R^x$;

$R^2$ es hidrógeno o $–C(O)R^y$;

$R^x$ y $R^y$ se seleccionan independientemente a partir de cicloalquilo, heteroarilo, heterociclilo, alcoxi, y alquilo, estando dicho alquilo sustituido por uno o más sustituyentes que se seleccionan independientemente a partir de arilo, alquenilo, cicloalquilo, heterociclilo, heteroarilo, $-OR^3$, $-C(O)OR^4$, $-NR^aR^b$, y $-C(O)NR^cR^d$,

en los que cualquiera de dichos arilo y heteroarilo puede estar opcionalmente sustituido con uno o más sustituyentes que se seleccionan

independientemente a partir de alquilo, haloalquilo, arilalquilo, heterociclilo, heterociclilalquilo, halógeno, ciano, nitro, $-C(O)OR^4$, $-OR^5$, $-NR^aR^b$, $(NR^aR^b)$alquilo, y (MeO)(HO)P(O)O-, y

en los que cualquiera de dichos cicloalquilo y heterociclilo puede opcionalmente estar condensado a un anillo aromático y puede estar opcionalmente sustituido con uno o más sustituyentes que se seleccionan independientemente a partir de alquilo, hidroxilo, halógeno, arilo, $-NR^aR^b$, oxo, y $-C(O)OR^4$;

$R^3$ es hidrógeno, alquilo, o arilalquilo;

$R^4$ es alquilo o arilalquilo;

$R^5$ es hidrógeno, alquilo, o arilalquilo;

$R^a$ y $R^b$ se seleccionan independientemente a partir de hidrógeno, alquilo, cicloalquilo, arilalquilo, heteroarilo, $-C(O)R^6$, $-C(O)OR^7$, $-C(O)NR^cR^d$, y $(NR^cR^d)$alquilo, o de forma alternativa, $R^a$ y $R^b$, junto con el átomo de nitrógeno al que están unidos, forman un anillo de cinco o seis miembros o estructura anular bicíclica con puente, en la que dicho anillo de cinco o seis miembros o estructura anular bicíclica con puente opcionalmente pueden contener uno o dos heteroátomos adicionales que se seleccionan independientemente a partir de nitrógeno, oxígeno, y azufre y pueden contener uno, dos, o tres sustituyentes que se seleccionan independientemente a partir de alquilo $C_1$ a $C_6$, haloalquilo $C_1$ a $C_4$, arilo, hidroxilo, alcoxi $C_1$ a $C_6$, haloalcoxi $C_1$ a $C_4$, y halógeno;

$R^6$ es alquilo;

$R^7$ es alquilo, arilalquilo, o haloalquilo; y

$R^c$ y $R^d$ se seleccionan independientemente a partir de hidrógeno, alquilo,

arilalquilo, y cicloalquilo.

17. Un compuesto, o una sal farmacéuticamente aceptable del mismo, que se selecciona a partir del grupo constituido por:

(1R)-2-((2S)-2-(4-(4-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenoxi) fenil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina;

(1R)-2-((2S)-2-(4-(4-(4-(2-((2S)-1-((2R)-2-hidroxi-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenoxi)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletanol;

(oxibis(4,1-fenilen-1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil((1R)-2-oxo-1-fenil-2,1-etanodiil)))biscarbamato de dimetilo;

(1R)-2-((2S)-2-(4-(3-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)fenoxi) fenil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina;

(1R)-2-((2S)-2-(4-(3-(4-(2-((2S)-1-((2R)-2-hidroxi-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)fenoxi)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletanol;

((1R)-2-((2S)-2-(4-(3-(4-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)fenoxi)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo;

(1R)-2-((2S)-2-(4-(4-((4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)bencil)oxi) fenil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina;

((1R)-2-((2S)-2-(4-(4-((4-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)bencil)oxi)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo;

(1R)-2-((2S)-2-(4-(4-(2-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)etil) fenil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina;

(1R,1'R)-2,2'-(1,2-etanodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil))bis(2-oxo-1-feniletanol);

(1,2-etanodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil ((1R)-2-oxo-1-fenil-2,1-etanodiil))) biscarbamato de dimetilo;

N',N'''-(1,2-etanodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil ((1R)-2-oxo-1-fenil-2,1-etanodiil)))bis(1-etilurea);

1-ciclopentil-3-((1R)-2-((2S)-2-(4-(4-(2-(4-(2-((2S)-1-((2R)-2-((ciclopentilcarbamoil) amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)etil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)urea;

(1R)-2-((2S)-2-(4-(4-(((4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)bencil)oxi) metil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina;

(1R)-2-((2S)-2-(4-(4-(((4-(2-((2S)-1-((2R)-2-hidroxi-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)bencil)oxi)metil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletanol;

(oxibis(metilen-4,1-fenilen-1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil ((1R)-2-oxo-1-fenil-2,1-etanodiil))) biscarbamato de dimetilo;

1-metil-3-((1R)-2-((2S)-2-(4-(4-(((4-(2-((2S)-1-((2R)-2-((metilcarbamoil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)bencil)oxi)metil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)urea;

1-etil-3-((1R)-2-((2S)-2-(4-(4-(((4-(2-((2S)-1-((2R)-2-((etilcarbamoil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)bencil)oxi)metil)fenil)-1H-imidazol-2-il)-1-

pirrolidinil)-2-oxo-1-feniletil)urea;

1-ciclopentil-3-((1R)-2-((2S)-2-(4-(4-(((4-(2-((2S)-1-((2R)-2-((ciclopentilcarbamoil) amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)bencil)oxi)metil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)urea;

(1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)bencil)oxi) metil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina;

(1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-hidroxi-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)bencil)oxi)metil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletanol;

(((1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)bencil)oxi)metil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo;

1-metil-3-((1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-((metilcarbamoil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)bencil)oxi)metil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)urea;

1-etil-3-((1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-((etilcarbamoil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)bencil)oxi)metil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)urea;

1-ciclopentil-3-((1R)-2-((2S)-2-(4-(3-(((4-(2-((2S)-1-((2R)-2-((ciclopentilcarbamoil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)bencil)oxi)metil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)urea;

(1,1':4',1''-terfenil-4,4''-diilbis(1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil ((1R)-2-oxo-1-fenil-2,1-etanodiil))) biscarbamato de dimetilo;

(1R)-2-((2S)-2-(4-(4''-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-

pirrolidinil)-1H-imidazol-5-il)-1,1':4',1''-terfenil-4-il)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina;

((1S)-1-(((2S)-2-(4-(4-((2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-4,5-dihidro-1H-nafto[1,2-d]imidazol-7-il)etinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

((1R)-2-((2S)-2-(4-(4-((2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-4,5-dihidro-1H-nafto[1,2-d]imidazol-7-il)etinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo;

((1R)-2-((2S)-2-(7-((4-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)-1H-nafto[1,2-d]imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo;

((1S)-1-(((2S)-2-(4-(4-((2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-nafto[1,2-d]imidazol-7-il)etinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-1-(((1R,3S,5R)-3-(4-(4-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-nafto[1,2-d]imidazol-7-il)etinil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

((1R)-2-((1R,3S,5R)-3-(7-((4-(2-((1R,3S,5R)-2-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)etinil)-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-feniletil)carbamato de metilo;

((1S)-1-(((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-4,5-dihidro-1H-nafto[1,2-d]imidazol-7-il)etinil)-4,5-dihidro-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-

2-metilpropil)carbamato de metilo;

((1S)-1-(((1R,3S,5R)-3-(7-((2-((3S)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-nafto[1,2-d]imidazol-7-il)etinil)-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-2-((1R,3S,5R)-3-(7-((2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-nafto[1,2-d]imidazol-7-il)etinil)-1H-nafto[1,2-d]imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo;

((1S)-1-(((2S)-2-(4-(4-((4-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil) carbamato de metilo;

(1,2-etinodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil ((1R)-2-oxo-1-fenil-2,1-etanodiil))) biscarbamato de dimetilo;

(1,2-etinodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo;

((1S)-1-(((1R,3S,5R)-3-(4-(4-((4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil) amino)-3-metilbutanoil)-2-azabiciclo[3.1.0] hex-3-il)-1H-imidazol-4-il)fenil)etinil) fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0] hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

(1,2-etinodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo [3.1.0]hexano-3,2-diil((2S)-1-oxo-1,2-butanodiil)))biscarbamato de dimetilo;

(1,2-etinodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo [3.1.0]hexano-3,2-diil((1S)-1-ciclobutil-2-oxo-2,1-etanodiil)))biscarbamato de dimetilo;

(1,2-etinodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo

[3.1.0]hexano-3,2-diil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo;

((1S)-1-(((1R,3S,5R)-3-(4-(4-((4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

(1S)-1-(((1R,3S,5R)-3-(4-cloro-5-(4-((4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-1-(((1R,3S,5R)-3-(4-cloro-5-(4-((4-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)fenil)etinil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-2-((1R,3S,5R)-3-(4-(4-((4-(4-cloro-2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)fenil)etinil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo;

(1,2-etinodiilbis(4,1-fenileno(4-cloro-1H-imidazol-5,2-diil)(1R,3S,5R)-2-azabiciclo[3.1.0]hexano-3,2-diil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo;

((1S)-1-(((1R,3S,5R)-3-(4-(4-((1S,2S)-2-(4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)ciclopropil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

((1S,2S)-1,2-ciclopropanodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0]hexano-3,2-diil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo;

((1S)-1-(((1R,3S,5R)-3-(4-(4-((1R,2R)-2-(4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)ciclopropil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

((1R,2R)-1,2-ciclopropanodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0]hexano-3,2-diil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo;

((1S)-1-(((2S,4S)-2-(4-(4-((1S,2S)-2-(4-(2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)fenil)ciclopropil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-1-(((2S,5S)-2-(4-(4-((4-(2-((2S,5S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil) carbonil)-2-metilpropil)carbamato de metilo;

(1,2-etinodiilbis(4,1-fenilen-1H-imidazol-4,2-diil((2S,5S)-5-metil-2,1-pirrolidinadiil)((2S)-1-oxo-1,2-butanodiil))) biscarbamato de dimetilo;

(1,2-etinodiilbis(4,1-fenilen-1H-imidazol-4,2-diil((2S,5S)-5-metil-2,1-pirrolidinadiil)((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo;

((1S)-1-(((2S,5S)-2-(4-(4-((4-(2-((2S,5S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-1-(((2S,4S)-2-(4-(4-((4-(2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

(1,2-etinodiilbis(4,1-fenilen-1H-imidazol-4,2-diil((2S,4S)-4-metil-2,1-pirrolidinadiil)((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo;

((1S)-1-(((2S,4S)-2-(4-(4-((4-(4-cloro-2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-5-il)fenil)etinil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-1-(((2S,4S)-2-(4-cloro-5-(4-((4-(4-cloro-2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-5-il)fenil)etinil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-2-((2S,4S)-2-(4-(4-((4-(4-cloro-2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-4-metil-2-pirrolidinil)-1H-imidazol-5-il)fenil)etinil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo;

(1,2-etinodiilbis(4,1-fenileno(4-cloro-1H-imidazol-5,2-diil)((2S,4S)-4-metil-2,1-pirrolidinadiil)((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo;

((1S)-2-((2S,4S)-2-(4-(4-((4-(2-((2S,4S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metil-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-4-metil-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo;

((1S)-1-(((1S,3S,5S)-3-(4-(4-((4-(2-((1S,3S,5S)-2-((2S)-2-

((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-5-metil-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-1-(((1R,3S,5R)-3-(4-(4-((E)-2-(4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil) amino)-3-metilbutanoil)-2-azabiciclo[3.1.0] hex-3-il)-1H-imidazol-4-il)fenil)vinil) fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0] hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

((E)-1,2-etenodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo [3.1.0]hexano-3,2-diil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil))) biscarbamato de dimetilo;

((1S)-2-((1R,3S,5R)-3-(4-(4-((E)-2-(4-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil) amino)-3-metilbutanoil)-2-azabiciclo[3.1.0] hex-3-il)-1H-imidazol-4-il)fenil)vinil) fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0] hex-2-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo;

((1S)-1-(((2S)-2-(4-(4-((4-(2-((2S)-4,4-difluoro-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-4,4-difluoro-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

(etino-1,2-diilbis(4,1-fenilen-1H-imidazol-5,2-diil((2S)-4,4-difluoropirrolidin-2,1-diil)((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)etano-2,1-diil)))biscarbamato de dimetilo;

((1R)-2-((2S)-2-(5-(4-((4-(2-((2S)-4,4-difluoro-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)pirrolidin-2-il)-1H-imidazol-5-il)fenil)etinil)fenil)-1H-imidazol-2-il)-4,4-difluoropirrolidin-1-il)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo;

(etino-1,2-diilbis(4,1-fenilen-1H-imidazol-5,2-diil((2S)-4,4-difluoropirrolidin-2,1-

diil)((1R)-2-oxo-1-(tetrahidro-2H-piran-4-il)etano-2,1-diil)))biscarbamato de dimetilo;

((1S)-1-(((3S)-3-(4-(4-((4-(2-((3S)-4-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-3-morfolinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-4-morfolinil)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-1-(((2S)-2-(4-(4-((4-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-piperidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-1-piperidinil)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-1-(((2S,4S)-4-hidroxi-2-(4-(4-((4-(2-((2S,4S)-4-hidroxi-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-1-(((1S,3S,5S)-3-(4-(4-((4-(2-((1S,3S,5S)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

(1,2-etinodiilbis(4,1-fenilen-1H-imidazol-4,2-diil(1S,3S,5S)-2-azabiciclo[3.1.0]hexano-3,2-diil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo;

((1S)-1-(((2S)-2-(4-(3-((3-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-2-metil-1-(((2S)-2-(4-(3-((3-(2-((2S)-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo;

(1,2-etinodiilbis(3,1-fenilen-1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo;

((1S)-1-(((1R,3S,5R)-3-(4-(3-((3-(2-((1R,3S,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo;

(1,2-etinodiilbis(3,1-fenilen-1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0]hexano-3,2-diil((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo;

((1S,2S)-1,2-ciclopropanodiilbis(4,1-fenilen-1H-imidazol-4,2-diil((2S,4S)-4-metil-2,1-pirrolidinadiil)((1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)-2,1-etanodiil)))biscarbamato de dimetilo;

((1S)-1-(((2S)-2-(4-(4-((4-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-4-metilen-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-4-metilen-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

((1S)-1-(((2S,4R)-4-hidroxi-2-(4-(4-((4-(2-((2S,4R)-4-hidroxi-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo;

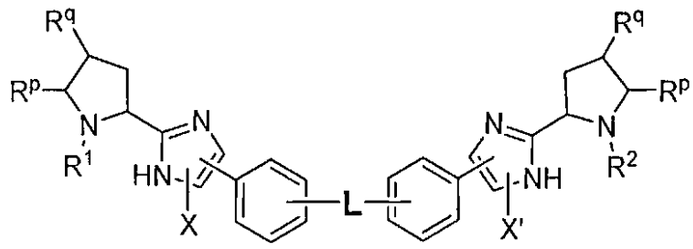
((1S)-1-(((2S)-2-(4-(4'-((4-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)fenil)etinil)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo; y los estereoisómeros y tautómeros correspondientes de los mismos.

18. Una composición que comprende un compuesto de la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, y un vehículo farmacéuticamente aceptable.

19. Un procedimiento de tratamiento de una infección por VHC en un paciente, que comprende administrar al paciente una cantidad terapéuticamente eficaz de un compuesto de la reivindicación 1, o una sal farmacéuticamente aceptable del mismo.

## RESUMEN

La presente divulgación se refiere a compuestos novedosos de la Fórmula (I) tal como se definen en la memoria descriptiva y a las composiciones que comprenden dichos compuestos novedosos. Estos compuestos son agentes antivirales útiles, especialmente para inhibir la función de la proteína NS5A codificada por el virus de la hepatitis C (VHC). Por lo tanto, la divulgación también se refiere a un procedimiento de tratamiento de enfermedades o afecciones relacionadas con VHC mediante el uso de estos compuestos novedosos o de una composición que comprende dichos compuestos novedosos.




(I)

Poder

**POD-02400**

A-

TRADUCCIÓN OFICIAL N° 2511031 de un documento escrito en inglés, el cual para su identificación se sella con el sello del Traductor. Esta es una Traducción Oficial efectuada el día 25 de noviembre de 2003 por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

---

Texto en inglés y en español mediante el cual **BRISTOL-MYERS SQUIBB COMPANY** domiciliada en Nueva York, Nueva York, otorga poder a **ALVARO CORREA ORDOÑEZ y/o OLGA GEORGETTE OTERO y/o RICARDO METKE y/o JUAN PABLO CONCHA**

Dado y suscrito en Nueva York, Nueva York el día 13 de noviembre de 2003

(firmado) Nadine P. Flynn, Subsecretaria

Firma de la persona que expide el poder

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ESTADO DE NUEVA YORK )
DONDADO DE NUEVA YORK ) declaración juramentada
ESTADOS UNIDOS DE AMÉRICA )

RECONOCIMIENTO

El 13 de noviembre del año 2003 compareció ante mí Nadine P. Flynn, a quien conozco, quien después de prestar el debido juramento, declaró y dijo que trabaja en 345 Park Avenue, Nueva York, Nueva York; que es la Subsecretaria de Bristol-Myers Squibb Company, la sociedad descrita en el anterior instrumento y que suscribió el mismo; y que lo firmó con la facultad que para ello le confirió la Junta Directiva de la mencionada sociedad.

(firmado) Gabriela Ullrich-Brown, Notario Público

JAIME A. GARAVITO B.
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

GABRIELA ULLRICH-BROWN
Notario Público, Estado de Nueva York
N° 31-4920138
Calificado en el Condado de Nueva York
Comisión vence el 28 de febrero de 2006

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N° 354118 Formato 1

ESTADO DE NUEVA YORK )

declaración juramentada

CONDADO DE NUEVA YORK )

(Aparece sello en tinta del Secretario de Condado del Condado de Nueva York)

YO, NORMAN GOODMAN, Secretario de Condado y Secretario de la Corte Suprema del Estado de Nueva York, en el Condado de Nueva York y para el mismo, siendo una Corte que guarda constancia de sus autos y que tiene un sello, CERTIFICO QUE

GABRIELA ULLRICH-BROWN

quien suscribe la declaración juramentada anexa, afirmación, certificado de reconocimiento o prueba, era en el momento de recibirlo un NOTARIO PÚBLICO en el Estado de Nueva York y para el mismo, debidamente comisionado, juramentado y calificado para actuar como tal; que de conformidad con la ley, se ha archivado en mi oficina una comisión o un certificado de carácter oficial y una firma autógrafa de dicho NOTARIO PÚBLICO; que en el momento de recibir dicha prueba, reconocimiento o juramento, estaba debidamente autorizado para recibirlos; que me encuentro familiarizado con la caligrafía de dicho NOTARIO PÚBLICO, o he comparado su firma en el instrumento anexo con la firma autógrafa de dicho NOTARIO PÚBLICO depositada en mi oficina y creo que la firma en el instrumento anexo es auténtica.

EN FE DE LO CUAL, he estampado mi firma y sello oficial hoy 17 DE NOVIEMBRE DE 2003.

COMISIÓN PAGADA: $3.00

(firmado) Norman Goodman, Secretario de Condado y Secretario de la Corte Suprema, Condado de Nueva York

(Aparece sello en relieve)

APOSTILLA

JAIME A. GARAVITO B.
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de fecha 11 de 1983
MINISTERIO DE JUSTICIA

1. País: Estados Unidos de América

   Este documento público

2. Ha sido firmado por Norman Goodman

3. Quien actúa en calidad de Secretario de Condado

4. Lleva el sello del Condado de Nueva York

Certificado

5. En Nueva York, Nueva York

6. El 17 de noviembre de 2003

7. Por el Secretario de Estado Encargado Especial, Estado de Nueva York

8. N° NYC-10092610B

9. Sello

10. Firma (firmado) James Bizzarri, Secretario de Estado Encargado Especial

(Aparece en relieve el Gran Sello del Estado de Nueva York)

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La anterior es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

Jaime Armando Garavito Burgos
c.c. N° 19.130.702 de Bogotá
Traductor e Intérprete Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

JAIME A. GARAVITO B.
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

691

RAISBECK, LARA, RODRÍGUEZ & RUEDA
Miembros de la Firma
BAKER & McKENZIE
ATTORNEYS AT LAW
APARTADO AEREO 3746
Teléfono: 634-1500

## POWER OF ATTORNEY

The undersigned.

BRISTOL-MYERS SQUIBB COMPANY

domiciled in New York, New York, U.S.A.

declares that it hereby grants to

ALVARO CORREA-ORDOÑEZ and/or OLGA GEORGETTE OTERO and/or RICARDO METKE and/or JUAN PABLO CONCHA

with domicile at Av. 82 No. 10-62, 6th floor, of Bogotá D.C., Colombia, a full and sufficient power of attorney to pursue before the competent authorities the following matters:

**Trademark registrations, renewals, mergers, changes of name, assignments, filing and prosecution of oppositions, deposit of commercial names, changes of address, filing and prosecution of cancellation actions, licenses of use, nullity actions and all judicial actions available for the prosecution of proceedings related to Intellectual Property matters,**

to which end it empowers them to take all necessary steps before said authorities for the objects stated, to file petitions, prepare descriptions, make protests, declarations, appeals and objections, pay imposts, apply for certifications, receive documents and securities, including facilities to enter into settlement agreements, abandon applications, renounce and collect refunds. Also, our attorneys are entitled to request cancellation of trademark registrations. To the said mandatories sufficient power is granted hereby to receive notifications for and 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 marks, and to do everything that may be required before administrative or judicial officers of any class, giving them likewise power to substitute these presents and revoke such substitutions if necessary.

I hereby ratify all actions previously taken on behalf of this company by the aforementioned attorneys with respect to the mentioned matters.

Done and suscribed in New York, NY

On the 13 day of November of 200 3

Signature of the person issuing the Power

Nadine P. Flynn
Assistant Secretary

## PODER

La abajo firmada.

BRISTOL-MYERS SQUIBB COMPANY

domiciliada en New York, New York, U.S.A.

declara por el presente otorgar a

ALVARO CORREA-ORDOÑEZ y/o OLGA GEORGETTE OTERO y/o RICARDO METKE y/o JUAN PABLO CONCHA

con domicilio en la Av. 82 No. 10-62 Piso 6 en Bogotá D.C., Colombia, poder especial amplio y suficiente, para adelantar ante las autoridades competentes los siguientes asuntos:

**Registro de marcas, renovaciones, fusiones, cambios de nombre, traspasos, presentación y tramitación de oposiciones, depósito de nombres comerciales, cambios de dirección, presentación y tramitación de acciones de cancelación, licencias de uso, acciones de nulidad y demás acciones judiciales, relacionadas con procesos de Propiedad Intelectual,**

a cuyo efecto los faculta para dar ante dichas autoridades todos los pasos necesarios al objeto indicado, elevar solicitudes, formular descripciones, protestas, declaraciones, apelaciones y reclamos, oblar impuestos, solicitar testimonios, recibir documentos y valores, transigir, desistir, renunciar y percibir. También nuestros apoderados están facultados para solicitar cancelación de registros de marca. Se concede a los expresados mandatarios poder suficiente 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 y demandas que por motivo de las marcas se presentaren, y hacer cuanto fuere necesario, ante las autoridades administrativas y judiciales de cualquier orden, dándoles así mismo facultad para sustituir el presente y en caso necesario revocar dichas sustituciones.

Igualmente, ratifico todo lo actuado hasta el momento en los mismos asuntos, por cualquiera de los mencionados apoderados en representación de ésta sociedad.

Dado y firmado en

A los días del mes de de 200

Firma de la persona que firma el Poder

ibb

NEW YORK COUNTY

No. 354118 Form 1

State of New York
County of New York, } ss.:

I, NORMAN GOODMAN, County Clerk and Clerk of the Supreme Court of the State of New York, in and for the County of New York, a Court of Record, having by law a seal,

DO HEREBY CERTIFY pursuant to the Executive Law of the State of New York, that

Gabriela Ulrich-Bellman

whose name is subscribed to the annexed affidavit, deposition, certificate of acknowledgment or proof, was at the time of taking the same a NOTARY PUBLIC in and for the State of New York duly commissioned, sworn and qualified to act as such; that pursuant to law, a commission or a certificate of his official character, with his autograph signature has been filed in my office; that at the time of taking such proof, acknowledgment or oath, he was duly authorized to take the same; that I am well acquainted with the handwriting of such NOTARY PUBLIC or have compared the signature on the annexed instrument with his autograph signature deposited in my office, and I believe that such signature is genuine.

IN WITNESS WHEREOF, I have hereunto set my hand affixed my official seal this

NOV 17 2003

FEE PAID $3.00

*County Clerk and Clerk of the Supreme Court, New York County*

STATE OF NEW YORK )

COUNTY OF NEW YORK ) ss.:

UNITED STATES OF AMERICA )

ACKNOWLEDGEMENT

On the 13th day of November in the year 2003 before me personally came Nadine P. Flynn, to me known, who being by me duly sworn, did depose and say that she works at 345 Park Avenue, New York, New York; that she is the Assistant Secretary of Bristol-Myers Squibb Company, the corporation described in and which executed the above instrument; and that she signed her name thereto by authority of the board of directors of said corporation.

COUNTY CLERK

Gabriela Ullrich-Brown
Notary Public

*GABRIELA ULLRICH-BROWN*
*Notary Public, State of New York*
*No. 31-4920138*
*Qualified in New York County*
*Commission Expires 2/28/06*

# Apostille

(Convention de La Haye du 5 Octobre 1961)

1. Country: **United States of America**

   This public document

2. has been signed by **Norman Goodman**

3. acting in the capacity of **County Clerk**

4. bears the seal/stamp of the county of **New York**

# Certified

5. At New York, New York 6. the 17th day of November 2003

7. by Special Deputy Secretary of State, State of New York

8. No. NYC-10092610B

9. Seal/Stamp 10. Signature

James Bizzarri
Special Deputy Secretary of State

SYL V/S

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-123611- -00000-0000

Fecha: 2011-09-21 16:56:50 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 694

Act. 411 PRESENTACION Folios: 687

**PATENTE DE INVENCIÓN** ☐ **MODELO DE UTILIDAD** ☐ **Art 33 Decisión 486/00**

- ☐ 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** ☑ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

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

Completa ☑ 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 ☐