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Organizacion y Digitalizacion CSA Ltda

Industria y Comercio

SUPERINTEN

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-098050- -00000-0000
Fecha: 2010-08-10 17:24:34 Dep: 2020 DIR NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 762

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 10-98050 1/3

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

51. **CLASIFICACIÓN INTERNACIONAL**

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

DOMICILIO PRINCETON, NEW JERSEY, ESTADOS UNIDOS

74. **APODERADO** ALVARO CORREA ORDOÑEZ

22. **BOGOTÁ, D.C.,** Agosto 10, 2010

(FORMA P-10)

12-09-2010

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-098050- -00000-0000
Fecha: 2010-08-10 17:24:34 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTE|YII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 762

ación

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

SOLICITUD DE :

(1)

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

[X] Capítulo I. [ ] Capítulo II.

(2) SOLICITANTE (71)

Nombre: **BRISTOL-MYERS SQUIBB COMPANY**

Dirección: Route 206 and Province Line Road Princeton, New Jersey 08543-4000, Estados Unidos de America

Nacionalidad o Domicilio: Estados Unidos de América

Lugar de Constitución: Estados Unidos de América

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 6

Teléfono: 6341500 Fax: 3762211

E-Mail: office.bogota@bakernet.com

IDENTIFICACION

C.C. [X] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número 79.143.366 Usaquén TP 20281

(4) VENTOR (ES) (72)

Nombre: BACHAND, Carol; BELEMA, Makonen; DEON, Daniel, H.; GOOD, Andrew, C.; GOODRICH, Jason; JAMES, Clint, A.; LAVOIE, Rico; LOPEZ, Omar, D.; MARTEL, Alain; MEANWELL, Nicholas, A.; NGUYEN, Van, N.; ROMINE, Jeffrey, Lee; RUEDIGER, Edward, H.; SNYDER, Lawrence, B.; ST. LAURENT, Denis, R.; YANG, Fukang; LANGLEY, David, R.; WANG, Gan; HAMANN, Lawrence, G.

Dirección: 119 Place Mercure Candiac, Québec J5R 1B1 (CA); c/o Bristol Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); 401-4905 Av. Colomb Brossard, Québec J4Z 3T2 (CA); 52 High Hill Road Wallingford, CT 06492 (US); c/o Bristol Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); 500 Boulevard Quinn Longueuil, Québec J4H 2N4 (CA); c/o Bristol Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); c/o Bristol Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); 29 Rue Monette Delson, Québec J5B 1G8 (CA); c/o Bristol Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); c/o Bristol Myers Squibb Company 5 Resear3ch Parkway Wallingford, CT 06492 (US); c/o Bristol Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); 133 St. Charles Greenfield Park, Québec J4V 2K3 (CA); c/o Bristol Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); c/o Bristol Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); c/o Bristol Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 (US); c/o Bristol Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); c/o Bristol Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 (US); 7 Whitney Street, North Grafton, Massachusetts 01536 (US)

Nacionalidad o Domicilio: Canadá y Estados Unidos de América

(5) PCT (85)

Solicitud Internacional No. PCT/US2008/053638 Fecha 12.02.2008

Publicación Internacional No. WO/2009/102318 Fecha 20.08.2009

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

(7) Clasificación Internacional (51) C07D 403/10, A61K 31/4164, A61P 31/22, C07D 403/14

(8) Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI [ ] NO [ ]			

(9) Comprobante de pago No. 10-46,262 – 10-54,910 – 10-54,911 – 10-63,394 – 10-63,390 **Fecha** 09-08, 2010

(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 documento de Poder General radicado en el Expediente No. 08 129.339
- [ ] Documento de cesión del inventor al solicitante o a su causante (ver Declaración)
- [ ] 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**

(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

2010/011

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 46,262
FECHA : JUNIO 8 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-098050- -00000-0000
Fecha: 2010-08-10 17:24:34 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 762

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	RECIBO DE CAJA			46215	09/06/2010	86,670,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	554,000.00
		TOTAL : $	554,000.00

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

4

2010/013

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 54,910
FECHA : JULIO 6 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-098050- -00000-0000
Fecha: 2010-08-10 17:24:34 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 762

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	380489826	06/07/2010	51,604,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	26,000.00
			TOTAL : $	26,000.00

SON: VEINTISEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

2010/013

5

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 54,911
FECHA : JULIO 6 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-098050- -00000-0000
Fecha: 2010-08-10 17:24:34 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve. 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 762

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	380489826	06/07/2010	51,604,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	26,000.00
			TOTAL : $	26,000.00

SON: VEINTISEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

2010/014

6

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 10 - 63,394
FECHA : AGOSTO 3 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-098050- -00000-0000
Fecha: 2010-08-10 17:24:34 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 762

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	353160824	02/08/2010	70,995,000.00

8

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99	OTROS SERVCIOS ADMINISTRATIVOS	70,000.00
			TOTAL : $	70,000.00

SON: SETENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

2010/014

7

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 63,390
FECHA : AGOSTO 3 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-098050- -00000-0000
Fecha: 2010-08-10 17:24:34 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 762

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	353160824	02/08/2010	70,995,000.00

8

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	295,000.00
		TOTAL : $	295,000.00

SON: DOSCIENTOS NOVENTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Industria y Comercio

SUPERINTENDENCIA

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

000008

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

(21) N° de solicitud: (22) Fecha de solicitud:

(51) Clasificación Internacional : C07D 403/10, A61K 31/4164, A61P 31/22, C07D 403/14

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

(72) Inventor(es) BACHAND, Carol; BELEMA, Makonen; DEON, Daniel, H.; GOOD, Andrew, C.; GOODRICH, Jason; JAMES, Clint, A.; LAVOIE, Rico; LOPEZ, Omar, D.; MARTEL, Alain; MEANWELL, Nicholas, A.; NGUYEN, Van, N.; ROMINE, Jeffrey, Lee; RUEDIGER, Edward, H.; SNYDER, Lawrence, B.; ST. LAURENT, Denis, R.; YANG, Fukang; LANGLEY, David, R.; WANG, Gan; HAMANN, Lawrence, G.

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad (31) ***No. Prioridad*** 32) ***Fecha*** (33) ***País***

(85) Fecha inicio fase nacional: 12-09-2010

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 12-02-2008
No. de solicitud: PCT/US2008/053638

(87) Publicación internacional
Fecha: 20.08.2009
N° publicación: WO/2009/102318

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

Industria y Comercio
SUPERINTENDENCIA

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

C00009

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

(21) N° de solicitud: (22) Fecha de solicitud:
(51) Clasificación Internacional: C07D 403/10, A61K 31/4164, A61P 31/22, C07D 403/14

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

(72) Inventor(es) BACHAND, Carol; BELEMA, Makonen; DEON, Daniel, H.; GOOD, Andrew, C.; GOODRICH, Jason; JAMES, Clint, A.; LAVOIE, Rico; LOPEZ, Omar, D.; MARTEL, Alain; MEANWELL, Nicholas, A.; NGUYEN, Van, N.; ROMINE, Jeffrey, Lee; RUEDIGER, Edward, H.; SNYDER, Lawrence, B.; ST. LAURENT, Denis, R.; YANG, Fukang; LANGLEY, David, R.; WANG, Gan; HAMANN, Lawrence, G.

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad (31) ***No. Prioridad*** 32) ***Fecha*** (33) ***País***

(85) Fecha límite inicio fase nacional: 12-09-2010
(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud: 12.02.2008
No. de solicitud PCT/US2008/053638

(87) Publicación internacional:
Fecha: 20.08.2009
No. Publicación: WO/2009/102318

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

(57) Resumen: La presente invención se refiere a composiciones de (4,4'-diimidazolil)bifenilos y a métodos para el tratamiento del virus de la hepatitis C (VHC). También se describen composiciones farmacéuticas que contienen estos compuestos y métodos para el uso de estos compuestos en el tratamiento de infección por VHC.

CONTINUA AL RESPALDO ...

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:	(51) Int Cl: C07D 403/10, A61K 31/4164, A61P 31/22, C07D 403/14
22) Fecha de solicitud:	(71)Solicitante(s) **BRISTOL-MYERS SQUIBB COMPANY**
(30) Prioridad (31) ***No.*** 32) ***Fecha*** (33) ***País***	(72) Inventor(es) BACHAND, Carol; BELEMA, Makonen; DEON, Daniel, H.; GOOD, Andrew, C.; GOODRICH, Jason; JAMES, Clint, A.; LAVOIE, Rico; LOPEZ, Omar, D.; MARTEL, Alain; MEANWELL, Nicholas, A.; NGUYEN, Van, N.; ROMINE, Jeffrey, Lee; RUEDIGER, Edward, H.; SNYDER, Lawrence, B.; ST. LAURENT, Denis, R.; YANG, Fukang; LANGLEY, David, R.; WANG, Gan; HAMANN, Lawrence, G.
	(74) Apoderado: **ALVARO CORREA ORDOÑEZ**
(85) Fecha limite inicio fase nacional: 12-09-2010 (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: 12.02.2008 No. de PCT/US2008/053638	(87) Publicación internacional Fecha: 20.08.2009 N° publicación: WO/2009/102318

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

Reivindicación(es): 1. Un compuesto caracterizado porque se selecciona de

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1S)-2-metil-1,1-propandiil)imino((2S)-1-oxo-1,2-propandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1S)-2-metil-1,1-propandiil)imino((2S,3R)-3-metoxi-1-oxo-1,2-butandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1S)-2-metil-1,1-propandiil)imino((2S)-3-metil-1-oxo-1,2-butandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1S)-2-metil-1,1-propandiil)imino((2S)-4-metoxi-1-oxo-1,2-butandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1R)-2-metil-1,1-propandiil)imino((2S)-3-metil-1-oxo-1,2-butandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1R)-2-metil-1,1-propandiil)imino((2S)-1-oxo-1,2-propandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1R)-2-metil-1,1-propandiil)imino((2S)-4-metoxi-1-oxo-1,2-butandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1R)-2-metil-1,1-propandiil)imino((2S,3R)-3-metoxi-1-oxo-1,2-butandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1R)-2-metil-1,1-propandiil)imino((2R)-3-metil-1-oxo-1,2-butandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1S)-2-metil-1,1-propandiil)imino((2R)-3-metil-1-oxo-1,2-butandiil)))biscarbamato de dimetilo;

N^2-(metoxicarbonil)-N-((1S)-1-(4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-metilpropil)-L-valinamida;

((1S,2R)-2-metoxi-1-(((2S)-2-(4-(4'-(2-((1S)-1-((N-(metoxicarbonil)-O-metil-L-treonil)amino)-2-metilpropil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo;

((1S)-3-metoxi-1-(((2S)-2-(4-(4'-(2-((1S)-1-((N-(metoxicarbonil)-O-metil-L-homoseril)amino)-2-metilpropil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo;

((1S)-2-((2S)-2-(4-(4'-(2-((1S)-1-((N-(metoxicarbonil)-L-alanil)amino)-2-metilpropil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo;

N^2-(metoxicarbonil)-N-((1R)-1-(4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-metilpropil)-L-valinamida;

((1S,2R)-2-metoxi-1-(((2S)-2-(4-(4'-(2-((1R)-1-((N-(metoxicarbonil)-O-metil-L-treonil)amino)-2-metilpropil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo; ...

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 August 2009 (20.08.2009)

PCT

(10) International Publication Number
WO 2009/102318 A1

(51) International Patent Classification:
C07D 403/10 (2006.01) *A61K 31/4164* (2006.01)
C07D 403/14 (2006.01) *A61P 31/22* (2006.01)

(21) International Application Number:
PCT/US2008/053638

(22) International Filing Date:
12 February 2008 (12.02.2008)

(25) Filing Language: English

(26) Publication Language: English

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(72) Inventors; and

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(54) Title: HEPATITIS C VIRUS INHIBITORS

(57) Abstract: The present disclosure relates to (4-4' -diimidazolyl) biphenyls compositions and methods for the treatment of hepatitis C virus (HCV) infection. Also disclosed are pharmaceutical compositions containing such compounds and methods for using these compounds in the treatment of HCV infection.

HEPATITIS C VIRUS INHIBITORS

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.

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.

Presently, the most effective HCV therapy employs a combination of alpha-interferon and ribavirin, leading to sustained efficacy in 40% of patients. Recent clinical results demonstrate that pegylated alpha-interferon is superior to unmodified alpha-interferon as monotherapy. However, even with experimental therapeutic regimens involving combinations of pegylated alpha-interferon and ribavirin, a substantial fraction of patients do not have a sustained reduction in viral load. Thus, there is a clear and long-felt need to develop effective therapeutics for treatment of HCV infection.

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.

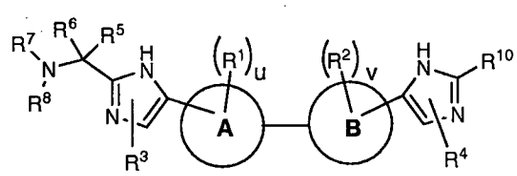
Considerable heterogeneity is found within the nucleotide and encoded amino acid sequence throughout the HCV genome. At least six major genotypes have been characterized, and more than 50 subtypes have been described. The major genotypes of HCV differ in their distribution worldwide, and the clinical significance of the genetic heterogeneity of HCV remains elusive despite numerous studies of the possible effect of genotypes on pathogenesis and therapy.

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, acting as a cofactor for the NS3 protease and possibly assisting in the membrane localization of NS3 and other viral replicase components. The complex formation of the NS3 protein with NS4A seems necessary to the processing events, enhancing the proteolytic efficiency at all of the sites. 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.

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 Tan, S.-L., Katzel, M.G. *Virology* 2001, *284*, 1-12; and in Park, K.-J.; Choi, S.-H, *J. Biological Chemistry* 2003.

In its first aspect the present disclosure provides a compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, wherein

u and v are independently 0, 1, 2, or 3;

A and B are independently selected from phenyl and a six-membered heteroaromatic ring containing one, two, or three nitrogen atoms;

each R^1 and R^2 is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

R^3 and R^4 are each independently selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, (NR^aR^b)carbonyl, and trialkylsilylalkoxyalkyl;

R^5 and R^6 are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and (NR^aR^b)alkyl; or,

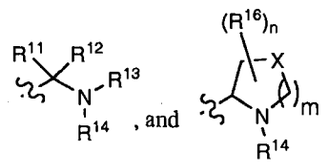
R^5 and R^6, together with the carbon atom to which they are attached, form a five or six membered saturated ring optionally containing one or two heteroatoms selected from NR^z, O, and S; wherein R^z is selected from hydrogen and alkyl;

R^7 is selected from hydrogen, R^9-C(O)-, and R^9-C(S)-;

R^8 is selected from hydrogen and alkyl;

R^9 is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, -NR^cR^d, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl;

R^{10} is selected from



; wherein

R^{11} and R^{12} are each independently selected from hydrogen, alkenyl, alkoxyalkyl, alkyl, haloalkyl, and (NR^aR^b)alkyl; or,

R^{11} and R^{12}, together with the carbon atom to which they are attached, form a five or six membered saturated ring optionally containing one or two heteroatoms selected from NR^z, O, and S; wherein R^z is selected from hydrogen and alkyl;

R^{13} is selected from hydrogen and alkyl;

R^{14} is selected from hydrogen, R^{15}-C(O)-, and R^{15}-C(S)-;

R^{15} is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, -NR^cR^d, (NR^cR^d)alkenyl,

(NR^cR^d)alkyl, and (NR^cR^d)carbonyl;

m is 0, 1, or 2;

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

X is selected from O, S, S(O), SO_2, CH_2, CHR^{16}, and $C(R^{16})_2$;

provided that when m is 0, X is selected from CH_2, CHR^{16}, and $C(R^{16})_2$;

each R^{16} is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^aR^b$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups.

In a first embodiment of the first aspect m is 0.

In a second embodiment of the first aspect u and v are each independently 0 or 1; and each R^1 and R^2 is independently selected from alkyl and halo.

In a third embodiment of the first aspect u and v are each 0.

In a fourth embodiment of the first aspect X is selected from CH_2 and CHR^{16}. In a fifth embodiment of the first aspect X is CH_2.

In a sixth embodiment of the first aspect R^3 and R^4 are each independently selected from hydrogen, haloalkyl, and trialkylsilylalkoxyalkyl. In a seventh embodiment R^3 and R^4 are each independently selected from hydrogen and haloalkyl.

In an eighth embodiment of the first aspect n is 0, 1, or 2; and, when present, each R^{16} is halo. In a ninth embodiment n is 0.

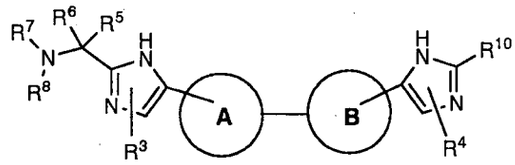
In a tenth embodiment of the first aspect R^5 and R^6 are independently selected from hydrogen and alkyl.

In an eleventh embodiment of the first aspect R^{11} and R^{12} are independently selected from hydrogen and alkyl.

In a twelfth embodiment of the first aspect at least one of R^7 and R^{14} is hydrogen.

In a thirteenth embodiment of the first aspect R^7 is R^9-C(O)-; and R^{14} is R^{15}-C(O)-. In a fourteenth embodiment R^9 and R^{15} are each independently selected from alkoxy, alkoxyalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, heterocyclyl, heterocyclylalkyl, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl. In a fifteenth embodiment R^9 and R^{15} are each independently selected from alkoxy, arylalkoxy, arylalkyl, and (NR^cR^d)alkyl.

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



(II),

or a pharmaceutically acceptable salt thereof, wherein

A and B are independently selected from phenyl and a six-membered heteroaromatic ring containing one, two, or three nitrogen atoms;

R^3 and R^4 are each independently selected from hydrogen, haloalkyl, and trialkylsilylalkoxyalkyl;

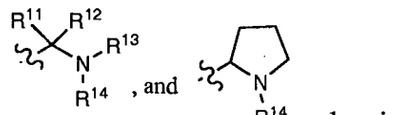
R^5 and R^6 are each independently selected from hydrogen, and alkyl;

R^7 is selected from hydrogen and R^9-C(O)-;

R^8 is selected from hydrogen and alkyl;

R^9 is independently selected from alkoxy, arylalkoxy, arylalkyl, and (NR^cR^d)alkyl;

R^{10} is selected from



; wherein

R^{11} and R^{12} are each independently selected from hydrogen and alkyl;

R^{13} is selected from hydrogen and alkyl;

R^{14} is selected from hydrogen and R^{15}-C(O)-; and

R^{15} is independently selected from alkoxy, arylalkoxy, arylalkyl, and (NR^cR^d)alkyl.

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. In a first embodiment of the third aspect, the composition comprises one or two additional compounds 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 one or two additional compounds 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 one or two additional compounds 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. In a first embodiment of the fourth aspect the method further comprises administering one or two additional compounds 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 adminstering one or two additional compounds 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.

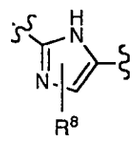
In a fifth embodiment of the fourth aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof and adminstering one or two additional compounds 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 portein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

Other embodiments of the present disclosure may comprise suitable combinations of two or more of embodiments and/or aspects disclosed herein.

Yet other embodiments and aspects of the disclosure will be apparent according to the description provided below.

The compounds of the present disclosure also exist as tautomers; therefore the present disclosure also encompasses all tautomeric forms.

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 accommodate a substitutent at any given location. For example, in the structure shown below



R^8 may be attached to either the carbon atom in the imidazole ring or, alternatively, R^8 may take the place of the hydrogen atom on the nitrogen ring to form an N-substituted imidazole.

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 (e.g., R^1, R^2, R^5, R^6, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. For example, when u is 2, each of the two R^1 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.

As used in the present specification, the following terms have the meanings indicated:

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, 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 "alkenyl," as used herein, refers to a straight or branched chain group of two to six carbon atoms containing at least one carbon-carbon double bond.

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

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

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

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

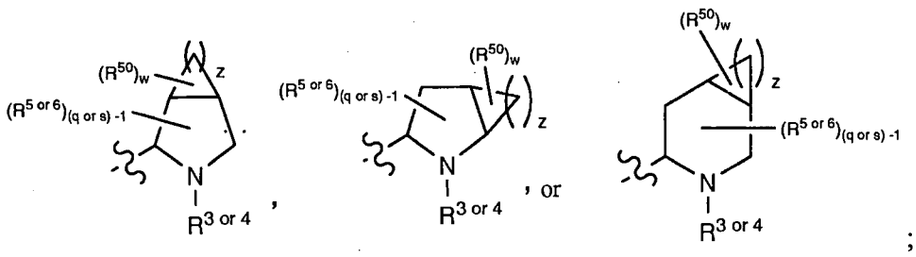
The term "alkoxyalkylcarbonyl," as used herein, refers to an alkoxyalkyl group attached to the parent molecular moiety through a carbonyl group.

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

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

The term "alkyl," as used herein, refers to a group derived from a straight or branched chain saturated hydrocarbon containing from one to six carbon atoms. In

the compounds of the present disclosure, when m and/or n is 1 or 2; X and/or Y is CHR^5 and/or CHR^6, respectively, and R^5 and/or R^6 is alkyl, each alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom to provide one of the structures shown below:



;

where z is 1, 2, 3, or 4, w is 0, 1, or 2, and R^{50} is alkyl. When w is 2, the two R^{50} alkyl groups may be the same or different.

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

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

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

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

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

The term "aryl," as used herein, refers to a phenyl group, or a bicyclic fused ring system wherein one or both of the rings is a phenyl group. Bicyclic fused ring systems consist of a phenyl group fused to a four- to six-membered aromatic or non-aromatic carbocyclic ring. The aryl groups of the present disclosure can be attached to the parent molecular moiety through any substitutable carbon atom in the group. Representative examples of aryl groups include, but are not limited to, indanyl, indenyl, naphthyl, phenyl, and tetrahydronaphthyl. The aryl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl,

hydroxy, hydroxyalkyl, nitro, $-NR^xR^y$, (NR^xR^y)alkyl, oxo, and $-P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

The term "arylalkenyl," as used herein, refers to an alkenyl group substituted with one, two, or three aryl groups.

The term "arylalkoxy," as used herein, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

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

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

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

The term "arylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three aryl groups. The alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, and $-NR^cR^d$, wherein the heterocyclyl is further optionally substitued with one or two substituents independently selected from alkoxy, alkyl, unsubstituted aryl, unsubstituted arylalkoxy, unsubstituted arylalkoxycarbonyl, halo, haloalkoxy, haloalkyl, hydroxy, and $-NR^xR^y$.

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

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

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

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

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

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

The terms "Cap" and "cap" as used herein, refer to the group which is placed on the nitrogen atom of the terminal nitrogen-containing ring, i.e., the pyrrolidine rings of compound 1e. It should be understood that "Cap" or "cap" can refer to the reagent used to append the group to the terminal nitrogen-containing ring or to the fragment in the final product, i.e., "Cap-51" or "The Cap-51 fragment found in LS-19".

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

The term "carboxy," as used herein, refers to $-CO_2H$.

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

The term "cycloalkyl," as used herein, refers to a saturated monocyclic, hydrocarbon ring system having three to seven carbon atoms and zero heteroatoms. Representative examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclopentyl, and cyclohexyl. The cycloalkyl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, hydroxyalkyl, nitro, and $-NR^xR^y$, wherein the aryl and the heterocyclyl are futher optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, hydroxy, and nitro.

The term "(cycloalkyl)alkenyl," as used herein, refers to an alkenyl group substituted with one, two, or three cycloalkyl groups.

The term "(cycloalkyl)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three cycloalkyl groups. The alkyl part of the (cycloalkyl)alkyl is further optionally substituted with one or two groups independently selected from hydroxy and $-NR^cR^d$.

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

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

The term "cycloalkylsulfonyl," as used herein, refers to a cycloalkyl group attached to the parent molecular moiety through a sulfonyl group.

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 "haloalkoxycarbonyl," as used herein, refers to a haloalkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "haloalkyl," as used herein, refers to an alkyl group substituted by one, two, three, or four halogen atoms.

The term "heterocyclyl," as used herein, refers to a four-, five-, six-, or seven-membered ring containing one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur. The four-membered ring has zero double bonds, the five-membered ring has zero to two double bonds, and the six- and seven-membered rings have zero to three double bonds. The term "heterocyclyl" also includes bicyclic groups in which the heterocyclyl ring is fused to another monocyclic heterocyclyl group, or a four- to six-membered aromatic or non-aromatic carbocyclic ring; as well as bridged bicyclic groups such as 7-azabicyclo[2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oc-2-tyl, and 2-azabicyclo[2.2.2]oc-3-tyl. The heterocyclyl groups of the present disclosure can be attached to the parent molecular moiety through any carbon atom or nitrogen atom in the group. Examples of heterocyclyl groups include, but are not limited to, benzothienyl, furyl, imidazolyl, indolinyl, indolyl, isothiazolyl, isoxazolyl, morpholinyl, oxazolyl, piperazinyl, piperidinyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrrolopyridinyl, pyrrolyl, thiazolyl, thienyl, thiomorpholinyl, 7-azabicyclo[2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oc-2-tyl, and 2-azabicyclo[2.2.2]oc-3-tyl. The heterocyclyl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^xR^y$, (NR^xR^y)alkyl, and oxo, wherein the alkyl part of the arylalkyl and the

heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

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

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

The term "heterocyclylalkoxycarbonyl," as used herein, refers to a heterocyclylalkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "heterocyclylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three heterocyclyl groups. The alkyl part of the heterocyclylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, aryl, halo, haloalkoxy, haloalkyl, hydroxy, and $-NR^cR^d$, wherein the aryl is further optionally substitued with one or two substituents independently selected from alkoxy, alkyl, unsubstituted aryl, unsubstitued arylalkoxy, unsubstituted arylalkoxycarbonyl, halo, haloalkoxy, haloalkyl, hydroxy, and $-NR^xR^y$.

The term "heterocyclylalkylcarbonyl," as used herein, refers to a heterocyclylalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "heterocyclylcarbonyl," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through a carbonyl group.

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

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

The term "heterocyclyloxycarbonyl," as used herein, refers to a heterocyclyloxy group attached to the parent molecular moiety through a carbonyl group.

The term "hydroxy," as used herein, refers to -OH.

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

The term "hydroxyalkylcarbonyl," as used herein, refers to a hydroxyalkyl group attached to the parent molecular moiety through a carbonyl group.

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. R^a and R^b are independently selected from hydrogen, alkenyl, and alkyl.

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^aR^b)carbonyl," as used herein, refers to an $-NR^aR^b$ group attached to the parent molecular moiety through a carbonyl group.

The term "$-NR^cR^d$," as used herein, refers to two groups, R^c and R^d, which are attached to the parent molecular moiety through a nitrogen atom. R^c and R^d are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, (NR^eR^f)alkyl, (NR^eR^f)alkylcarbonyl, (NR^eR^f)carbonyl, (NR^eR^f)sulfonyl, -C(NCN)OR', and -C(NCN)NR^xR^y, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

The term "(NR^cR^d)alkenyl," as used herein, refers to an alkenyl group substituted with one, two, or three $-NR^cR^d$ groups.

The term "(NR^cR^d)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three -NR^cR^d groups. The alkyl part of the (NR^cR^d)alkyl is further optionally substituted with one or two additional groups selected from alkoxy, alkoxyalkylcarbonyl, alkoxycarbonyl, alkylsulfanyl, arylalkoxyalkylcarbonyl, carboxy, heterocyclyl, heterocyclylcarbonyl, hydroxy, and (NR^eR^f)carbonyl; wherein the heterocyclyl is further optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

The term "(NR^cR^d)carbonyl," as used herein, refers to an -NR^cR^d group attached to the parent molecular moiety through a carbonyl group.

The term "-NR^eR^f," as used herein, refers to two groups, R^e and R^f, which are attached to the parent molecular moiety through a nitrogen atom. R^e and R^f are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, (NR^xR^y)alkyl, and (NR^xR^y)carbonyl.

The term "(NR^eR^f)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three -NR^eR^f groups.

The term "(NR^eR^f)alkylcarbonyl," as used herein, refers to an (NR^eR^f)alkyl group attached to the parent molecular moiety through a carbonyl group.

The term "(NR^eR^f)carbonyl," as used herein, refers to an -NR^eR^f group attached to the parent molecular moiety through a carbonyl group.

The term "(NR^eR^f)sulfonyl," as used herein, refers to an -NR^eR^f group attached to the parent molecular moiety through a sulfonyl group.

The term "-NR^xR^y," as used herein, refers to two groups, R^x and R^y, which are attached to the parent molecular moiety through a nitrogen atom. R^x and R^y are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted heterocyclyl, and ($NR^{x'}R^{y'}$)carbonyl, wherein $R^{x'}$ and $R^{y'}$ are independently selected from hydrogen and alkyl.

The term "(NR^xR^y)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three -NR^xR^y groups.

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 R is alkyl. The R groups may be the same or different.

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

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

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

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 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, dihydrobromide, diydrochloride, dihydroiodide, 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 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 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 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. Treatment may be 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 *Pharmaceutical Research* 1986, *3*(6), 318.

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

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* 2003, *38*, 1282; *Biochem. Biophys. Res. Commun.* 2004, *313*, 42; *J. Gastroenterol.* 2003, *38*, 567).

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		Cyclophilin Inhibitor	Novartis
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 Phamaceuticals Inc., New York, NY
Summetrel	Antiviral	antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
GS-9132 (ACH-806)	Antiviral	HCV Inhibitor	Achillion / Gilead
Pyrazolopyrimidine compounds and salts From WO-2005047288 26 May 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
XTL-6865 (XTL-002)	Antiviral	monoclonal antibody	XTL Biopharmaceuticals Ltd., Rehovot, Isreal
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

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Ribavirin	Antiviral	ribavirin	Schering-Plough Corporation, Kenilworth, NJ
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
IFN-β and EMZ701	Interferon	IFN-β and EMZ701	Transition Therapeutics Inc., Ontario, Canada

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Rebif	Interferon	IFN-β1a	Seróno, 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 Biopharmiceuticals 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
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

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
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

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.

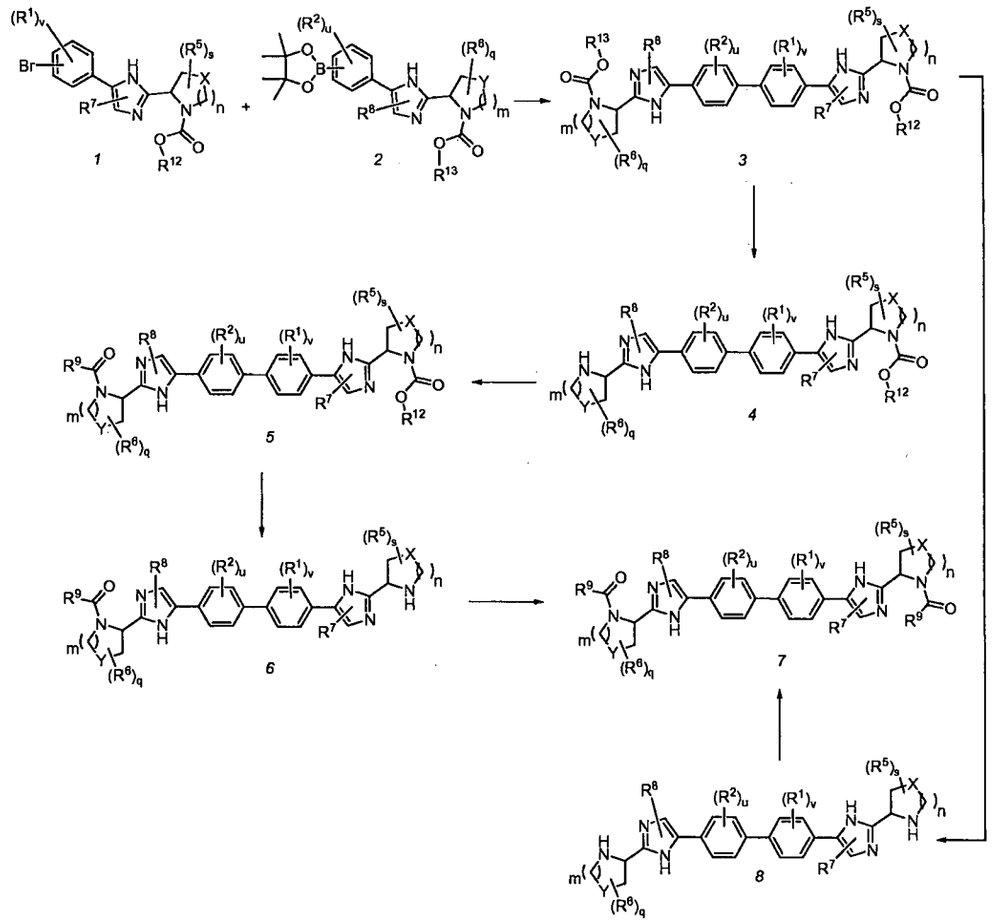
This disclosure is intended to encompass compounds having formula (I) when prepared by synthetic processes or by metabolic processes including those occurring in the human or animal body (*in vivo*) or processes occurring *in vitro*.

The abbreviations used in the present application, including particularly in the illustrative schemes and examples which follow, are well-known to those skilled in the art. Some of the abbreviations used are as follows: HATU for O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; Boc or BOC for tert-butoxycarbonyl; NBS for N-bromosuccinimide; tBu or t-Bu for tert-butyl; SEM for -(trimethylsilyl)ethoxymethyl; DMSO for dimethylsulfoxide; MeOH for methanol; TFA for trifluoroacetic acid; RT for room temperature or retention time (context will dictate); t_R for retention time; EDCI for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DMAP for 4-dimethylaminopyridine; THF for tetrahydrofuran; DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene; *t*-Bu; DEA for diethylamine; HMDS for hexamethyldisilazide; DMF for N,N-dimethylformamide; Bzl for benzyl; EtOH for ethanol; iPrOH or i-PrOH for isopropanol; Me_2S for dimethylsulfide; Et_3N or TEA for triethylamine; Ph for phenyl; OAc for acetate; EtOAc for ethyl acetate; dppf for 1,1'-bis(diphenylphosphino)ferrocene; iPr_2EtN or DIPEA for diisopropylethylamine; Cbz for carbobenzyloxy; n-BuLi for n-butyllithium; ACN for acetonitrile; h or hr for hours; m or min for minutes; s for seconds; LiHMDS for lithium hexamethyldisilazide; DIBAL for diisobutyl aluminum hydride; TBDMSCl for tert-butyldimethylsilyl chloride; Me for methyl; ca. for about; OAc for acetate; iPr for isopropyl; Et for ethyl; Bn for benzyl; and HOAT for 1-hydroxy-7-azabenzotriazole.

The compounds and processes of the present disclosure will be better understood in connection with the following synthetic schemes which illustrate the methods by which the compounds of the present disclosure may be prepared. Starting materials can be obtained from commercial sources or prepared by well-established literature methods known to those of ordinary skill in the art. It will be readily apparent to one of ordinary skill in the art that the compounds defined above can be synthesized by substitution of the appropriate reactants and agents in the syntheses shown below. It will also be readily apparent to one skilled in the art that the selective protection and deprotection steps, as well as the order of the steps themselves, can be carried out in varying order, depending on the nature of the variables to successfully complete the syntheses below. The variables are as defined above unless otherwise noted below.

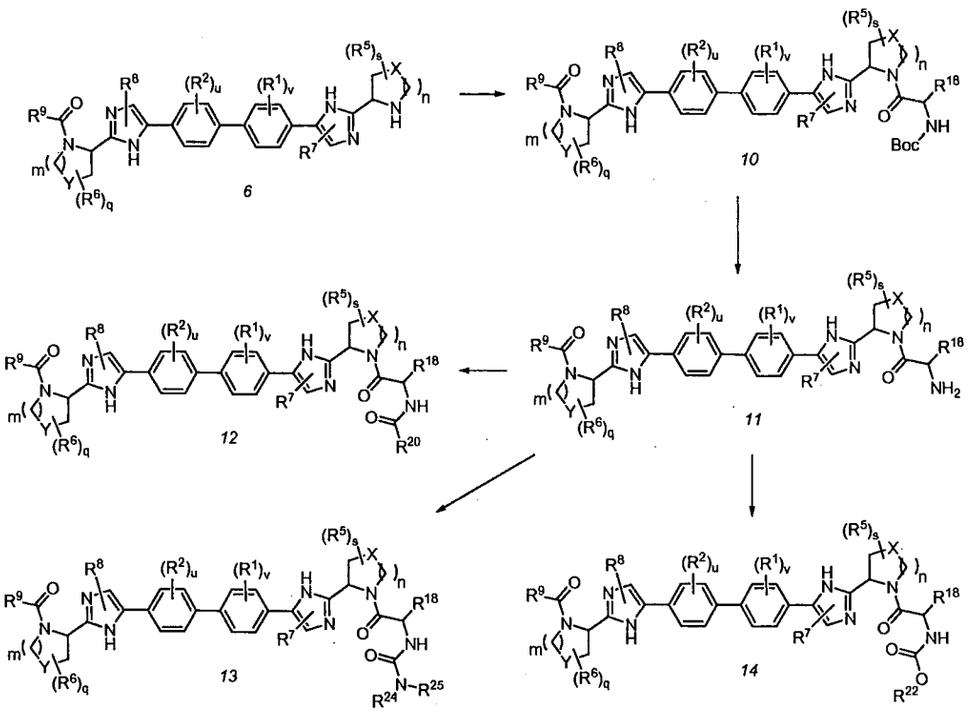
Scheme 1: Symmetric or Asymmetric Biphenyls

Aryl halide *1* and boronic ester *2* can be coupled to produce biaryl *3* using standard Suzuki-Miayura coupling conditions (*Angew Chem. Int. Ed. Engl* 2001, 40, 4544). It should be noted that the boronic acid analog of *2* may be used in place of the ester. Mono-deprotection of the pyrrolidine moiety may be accomplished when R^{12} and R^{13} are different. When R^{12} = benzyl, and R^{13} = t-butyl treatment to hydrogenolytic conditions produces *4*. For example, Pd/C catalyst in the presence of a base such as potassium carbonate can be used. Acylation of *4* can be accomplished under standard acylation conditions. A coupling reagent such as HATU in combination with an amine base such as Hunig's base can be used in this regard. Alternatively, *4* may be reacted with an isocyanate or carbamoyl chloride to provide compounds of formula *5* where R^9 is an amine. Further deprotection of *5* can be accomplished by treatment with strong acid such as HCl or trifluoroacetic acid. Standard conditions analogous to those used to convert *4* to *5* can be used to prepare *7* from *6*. In another embodiment where $R^{12} = R^{13}$ = t-Bu, direct conversion to *8* can be accomplished by treatment of *3* with strong acid such as HCl or trifluoroacetic acid. Conversion of *8* to *7* is accomplished in analogous fashion to the methods used to prepare *5* from *4* or *7* from *6*. In this instance however, the caps in *7* will be identical.



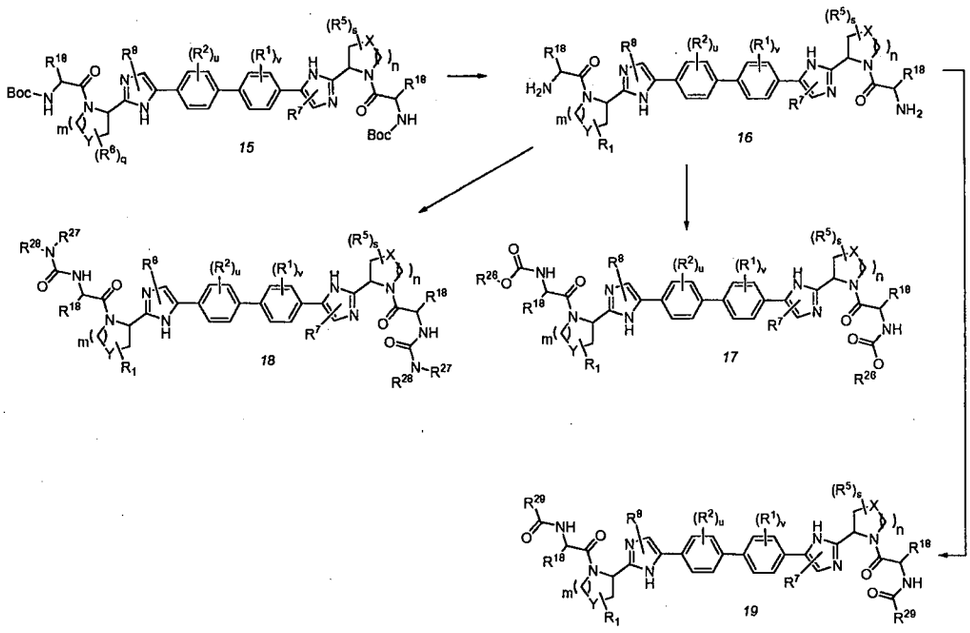
Scheme 2: Asymmetrically Capped Biphenyls

Conversion of *6* (from Scheme 1) to *10* can be done using standard amide coupling conditions such as HATU with an amine base, such as Hunig's base. Deprotection can be accomplished with strong acid such as HCl or trifluoroacetic acid affording *11*. Compound *11* can then be converted to *12*, *13*, or *14* using an acid chloride, an isocyanate or carbamoyl chloride, or a chloroformate respectively.



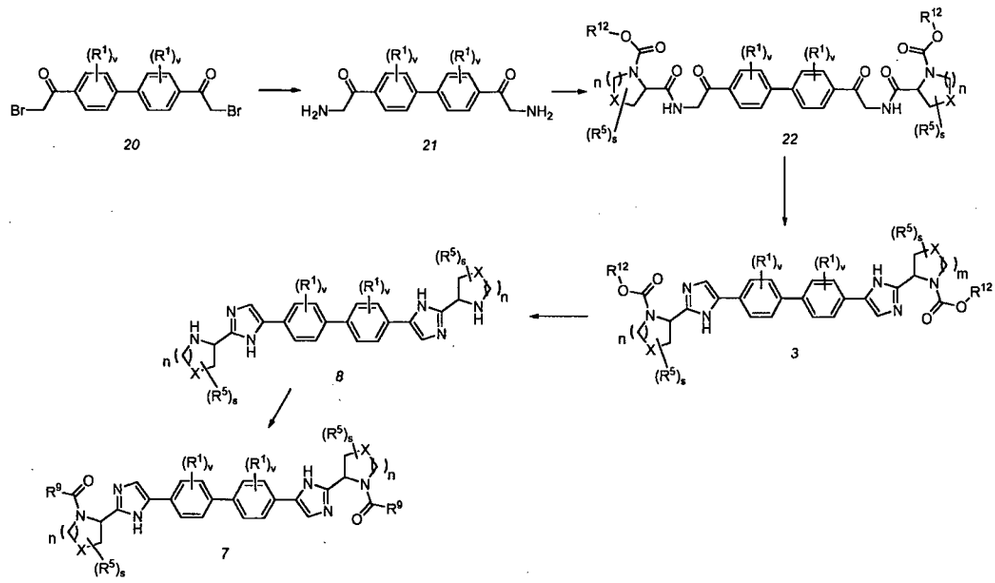
Scheme 3: Symmetric Cap Elaborated Biphenyls

Compound *15* (*15* = *7* (Scheme 1) wherein each R^9 is -CH(NHBoc)R^{18})can be converted to *16 via* treatment with strong acid such as HCl or trifluoroacetic acid. Compounds *17*, *18*, and *19* can be prepared from *16* by treating *16* with an appropriate chloroformate, isocyanate or carbamoyl chloride, or an acid chloride respectively.



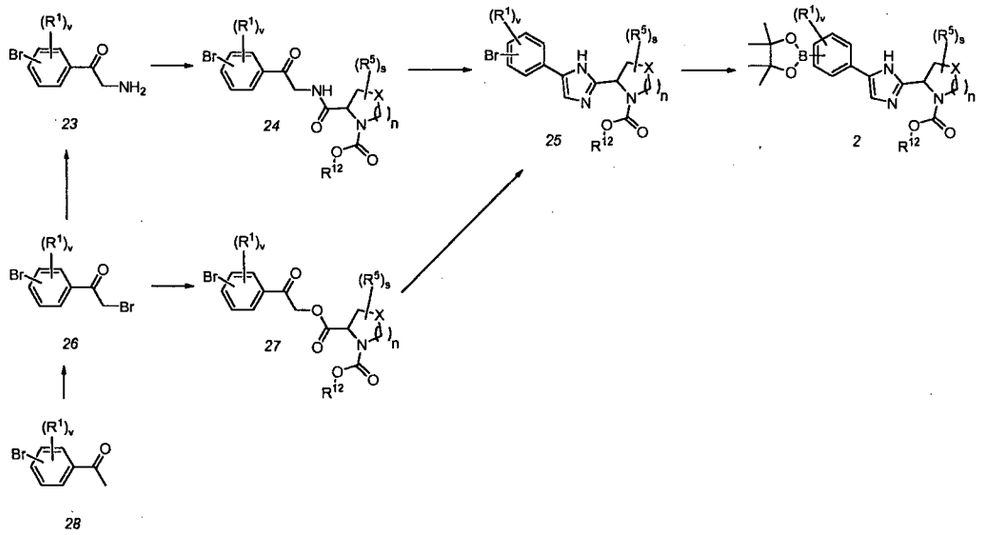
Scheme 4: Symmetric Biphenyls

Symmetrical biphenyl analogs (compounds of formula *7* where both halves of the molecule are equivalent) can be synthesized starting from bromoketone *20*. Amination by displacement with a nucleophile such as azide, phthalimide or preferably sodium diformylamide (Yinglin and Hongwen, *Synthesis* 1990, 122) followed by deprotection affords *21*. Condensation under standard amination conditions such as HATU and Hunig's base with an appropriately protected amino acid provides *22*. Heating with ammonium acetate under thermal or microwave conditions results in the formation of *3* which can be deprotected with strong acid such as HCl or trifluoroacetic acid ($R^{12} = R^{13}$ = t-Bu) or by hydrogenolysis with hydrogen gas and a transition metal catalyst such as Pd/C ($R^{12} = R^{13}$ = benzyl). Acylation can be affected with a carboxylic acid (R^9CO_2H) in a manner similar to the conversion of *21* to *22*. Urea formation can be accomplished by treatment with an appropriate isocycante ($R^9 = R^{24}R^{25}N$; R^{25} =H) or carbamoyl chloride ($R^9 = R^{24}R^{25}N$; R^{25} is other than hydrogen).



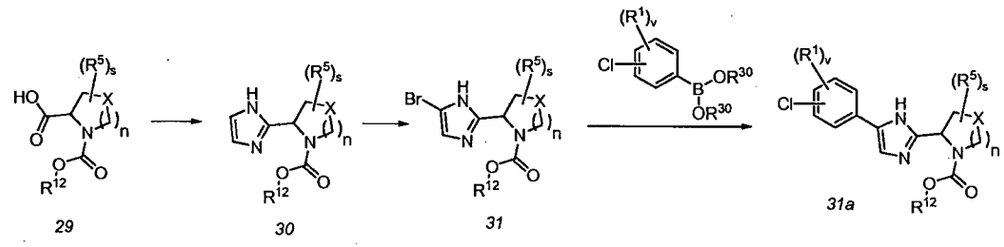
Scheme 5: Starting Materials 25 and 2

Scheme 5 describes the preparation of some of the starting materials required for the synthetic sequences depicted in Schemes 1-4. Key intermediate *25* (analogous to *1* in Scheme 1) is prepared from keto-amide *24* or keto-ester *27 via* heating with ammonium acetate under thermal or microwave conditions. Keto-amide *24* can be prepared from *23 via* condensation with an appropriate cyclic or acyclic amino acid under standard amide formation conditions. Bromide *26* can give rise to *23* by treatment with a nucleophile such as azide, phthalimide or sodium diformylamide (*Synthesis* 1990, 122) followed by deprotection. Bromide *26* can also be converted to *27* by reacting with an appropriate cyclic or acyclic N-protected amino acid in the presence of base such as potassium carbonate or sodium bicarbonate. Bromination of *28* with a source of bromonium ion such as bromine, NBS, or CBr_4 results in the formation of *26*. Bromide *25* can be converted to boronic ester *2 via* treatment with bis-pinacalotodiboron under palladium catalysis according to the method described in *Journal of Organic Chemistry* 1995, *60*, 7508, or variations thereof.



Scheme 6: Starting Material 31a

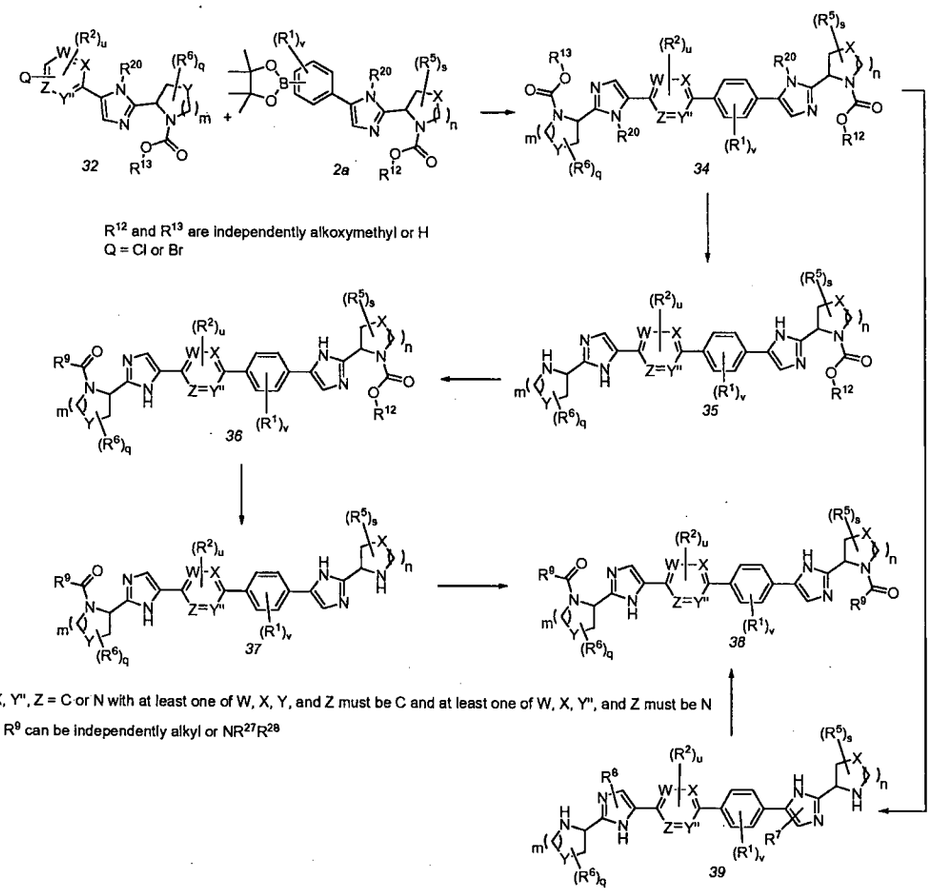
In another embodiment, starting materials such as *31a* (analogous to *25* in Scheme 5 and *1* in Scheme 1) may be prepared by reacting bromoimidazole derivatives *31* under Suzuki-type coupling conditions with a variety of chloro-substituted aryl boronic acids which can either be prepared by standard methodologies (see, for example, *Organic Letters* 2006, *8*, 305 and references cited therein) or purchased from commercial suppliers. Bromoimidazole *31* can be obtained by brominating imidazole *30* with a source of bromonium ion such as bromine, CBr_4, or N-bromosuccinimide. Imidazole *30* can be prepared from N-protected amino acids which are appropriately substituted by reacting with glyoxal in a methanolic solution of ammonium hydroxide.



Scheme 7: Heteroaryls

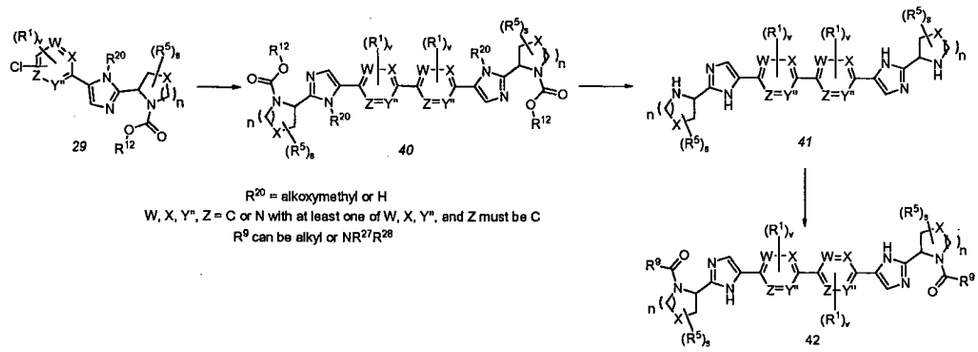
In yet another embodiment of the current disclosure, aryl halide *32* can be coupled under Suzuki-Miyaura palladium catalyzed conditions to form the heteroaryl derivative *34*. Compound *34* can be elaborated to *35* by treatment to hydrogenolytic conditions with hydrogen and a transition metal catalyst such as palladium on carbon

(R^{13} = benzyl). Acylation of *35* can be accomplished with an appropriate acid chloride (R^9COCl) in the presence of a base such as triethylamine, with an appropriately substituted carboxylic acid (R^9CO_2H) in the presence of a standard coupling reagent such as HATU, or with an isoscyanate ($R^{27}NCO$ wherein R^9 = $R^{27}R^{28}N$-; R^{28} =H)or carbamoyl chloride ($R^{27}R^{28}NCOCl$ wherein $R^9 = R^{27}R^{28}N$-). Compound *37* can be prepared from 36 (R^{12} = t-Bu) *via* treatment with strong acid such as HCl or trifluoroacetic acid. Acylation of the resulting amine in *37* to give *38* can be accomplished as in the transformation of *35* to *36*. In cases where $R^{12} = R^{13}$, *34* can be directly transformed into *39* by treatment with strong acid such as HCl or trifluoroacetic acid ($R^{12} = R^{13}$ = t-Bu) or by employing hydrogenolytic conditions with hydrogen and a transition metal catalyst such as palladium on carbon ($R^{12} = R^{13}$ = benzyl). Acylation of *39* can be accomplished in analogous fashion to that described for the transformation of *35* to *36*.



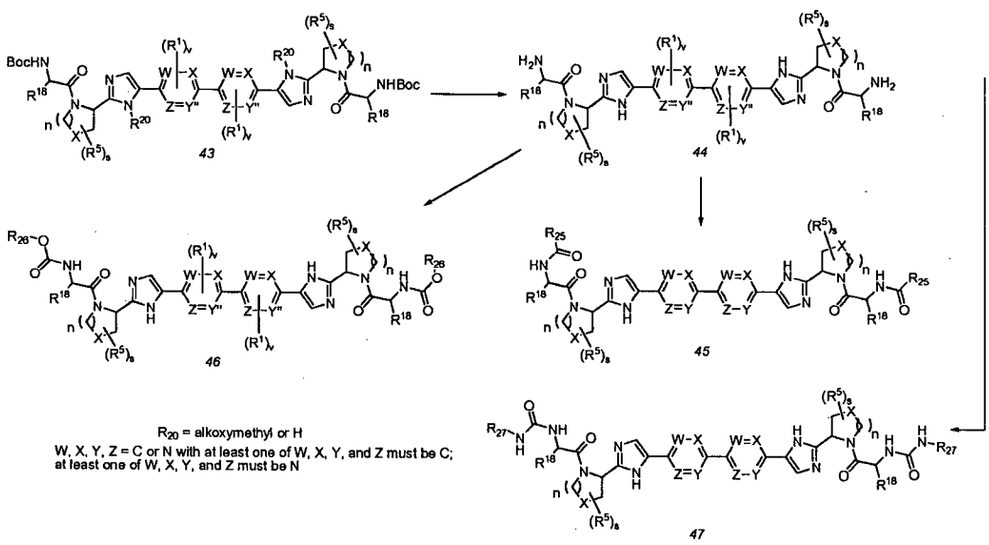
Scheme 8

Heteroaryl chloride *29* can be converted to symmetrical analog *40 via* treatment with a source of palladium such as dichlorobis(benzonitrile) palladium in the presence of tetrakis(dimethylamino)ethylene at elevated temperature. Removal of the SEM ether and Boc carbamates found in *40* can be accomplished in one step by treatment with a strong acid such as HCl or trifluoroacetic acid providing *41*. Conversion to *42* can be accomplished in similar fashion to the conditions used to convert *38* to *39* in Scheme 7.



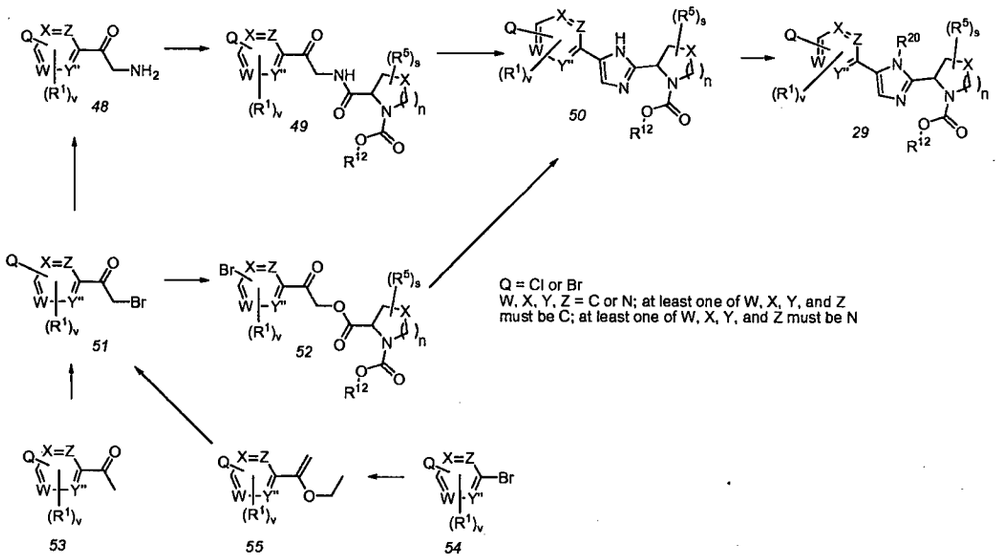
Scheme 9: Symmetric Cap Substituted Heteroaryls

Compound *43* (analogous to *42* wherein R_{23} = -CH(NHBoc)R_{24}) may be elaborated to *45*, *46*, and *47 via* similar methodologies to those described in Scheme 3. In cases where R_{20} = alkoxymethyl (ie; SEM), removal can be accomplished simultaneously with removal of the Boc carbamate (cf; *43* to *44*) using strong acid such as HCl or trifluoroacetic acid.



Scheme 10: Starting Material 29

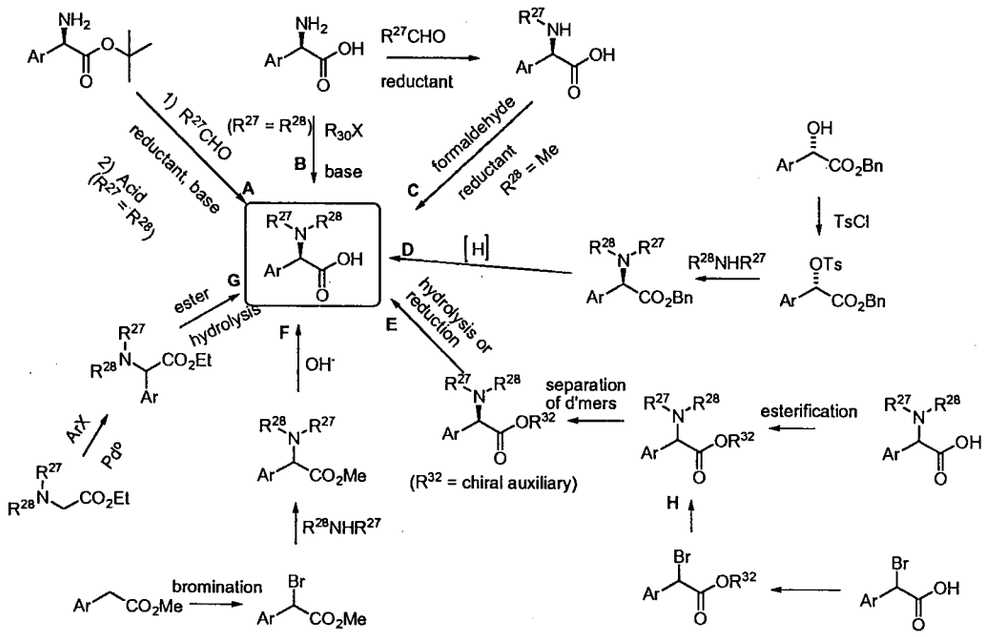
Heteroaryl bromides *54* may be reacted with a vinyl stannane such as tributyl(1-ethoxyvinyl)tin in the presence of a source of palladium such as dichlorobis(triphenylphosphine)palladium (II) to provide *55* which can be subsequently transformed into bromoketone *51 via* treatment with a source of bromonium ion such as N-bormosuccinimide, CBr_4, or bromine. Alternatively, keto-substituted heteroaryl bromides *53* may be directly converted to *51 via* treatment with a source of bromonium ion such as bromine, CBr_4, or N-bromosuccinimide. Bromide *51* can be converted to aminoketone *48 via* addition of sodium azide, potassium phthalimide or sodium diformylamide (*Synthesis* 1990 122) followed by deprotection. Aminoketone *48* can then be coupled with an appropriately substituted amino acid under standard amide formation conditions (i.e.; a coupling reagent such as HATU in the presence of a mild base such as Hunig's base) to provide *49*. Compound *49* can then be further transformed into imidazole *50 via* reacting with ammonium acetate under thermal or microwave conditions. Alternatively, *51* can be directly reacted with an appropriately substituted amino acid in the presence of a base such as sodium bicarbonate or potassium carbonate providing *52* which can in turn be reacted with ammonium acetate under thermal or microwave conditions to provide *50*. Imidazole *50* can be protected with an alkoxylmethyl group by treatment with the appropriate alkoxymethyl halide such as 2-(trimethylsilyl)ethoxymethyl chloride after first being deprotonated with a strong base such as sodium hydride.



Scheme 11: Substituted Phenylglycine Derivatives

Substituted phenylglycine derivatives can be prepared by a number of methods shown below. Phenylglycine t-butyl ester can be reductively alkylated (pathyway A) with an appropriate aldehyde and a reductant such as sodium cyanoborohydride in acidic medium. Hydrolysis of the t-butyl ester can be accomplished with strong acid such as HCl or trifluoroacetic acid. Alternatively, phenylglycine can be alkylated with an alkyl halide such as ethyl iodide and a base such as sodium bicarbonate or potassium carbonate (pathway B). Pathway C illustrates reductive alkylation of phenylglycine as in pathway A followed by a second reductive alkylation with an alternate aldehyde such as formaldehyde in the presence of a reducing agent and acid. Pathway D illustrates the synthesis of substituted phenylglycines *via* the corresponding mandelic acid analogs. Conversion of the secondary alcohol to a competent leaving group can be accomplished with p-toluensulfonyl chloride. Displacement of the tosylate group with an appropriate amine followed by reductive removal of the benzyl ester can provide substituted phenylglycine derivatives. In pathway E a racemic substituted phenylglycine derivative is resolved by esterification with an enantiomerically pure chiral auxiliary such as but not limited to (+)-1-phenylethanol, (-)-1-phenylethanol, an Evan's oxazolidinone, or enantiomerically pure pantolactone. Separation of the diastereomers is accomplished *via* chromatography (silica gel, HPLC, crystallization,

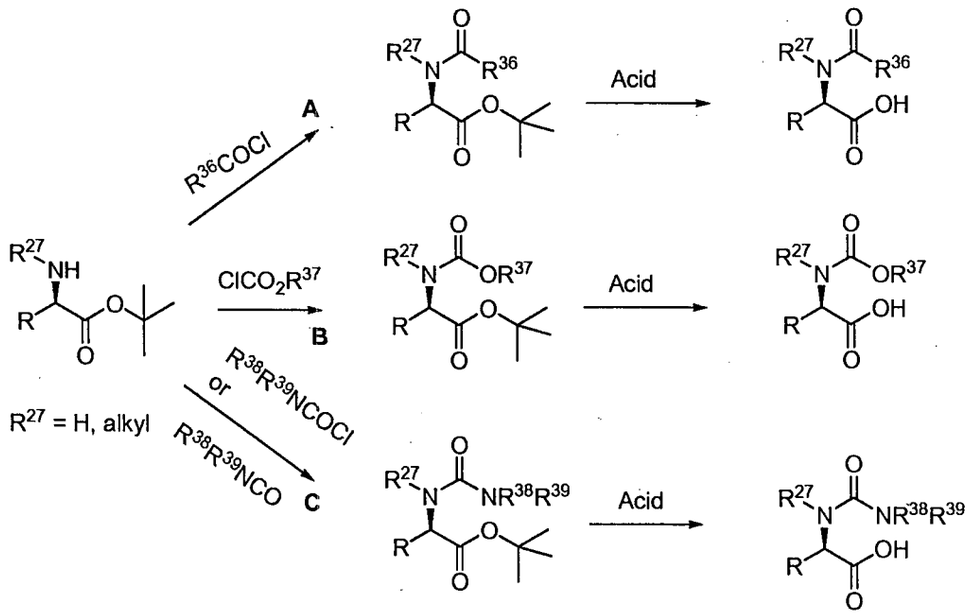
etc) followed by removal of the chiral auxiliary providing enantiomerically pure phenylglycine derivatives. Pathway H illustrates a synthetic sequence which intersects with pathway E wherein the aforementioned chiral auxiliary is installed prior to amine addition. Alternatively, an ester of an arylacetic acid can be brominated with a source of bromonium ion such as bromine, N-bromosuccinimide, or CBr_4. The resultant benzylic bromide can be displaced with a variety of mono- or disubstituted amines in the presence of a tertiary amine base such as triethylamine or Hunig's base. Hydrolysis of the methyl ester *via* treatment with lithium hydroxide at low temperature or 6N HCl at elevated temperature provides the substituted phenylglycine derivatives. Another method is shown in pathway G. Glycine analogs can be derivatized with a variety of aryl halides in the presence of a source of palladium (0) such as palladium bis(tributylphosphine) and base such as potassium phosphate. The resultant ester can then be hydrolyzed by treatment with base or acid. It should be understood that other well known methods to prepare phenylglycine derivatives exist in the art and can be amended to provide the desired compounds in this description. It should also be understood that the final phenylglycine derivatives can be purified to enantiomeric purity greater than 98%ee *via* preparative HPLC.



Scheme 12: Acylated Amino Acid Derivatives

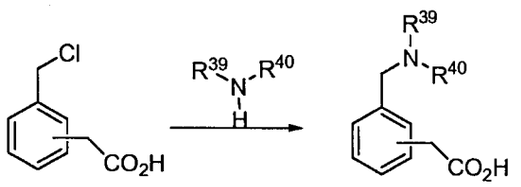
In another embodiment of the present disclosure, acylated phenylglycine derivatives may be prepared as illustrated below. Phenylglycine derivatives wherein

the carboxylic acid is protected as an easily removed ester, may be acylated with an acid chloride in the presence of a base such as triethylamine to provide the corresponding amides (pathway A). Pathway B illustrates the acylation of the starting phenylglycine derivative with an appropriate chloroformate while pathway C shows reaction with an appropriate isocyanate or carbamoyl chloride. Each of the three intermediates shown in pathways A – C may be deprotected by methods known by those skilled in the art (ie; treatment of the t-butyl ester with strong base such as HCl or trifluoroacetic acid).



Scheme 13

Amino-substituted phenylacetic acids may be prepared by treatment of a chloromethylphenylacetic acid with an excess of an amine.



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. The LC conditions employed in determining the retention time (RT) were:

Condition 1

Column = Phenomenex-Luna 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
Slovent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition 2

Column = Phenomenex-Luna 4.6X50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 2 min
Stop time = 3 min
Flow Rate = 5 mL/min
Wavelength = 220 nm
Slovent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition 3

Column = HPLC 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

Slovent A = 0.1% TFA in 10% methanol/90%H_2O

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

Condition M1

Column: Luna 4.6X 50 mm S10

Start %B = 0

Final %B = 100

Gradient time = 3 min

Stop time = 4 min

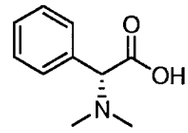
Flow rate = 4 mL/min

Solvent A: = 95% H_20: 5% CH_3CN, 10 mm Ammonium acetate

Solvent B: = 5% H_2O : 95% CH_3CN; 10 mm Ammonium acetate

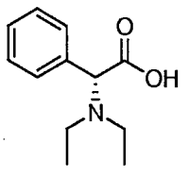
Synthesis of common caps

Cap-1



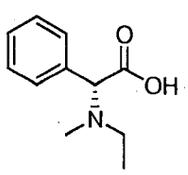
A suspension of 10% Pd/C (2.0g) in methanol (10 mL) was added to a mixture of (R)-2-phenylglycine (10g, 66.2 mmol), formaldehyde (33 mL of 37% wt. in water), 1N HCl (30 mL) and methanol (30 mL), and exposed to H_2 (60 psi) for 3 hours. The reaction mixture was filtered through diatomaceous earth (Celite®), 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]. ^1H 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. 1): 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 MeOH (100 mL), and stirred for 5 min. Acetaldehyde (10 mL) was added drop-wise over 10 min and stirring was continued at the same cooled temperature for 45 min and at ambient temperature for ~6.5 hr. The reaction mixture was cooled back with ice-water bath, treated with water (3 mL) and then quenched with a drop-wise addition of concentrated HCl over ~ 45 min until the pH of the mixture is ~ 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 over night, 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). ^1H NMR (DMSO-d_6, δ = 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. 1): RT = 0.43 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{18}NO_2$: 208.13; found 208.26

Cap-3

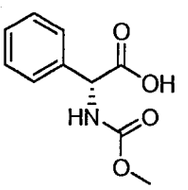


Acetaldehyde (5.0 mL, 89.1 mmol) and a suspension of 10% Pd/C (720 mg) in methanol/H_2O (4mL/1 mL) was sequentially added to a cooled (~ 15 °C) mixture of (R)-2-phenylglycine (3.096g, 20.48 mmol), 1N HCl (30 mL) and methanol (40 mL). The cooling bath was removed and the reaction mixture was stirred under 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. 1): 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. 1): 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

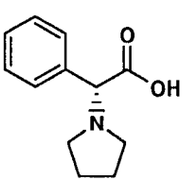


$ClCO_2Me$ (3.2 mL, 41.4 mmol) was added dropwise to a cooled (ice/water) THF (410 mL) semi-solution of (R)-tert-butyl 2-amino-2-phenylacetate/HCl (9.877 g, 40.52 mmol) and diisopropylethylamine (14.2 mL, 81.52 mmol) over 6 min, and stirred at similar temperature for 5.5 hours. The volatile component 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. 1): 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. 1): 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.

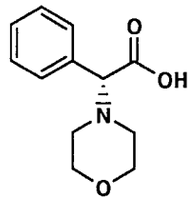
Cap-5



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

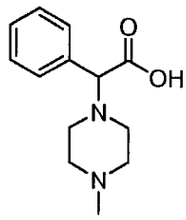
HPLC (water/methanol/TFA) to provide the TFA salt of *Cap*-5 as a semi-viscous white foam (1.0 g). ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) δ 10.68 (br s, 1H), 7.51 (m, 5H), 5.23 (s, 1H), 3.34 (app br s, 2H), 3.05 (app br s, 2H), 1.95 (app br s, 4H); RT = 0.30 min (Cond. 1); >98% homogeneity index; LC/MS: 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 min (Cond. 1); >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. 3); >90% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{22}H_{20}NaO_5S$: 419.09; found 419.04.

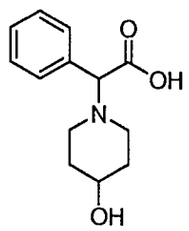
A THF (75 mL) solution of benzyl 2-phenyl-2-(tosyloxy)acetate (6.0 g, 15.1 mmol), 1-methylpiperazine (3.36 mL, 30.3 mmol) and N,N-diisopropylethylamine (13.2 mL, 75.8 mmol) was heated at 65 °C for 7 hours. The reaction was allowed to cool to ambient temperature and the volatile component was removed *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. 3); >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 min. 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. bs, 2H), 2.48-2.32 (m, 6H), 2.19 (s, 3H); RT = 0.31 (Cond. 2); >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.

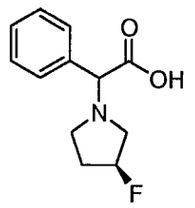
Cap-8



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. 2); >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.

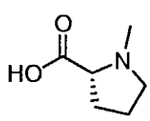
Cap-9



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 stereiosmers 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. 1); >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. 1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; found 224.14.

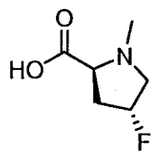
Cap-10



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

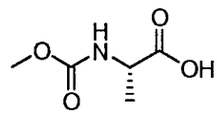
hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and concentrated *in vacuo* to provide *Cap*-10 as an off-white solid (2.15 g). ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) 3.42 (m, 1H), 3.37 (dd, *J* = 9.4, 6.1, 1H), 2.85-2.78 (m, 1H), 2.66 (s, 3H), 2.21-2.13 (m, 1H), 1.93-1.84 (m, 2H), 1.75-1.66 (m, 1H). RT = 0.28 (Cond. 2); >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. 2); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{11}FNO_2$: 148.08; found 148.06.

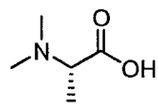
Cap-12



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),

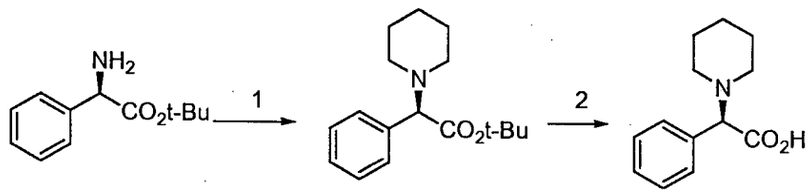
filtered, and concentrated *in vacuo* to provide a colorless oil (2.58 g). 500 mg of this material was purified by a reverse phase HPLC (H_2O/methanol/TFA) to provide 150 mg of *Cap*-12 as a colorless oil . ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) 7.44 (d, J = 7.3, 0.8H), 7.10 (br s, 0.2H), 3.97 (m, 1H), 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



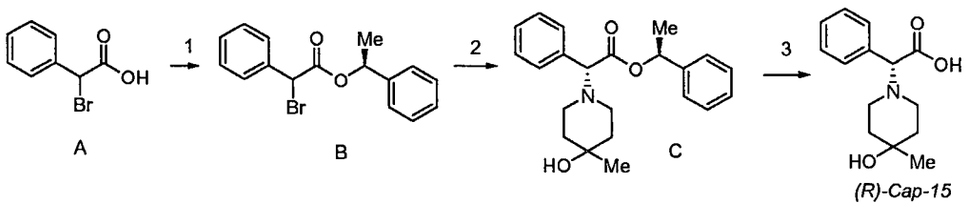
Cap-14

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}HNMR (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}HNMR (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

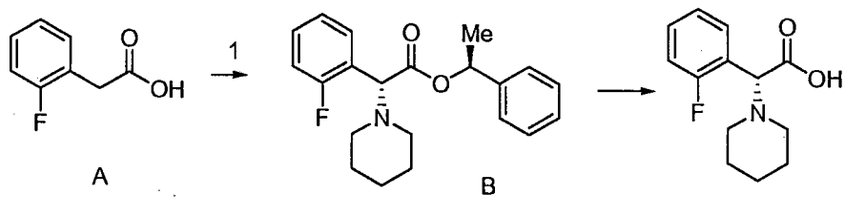
yellow oil. Flash chromatography (SiO_2/ hexane-ethyl acetate, 4:1) of this oil provided the title compound (11.64 g, 73%) as a white solid. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.53-7.17 (m, 10H), 5.95 (q, J = 6.6 Hz, 0.5H), 5.94 (q, J = 6.6 Hz, 0.5H), 5.41 (s, 0.5H), 5.39 (s, 0.5H), 1.58 (d, J = 6.6 Hz, 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}HNMR (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}HNMR (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

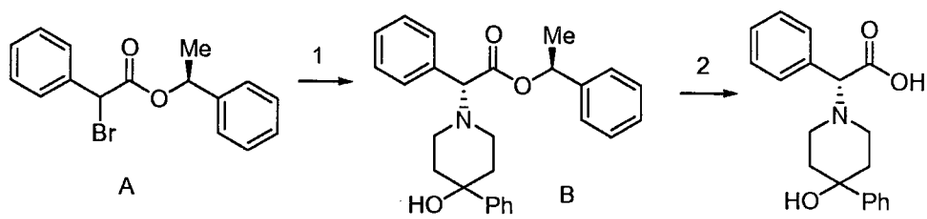
Step 1; (S)-1-Phenylethyl 2-(2-fluorophenyl)acetate: A mixture of 2-fluorophenylacetic acid (5.45 g, 35.4 mmol), (S)-1-phenylethanol (5.62 g, 46.0 mmol), EDCI (8.82 g, 46.0 mmol) and DMAP (0.561 g, 4.60 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 12 hours. The solvent was then concentrated 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}HNMR (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}HNMR) 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}HNMR (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%). ^{1}HNMR (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

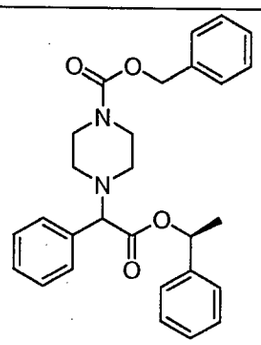


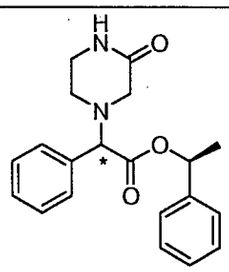
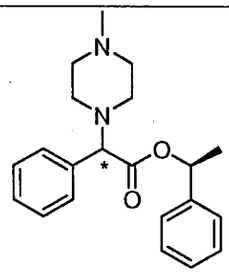
(R)-Cap-17

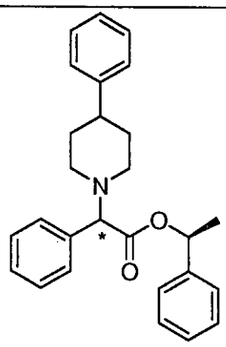
Step 1; (S)-1-Phenylethyl (R)-2-(4-hydroxy-4-phenylpiperidin-1-yl)- 2-phenylacetate: To a solution of (S)-1-phenylethyl 2-bromo-2-phenylacetate (1.50 g, 4.70 mmol) in THF (25 mL) was added triethylamine (1.31 mL, 9.42 mmol), followed by tetrabutylammonium iodide (0.347 g, 0.94 mmol). The reaction mixture 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 ^{1}HNMR. 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}HNMR (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: ^{1}HNMR (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 employing step 1 in the synthesis of *Cap*-17.

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: $C_{28}H_{30}N_2O_4$ 458.55; Found: 459.44 $(M+H)^+$.

		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: $C_{28}H_{30}N_2O_4$ 458.55; Found: 459.44 $(M+H)^+$.
Intermediate -17b		Diastereomer 1: RT = 11.76 min (Cond'n II); LCMS: Anal. Calcd. for: $C_{20}H_{22}N_2O_3$ 338.4 Found: 339.39 $(M+H)^+$; Diastereomer 2: RT = 10.05 min (Cond'n II); LCMS: Anal. Calcd. for: $C_{20}H_{22}N_2O_3$ 338.4; Found: 339.39 $(M+H)^+$.
Intermediate -17c		Diastereomer 1: T_R = 4.55 min (Cond'n I); LCMS: Anal. Calcd. for: $C_{21}H_{26}N_2O_2$ 338.44 Found: 339.45 $(M+H)^+$; Diastereomer 2: T_R = 6.00 min (Cond'n I); LCMS: Anal. Calcd. for: $C_{21}H_{26}N_2O_2$ 338.44 Found: 339.45 $(M+H)^+$.

Intermediate -17d		Diastereomer 1: RT = 7.19 min (Cond'n I); LCMS: Anal. Calcd. for: $C_{27}H_{29}NO_2$ 399.52 Found: 400.48 $(M+H)^+$; Diastereomer 2: RT = 9.76 min (Cond'n I); LCMS: Anal. Calcd. for: $C_{27}H_{29}NO_2$ 399.52 Found: 400.48 $(M+H)^+$.

Chiral SFC Conditions for determining retention time for intermediates 17b-17d

Condition 1

Column: Chiralpak AD-H Column, 4.6X250 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

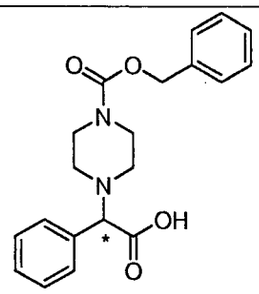
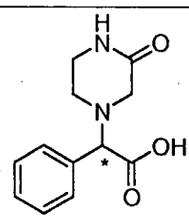
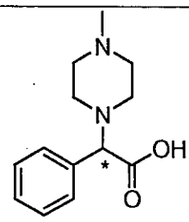
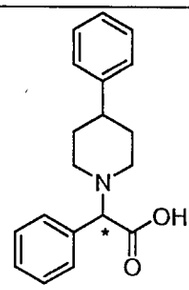
Condition 2

Column: Chiralcel OD-H Column, 4.6X250 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; found: 312 $(M+H)^+$.

The following carboxylic acids were prepared in a similar fashion:

Cap-17a		RT = 2.21 (Cond'n II); ^1H 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: $C_{20}H_{22}N_2O_4$ 354.40; Found: 355.38 $(M+H)^+$.
Cap-17b		RT = 0.27 (Cond'n III); LCMS: Anal. Calcd. for: $C_{12}H_{14}N_2O_3$ 234.25; Found: 235.22 $(M+H)^+$.
Cap-17c		RT = 0.48 (Cond'n II); LCMS: Anal. Calcd. for: $C_{13}H_{18}N_2O_2$ 234.29; Found: 235.31 $(M+H)^+$.
Cap-17d		RT = 2.21 (Cond'n I); LCMS: Anal. Calcd. for: $C_{19}H_{21}NO_2$ 295.38; Found: 296.33 $(M+H)^+$.

LCMS Conditions for determining retention time for Caps 17a-17d

Condition 1

Column: Phenomenex-Luna 4.6 X 50 mm S10

Start % B = 0

Final % 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 2

Column: Waters-Sunfire 4.6 X 50 mm S5

Start % B = 0

Final % 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 3

Column: Phenomenex 10μ 3.0 X 50 mm

Start % B = 0

Final % B = 100

Gradient Time = 2 min

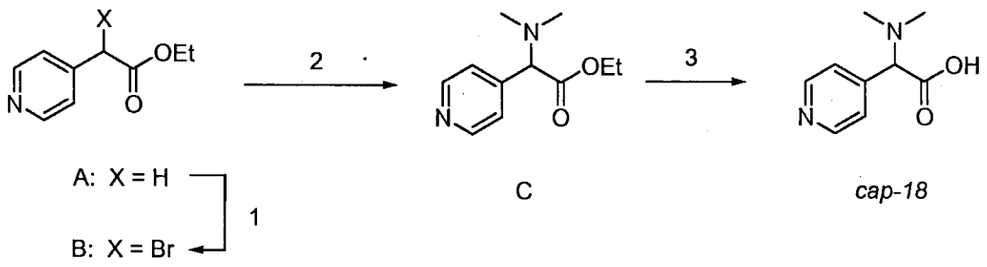
Flow Rate = 4 mL/min

Wavelength = 220

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

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

Cap-18



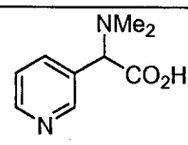
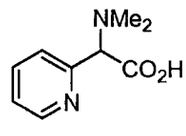
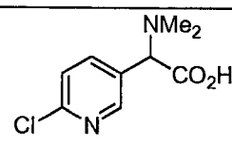
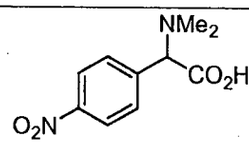
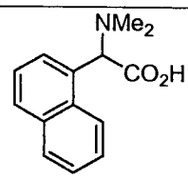
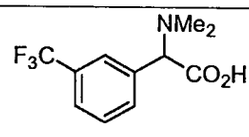
Step 1; (R,S)-Ethyl 2-(4-pyridyl)-2-bromoacetate: To a solution of ethyl 4-pyridylacetate (1.00 g, 6.05 mmol) in dry THF (150 mL) at 0 °C under argon was added DBU (0.99 mL, 6.66 mmol). The reaction mixture was allowed to warm to room temperature over 30 minutes and then it was cooled to -78 °C. To this 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. ^{1}HNMR (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 $(M+H)^+$.

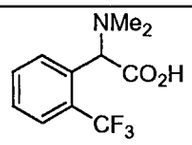
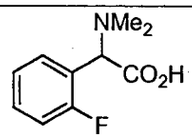
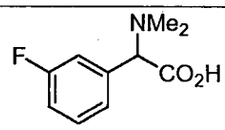
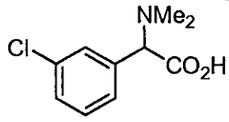
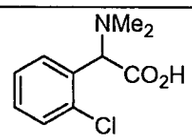
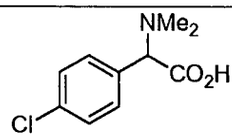
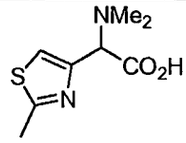
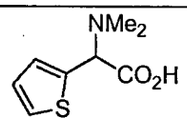
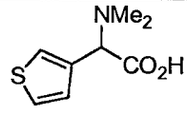
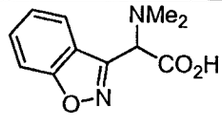
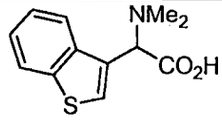
Step 2; (R,S)-Ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate: To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-bromoacetate (1.40 g, 8.48 mmol) in DMF (10 mL) at room temperature was added dimethylamine (2M in THF, 8.5 mL, 17.0 mmol). After completion of the reaction (as judged by tlc) the volatiles were 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}HNMR (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 $(M+H)^+$.

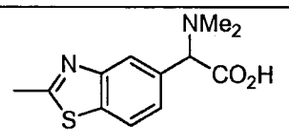
Step 3; (R,S)-2-(4-Pyridyl)-2-(N,N-dimethylamino)acetic acid: To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate (0.200 g, 0.960 mmol) in a mixture of THF-methanol-H_2O (1:1:1, 6 mL) was added powdered LiOH (0.120 g,

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}HNMR (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).

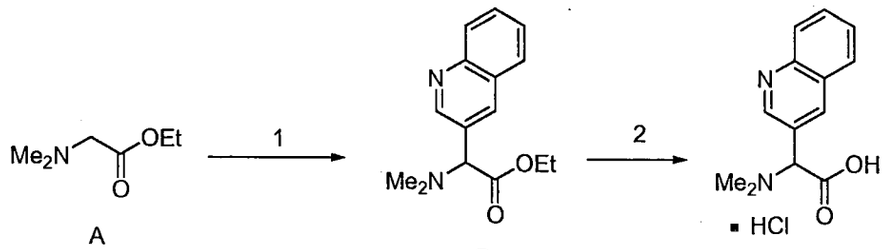
The following examples were prepared in similar fashion using the method described above.

Cap-19		LCMS: Anal. Calcd. for $C_9H_{12}N_2O_2$: 180; found: 181 $(M+H)^+$.
Cap-20		LCMS: no ionization. ^{1}HNMR (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 $C_{14}H_{15}NO_2$: 247; found: 248 $(M+H)^+$.
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 $C_{10}H_{12}FNO_2$: 247; found: 248 $(M+H)^+$.
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, 215; found: 214, 217 $(M+H)^+$.
Cap-29		LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213, 215; found: 214, 217 $(M+H)^+$.
Cap-30		LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213, 215; found: 214, 217 $(M+H)^+$.
Cap-31		LCMS: Anal. Calcd. for $C_8H_{11}N_2O_2S$: 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 $(M+H)^+$.

Cap-37



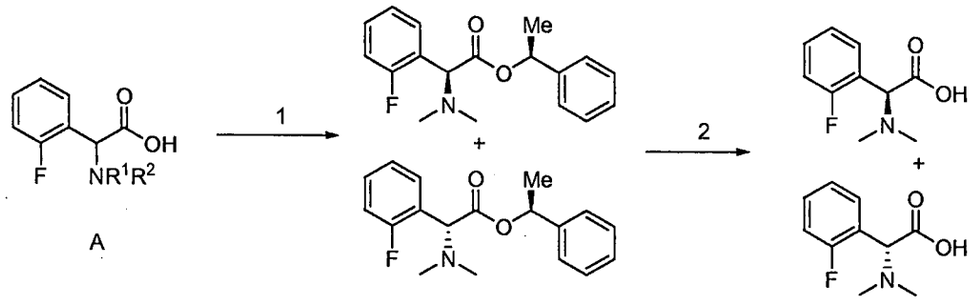
cap-37

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. ^{1}HNMR (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}HNMR (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}HNMR (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%). ^{1}HNMR (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.

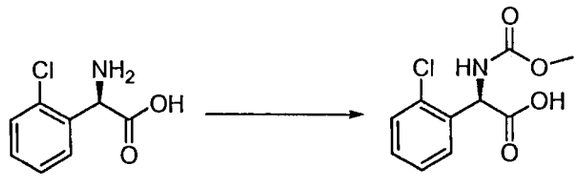
Cap-39



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%). ^{1}H 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, 215; found: 214, 216 $(M+H)^+$.

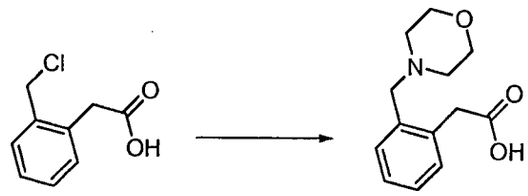
Cap-40



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, 245; found: 244, 246 $(M+H)^+$.

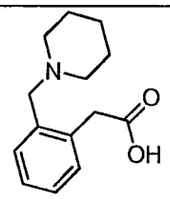
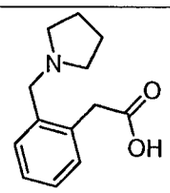
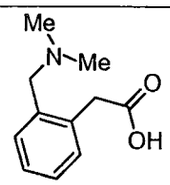
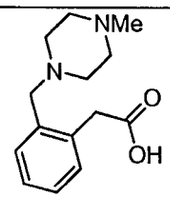
Cap-41



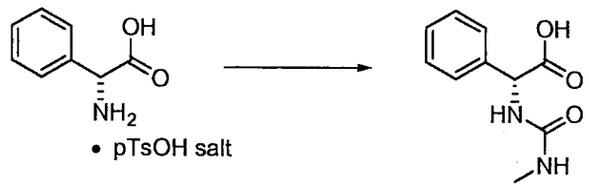
cap-41

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}HNMR (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 caps 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-45

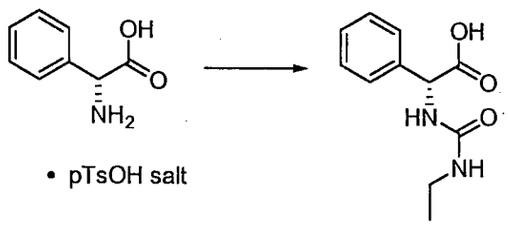


Cap-45

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

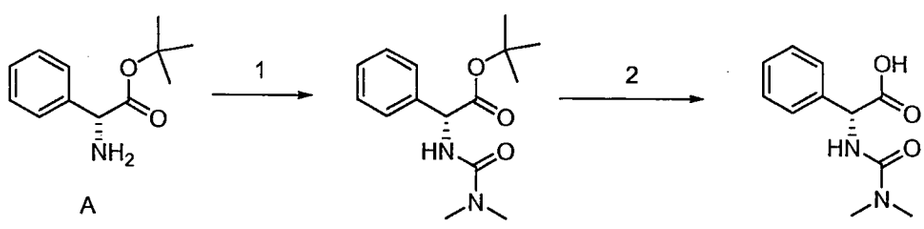


cap-46

The desired product was prepared according to the method described for *Cap-45*. ^{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 209.121 $(M+H)^+$.

HPLC XTERRA C-18 3.0 × 506 mm, 0 to 100% B over 2 minutes, 1 minutes 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

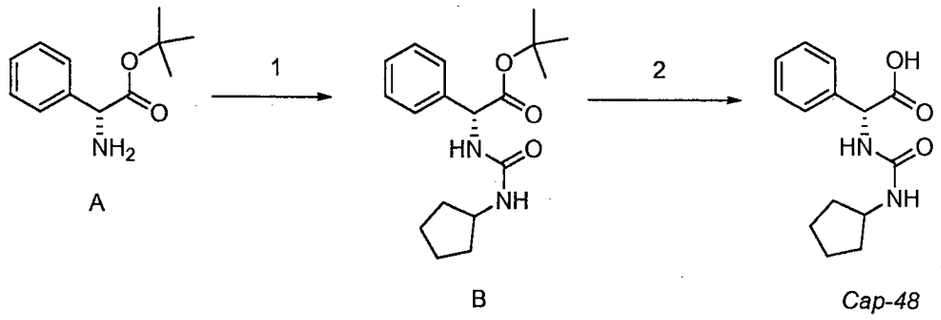


Step 1; (R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate: To a stirred solution of (R)-tert–butyl-2-amino-2-phenylacetate (1.0 g, 4.10 mmol) and Hunig's

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. ^1H 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 minutes 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 h. 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. ^1H 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 minutes 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. ^{1}H 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 minutes 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 minutes 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.

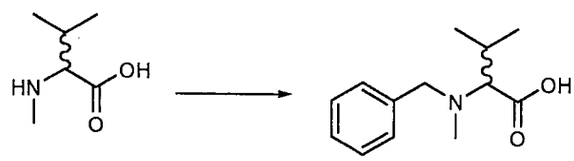
Cap-49



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. ^1H 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: $C_{10}H_{13}NO_2$ 179.22; Found: 180.20 $(M+H)^+$.

Cap-50

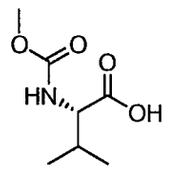


Cap-50

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,

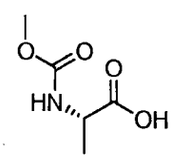
detection at 220 nm, flow rate 40 mL/min, 20 to 80% B over 6 min; A = 90% water, 10 % methanol, 0.1% TFA, B = 10% water, 90 % methanol, 0.1% TFA) to provide 2-(benzyl(methyl)amino)-3-methylbutanoic acid, TFA salt (126 mg, 19%) as a colorless wax. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.98 (d, 3H) 1.07 (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: $C_{13}H_{19}NO_2$ 221.30; 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 drop-wise 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 ($MgSO_4$), filtered, and concentrated *in vacuo* to afford *Cap*-51 as a white solid (6 g). ^{1}H NMR for the dominant rotamer (DMSO-d_6, δ = 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

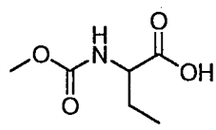
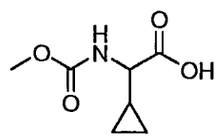
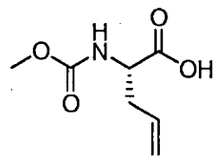
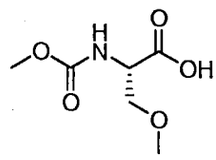
Cap-52

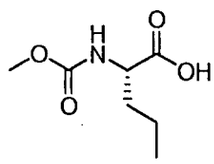
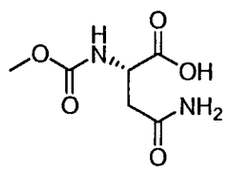
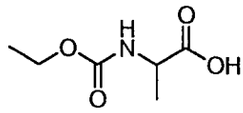
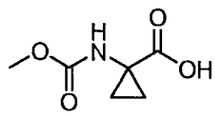
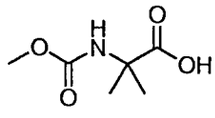


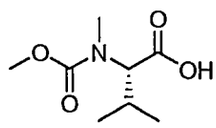
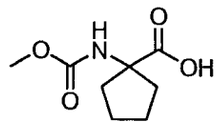
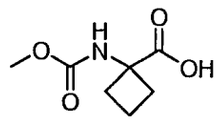
Cap-52 was synthesized from L-alanine according to the procedure described for the synthesis of *Cap*-51. For characterization purposes, a portion of the crude material was purified by a reverse phase HPLC (H_2O/MeOH/TFA) to afford *Cap*-52 as a colorless viscous oil. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 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).

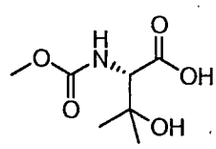
Cap-53 to -64 were prepared from appropriate starting materials according to the procedure described for the synthesis of *Cap*-51, with noted modifications if any.

Cap	Structure	Data
Cap-53a: (R) *Cap-53b*: (S)		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 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 (bs, 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

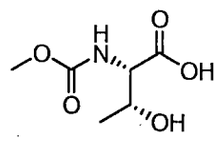


Methyl chloroformate (0.65 mL, 8.39 mmol) was added dropwise over 5 min to a cooled (ice-water) mixture of Na_2CO_3 (0.449 g, 4.23 mmol), NaOH (8.2 mL of 1M/H_2O, 8.2 mmol) and (*S*)-3-hydroxy-2-(methoxycarbonylamino)-3-methylbutanoic acid (1.04 g, 7.81 mmol). The reaction mixture was stirred for 45 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, δ = 2.5 ppm, 400 MHz): δ 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).

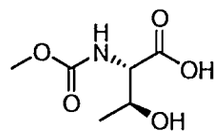
Cap-66 and -67 were prepared from appropriate commercially available starting materials by employing the procedure described for the synthesis of *Cap*-65.

Cap-66



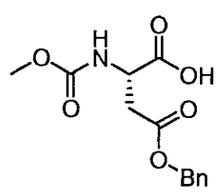
^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.58 (br s, 1H), 7.07 (d, *J* = 8.3, 0.13H), 6.81 (d, *J* = 8.8, 0.67H), 4.10-4.02 (m, 1.15H), 3.91 (dd, *J* = 9.1, 3.5, 0.85H), 3.56 (s, 3H), 1.09 (d, *J* = 6.2, 3H). [Note: only the dominant signals of NH were noted]

Cap-67



^{1}H NMR (DMSO-d_6, δ = 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]

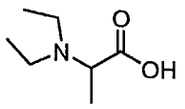
Cap-68



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.

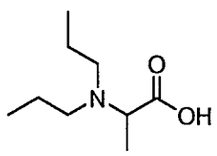
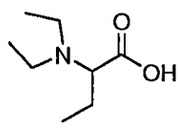
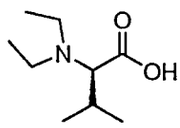
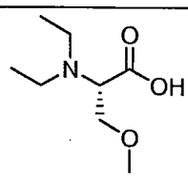
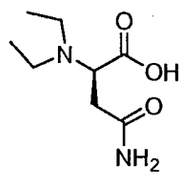
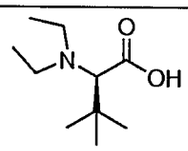
Cap-69a and -69b



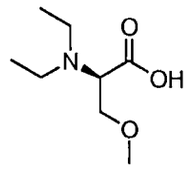
Cap-69a: (R)-enantiomer
Cap-69b: (S)-enantiomer

$NaCNBH_3$ (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. ^{1}H 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).

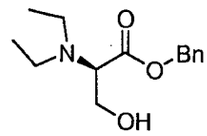
Cap-70 to -74x were prepared according to the procedure described for the synthesis of *Cap*-69 by employing appropriate starting materials.

Cap-70a: (R) *Cap-70b*: (S)		^{1}H 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)		^{1}H 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		^{1}H 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		^{1}H 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



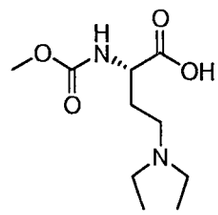
$NaBH_3CN$ (1.6 g, 25.5 mmol) was added to a cooled (ice/water bath) water (25 ml)/methanol (15 ml) solution of H-D-Ser-OBzl HCl (2.0 g, 8.6 mmol). Acetaldehyde (1.5 ml, 12.5 mmol) was added drop-wise over 5 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition 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). ^1H 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

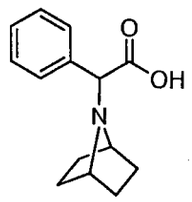


$NaCNBH_3$ (1.60 g, 24.2 mmol) was added in batches to a chilled (~15 °C) water/MeOH (12 mL each) solution of (*S*)-4-amino-2-(tert-butoxycarbonylamino) butanoic acid (2.17 g, 9.94 mmol). A few minutes later acetaldehyde (2.7 mL, 48.1 mmol) was added drop-wise over 2 min, the cooling bath was removed, 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, δ = 3.29 ppm, 400 MHz): δ 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.

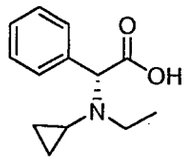
Cap-77a and -77b



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 $[M+H]^+$ $C_{14}H_{18}BrNO_2$: 232.13; found 232.18. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{18}BrNO_2$: 232.1338; found 232.1340.

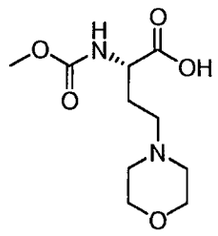
Cap-78



$NaCNBH_3$ (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). ^1H 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



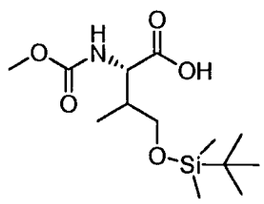
Ozone was bubbled through a cooled (-78 °C) CH_2Cl_2 (5.0 mL) solution *Cap*-55 (369 mg, 2.13 mmol) for about 50 min until the reaction mixture attained a tint of blue color. Me_2S (10 pipet drops) was added, and the reaction mixture was stirred for 35 min. The -78 °C bath was replaced with a -10 °C 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, δ = 2.5 ppm, 400 MHz): δ 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, δ = 2.5 ppm, 400 MHz): δ 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 (^1H 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 ^1H NMR data (DMSO-d_6, δ = 2.5 ppm, 400 MHz): major diastereomer, δ 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, δ 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, δ = 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, δ = 2.5 ppm, 400 MHz), 7.82 (d, *J* = 3.0, 1H), 7.80 (d, *J* = 3.1, 1H), 7.39-7.10 (m,

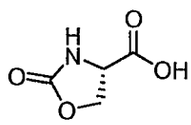
16H), 4.66 (d, J = 12.4, 1H), 4.39 (d, J = 12.4, 1H), 3.61 (dd, J = 9.9, 5.6, 1H), 3.45 (d, J = 9.5, 1H), 3.41 (dd, J = 10, 6.2, 1H), 2.55 (dd, J = 9.5, 7.3, 1H), 1.74 (m, 1H), 0.77 (s, 9H), 0.61 (d, J = 7.1, 3H), -0.06 (s, 3H), -0.08 (s, 3H).

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, δ = 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, δ = 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, δ = 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: ^{1}H NMR ($CDCl_3$, δ = 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.

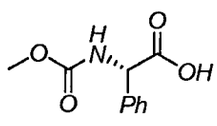
Cap-81



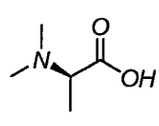
Prepared according to the protocol described by Falb et al. *Synthetic Communications* 1993, *23*, 2839.

Cap-82 to Cap-85

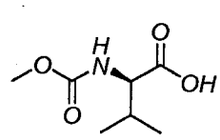
Cap-82 to *Cap*-85 were synthesized from appropriate starting materials according to the procedure described for *Cap*-51. The samples exhibited similar spectral profiles as that of their enantiomers (i.e., *Cap*-4, *Cap*-13, *Cap*-51 and *Cap*-52, respectively)



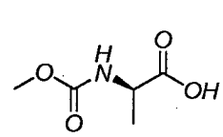
Cap-82



Cap-83

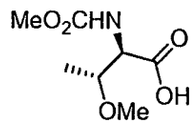


Cap-84



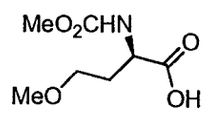
Cap-85

Cap-86



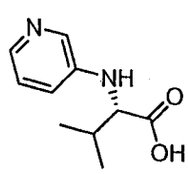
To a mixture of O-methyl-L-threonine (3.0 g, 22.55 mmol), NaOH (0.902 g, 22.55 mmol) in H_2O (15 mL) was added $ClCO_2Me$ (1.74 mL, 22.55 mmol) dropwise at 0°C. The mixture was allowed to stir for 12 h and acidified to pH 1 using 1N HCl. The aqueous phase was extracted with EtOAc and (2x250 mL) and 10% 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



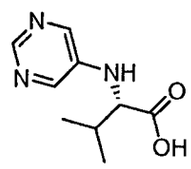
To a mixture of L-homoserine (2.0 g, 9.79 mmol), Na_2CO_3 (2.08 g, 19.59 mmol) in H_2O (15 mL) was added $ClCO_2Me$ (0.76 mL, 9.79 mmol) dropwise at 0°C. The mixture was allowed to stir for 48 h and acidified to pH 1 using 1N HCl. The aqueous phase was extracted with EtOAc and (2X250 mL) and the combined organic phases were concentrated under *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 $(M+H)^+$.

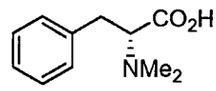
Cap-89



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

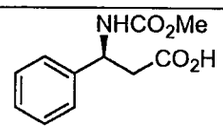
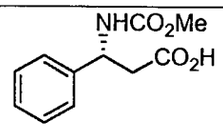
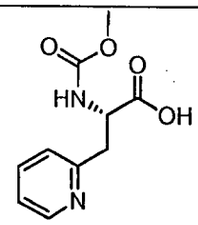
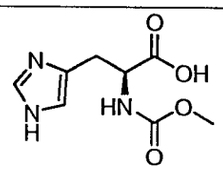
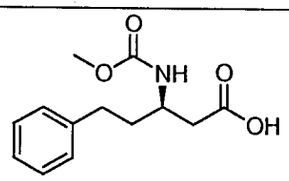
could not be estimated. The material was used as is in subsequent reactions. LCMS: Anal. Calcd. for $C_9H_{13}N_3O_2$: 195; found: 196 $(M+H)^+$.

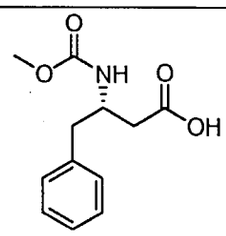
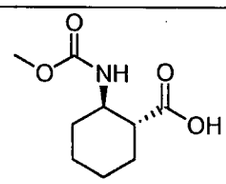
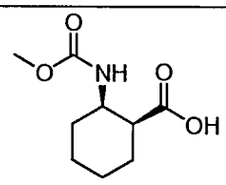
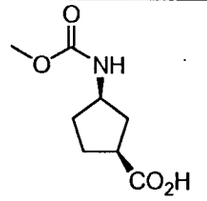
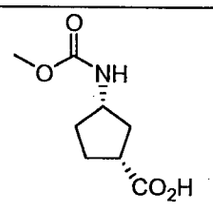
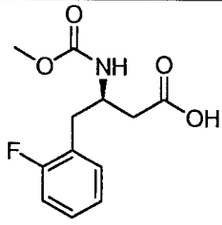
Cap–90

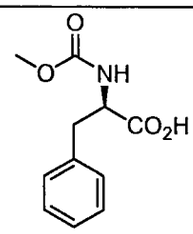
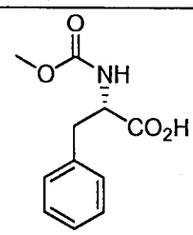
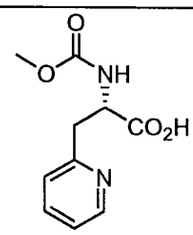
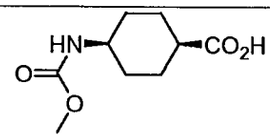
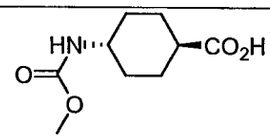
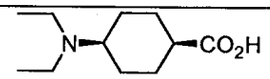


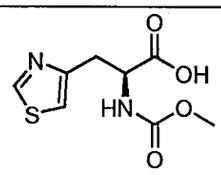
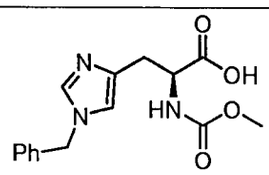
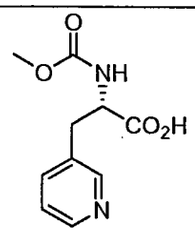
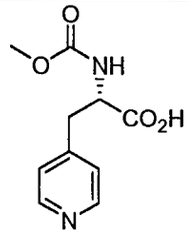
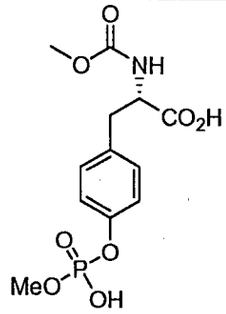
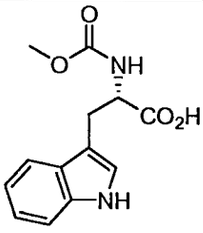
Cap-90 was prepared according to the method described for the preparation of *Cap*-1. The crude material was used as is in subsequent steps. LCMS: Anal. Calcd. for $C_{11}H_{15}NO_2$: 193; found: 192 $(M-H)^-$.

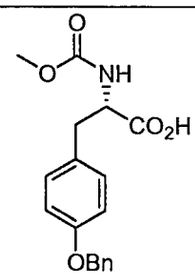
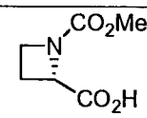
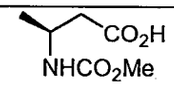
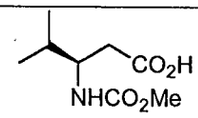
The following caps were prepared according to the method of *Cap*-51:

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 $(M+H)^+$.

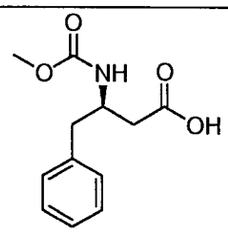
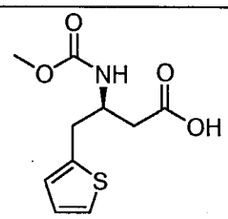
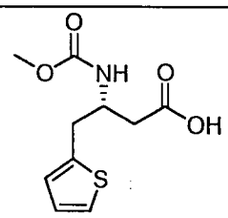
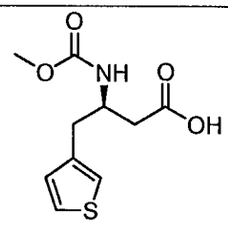
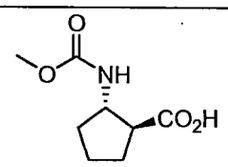
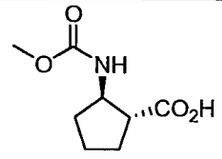
Cap-101		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$.
Cap-102		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$
Cap-103		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-104		^{1}HNMR (400 MHz, CD_3OD) δ 3.60 (s, 3H), 3.50 – 3.53 (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 following the procedure described		^{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

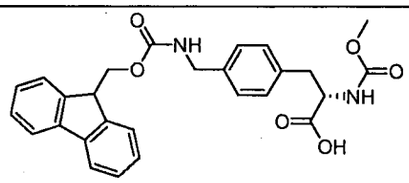
for Cap-2))		dt J = 4.0, 12.9 Hz, 2H), 1.26 (t, J = 7.3 Hz, 6H).
Cap-107		LCMS: Anal. Calcd. for $C_8H_{10}N_2O_4S$: 230; found: 231 $(M+H)^+$.
Cap-108		LCMS: Anal. Calcd. for $C_{15}H_{17}N_3O_4$: 303; found: 304 $(M+H)^+$.
Cap-109		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
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).

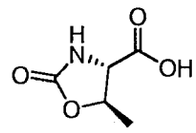
Cap-117 to Cap-123

For the preparation of caps *Cap*-117 to *Cap*-123 the the Boc amino acids were commercially available 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 for *Cap*-51.

Cap	Structure	LCMS
Cap-117		LCMS: Anal. Calcd. for $C_{12}H_{15}NO_4S$: 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 (400 MHz, $CDCl_3$) δ 5.28 and 5.12 (s, br, 1H), 3.66 (s, 3H), 2.64 – 2.74 (m, 1H), 1.86 - 2.12 (m, 3H), 1.67 – 1.74 (m, 2H), 1.39 – 1.54 (m, 1H).

Cap-123		LCMS: Anal. Calcd. for $C_{27}H_{26}N_2O_6$: 474; found: 475 $(M+H)^+$.

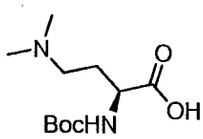
Preparation of *Cap*-124 . (4S,5R)-5-methyl-2-oxooxazolidine-4-carboxylic acid



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 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 $(M+H)^+$.

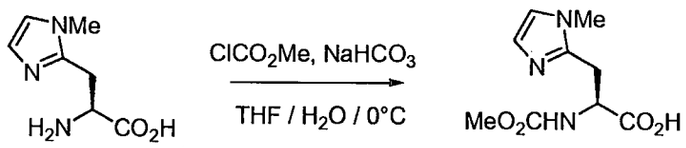
Preparation of *Cap*-125. (S)-2-(tert-butoxycarbonylamino)-4-(dimethylamino)butanoic acid.



cap-125

Cap-125 was prepared according to the procedure for the preparation of *Cap*-1. The crude product was used as is in subsequent reactions. LCMS: Anal. Calcd. for $C_{11}H_{22}N_2O_4$: 246; found: 247 $(M+H)^+$.

Preparation of (S)-2-(methoxycarbonylamino)-3-(1-methyl-1H-imidazol-2-yl)propanoic acid (*Cap*-126).



cj-25 *cap-126*

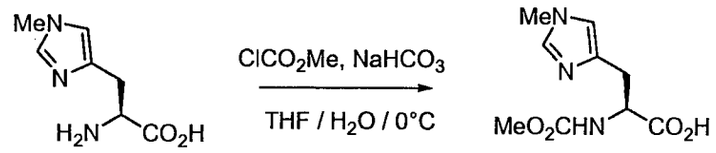
This procedure is a modification of that used to prepare *Cap*-51. To a suspension of (S)-2-amino-3-(1-methyl-1H-imidazol-2-yl)propanoic acid (0.80 g, 4.70 mmol) in THF (10mL) and H_2O (10 mL) at 0°C was added $NaHCO_3$ (0.88 g, 10.5 mmol). The resulting mixture was treated with $ClCO_2Me$ (0.40 mL, 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 ^1H 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 ^1H 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 $C_{17}H_{15}NO_2$: 392; found: 393 $(M+H)^+$.

Preparation of (S)-2-(methoxycarbonylamino)-3-(1-methyl-1H-imidazol-4-yl)propanoic acid (*Cap*-127).



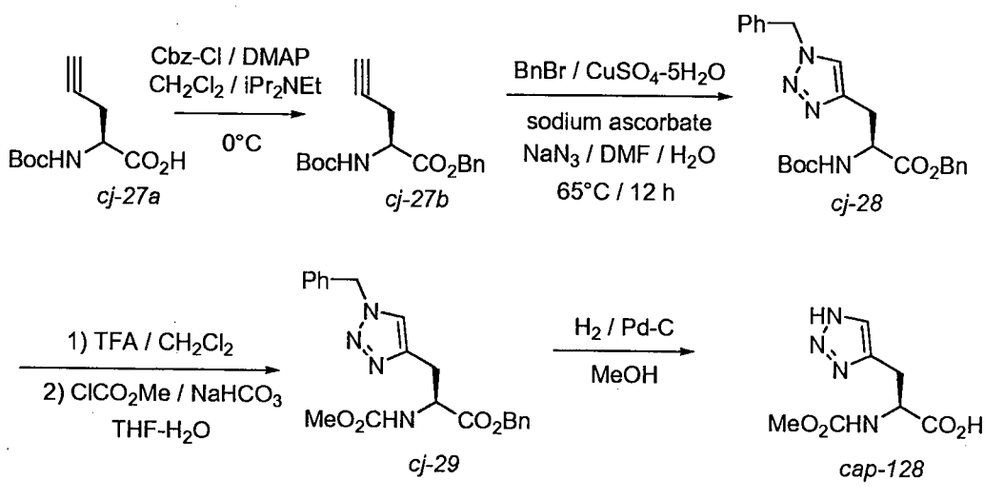
cj-26 *cap-127*

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).

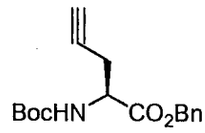
LCMS: Anal. Calcd. for $C_{17}H_{15}NO_2$: 392; found: 393 $(M+H)^+$.

Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-1,2,3-triazol-4-yl)propanoic acid (*Cap*-128).



cj-27a *cj-27b* *cj-28* *cj-29* *cap-128*

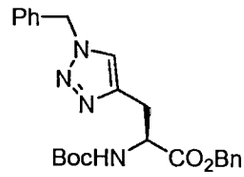
Step 1. Preparation of (S)-benzyl 2-(tert-butoxycarbonylamino)pent-4-ynoate (cj-27b).



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).

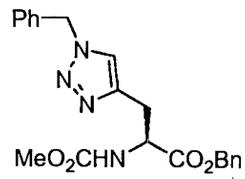


cj-28

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 $(M+H)^+$.

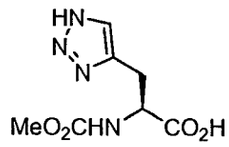
Step 2. Preparation of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(methoxycarbonylamino)propanoate (cj-29).



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 3. Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-1,2,3-triazol-4-yl)propanoic acid (*Cap*-128).

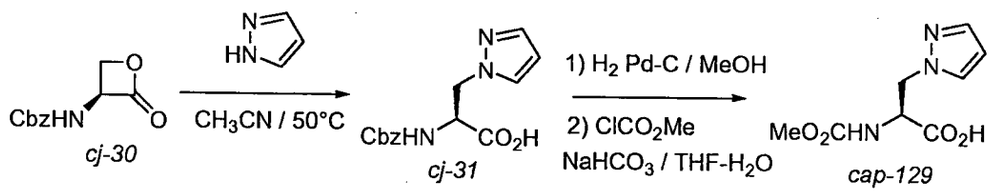


Cap-128

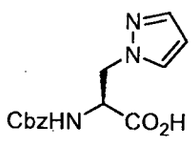
(S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(methoxycarbonylamino)propanoate (502 mg, 1.11 mmol) was hydrogenated in the presence of Pd-C (82 mg) in MeOH (5 mL) at atmospheric pressure for 12h. The mixture was filtered through diatomaceous earth (Celite®) and concentrated *in vacuo*. (S)-2-(methoxycarbonylamino)-3-(1H-1,2,3-triazol-4-yl)propanoic 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 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). LCMS: Anal. Calcd. for $C_7H_{10}N_4O_4$: 214; found: 215 $(M+H)^+$.

Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (*Cap*-129).



Step 1. Preparation of (S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (cj-31).



cj-31

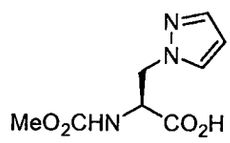
A suspension of (S)-benzyl 2-oxooxetan-3-ylcarbamate (0.67 g, 3.03 mmol), and pyrazole (0.22 g, 3.29 mmol) in CH_3CN (12 mL) was heated at 50°C for 24h. The

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).

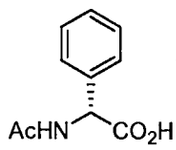


cap-129

(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 rxn 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 extract 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. N-Acetyl –(R)-Phenylglycine



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.

EXAMPLES

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.

Solution percentages express a weight to volume relationship, and solution ratios express a volume to volume relationship, unless stated otherwise. Nuclear magnetic resonance (NMR) spectra were recorded either on a Bruker 300, 400, or 500 MHz spectrometer; the chemical shifts (δ) are reported in parts per million. Flash chromatography was carried out on silica gel (SiO_2) according to Still's flash chromatography technique (*J. Org. Chem.* **1978**, *43*, 2923).

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. The LC conditions employed in determining the retention time (RT) were:

Condition 1

Column = Phenomenex-Luna 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%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition 2

Column = Phenomenex-Luna 4.6X50 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 3

Column = HPLC 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

Method A: LCMS – Xterra MS C-18 3.0 x 50mm, 0 to 100% B over 30.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate.

Method B: HPLC – X-Terra C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA

Method C: HPLC – YMC C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.2% H_3PO_4, B = 90% methanol 10% water 0.2% H_3PO_4.

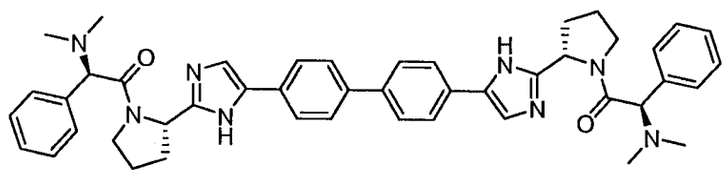
Method D: HPLC – Phenomenex C-18 4.6 x 150mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.2% H_3PO_4, B = 90% methanol 10% water 0.2% H_3PO_4

Method E: LCMS – Gemini C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate.

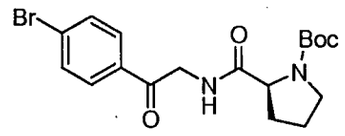
Method F: LCMS-Luna C-18 3.0 x 50mm, 0 to 100% B over 7.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate.

Example 1

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)



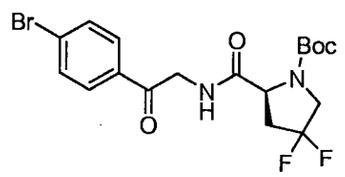
Example 1, Step a



1a

N,N-Diisopropylethylamine (18 mL, 103.3 mmol) was added dropwise, over 15 minutes, to a heterogeneous mixture of *N*-Boc-L-proline (7.139 g, 33.17 mmol), HATU (13.324 g, 35.04 mmol), the HCl salt of 2-amino-1-(4-bromophenyl)ethanone (8.127 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 ketoamide 1a as a white solid (12.8 g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 8.25-8.14 (m, 1H), 7.92 (br d, J = 8.0, 2H), 7.75 (br d, J = 8.6, 2H), 4.61 (dd, J = 18.3, 5.7, 1H), 4.53 (dd, J = 18.1, 5.6, 1H), 4.22-4.12 (m, 1H), 3.43-3.35 (m, 1H), 3.30-3.23 (m, 1H), 2.18-2.20 (m, 1H), 1.90-1.70 (m, 3H), 1.40/1.34 (two app br s, 9H). LC (Cond. 1): RT = 1.70 min; LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{18}H_{23}BrN_2NaO_4$: 433.07; found 433.09.

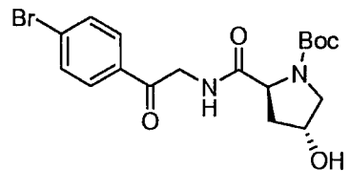
Analogous compounds such as intermediate 1-1a to 1-5a can be prepared by incorporating the appropriately substituted amino acid and aryl bromide isomer.



1-1a

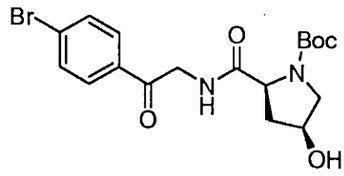
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.35/1.40 (two br s, 9H), 2.27-2.42 (m, 1H), 2.73-2.95 (m, 1H), 3.62-3.89 (m, 2H), 4.36-4.50 (m, 1H), 4.51-4.60 (m, 1H), 4.62-4.73 (m, 1H), 7.75 (d, J=8.24 Hz, 2H), 7.92 (d, J=7.63 Hz, 2H), 8.31-8.49 (m, 1H). HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 4 minutes, 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 = 1.59 minutes, 99% homogeneity index. LCMS: Anal. Calcd. for $C_{18}H_{21}BrF_2N_2O_4$: 446.06; found: 445.43 $(M-H)^-$.



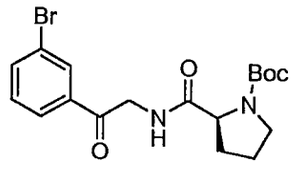
1-2a

^1H NMR (500 MHz, DMSO-d_6) δ ppm (8.25 1H, s), 7.91 (2H, d, *J*=8.24Hz), 7.75 (2H, d, *J*=8.24 Hz), 4.98 (1H, s), 4.59-4.63 (1H, m), 4.46-4.52 (1H, m), 4.23 (1H, m), 3.37 (1H, s), 3.23-3.28 (1H, m), 2.06 (1H, m), 1.88 (1H, s), 1.38 (3H, s), 1.33 (6H, s). LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA mobile phase, RT = 3.34 minutes, Anal Calcd. for $C_{18}H_{23}BrN_2O_5$ 427.30; found 428.08 $(M+H)^+$.



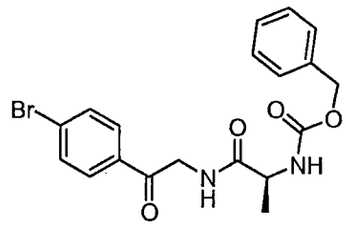
1-3a

^1H NMR (500 MHz, DMSO-d_6) δ ppm 8.30 (1H, s) 7.93-7.96 (2H, m) 7.76 (2H d, *J*=8.24 Hz) 5.13 (1H, s) 4.66-4.71 (1H, m) 4.52-4.55 (1H, m) 4.17 (1H, m) 3.51 (1H, s) 3.16-3.19 (1H, m) 2.36 (1H, m) 1.78 (1H, s) 1.40 (s, 3H), 1.34 (s, 6H). LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, RT= 3.69 minutes, Anal Calcd. for $C_{18}H_{23}BrN_2O_5$ 427.30; found 428.16 $(M+H)^+$.



1-4a

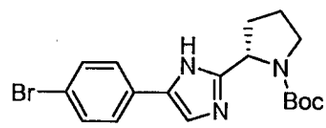
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.29-1.47 (m, 9H), 1.67-1.90 (m, 3H), 2.00-2.20 (m, 1H), 3.23-3.30 (m, 1H), 3.34-3.44 (m, 1H), 4.16 (dd, 1H), 4.57 (q, 2H), 7.51 (t, *J*=7.78 Hz, 1H), 7.86 (dd, *J*=7.93, 1.22 Hz, 1H), 7.98 (d, *J*=7.63 Hz, 1H), 8.11 (s, 1H), 8.15-8.29 (m, 1H). LC/MS $(M+Na)^+$ = 433.12/435.12.



1-5a

LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 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, 220nm, 5 μL injection volume. RT = 1.93 min; LRMS: Anal. Calcd. for $C_{19}H_{18}BrN_2O_4$ 418.05; found: 419.07 $(M+H)^+$.

Example 1, Step b



1b

A mixture of ketoamide 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 an 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 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 imidazole 1b. ^{1}H NMR (DMSO-

d_6, δ = 2.5 ppm, 400 MHz): δ 12.17/11.92/11.86 (m, 1H), 7.72-7.46/7.28 (m, 5H), 4.86-4.70 (m, 1H), 3.52 (app br s, 1H), 3.36 (m, 1H), 2.30-1.75 (m, 4H), 1.40/1.15 (app br s, 9H). LC (Cond. 1): RT = 1.71 min; >98% homogeneity index; LC/MS: 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 1b were assessed using 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

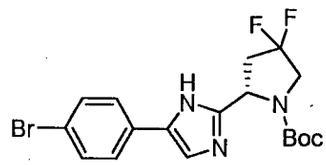
Solvent: 2% ethanol/heptane (isocratic)

Flow rate: 1 mL/min

Wavelength: either 220 or 254 nm

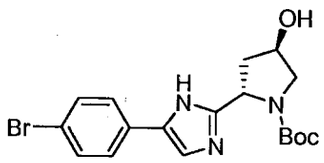
Relative retention time: 2.83 minutes (*R*), 5.34 minutes (*S*)

Analogous compounds such as intermediates 1-1b to 1-4b can be prepared by incorporating the appropriate ketoamide.



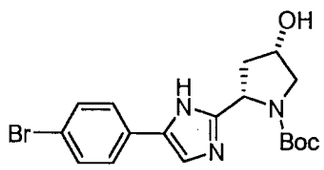
1-1b

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.17/1.40 (two br s, 9H), 2.50-2.74 (m, *J*=25.64 Hz, 1H), 2.84-3.07 (m, 1H), 3.88 (d, *J*=10.07 Hz, 2H), 5.03 (s, 1H), 7.50 (d, *J*=8.55 Hz, 2H), 7.60 (s, 1H), 7.70 (d, *J*=8.55 Hz, 2H), 12.10 (s, 1H). HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 4 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 = 1.59 minutes, 99% homogeneity index; LCMS: Anal. Calcd. for $C_{18}H_{20}BrF_2N_3O_2$: 428.27; found: 428.02 $(M)^+$.



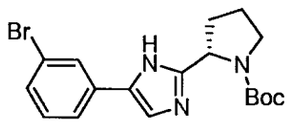
1-2b

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.89-11.99 (1H, m), 7.68 (2H, d, *J*=8.54 Hz), 7.52-7.59 (1H, m), 7.48 (2H, d, *J*=8.54 Hz), 4.80 (1H, m), 4.33 (1H, s), 3.51-3.60 (1H, m), 3.34 (1H, d, *J*=10.99 Hz), 2.14 (1H, s), 1.97-2.05 (1H, m), 1.37 (3H, s), 1.10 (6H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, (RT= 3.23 min) Anal Calcd. for $C_{18}H_{22}BrN_3O_3$ 408.30; found 409.12 $(M+H)^+$.



1-3b

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.06-12.24 (1H, m), 7.58-7.69 (5H, m), 4.84-4.95 (1H, m), 4.34 (1H, s), 3.61 (1H, s), 3.34-3.40 (1H, m), 2.52 (1H, s), 1.92-2.20 (1H, m), 1.43 (3H, s), 1.22 (6H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, (RT= 3.41 min) Anal Calcd. for $C_{18}H_{22}BrN_3O_3$ 408.30; found 409.15 $(M+H)^+$.



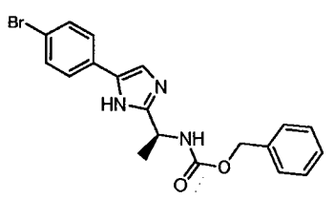
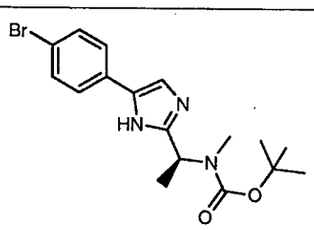
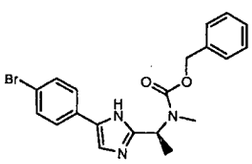
1-4b

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.98-1.51 (m, 9H), 1.82-2.12 (m, 3H), 2.31-2.48 (m, 1H), 3.30-3.51 (m, 1H), 3.52-3.66 (m, 1H), 4.88-5.16 (m, 1H), 7.47 (t, *J*=7.93 Hz, 1H), 7.61 (d, *J*=7.93 Hz, 1H), 7.81 (d, *J*=7.93 Hz, 1H), 8.04 (s, 1H), 8.12 (d, *J*=28.38 Hz, 1H), 14.65 (s, 1H). LC/MS $(M+H)^+$ = 391.96/393.96.

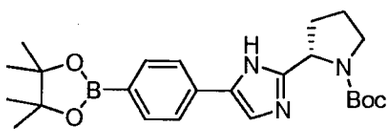
Additional imidazole analogs made following procedures similar to those described above.

LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

Condition 2: Phenomenex LUNA C-18 4.6 × 50 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, 220nm, 5 μL injection volume.

Example	*Structure*	*Data*
1-5b		RT = 1.70 minutes (condition 2, 98%); LRMS: Anal. Calcd. for $C_{19}H_{18}BrN_3O_2$ 399.05; found: 400.08 $(M+H)^+$.
1-6b		RT = 1.64 minutes (condtion 2, 98%); LRMS: Anal. Calcd. for $C_{17}H_{22}N_3O_2$ 379.09; found: 380.06 $(M+H)^+$.
1-7b		RT = 2.28 minutes (95%); LRMS: Anal. Calcd. for $C_{20}H_{21}BrN_3O_2$ 414.08; found: 414.08 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{20}H_{21}BrN_3O_2$ 414.0817; found: 414.0798 $(M+H)^+$.

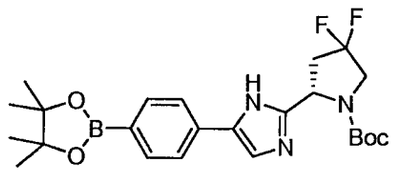
Example 1, Step c



1c

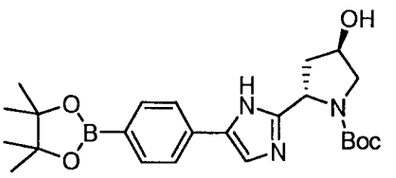
$Pd(Ph_3P)_4$ (469 mg, 0.406 mmol) was added to a pressure tube containing a mixture of bromide 1b (4.008 g, 10.22 mmol), bis(pinacolato)diboron (5.422 g, 21.35 mmol), potassium acetate (2.573g, 26.21 mmol) and 1,4-dioxane (80 mL). The reaction flask was purged with nitrogen, capped and heated with an oil bath at 80 °C for 16.5 hours. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The crude material was partitioned carefully between CH_2Cl_2 (150 mL) and an aqueous medium (50 mL water + 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 boronate 1c, contaminated with pinacol, as an off-white dense solid; the relative mole ratio of 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 (DMSO-d_6, δ= 2.5 ppm, 400 MHz): 12.22/11.94/ 11.87 (m, 1H), 7.79-7.50/ 7.34-7.27 (m, 5H), 4.86-4.70 (m, 1H), 3.52 (app br s, 1H), 3.36 (m, 1H), 2.27-1.77 (m, 4H), 1.45-1.10 (m, 21H). LC (Cond. 1): RT = 1.64 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{35}BN_3O_4$: 440.27; found 440.23.

Analogous compounds such as intermediates 1-1c to 1-4c can be prepared by incorporating the appropriate aryl bromide.



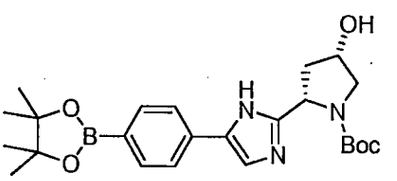
1-1c

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.16 (s, 8H), 1.29 (s, 13H), 2.51-2.72 (m, 1H), 2.84-3.03 (m, 1H), 3.79-4.00 (m, 2H), 4.88-5.21 (m, 1H), 7.62 (d, *J*=7.93 Hz, 2H), 7.67 (s, 1H), 7.76 (d, *J*=7.93 Hz, 2H), 12.11/12.40 (two br s, 1H). HPLC GEMINI C-18 4.6 × 50 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 95% water, 5% acetonitrile, 0.1% NH_4OAc, B = 5% water, 95% acetonitrile, 0.1% NH_4OAc, RT = 1.62 minutes, 99% homogeneity index. LCMS: Anal. Calcd. for $C_{34}H_{32}BF_2N_3O_4$: 475.34; found: 474.78 $(M-H)^-$.



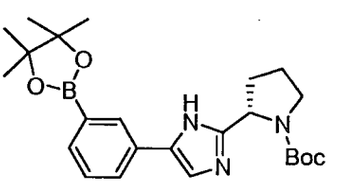
1-2c

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.97 (1H, m), 7.62-7.75 (5H, m), 5.05 (1H d, *J*=3.36 Hz), 4.82 (m, 1H), 4.35 (m, 1H), 3.58 (1H, m), 2.389 (1H, s), 2.17 (1 H, m), 1.38 (3H, s), 1.30 (12H, s), 1.1 (6H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate, RT= 3.63 minutes, Anal. Calcd. for $C_{24}H_{34}BN_3O_5$ 455.30; found 456.31 $(M+H)^+$.



1-3c

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.05-12.24 (1H, m), 7.61-7.73 (5H, m), 4.83-5.01 (1H, m), 4.33 (1H, s), 3.54-3.63 (1H, m), 3.39-3.80 (1H, m), 2.38-2.49 (1H, m), 1.98-2.01 (1H, m), 1.42 (3H, s), 1.34 (12H, s), 1.21 (6H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, RT= 3.64 minutes, Anal. Calcd. for $C_{24}H_{34}BN_3O_5$ 455.30; found 456.30 $(M+H)^+$.



1-4c

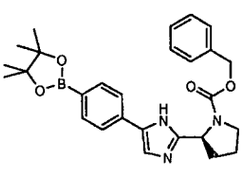
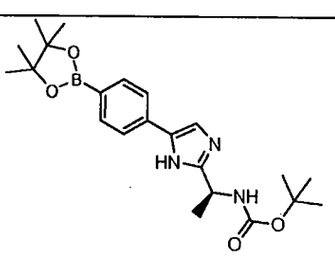
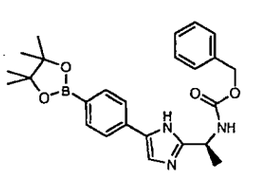
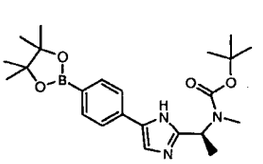
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.02-1.54 (m, 21H), 1.75-2.07 (m, 3H), 2.09-2.33 (m, 1H), 3.32-3.44 (m, 1H), 3.55 (s, 1H), 4.69-4.94 (m, 1H), 7.33 (t, *J*=7.32 Hz,

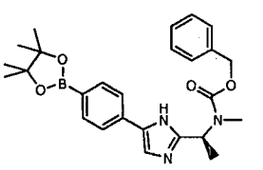
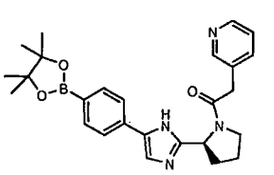
1H), 7.41-7.57 (m, 2H), 7.84 (d, *J*=7.32 Hz, 1H), 8.08 (s, 1H), 11.62-12.07 (m, 1H). LC/MS $(M+H)^+$ = 440.32.

Additional boronic esters: Conditions for 1-5c through 1-10c

LCMS conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

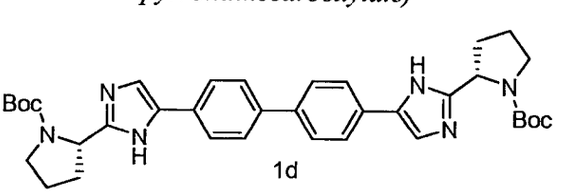
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

1-5c		RT = 1.84 minutes (condition 2); LCMS: Anal. Calcd. for $C_{27}H_{32}BN_3O_4$ 473; found: 474 $(M+H)^+$.
1-6c		RT = 1.84 minutes (condition 2); LCMS: Anal. Calcd. for $C_{22}H_{32}BN_3O_4$ 413; found: 414 $(M+H)^+$.
1-7c		RT = 1.85 minutes (condition 2); LRMS: Anal. Calcd. for $C_{25}H_{31}BN_3O_4$ 448; found: 448 $(M+H)^+$.
1-8c		RT = 2.49 (76%, boronic ester) and 1.81 (21.4%, boronic acid); LCMS: Anal. Calcd. for $C_{23}H_{35}N_3O_4B$ 428.27; found: 428.27 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{23}H_{35}N_3O_4B$ 428.2721; found:

		428.2716 $(M+H)^+$.
1-9c		RT = 2.54 (74.2%, boronic ester) and 1.93 (25.8%, boronic acid); LRMS: Anal. Calcd. for $C_{26}H_{33}N_3O_4B$ 462.26; found: 462.25 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{26}H_{33}N_3O_4B$ 462.2564; found: 462.2570 $(M+H)^+$.
1-10c		RT = 1.91 (64.5 %, boronic ester) and 1.02 (33.8 %, boronic acid); LRMS: Anal. Calcd. for $C_{26}H_{32}N_4O_3{}^{10}B$ 458.26; found: 458.28 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{26}H_{32}N_4O_3{}^{10}B$ 458.2604; found: 458.2617 $(M+H)^+$.

Example 1, Step d

di-tert-butyl (2S,2'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))di(1-pyrrolidinecarboxylate)



1d

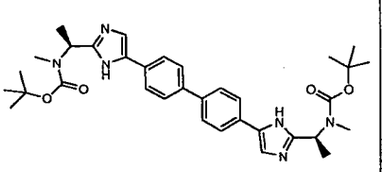
$Pd(Ph_3P)_4$ (59.9 mg, 0.0518 mmol) was added to a mixture of bromide 1b (576.1 mg, 1.469 mmol), boronate 1c (621.8 mg, 1.415 mmol), $NaHCO_3$ (400.4 mg, 4.766 mmol) in 1,2-dimethoxyethane (12 mL) and water (4 mL). The reaction mixture was flushed with nitrogen, heated with an oil bath at 80 °C for 5.75 hours, and then the volatile component was removed *in vacuo*. The residue was partitioned

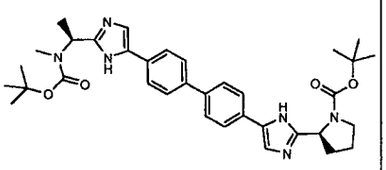
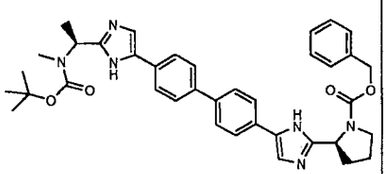
between 20% methanol/ $CHCl_3$ (60 mL) and water (30 mL), and the aqueous phase was extracted with 20% methanol/$CHCl_3$ (30 mL). The combined organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. A silica gel mesh was prepared from the resulting crude material and submitted to flash chromatography (ethyl acetate) to provide dimer 1d, contaminated with Ph_3PO, as an off-white solid (563 mg). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.21-12-16/11.95-11.78 (m, 2H), 7.85-7.48/ 7.32-7.25 (m, 10H), 4.90-4.71 (m, 2H), 3.60-3.32 (m, 4H), 2.30-1.79 (m, 8H), 1.46-1.10 (m, 18H). LC (Cond. 1b): RT = 1.77 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{45}BN_6O_4$: 625.35; found 625.48.

Additional biphenyl analogs were prepared similarly.

LC conditions for Examples 1-5d through 1-7d: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

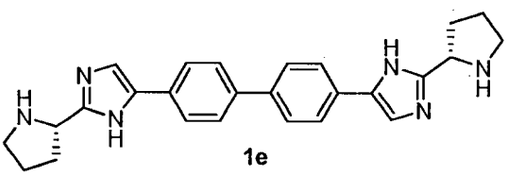
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

Example	*Compound Name*	*Structure*	*Characterization Data*
1-5d	di-tert-butyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S)-1,1-ethanediyl))bis(methylcarbamate)	 Prepared from 1-8c and 1-6b	RT = 1.64 minutes (>95%); Condition 2; LCMS: Anal. Calcd $C_{34}H_{45}N_6O_4$ 601.35; found: 601.48 $(M+H)^+$; LRMS: Anal. Calcd. for $C_{34}H_{44}N_6O_4$ 600.34; found: 601.32 $(M+H)^+$.

1-6d	tert-butyl (2S)-2-(5-(4'-(2-((1S)-1-((tert-butoxycarbonyl)(methyl)amino)ethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from 1-8c and 1b	RT = 1.63 minutes (>95%); Condition 2; LCMS: Anal. Calcd $C_{35}H_{45}N_6O_4$ 613.34; found: 613.56 $(M+H)^+$; LRMS: Anal. Calcd. for $C_{35}H_{44}N_6O_4$ 612.34; found: 613.33 $(M+H)^+$.
1-7d	benzyl (2S)-2-(5-(4'-(2-((1S)-1-((tert-butoxycarbonyl)(methyl)amino)ethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from 1-6b and 1-5c	RT = 1.65 minutes (>95%); Condition 2; LCMS: Anal. Calcd $C_{38}H_{43}N_6O_4$ 647.33; found: 647.44 $(M+H)^+$; LRMS: Anal. Calcd. for $C_{38}H_{42}N_6O_4$ 646.33; found: 647.34 $(M+H)^+$.

Example 1, Step e

5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole)

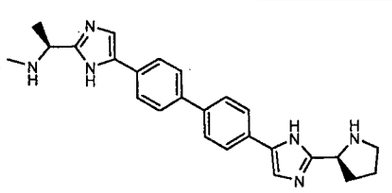
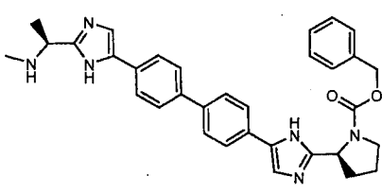
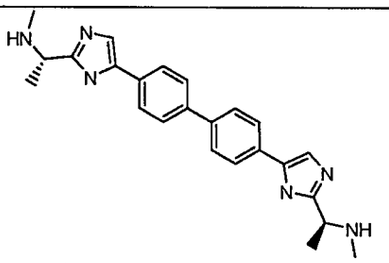


1e

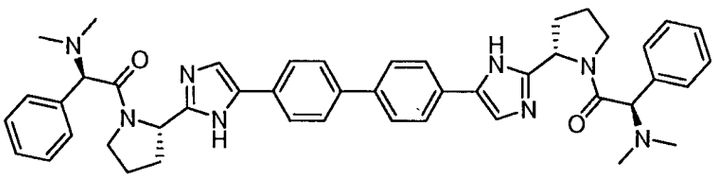
A mixture of carbamate 1d (560 mg) and 25% TFA/CH_2Cl_2 (9.0 mL) was stirred at ambient condition for 3.2 hours. The volatile component was removed *in vacuo*, and the resulting material was free based using an MCX column (methanol wash; 2.0 M NH_3/methanol elution) to provide pyrrolidine 1e as a dull yellow solid (340 mg). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 11.83 (br s, 2H), 7.80 (d,

J = 8.1, 4H), 7.66 (d, J = 8.3, 4H), 7.46 (br s, 2H), 4.16 (app t, J = 7.2, 2H), 2.99-2.69 (m, 6H), 2.09-2.00 (m, 2H), 1.94-1.66 (m, 6H). LC (Cond. 1): RT = 1.27 min; > 98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{29}N_6$: 425.25; found 425.25; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{29}N_6$: 425.2454; found 425.2448

Additional analogs were prepared similarly:

Example	Compound Name	Structure	Data
1-5e		 Prepared from 1-6d	RT = 1.37 min; LCMS: Anal. Calcd. for $C_{25}H_{28}N_6$ 412; found: 413 $(M+H)^+$.
1-6e		 Prepared from 1-7d	RT = 1.43 min; LCMS: Anal. Calcd. for $C_{33}H_{35}N_6O_2$ 547; found: 547 $(M+H)^+$.
1-7e		 Prepared from 1-5d	RT = 1.12 min; LRMS: Anal. Calcd. for $C_{24}H_{28}N_6$ 400.24; found: 401.22 $(M+H)^+$.

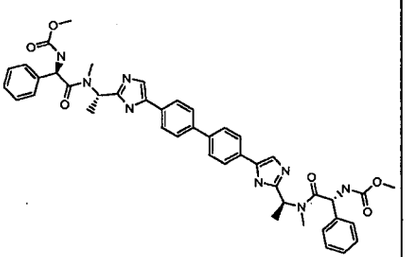
LC Conditions for 1-5e through 1-7e: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

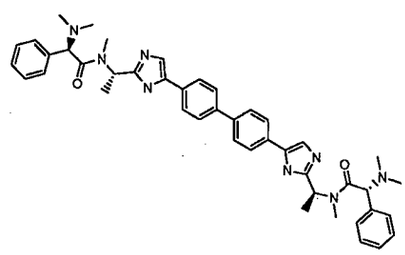
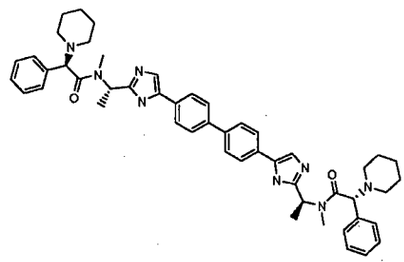
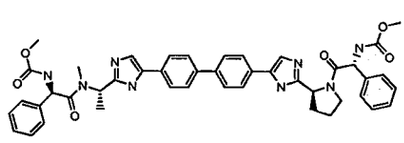


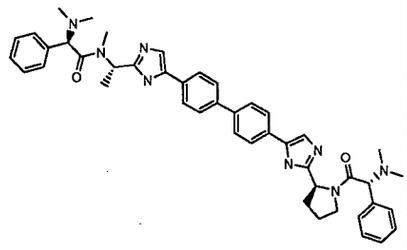
Example 1

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)

HATU (44.6 mg, 0.117 mmol) was added to a mixture of pyrrolidine 1e (22.9 mg, 0.054 mmol), diisopropylethylamine (45 μL, 0.259 mmol) and *Cap*-1 (28.1 mg, 0.13 mmol) in DMF (1.5 mL), and the resulting mixture was stirred at ambient for 90 minutes. The volatile component was removed *in vacuo*, and the residue was purified first by MCX (methanol wash; 2.0 M NH_3/methanol elution) and then by a reverse phase HPLC system (H_2O/methanol/TFA) to provide the TFA salt of Example 1 as an off-white foam (44.1 mg). ^{1}H NMR (DMSO-d_6, δ= 2.5 ppm, 400 MHz): δ 10.25 (br s, 2H), 8.20-7.10 (m, 20H), 5.79-5.12 (m, 4H), 4.05-2.98 (m, 4H), 2.98-2.62 (m, 6H), 2.50-1.70 (m, 14H), [Note: the signal of the imidazole NH was too broad to assign a chemical shift]; LC (Cond. 1): RT = 1.40 min; > 98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{51}N_8O_2$: 747.41; found 747.58

Example	*Compound Name*	*Structure*	*Characterization Data*
24-18-1	dimethyl (4,4'-biphenyldiylbis(1 H-imidazole-5,2-diyl(1S)-1,1-ethanediyl(methylimino)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 from 1-7e and *Cap*-4	RT = 1.55 min[1]; LRMS: Anal. Calcd. for $C_{44}H_{46}N_8O_6$ 782.35; found: 783.37 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{44}H_{47}N_8O_6$ 783.3619 found: 783.3630 $(M+H)^+$.

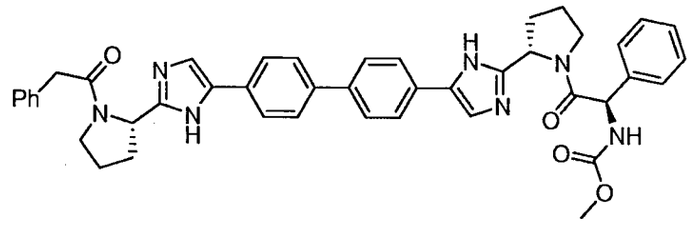
24-18-2	(2R,2'R)-N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S)-1,1-ethanediyl))bis(2-(dimethylamino)-N-methyl-2-phenylacetamide)	 from 1-7e and *Cap*-1	RT = 1.16 min[1]; LRMS: Anal. Calcd. for $C_{44}H_{50}N_8O_2$ 722.41; found: 723.41 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{44}H_{51}N_8O_2$ 723.4135 found: 723.4152 $(M+H)^+$.
24-18-3	(2R,2'R)-N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S)-1,1-ethanediyl))bis(N-methyl-2-phenyl-2-(1-piperidinyl)acetamide)	 from 1-7e and *Cap*-14	RT = 1.28 min[1]; LRMS: Anal. Calcd. for $C_{50}H_{58}N_8O_2$ 802.47; found: 803.50 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{50}H_{59}N_8O_2$ 803.4761 found: 803.4778 $(M+H)^+$.
24-18-4	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((1S)-1-(((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)(methyl)amino)ethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from 1-5e and *Cap*-4	RT = 1.53 min[1]; LRMS: Anal. Calcd. for $C_{45}H_{46}N_8O_6$ 794.35; found: 795.39 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{45}H_{47}N_8O_6$ 795.3619 found: 795.3616 $(M+H)^+$.

24-18-5	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)ethyl)-N-methyl-2-phenylacetamide	 Prepared from 1-5e and *Cap*-1	RT = 1.21[1]; LRMS: Anal. Calcd. for $C_{45}H_{50}N_8O_2$ 734.41; found: 735.46 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{45}H_{51}N_8O_2$ 735.4135 found: 735.4136 $(M+H)^+$.

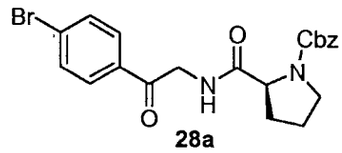
[1]LC Conditions for 24-18-1 through 24-18-5: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example 28

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate



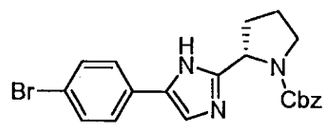
Example 28, Step a



28a

HATU (19.868g, 52.25 mmol) was added to a heterogeneous mixture of *N*-Cbz-L- proline (12.436 g, 49.89 mmol) and the HCl salt of 2-amino-1-(4-bromophenyl) ethanone (12.157 g, 48.53 mmol) in DMF (156 mL). The mixture was lowered in an ice-water bath, and immediately afterward *N,N*-diisopropylethylamine (27 mL, 155 mmol) was added dropwise to it over 13 minutes. After the addition of the base was completed, the cooling bath was removed and the reaction mixture was stirred for an additional 50 minutes. The volatile component was removed *in vacuo*; water (125 mL) was added to the resulting crude solid and stirred for about 1 hour. The off-white solid was filtered and washed with copious water, and dried *in vacuo* to provide ketoamide 28a as a white solid (20.68 g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 8.30 (m, 1H), 7.91 (m, 2H), 7.75 (d, J = 8.5, 2H), 7.38-7.25 (m, 5H), 5.11-5.03 (m, 2H), 4.57-4.48 (m, 2H), 4.33-4.26 (m, 1H), 3.53-3.36 (m, 2H), 2.23-2.05 (m, 1H), 1.94-1.78 (m, 3H); LC (Cond. 1): RT = 1.65 min; 98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{22}BrN_2O_4$: 445.08; found 445.31.

Example 28, Step b



28b

Ketoamide 28a (10.723g, 24.08 mmol) was converted to 28b according to the procedure described for the synthesis of carbamate 1b, with the exception that the crude material was purified by flash chromatography (sample was loaded with eluting solvent; 50% ethyl acetate/hexanes). Bromide 28b was retrieved as an off-white foam (7.622 g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.23/12.04/11.97 (m, 1H), 7.73-6.96 (m, 10H), 5.11-4.85 (m, 3H), 3.61 (m, 1H), 3.45 (m, 1H), 2.33-184(m, 4H). LC (Cond.1): RT = 1.42 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{21}BrN_3O_2$: 426.08; found 426.31; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{21}BrN_3O_2$: 426.0817; found: 426.0829. The optical purity of 28b was assessed using the following chiral HPLC methods, and an ee of 99% was observed.

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

Solvent: 20% ethanol/heptane (isocratic)

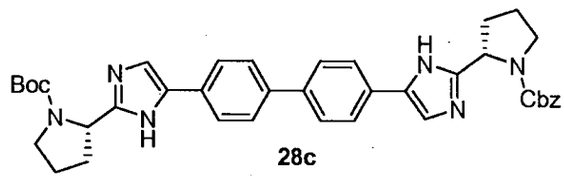
Flow rate: 1 mL/min

Wavelength: 254 nm

Relative retention time: 1.82 minutes (*R*), 5.23 minutes (*S*)

Example 28, Step c

benzyl tert-butyl (2S,2'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))di(1-pyrrolidinecarboxylate)

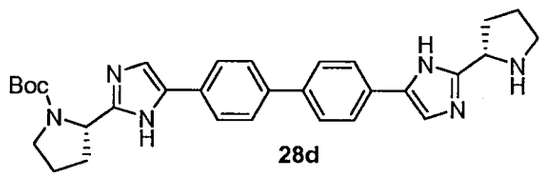


28c

$Pd(Ph_3P)_4$ (711.4 mg, 0.616 mmol) was added to a mixture of boronate ester 1c (7.582 g, ~ 17 mmol), bromide 28b (7.62 g, 17.87 mmol), $NaHCO_3$ (4.779 g, 56.89 mmol) in 1,2-dimethoxyethane (144 mL) and water (48 mL). The reaction mixture was purged with N_2 and heated with an oil bath at 80 °C for 15.5 hours, and then the volatile component was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting material was submitted to flash chromatography (sample was loaded as a silica gel mesh; ethyl acetate used as eluent) to provide biphenyl 28c as an off-white foam containing Ph_3PO impurity (7.5 g). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.24-12.19 (m, 0.36H), 12.00-11.82 (m, 1.64H), 7.85-6.98 (15H), 5.12-4.74 (4H), 3.68-3.34(4H), 2.34-1.79 (8H), 1.41/1.17 (two br S, 9H); LC (Cond.1): RT = 1.41 minutes; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{43}N_6O_4$: 659.34; found 659.52; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{43}N_6O_4$: 659.3346; found 659.3374.

Example 28, Step d

tert-butyl (2S)-2-(5-(4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate



28d

K_2CO_3 (187.8 mg, 1.36 mmol) was added to a mixture of catalyst (10% Pd/C; 205.3 mg), carbamate 28c (1.018 g, ~ 1.5 mmol), methanol (20 mL) and 3 pipet-drops of water. A balloon of H_2 was attached and the mixture was stirred for 6 hours. Then, additional catalyst (10% Pd/C, 100.8 mg) and K_2CO_3 (101.8 mg, 0.738 mmol) were added and stirring continued for 3.5 hours. During the hydrogenation process, the balloon of H_2 was changed at intervals three times. The reaction mixture was filtered through a pad of diatomaceous earth (Celite® 521), and the filterate was removed *in vacuo*. The resulting crude material was submitted to flash chromatography using a short column (sample was loaded as a silica gel mesh; 0-20% methanol/CH_2Cl_2 used as eluent) to provide 28d as a light-yellow foam (605.6 mg). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.18/11.89/11.82 (three br s, 2H), 7.83-7.29 (m, 10H), 4.89-4.73 (m, 1H), 4.19 (app t, J = 7.2, 1H), 3.55 (app br s, 1H), 3.40-3.35 (m, 1H), 3.02-2.96 (m, 1H), 2.91-2.84(m, 1H), 2.30-1.69(m, 8H), 1.41/1.16 (two br s, 9H). Note: the signal of pyrrolidine NH appears to have overlapped with signals in the 3.6-3.2 ppm region; LC (Cond.1): RT = 1.21 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{31}H_{37}N_6O_2$: 525.30; found 525.40.

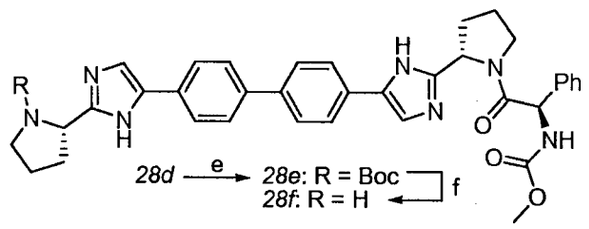
Example 28, Step e-f

Example 28 step e

tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate

Example 28 step f

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate

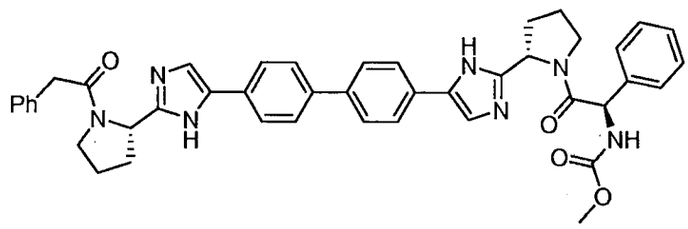


Step e: HATU (316.6 mg, 0.833 mmol) was added to a DMF (7.0 mL) solution of pyrrolidine 28d (427 mg, 0.813 mmol), *Cap*-4 (177.6 mg, 0.849 mmol) and diisopropylethylamine (0.32 mL, 1.84 mmol), and the reaction mixture was stirred for 45 minutes. The volatile component was removed *in vacuo*, and the residue was partitioned between CH_2Cl_2 (50 mL) and an aqueous medium (20 mL H_2O + 1 mL saturated $NaHCO_3$ solution). The aqueous phase was re-extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography (silica gel; ethyl acetate) to provide 28e as a yellow foam (336 mg). LC (Cond. 1): RT = 1.68min; 91% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{46}N_7O_5$: 716.35; found 716.53.

Step f: Carbamate 28e was elaborated to amine 28f by employing the procedure described in the conversion of 1d to 1e. LC (Cond. 1): RT = 1.49min; >98% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{38}N_7O_3$: 616.30; found 616.37; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{38}N_7O_3$: 616.3036; found 616.3046.

Example 28

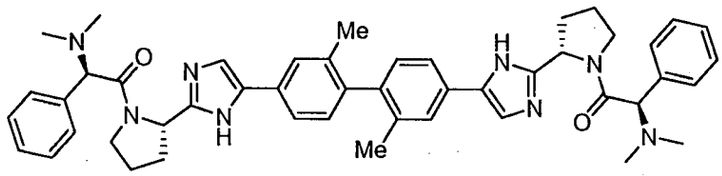
methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate



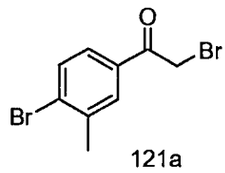
Amine 28f was converted to the TFA salt of Example 28 by employing the last step of the synthesis of Example 1. ^{1}H NMR (DMSO-d_6, δ= 2.5 ppm, 400 MHz): δ 8.21-7.03 (m, 21H), 5.78-5.14 (3H), 3.98-3.13 (m, 9H; includes the signal for OCH_3 at 3.54 & 3.53), 2.45-1.72 (m, 8H). LC (Cond. 1): RT = 1.66 minutes, >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{44}N_7O_4$: 734.35; found 734.48; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{44}N_7O_4$: 734.3455; 734.3455.

Example 121

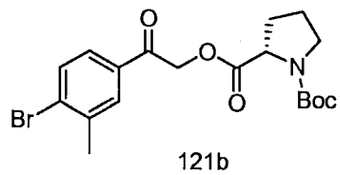
(1R,1'R)-2,2'-((2,2'-dimethyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)



Example 121, Step a-b



121a



121b

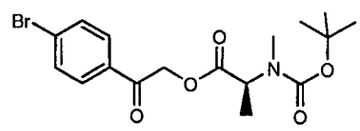
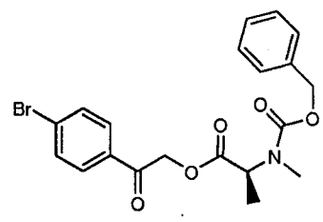
$PdCl_2(Ph_3P)_2$ (257 mg, 0.367 mmol) was added to a dioxane (45 mL) solution of 1-bromo-4-iodo-2-methylbenzene (3.01 g, 10.13 mmol) and tri-*n*-butyl(1-ethoxyvinyl)stannane (3.826 g, 10.59 mmol) and heated at 80 °C for ~17 hours. The reaction mixture was treated with water (15 mL), cooled to ~0 °C (ice/water), and

then NBS (1.839 g, 10.3 mmol) was added in batches over 7 minutes. After about 25 minutes of stirring, the volatile component was removed *in vacuo*, and the residue was partitioned between CH_2Cl_2 and water. 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 crude material was purified by a gravity chromatography (silica gel; 4% ethyl acetate/hexanes)to provide bromide 121a as a brownish-yellow solid (2.699 g); the sample is impure and contains stannane-derived impurities, among others. ^{1}H NMR ($CDCl_3$, δ = 7.24, 400 MHz): 7.83 (s, 1H), 7.63 (s, 2H), 4.30 (s, 2H), 2.46 (s, 3H).

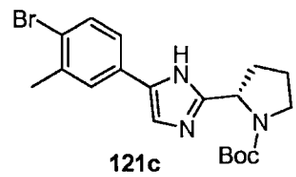
A CH_3CN (15 mL) solution of 121a (2.69 g, < 9.21 mmol) was added dropwise over 3 minutes to a CH_3CN (30 mL) solution of (*S*)-Boc-proline (2.215 g, 10.3 mmol) and triethylamine (1.40 mL, 10.04 mmol), and stirred for 90 minutes. The volatile component was removed *in vacuo*, and the residue was partitioned between water and CH_2Cl_2, and the organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified by a flash chromatography (silica gel; 15-20% ethyl acetate/hexanes) to provide 121b as a colorless viscous oil (2.74g). ^{1}H NMR (DMSO-d_6, δ = 2.50, 400 MHz): δ 7.98 (m, 1H), 7.78 (d, J = 8.3, 1H), 7.72-7.69 (m, 1H), 5.61-5.41 (m, 2H), 4.35-4.30 (m, 1H), 3.41-3.30 (m, 2H), 2.43 (s, 3H), 2.33-2.08 (m, 2H), 1.93-1.83 (m, 2H), 1.40/1.36 (s, 9H); LC (Cond. 1): RT = 1.91 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{19}H_{24}BrNNaO_5$ 448.07; found 448.10.

Additional keto-esters can be prepared in analogous fashion.

LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.
Condition 2: Phenomenex LUNA C-18 4.6 × 50 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, 220nm, 5 µL injection volume.

Example	*Structure*	*Data*
121b-1		RT = 2.15 minutes (condition 2, 98%); LRMS: Anal. Calcd. for $C_{17}H_{22}NO_5$ 399.07; found: 400.10 $(M+H)^+$.
121b-2		RT = 2.78 minutes (condition 1, >90%); LRMS: Anal. Calcd. for $C_{20}H_{20}{}^{37}BrNO_5$ 435.05 found: 458.02 $(M+Na)^+$.

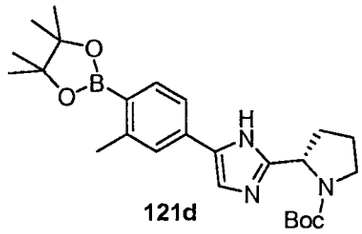
Example 121, Step c



121c

A mixture of ketoester 121b (1.445 g, 3.39 mmol) and NH_4OAc (2.93 g, 38.0 mmol) in xylenes (18 mL) was heated with a microwave at 140 °C for 80 minutes. The volatile component was removed *in vacuo*, and the residue was carefully partitioned between CH_2Cl_2 and water, where enough saturated $NaHCO_3$ solution was added to neutralize the aqueous medium. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by a flash chromatography (silica gel, 40% ethyl acetate/hexanes) to provide imidzaole 121c as an off-white solid (1.087 g). ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 12.15/11.91/11.84 (br s, 1H), 7.72-7.24 (m, 4H), 4.78 (m, 1H), 3.52 (m, 1H), 3.38-3.32 (m, 1H), 2.35 (s, 3H), 2.28-1.77 (m, 4H), 1.40/1.14 (s, 9H); LC (Cond. 1): RT = 1.91 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{19}H_{25}BrN_3O_2$ 405.96; found 406.11.

Example 121, Step d



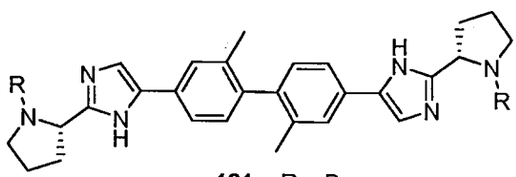
121d

$PdCl_2dppf{\cdot}CH_2Cl_2$ (50.1 mg, 0.061 mmol) was added to a pressure tube containing a mixture of bromide 121c (538.3 mg, 1.325 mmol), bis(pinacolato)diboron (666.6 mg, 2.625 mmol), potassium acetate (365.8 mg, 3.727 mmol) and DMF (10 mL). The reaction mixture was flushed with N_2 and heated at 80 °C for 24.5 hours. The volatile component was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and water, where enough saturated $NaHCO_3$ solution was added to make the pH of the aqueous medium neutral. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting material was purfied by a Biotage system (silica gel, 40-50% ethyl acetate/hexanes) to provide boronate 121d as a white foam (580 mg). According to ^1H NMR the sample contains residual pinacol in a product/pinacol ratio of ~3. ^1H NMR (DMSO-d_6, $\delta = 2.50$, 400 MHz): δ 12.16/11.91/11.83 (br s, 1H), 7.63-7.25 (m, 4H), 4.78 (m, 1H), 3.53 (m, 1H), 3.39-3.32 (m, 1H), 2.48/2.47 (s, 3H), 2.28-1.78 (m, 4H), 1.40/1.14/1.12 (br s, 9H), 1.30 (s, 12H); LC (Cond. 1): RT = 1.62 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{37}BN_3O_4$ 454.29; found 454.15

Example 121, Step e

and

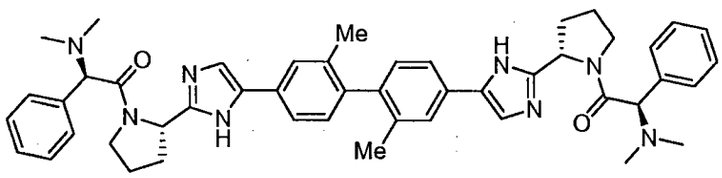
Example 121, Step f



121e: R = Boc
121f: R = H

Carbamate 121e was prepared from bromide 121c and boronate 121d according to the preparation of dimer 1d; LC (Cond. 1): RT = 1.43 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{49}N_6O_4$ 653.38; found 653.65.

The deprotection of carbamate 121e, according to the preparation of pyrrolidine 1e, provided 121f as an off-white foam. ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 11.79 (br s, 2H), 7.66 (s, 2H), 7.57 (d, J = 7.8, 2H), 7.41 (br s, 2H), 7.02 (d, J = 7.8, 2H), 4.15 (app t, J = 7.2, 2H), 3.00-2.94 (m, 2H), 2.88-2.82 (m, 2H), 2.09-2.01 (m, 2H), 2.04 (s, 6H), 1.93-1.85 (m, 2H), 1.82-1.66 (m, 4H). Note: although broad signals corresponding to the pyrrolidine NH appear in the 2.8-3.2 ppm region, the actual range for their chemical shift could not be determined. LC (Cond. 1): RT = 1.03 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{28}H_{33}N_6$ 453.28; found 453.53

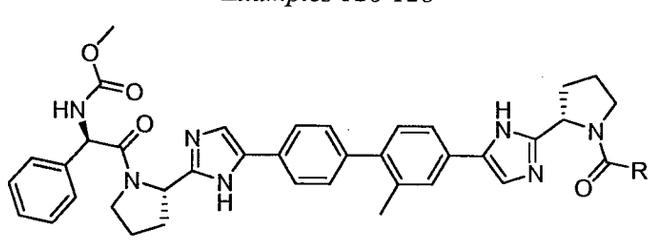


Example 121

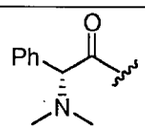
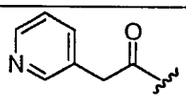
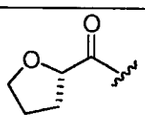
(1R,1'R)-2,2'-((2,2'-dimethyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)

Example 121 (TFA salt) was synthesized from 121f according to the preparation of Example 1 from 1e; LC (Cond. 1): RT = 1.14 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{55}N_8O_2$ 775.45; 775.75; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{55}N_8O_2$ 775.4448; found 775.4473

Examples 126-128



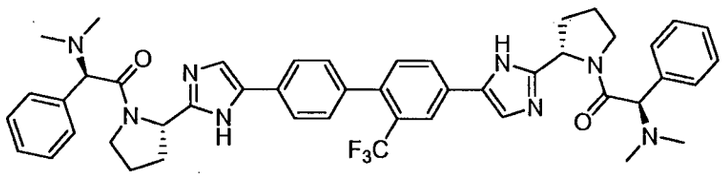
Example 126-128 were prepared starting from bromide 28b and boronate 121d by using the methods described in Example 28 starting with step c.

Example	*Compound Name*		*RT (LC-Cond.); % homogeneity index; MS data*
126	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2'-methyl-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap-1*	1.22min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{51}N_8O_4$: 791.40; found 791.70; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{51}N_8O_4$: 791.4033; found 791.4061
127	methyl ((1R)-2-((2S)-2-(5-(2'-methyl-4'-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.19 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_8O_4$: 749.36; found 749.62; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_8O_4$: 749.3564; found 749.3592
128	methyl ((1R)-2-((2S)-2-(5-(2'-methyl-4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-		1.27 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}N_7O_5$: 728.36; found 728.59; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}N_7O_5$: 728.3560; found 728.3593

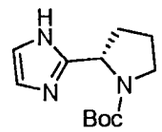
	phenylethyl)carbamate		

Example 130

(1R,1'R)-2,2'-((2-(trifluoromethyl)-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)



Example 130, Step a



130a

Glyoxal (2.0 mL of 40% in water) was added dropwise over 11 minutes to a methanol solution of NH_4OH (32 mL) and (S)-Boc-prolinal (8.564 g, 42.98 mmol) and stirred at ambient temperature for 19 hours. The volatile component was removed *in vacuo* and the residue was purified by a flash chromatography (silica gel, ethyl acetate) followed by a recrystallization (ethyl acetate, room temperature) to provide imidazole 130a as a white fluffy solid (4.43g). ^{1}H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 11.68/11.59 (br s, 1H), 6.94 (s, 1H), 6.76 (s, 1H), 4.76 (m, 1H), 3.48 (m, 1H), 3.35-3.29 (m, 1H), 2.23-1.73 (m, 4H), 1.39/1.15 (s, 9H). LC (Cond. 1): RT = 0.87 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{20}N_3O_2$ 238.16; found 238.22. Imidazole 130a had an ee of 98.9% when analyzed under chiral HPLC condition noted below.

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

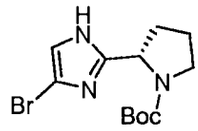
Solvent: 1.7% ethanol/heptane (isocratic)

Flow rate: 1 mL/min

Wavelength: either 220 or 256 nm

Relative retention time: 3.25min (*R*), 5.78 minutes (*S*)

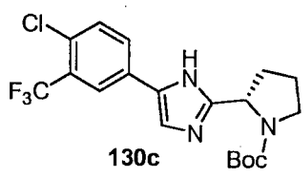
Example 130, Step b



130b

N-Bromosuccinimide (838.4 mg, 4.71 mmol) was added in batches, over 15 minutes, to a cooled (ice/water) CH_2Cl_2 (20 mL) solution of imidazole 130a (1.0689 g, 4.504 mmol), and stirred at similar temperature for 75 minutes. The volatile component was removed *in vacuo*. The crude material was purified by a reverse phase HPLC system (H_2O/methanol/TFA) to separate bromide 130b from its dibromo-analog and the non-consumed starting material. The HPLC elute was neutralized with excess NH_3/methanol and the volatile component was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted with water. The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide 130b as a white solid (374 mg). ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 12.12 (br s, 1H), 7.10 (m, 1H), 4.70 (m, 1H), 3.31 (m, 1H; overlapped with water signal), 2.25-1.73 (m, 4H), 1.39/1.17 (s, 3.8H + 5.2H). LC (Cond. 1): RT = 1.10 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{19}BrN_3O_2$ 316.07; found 316.10.

Example 130, Step c

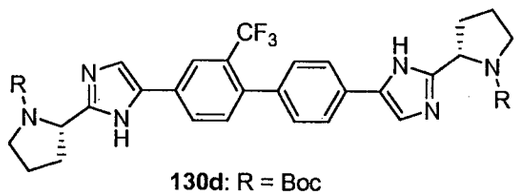


130c

$Pd(Ph_3P)_4$ (78.5 mg, 0.0679 mmol) was added to a mixture of bromide 130b (545 mg, 1.724 mmol), 2-(4-chloro-3-(trifluoromethyl)phenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (542.8 mg, 1.771 mmol) (commercially available), $NaHCO_3$ (477 mg, 5.678 mmol) in 1,2-dimethoxyethane (12.5 mL) and water (4.2 mL). The reaction mixture was purged with nitrogen, heated with an oil bath at 80 °C for 27 hours, and then the volatile component was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and water, and the organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified by a

Biotage system (silica gel, 40-50% ethyl acetate/hexanes) followed by a reverse phase HPLC (water/ methanol/TFA). The HPLC elute was treated with excess NH_3/methanol and concentrated. The residue was partitioned between water and CH_2Cl_2, and the organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide 130c as a white foam (317.4 mg). ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 12.36/12.09/12.03 (br s, 1H), 8.15 (d, J = 1.8, 0.93H), 8.09 (br s, 0.07H), 8.01 (dd, J = 8.3/1.3, 0.93H), 7.93 (m, 0.07H), 7.74 (m, 1H), 7.66 (d, J = 8.3, 0.93H), 7.46 (m, 0.07H), 4.80 (m, 1H), 3.53 (m, 1H), 3.36 (m, 1H), 2.30-1.77 (m, 4h), 1.40/1.15 (s, 3.8H+5.2H). LC (Cond. 1): RT = 1.52 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{19}H_{22}ClF_3N_3O_2$ 416.14; found 416.17.

Example 130, Step d-e



130d: R = Boc
130e: R = H

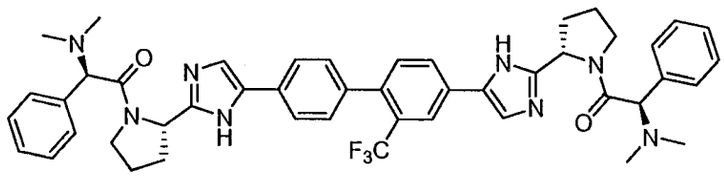
$Pd[P(t\text{-}Bu)_3]_2$ (48 mg, 0.094 mmol) was added to a mixture of chloride 130c (245 mg, 0.589 mmol), boronate 1c (277.1 mg, 0.631 mmol), KF (106.7 mg, 1.836 mmol) in DMF (6 mL), and heated at 110 °C for ~30 hours. The volatile component was removed *in vacuo*, and the residue was partitioned between CH_2Cl_2 (50 mL), water (20 mL) and saturated $NaHCO_3$ (1 mL). The aquous layer was extracted with CH_2Cl_2 (2x), and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting material was purified by a Biotage system (silica gel, ethyl acetate) to provide carbamate 130d as an off-white foam (297 mg). LC (Cond. 1): RT = 1.44 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{44}F_3N_6O_4$ 693.34; found 693.34.

The deprotection of 130d, which was conducted according to the preparation of pyrrolidine 1e, provideed 130e as a light yellow foam. ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 11.88 (br s, 2H), 8.16 (d, J = 1.5, 1H), 8.02 (d, J = 7.8, 1H), 7.78 (d, J = 8.1, 2H), 7.66 (br s, 1H), 7.48 (br s, 1H), 7.37 (d, J = 8.1, 1H), 7.28 (d, J = 8.3, 2H), 4.18 (m, 2H), 2.99-2.93 (m, 2H), 2.89-2.83 (m, 2H), 2.11-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.82-1.67 (m, 4H). Note: although broad signals corresponding to the

pyrrolidine NH appear in the 2.8-3.2 ppm region, the actual range for their chemical shift could not be determined. LC (Cond. 1): RT = 1.12 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{28}F_3N_6$ 493.23; found 493.14.

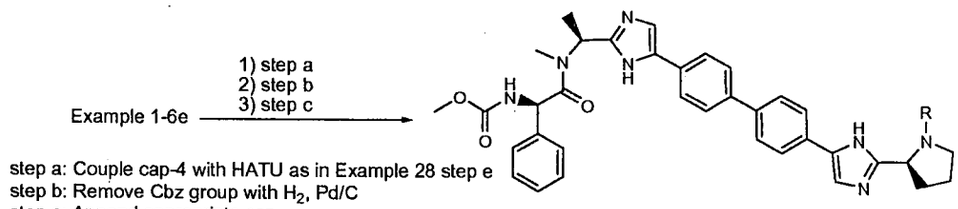
Example 130

(1R,1'R)-2,2'-((2-(trifluoromethyl)-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)



Example 130 (TFA salt) was prepared from 130e and *Cap*-1 according to the preparation of Example 1 from pyrrolidine 1e. LC (Cond. 1): RT = 1.17 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{50}F_3N_8O_2$ 815.40; found 815.44; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{50}F_3N_8O_2$ 815.4009; found 815.4013

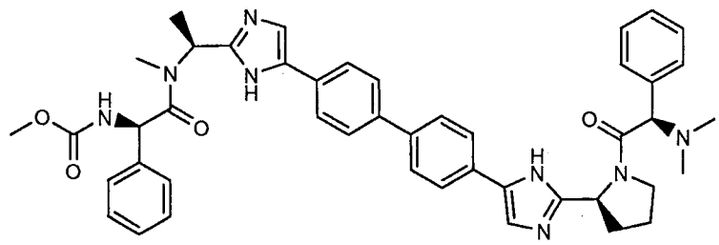
Example 131.1-1 to 131.1-2



Examples 131.1-1 through 131.1-2 were prepared in similar fashion to example 28 *via* the intermediacy of intermediate 1-6e after appending *Cap*-4.

Example 131.1-1

methyl ((1R)-2-(((1S)-1-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)ethyl)(methyl)amino)-2-oxo-1-phenylethyl)carbamate



Cap-1 was appended after the CBz carbamate was removed from 1-6e with $Pd/C/H_2$.

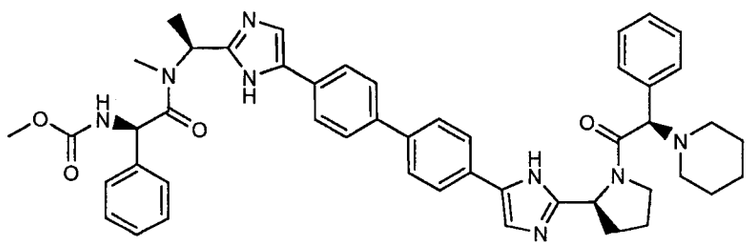
LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume. t_R = 1.42 min

LRMS: Anal. Calcd. for $C_{45}H_{49}N_8O_4$ 765.39; found: 765.38 $(M+H)^+$.

HRMS: Anal. Calcd. for $C_{45}H_{49}N_8O_4$ Calcd 765.3877 found: 765.3905 $(M+H)^+$.

Example 131.1-2

methyl ((1R)-2-(methyl((1S)-1-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)ethyl)amino)-2-oxo-1-phenylethyl)carbamate



Cap-14 was appended after the CBz carbamate was removed from 1-6e with $Pd/C/H_2$.

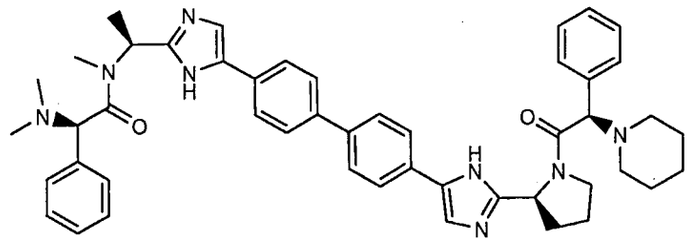
LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume. t_R = 1.45 min (>95 %)

LRMS: Anal. Calcd. for $C_{48}H_{52}N_8O_4$ 805.42; found: 805.41 $(M+H)^+$.

HRMS: Anal. Calcd. $C_{48}H_{52}N_8O_4$ Calcd 805.4190 found: 805.4214 $(M+H)^+$.

Example 131.2

(2R)-2-(dimethylamino)-N-methyl-2-phenyl-N-((1S)-1-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)ethyl)acetamide



Example 131.2 was prepared in similar fashion to example 131.1-1 and example 131.1-2 *via* the intermediacy of intermediate 1-6e after appending *Cap*-1. *Cap*-14 was appended after the CBz carbamate was removed with $Pd/C/H_2$.

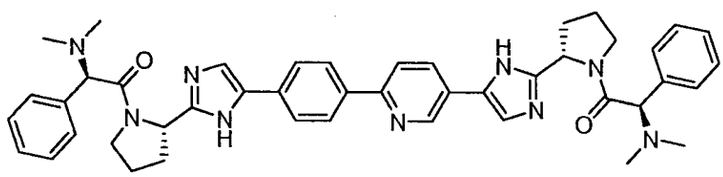
LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume. t_R = 1.28 min

LRMS: Anal. Calcd. for $C_{48}H_{54}N_8O_2$ 775.44; found: 775.45 $(M+H)^+$.

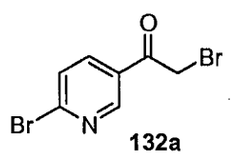
HRMS: Anal. Calcd. $C_{48}H_{54}N_8O_2$ Calcd 775.4448 found: 775.4460 $(M+H)^+$.

Example 132

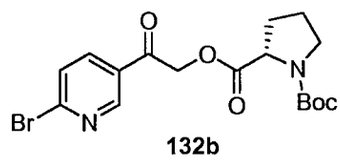
(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine



Example 132, Step a-b



132a



132b

A CH_2Cl_2 (10 mL) solution of Br_2 (7.63 g, 47.74 mmol) was added-drop wise over 5 min to a cooled (ice/water) CH_2Cl_2 (105 mL) solution of 1-(6-bromopyridine-3-yl)ethanone (9.496 g, 47.47 mmol) and 48% HBr (0.4 mL). The cooling bath was removed 40 min later, and stirring was continued at ambient temperature for about 66 hr. The cake of solid that formed was filtered, washed with CH_2Cl_2 and dried *in vacuo* to afford impure 132a as an off-white solid (15.94 g).

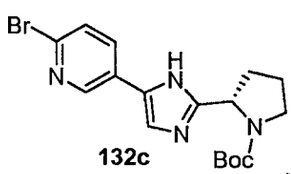
Boc-L-proline (9.70 g, 45.06 mmol) was added in one batch to a heterogeneous mixture of crude 132a (15.4 g) and CH_3CN (150 mL), and immediately afterward Et_3N (13.0 mL, 93.2 mmol) was added drop-wise over 6 min. The reaction mixture was stirred for 50 min, the volatile component was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and water. The CH_2Cl_2 layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*, and the resultant material was purified by flash chromatography (silica gel; sample was loaded with eluting solvent; 25% EtOAc/hexanes) to afford 132b as a highly viscous yellow oil (11.44g). ^1H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 8.95 (m, 1H), 8.25-8.21 (m, 1H), 7.88 (d, J = 8.3, 1H), 5.65-5.46 (m, 2H), 4.36-4.31 (m, 1H), 3.41-3.29 (m, 2H), 2.36-2.22 (m, 1H), 2.14-2.07 (m, 1H), 1.93-1.83 (m, 2H), 1.40 & 1.36 (two s, 9H).

LC (Cond. 1): RT = 2.01 min; >90% homogeneity index

LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{17}H_{21}NaBrN_2O_5$: 435.05; found 435.15

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{17}H_{22}BrN_2O_5$: 413.0712; found 413.0717

Example 132, Step c



132c

A mixture of ketoester 132b (1.318 g, 3.19 mmol) and NH_4OAc (2.729 g, 35.4 mmol) in xylenes (18 mL) was heated with a microwave at 140 °C for 90 min.

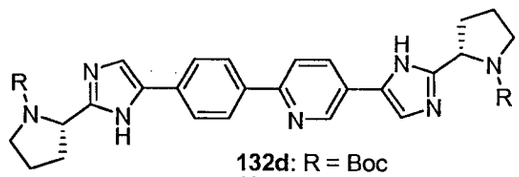
The volatile component was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and water, where enough saturated $NaHCO_3$ solution was added to neutralize the aqueous medium. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified by a Biotage system (silica gel; 50% EtOAc/hexanes) to afford imidzaole 132c as an off-white foam (1.025 g). ^{1}H NMR (DMSO, δ = 2.5 ppm, 400 MHz): 12.33/12.09/12.02 (br m, 1H), 8.74 (d, J = 2.3, 0.93H), 8.70 (app br s, 0.07H), 8.03/7.98 (dd for the first peak, J = 8.3, 1H), 7.69/7.67 (br m, 1H), 7.58/7.43 (d for the first peak, J = 8.3, 1H), 4.80 (m, 1H), 3.53 (m, 1H), 3.36 (m, 1H), 2.33-2.11 (m, 1H), 2.04-1.79 (m, 3H), 1.39/1.15 (app br s, 3.9H+5.1H).

LC (Cond.1): RT = 1.52 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{17}H_{22}BrN_4O_2$: 393.09; found 393.19

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{17}H_{22}BrN_4O_2$: 393.0926; found 393.0909

Example 132, Step d-e



132d: R = Boc
132e: R = H

$Pd(Ph_3P)_4$ (115.1 mg, 0.10 mmol) was added to a mixture of bromide 132c (992mg, 2.52 mmol), boronate 1c (1.207 g, 2.747 mmol), $NaHCO_3$ (698.8 mg, 8.318 mmol) in 1,2-dimethoxyethane (18 mL) and water (4 mL). The reaction mixture was flushed with nitrogen, heated with an oil bath at 90 °C for 37 hr and allowed to cool to ambient temperature. The suspension that formed was filtered and washed with water followed by 1,2-dimethoxyethane, and dried *in vacuo*. A silica gel mesh was prepared from the crude solid and submitted to flash chromatography (silica gel; EtOAc) to afford carbamate 132d as a white solid, which yellowed slightly upon standing at ambient conditions (1.124g). ^{1}H NMR indicated that the sample contains residual MeOH in a product/MeOH mole ratio of 1.3.

LC (Cond. 1): RT = 1.71 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{44}N_7O_4$: 626.35; found 626.64

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{44}N_7O_4$: 626.3455; 626.3479

Carbamate 132d (217 mg) was treated with 25% TFA/CH_2Cl_2 (3.6 mL) and stirred at ambient condition for 6 hr. The volatile component was removed *in vacuo*, and the resultant material was free based by MCX column (MeOH wash; 2.0 M NH_3/MeOH elution) to afford 132e as a dull yellow foam that solidified gradually upon standing (150.5 mg; mass is above theoretical yield). ^{1}H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 11.89 (very broad, 2H), 9.01 (d, J = 1.8, 1H), 8.13 (dd, J = 8.3, 2.2, 1H), 8.07 (d, J = 8.6, 2H), 7.92 (d, J = 8.3, 1H), 7.83 (d, J = 8.5, 2H), 7.61 (br s, 1H), 7.50 (br s, 1H), 4.18 (m, 2H), 3.00-2.93 (m, 2H), 2.90-2.82 (m, 2H), 2.11-2.02 (m, 2H), 1.94-1.85 (m, 2H), 1.83-1.67 (m, 4H). [Note: the exchangeable pyrrolidine hydrogens were not observed]

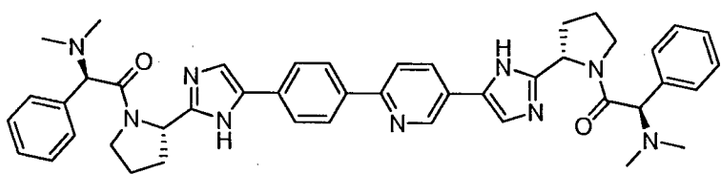
LC (Cond. 1): RT = 1.21min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{28}N_7$: 426.24; found 426.40

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{28}N_7$: 426.2406; found 426.2425

Example 132

(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine



HATU (41.4 mg, 0.109 mmol) was added to a mixture of pyrrolidine 132e (23.1 mg, 0.054 mmol), (i-Pr)$_2$EtN (40 μL, 0.23 mmol) and *Cap*-1 (25.3 mg, 0.117 mmol) in DMF (1.5 mL), and the mixture was stirred at ambient for 1 hr. The volatile component was removed *in vacuo*, and the residue was purified first by MCX (MeOH wash; 2.0 M NH_3/MeOH elution) and then by a reverse phase HPLC (H_2O/MeOH/TFA) to afford the TFA salt of Example 132 as a yellow foam (39.2 mg).

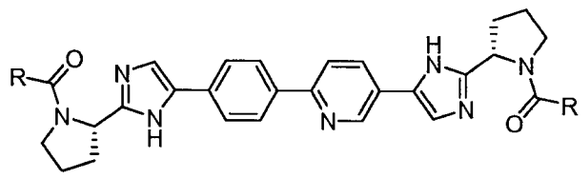
LC (Cond. 1): RT = 1.37min; >98% homogeneity index

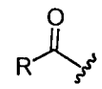
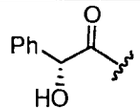
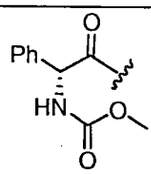
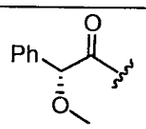
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}N_9O_2$: 748.41; found 748.53

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}N_9O_2$: 748.4087; found 748.4090

Example 133-135 were prepared as TFA salts from 132e by using the same method of preparations as Example 132 and appropriate reagents.

Example 133-135

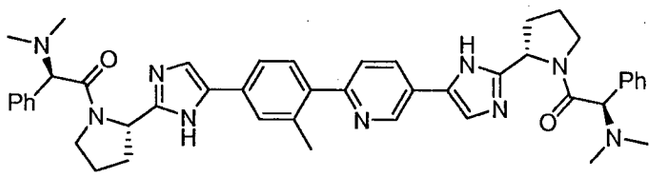


Example	*Compound Name*		*RT (LC-Cond.); % homogeneity index; MS data*
133	(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanol		1.49 min (Cond. 1); >98% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{40}N_7O_4$: 694.31; found 694.42 HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{40}N_7O_4$: 694.3142, found: 694.3164
134	methyl ((1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap-4*	1.60 min (Cond. 1); >98% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{46}N_9O_6$: 808.36; found 808.51 HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{46}N_9O_6$: 808.3571; found 808.3576
135	5-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-(4-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-		1.60 min (Cond. 1); >98% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{44}N_7O_4$: 722.35; found 722.40 HRMS: Anal. Calcd. for

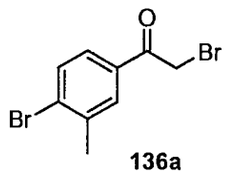
	pyrrolidinyl)-1H-imidazol-5-yl)phenyl)pyridine		$[M+H]^+$ $C_{43}H_{44}N_7O_4$: 722.3455; found 722.3464

Example 136

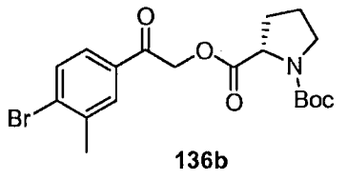
(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-methylphenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine



Example 136, Steps a and b



136a



136b

$PdCl_2(Ph_3P)_2$ (257 mg, 0.367 mmol) was added to a dioxane (45 mL) solution of 1-bromo-4-iodo-2-methylbenzene (3.01 g, 10.13 mmol) and tri-*n*-butyl(1-ethoxyvinyl)stannane (3.826 g, 10.59 mmol) and heated at 80 °C for ~17 hr. The reaction mixture was treated with water (15 mL), cooled to ~0 °C (ice/water), and then NBS (1.839 g, 10.3 mmol) was added in batches over 7 min. About 25 min of stirring, the volatile component was removed *in vacuo*, and the residue was partitioned between CH_2Cl_2 and water. 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 crude material was purified by a gravity chromatography (silica gel; 4% EtOAc/hexanes)to afford bromide 136a as a brownish-yellow solid (2.699 g); the sample is impure and contains stannane-derived impurities, among others. ^{1}H NMR ($CDCl_3$, δ = 7.24, 400 MHz): 7.83 (s, 1H), 7.63 (s, 2H), 4.30 (s, 2H), 2.46 (s, 3H).

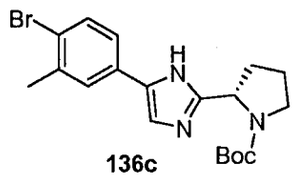
An CH_3CN (15 mL) solution of 136a (2.69 g, < 9.21 mmol) was added drop wise over 3 min to a CH_3CN (30 mL) solution of (*S*)-Boc-proline (2.215 g, 10.3 mmol) and Et_3N (1.40 mL, 10.04 mmol), and stirred for 90 min. The volatile

component was removed *in vacuo*, and the residue was partitioned between water and CH_2Cl_2, and the organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resultant crude material was purified by a flash chromatography (silica gel; 15-20% EtOAc/hexanes) to afford 136b as a colorless viscous oil (2.74g). ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 7.98 (m, 1H), 7.78 (d, J = 8.3, 1H), 7.72-7.69 (m, 1H), 5.61-5.41 (m, 2H), 4.35-4.30 (m, 1H), 3.41-3.30 (m, 2H), 2.43 (s, 3H), 2.33-2.08 (m, 2H), 1.93-1.83 (m, 2H), 1.40/1.36 (s, 9H).

LC (Cond. 1): RT = 1.91 min; >95% homogeneity index

LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{19}H_{24}BrNNaO_5$ 448.07; found 448.10

Example 136, Step c



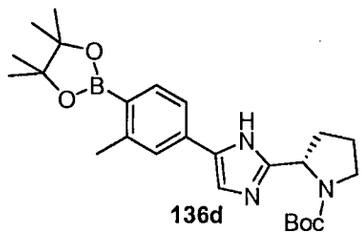
136c

A mixture of ketoester 136b (1.445 g, 3.39 mmol) and NH_4OAc (2.93 g, 38.0 mmol) in xylenes (18 mL) was heated with a microwave at 140 °C for 80 min. The volatile component was removed *in vacuo*, and the residue was carefully partitioned between CH_2Cl_2 and water, where enough saturated $NaHCO_3$ solution was added to neutralize the aqueous medium. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude was purified by a flash chromatography (silica gel, 40% EtOAc/hexanes) to afford imidzaole 136c as an off-white solid (1.087 g). ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 12.15/11.91/11.84 (br s, 1H), 7.72-7.24 (m, 4H), 4.78 (m, 1H), 3.52 (m, 1H), 3.38-3.32 (m, 1H), 2.35 (s, 3H), 2.28-1.77 (m, 4H), 1.40/1.14 (s, 9H).

LC (Cond. 1): RT = 1.91 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{19}H_{25}BrN_3O_2$ 405.96; found 406.11

Example 136, Step d



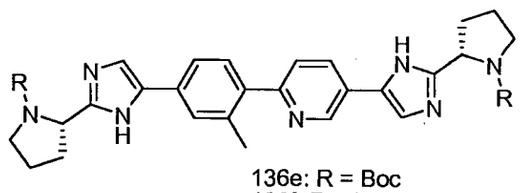
136d

$PdCl_2dppf.CH_2Cl_2$ (50.1 mg, 0.061 mmol) was added to a pressure tube containing a mixture of bromide 136c (538.3 mg, 1.325 mmol), bis(pinacolato)diboron (666.6 mg, 2.625 mmol), KOAc (365.8 mg, 3.727 mmol) and DMF (10 mL). The reaction mixture was flushed with N_2 and heated at 80 °C for 24.5 hr. The volatile component was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and water, where enough saturated $NaHCO_3$ solution was added to make the pH of the aqueous medium neutral. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting material was purfied by a Biotage system (silica gel, 40-50% EtOAc/hexanes) to afford boronate 136d as a white foam (580 mg). According to ^1H NMR the sample contains residual pinacol in a product/pinacol ratio of ~3. ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 12.16/11.91/11.83 (br s, 1H), 7.63-7.25 (m, 4H), 4.78 (m, 1H), 3.53 (m, 1H), 3.39-3.32 (m, 1H), 2.48/2.47 (s, 3H), 2.28-1.78 (m, 4H), 1.40/1.14/1.12 (br s, 9H), 1.30 (s, 12H).

LC (Cond. 1): RT = 1.62 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{37}BN_3O_4$ 454.29; found 454.15

Example 136, Step e-f



136e: R = Boc
136f: R = H

Biaryl 136e was prepared from bromide 132c and boronate 136d according to the coupling condition described for the preparation of biaryl 132d.

LC (Cond. 1a): RT = 1.32 min; >90% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{45}N_7O_4$ 640.36; found 640.66

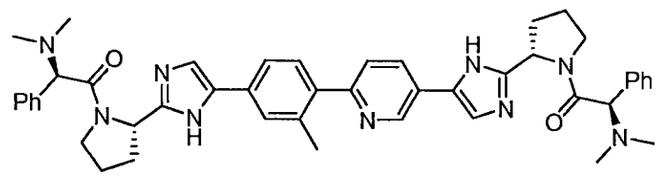
The deprotection of biaryl 136e was done according to the preparation of pyrrolidine 132e to afford 136f as a light yellow foam. ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 11.88 (br s, 2H), 9.02 (d, J = 2, 1H), 8.12 (dd, J = 8.4, 2.3, 1H), 7.67 (s, 1H), 7.64-7.62 (m, 2H), 7.50 (d, J = 8.3, 1H), 7.46 (br s, 1H), 7.40 (d, J = 7.8, 1H), 4.21-4.14 (m, 2H), 3.00-2.93 (m, 2H), 2.90-2.82 (m, 2H), 2.40 (s, 3H), 2.11-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.82-1.66 (m, 4H). [Note: the signal for the pyrrolidine NH appears in the region 3.22-2.80 and is too broad to make a chemical shift assignment.]

LC (Cond. 1): RT = 0.84 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{30}N_7$ 440.26; found 440.50

Example 136

(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-methylphenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine



Example 136 (TFA salt) was synthesized from 136f according to the preparation of Example 132 from 132e.

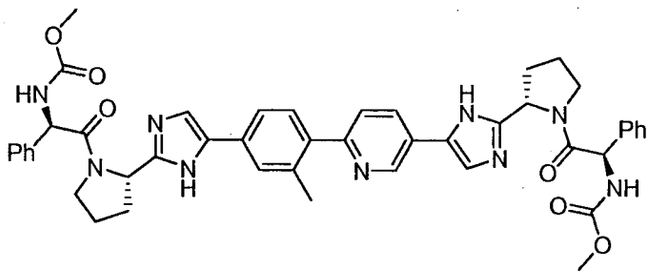
1.05 min (Cond.1); >98%

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{52}N_9O_2$: 762.42, found: 762.77

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{52}N_9O_2$: 762.4244; found 762.4243

Example 138

methyl ((1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-methylphenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate



Example 138 was prepared similarly from pyrrolidine 136f and *Cap*-4.

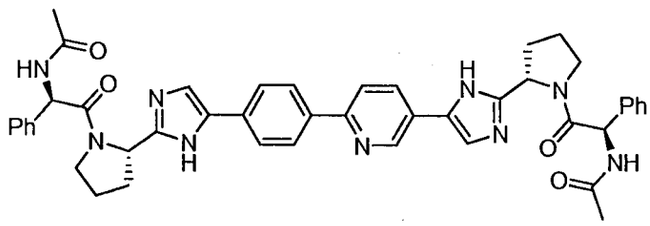
1.60 min (Cond. 1); >98%

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{48}N_9O_6$: 822.37; found 822.74

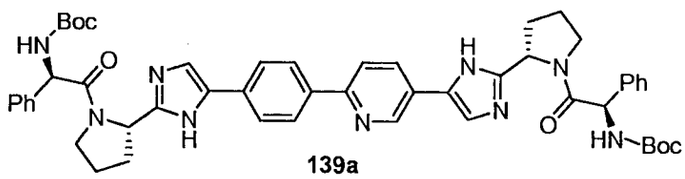
HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{48}N_9O_6$: 822.3728; found 822.3760

Example 139

N-((1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-acetamido-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)acetamide



Example 139, Step a



139a

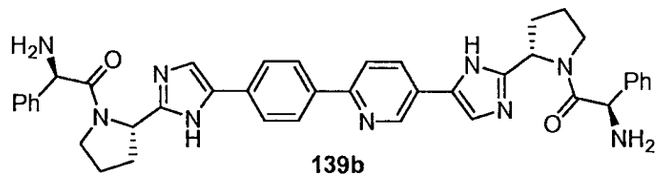
HATU (99.8 mg, 0.262 mmol) was added to a mixture of 132e (54.1 mg, 0.127 mmol), (*R*)-2-(*t*-butoxycarbonylamino)-2-phenylacetic acid (98.5 mg, 0.392 mmol) and *i*-Pr_2EtN (100 μL, 0.574 mol), and the reaction mixture was stirred for 70

min. The volatile component was removed *in vacuo*, and the residue was purified by a reverse phase HPLC (H_2O/MeOH/TFA), where the HPLC elute was treated with excess 2.0 N NH_3/MeOH before the removal of the volatile component *in vacuo*. The resulting material was partitioned between CH_2Cl_2 and water, and the aqueous phase was extracted with CH_2Cl_2 (2x). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Carbamate 139a was obtained as a white film of foam (82.3 mg).

LC (Cond. 1): RT = 1.97 min; >95% homogeneity index.

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{58}N_9O_6$: 892.45; found 892.72

Example 139b, Step b



139b

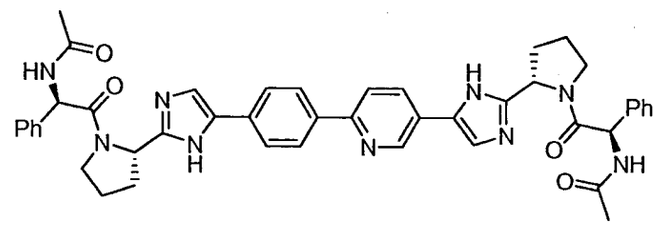
Carbamate 139a was deprotected to amine 139b by using the procedure described for the preparation of pyrrolidine 132e from 132d.

LC (Cond. 1): RT = 1.37 min; >95% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{42}N_9O_2$: 692.35; found 692.32

Example 139

N-((1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-acetamido-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)acetamide



Acetic anhydride (20 μL, 0.212 mmol) was added to a DMF (1.5 mL) solution of 139b (31.2 mg, 0.045 mmol), and the reaction mixture was stirred for 1 hr. NH_3/MeOH (1.0 mL of 2N) was added to the reaction mixture and stirring continued for 100 min. The volatile component was removed *in vacuo* and the

resulting crude material was purified by a reverse phase HPLC (H_2O/MeOH/TFA) to afford the TFA salt of Example 139 as a light yellow solid (24.1 mg).

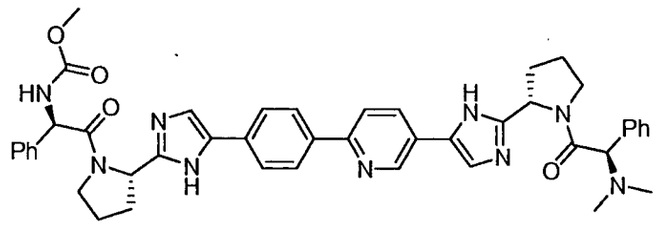
LC (Cond. 1): RT = 1.53 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{46}N_9O_4$: 776.37; found 776.38

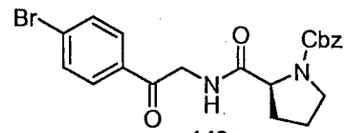
HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{46}N_9O_4$: 776.3673; found 776.3680

Example 140

methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate



Example 140, Step a



140a

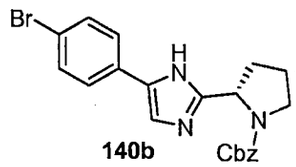
HATU (19.868g, 52.25 mmol) was added to a heterogeneous mixture of *N*-Cbz-L-proline (12.436 g, 49.89 mmol) and the HCl salt of 2-amino-1-(4-bromophenyl) ethanone (12.157 g, 48.53 mmol) in DMF (156 mL). The mixture was lowered in an ice-water bath, and immediately afterward *N,N*-diisopropylethylamine (27 mL, 155 mmol) was added drop wise to it over 13 min. After the addition of the base was completed, the cooling bath was removed and the reaction mixture was stirred for an additional 50 min. The volatile component was removed *in vacuo*; water (125 mL) was added to the resultant crude solid and stirred for about 1 hr. The off-white solid was filtered and washed with copious water, and dried *in vacuo* to afford ketoamide 140a as a white solid (20.68 g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 8.30 (m, 1H), 7.91 (m, 2H), 7.75 (d, J = 8.5, 2H), 7.38-7.25 (m, 5H), 5.11-5.03 (m, 2H),

4.57-4.48 (m, 2H), 4.33-4.26 (m, 1H), 3.53-3.36 (m, 2H), 2.23-2.05 (m, 1H), 1.94-1.78 (m, 3H).

LC (Cond. 1): RT = 1.65 min; 98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{22}BrN_2O_4$: 445.08; found 445.31

Example 140, Step b



140b

Ketoamide 140a (10.723g, 24.08 mmol) was converted to 140b according to the procedure described for the synthesis of carbamate 132c, with the exception that the crude material was purified by flash chromatography (silica gel; 50% EtOAc/hexanes). Bromide 140b was retrieved as an off-white foam (7.622 g). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.23/12.04/11.97 (m, 1H), 7.73-6.96 (m, 10H), 5.11-4.85 (m, 3H), 3.61 (m, 1H), 3.45 (m, 1H), 2.33-184(m, 4H).

LC (Cond.1): RT = 1.42 min; >95% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{21}BrN_3O_2$: 426.08; found 426.31

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{21}H_{21}BrN_3O_2$: 426.0817; found: 426.0829

The optical purity of 140b was assessed using the following chiral HPLC methods, and an ee of 99% was observed.

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

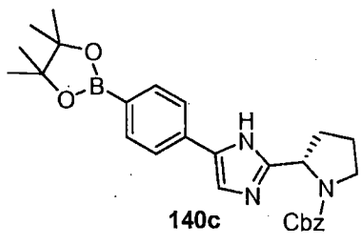
Solvent: 20% ethanol/heptane (isocratic)

Flow rate: 1 ml/min

Wavelength: 254 nm

Relative retention time: 1.82 min (*R*), 5.23 min (*S*)

Example 140, Step c



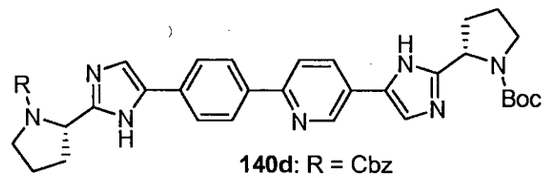
140c

$Pd(Ph_3P)_4$ (208 mg, 0.180 mmol) was added to a pressure tube containing a mixture of bromide 140b (1.80 g, 4.22 mmol), bis(pinacolato)diboron (2.146 g, 8.45 mmol), KOAc (1.8 g, 11.0 mmol) and 1,4-dioxane (34 mL). The reaction flask was purged with nitrogen, capped and heated with an oil bath at 80 °C for 23 hr. The volatile component was removed *in vacuo*, and the residue was partitioned carefully between CH_2Cl_2 (70 mL) and an aqueous medium (22 mL water + 5 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 oily resdue was crystallized from EtOAc/hexanes to afford two crops of boronate 140c as a yellow solid (1.52 g). The mother liquor was evaporated *in vacuo* and the resulting material was purified by flash chromatography (silica gel; 20-35% EtOAc/CH_2Cl_2) to afford additional 140c as an off-white solid, containing residual pinacol (772 mg).

LC (Cond. 1): RT = 1.95 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{33}BN_3O_4$: 474.26; found 474.31

Example 140, Steps d-e



140d: R = Cbz
140e: R = H

Arylbromide 132c was coupled with boronate 140c to afford 140d by using the same procedure described for the synthesis of biaryl 132d. The sample contains the desbromo version of 132c as an impurity. Proceeded to the next step without further purification.

LC (Cond. 1): RT = 1.72 min; ~85% homogeneity index

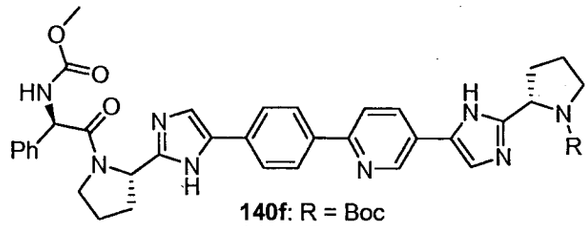
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{42}N_7O_4$: 660.33; found 660.30

A mixture of 10% Pd/C (226 mg), biaryl 140d (1.25 g) and MeOH (15 mL) was stirred under a balloon of hydrogen for ~160 hr, where the hydrogen supply was replenished periodically as needed. The reaction mixture was filtered through a pad of diatomaceous earth (Celite®), and the filtrate was evaporated *in vacuo* to afford crude 140e as a yellowish-brown foam (911 mg). Proceeded to the next step without further purification.

LC (Cond. 1): RT = 1.53 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{30}H_{36}N_7O_2$: 526.29; found 526.23

Example 140, Steps f-g



140f: R = Boc
140g: R = H

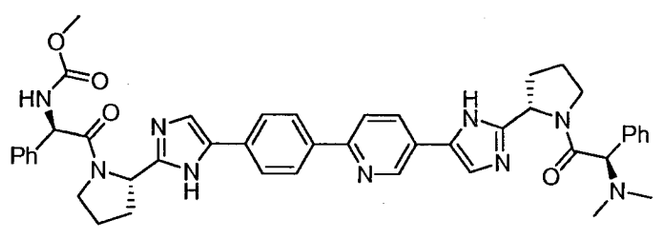
Pyrrolidine 140g was prepared from 140e and *Cap*-4, *via* the intermediacy of carbamate 140f, by sequentially employing the amide forming and Boc-deprotection protocols used in the synthesis of Example 132.

LC (Cond. 1): RT = 1.09 min; ~94% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{37}N_8O_3$: 617.30; found 617.38

Example 140

methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate



The TFA salt of Example 140 was synthesized from pyrrolidine 140g and *Cap*-1 by using the procedure described for the preparation of Example 132 from intermediate 132e.

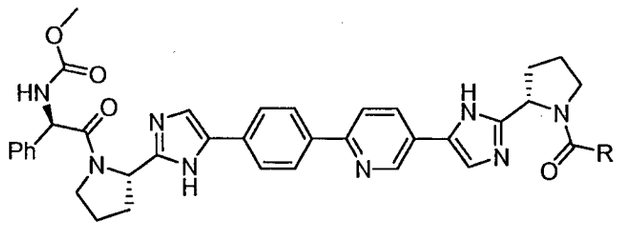
1.15 min (Cond. 1); >98% homogeneity index

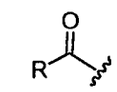
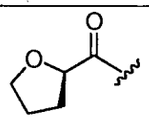
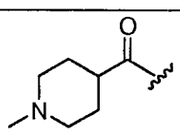
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{40}N_7O_4$: 778.38; found 778.48

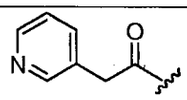
HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{40}N_7O_4$: 778.3829; found 778.3849

The TFA salt of Example 141-143 were synthesized from intermediate 140g and appropriate reagents in a similar manner.

Examples 141-143

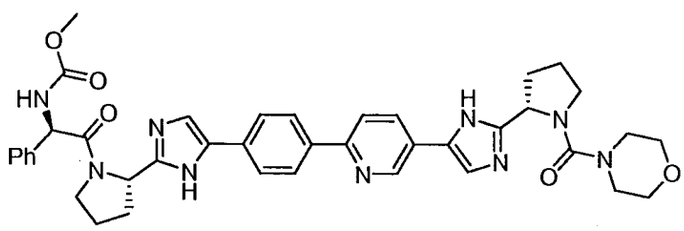


Example	*Compound Name*		*RT (LC-Cond.); % homogeneity index; MS data*
141	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.15 min (Cond. 1); >98% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{43}N_8O_5$: 715.34; found 715.44 HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{43}N_8O_5$: 715.3356; found 715.3381
142	methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((1-methyl-4-piperidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-		1.07 min (Cond. 1); >98% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{48}N_9O_4$: 742.38; found 742.48

	5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{48}N_9O_4$: 742.3829; found 742.3859
143	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4-(5-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.09 min (Cond. 1); >98% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{42}N_9O_4$: 736.34; found 736.44 HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{42}N_9O_4$: 736.3360; 736.3344

Example 144

methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-(4-morpholinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate



A DMF (1.5 mL) solution of morpholine-4-carbonyl chloride (8.5 mg, 0.057 mmol) was added to a mixture of *i*-Pr_2EtN (20 μL, 0.115 mmol) and 140g (27.3 mg, 0.044 mmol), and stirred for 100 min. The volatile component was removed *in vacuo* and the residue was purified by a reverse phase HPLC (H_2O/MeOH/TFA) to afford the TFA salt of Example 144 as a yellow foam (34.6 mg).

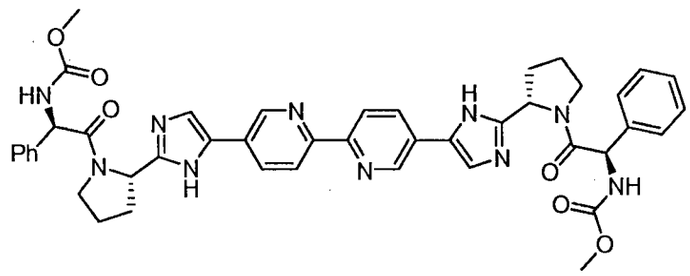
1.17 min (Cond. 1); >98%

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{44}N_9O_5$: 730.35; found 730.42

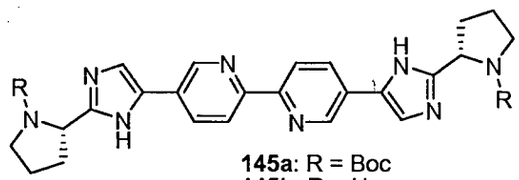
HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{44}N_9O_5$: 730.3465; found 730.3477

Example 145

dimethyl (2,2'-bipyridine-5,5'-diylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate



Example 145, Step a-b



145a: R = Boc
145b: R = H

$Pd(Ph_3P)_4$ (9.6 mg, 0.008 mmol) and LiCl (28 mg, 0.67 mmol) were added to a mixture of arylbromide 132c (98.7 mg, 0.251 mmol) and hexamethylditin (51.6 mg, 0.158 mmol), and heated at 80 °C for ~ 3 days. The volatile component was removed *in vacuo* and the resultant crude material was purified by flash chromatography (silica gel; 0-10% MeOH/EtOAc) followed by a reverse phase HPLC (H_2O/MeOH/TFA). The HPLC elute was neutralized with excess 2.0 N NH_3/MeOH, and the volatile component was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and water, and the aqueous phase was washed with CH_2Cl_2 (2x). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford carbamate 145a as a film of oil (8.7 mg).

LC (Cond. 1): RT = 1.68 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{43}N_8O_4$: 627.34; found 627.47

Carbamate 145a was elaborated to pyrrolidine 145b according to the preparation of 132e from 132d. ^1H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 12.02 (br signal, 2H), 9.04 (d, J = 1.6, 2H), 8.34 (d, J = 8.3, 2H), 8.20 (dd, J = 8.3, 2.3, 2H), 7.67 (br s,

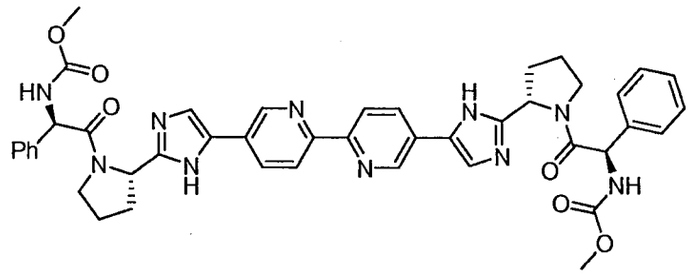
1H), 4.21 (m, 2H), 3.00-2.85 (m, 4H), 2.12-2.04 (m, 2H), 1.95-1.68 (m, 6H). [Note: the pyrrolidine-NH signal was not observed].

LC (Cond.1): RT = 1.17 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{27}N_8$: 427.24; found 427.13

Example 145

dimethyl (2,2'-bipyridine-5,5'-diylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate



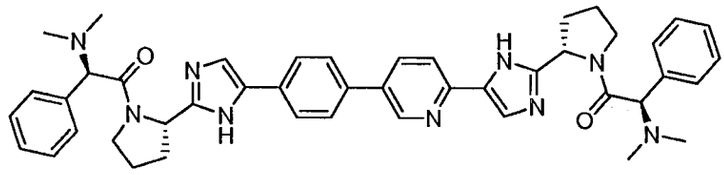
Example 145 (TFA salt) was synthesized from 145b according to the preparation of Example 132 from 132e.

LC (Cond. 1): RT = 1.63 min; 98% homogeneity index

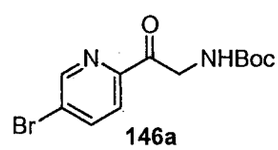
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_{10}O_6$: 809.35; found 809.40

Example 146

(1R)-2-((2S)-2-(5-(5-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-2-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine



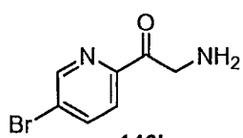
Example 146, Step a



146a

n-BuLi (12.0 mL of 2.5M/hexanes, 30 mmol) was added drop-wise over 15 min to a cooled (-78 °C) toluene (300 mL) semi-solution of 2,5-dibromopyridine (6.040 g, 25.5 mmol), and stirred for 2.5 hr. *t*-Butyl 2-(methoxy(methyl)amino)-2-oxoethylcarbamate (2.809 g, 12.87 mmol) was added in batches over 7 min, and stirring continued for 1.5 hr at -78 °C. The -78 °C bath was replaced with -60 °C bath, which was allowed to warm up to -15 °C over 2.5 hr. The reaction was quenched with saturated NH_4Cl solution (20 mL), and the mixture was allowed to thaw to ambient temperature and the organic layer was separated and evaporated *in vacuo*. The resulting crude material was purified by flash chromatography (silica gel; 15 % EtOAc/hexanes) to afford a reddish brown semisolid, which was washed with hexanes to removed the colored residue. Pyridine 146a was retrieved as an ash colored solid (842 mg). ^{1}H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 8.89 (d, J = 2.3, 1H), 8.30 (dd, J = 8.4, 2.4, 1H), 7.90 (d, J = 8.3, 1H), 7.03(br t, J = 5.7; 0.88H), 6.63 (app br s, 0.12H), 4.55 (d, J = 5.8, 2H), 1.40/1.28 (two app s, 7.83H + 1.17H).
LC (Cond. 1): RT = 2.00 min; >95% homogeneity index
LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{12}H_{15}BrNaN_2O_3$: 337.02; found 337.13

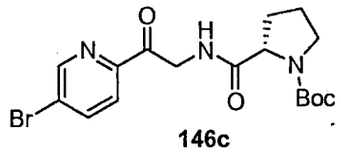
Example 146, Step b



146b

48% HBr (1.0 mL) was added drop-wise to a dioxane (5.0 mL) solution of carbamate 146a (840 mg, 2.66 mmol) over 3 min, and the reaction mixture was stirred at ambient temperature for 17.5 hr. The precipitate was filtered and washed with dioxane, and dried *in vacuo* to afford amine the HBr salt of 146b as an off-white solid (672.4 mg; the exact mole equivalent of the HBr salt was not determined). ^{1}H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 8.95 (d, J = 2.3, 1 H), 8.37 (dd, J = 8.4, 2.3, 1H), 8.2 (br s, 3H), 8.00 (d, J = 8.3, 1H), 4.61 (s, 2H).
LC (Cond. 1): RT = 0.53 min
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_7H_8BrN_2O$: 214.98; found 215.00

Example 146, Step c



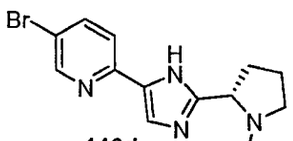
146c

i-Pr_2EtN (2.3 mL, 13.2 mmol) was added drop-wise over 15 min to a heterogonous mixture of amine 146b (1.365g), (*S*)-Boc-proline (0.957 g, 4.44 mmol) and HATU (1.70 g, 4.47 mmol) in DMF (13.5 mL), and stirred at ambient temperature for 1 hr. The volatile component was removed *in vacuo* and the residue was partitioned between EtOAc (40 mL) and an aqueous medium (20 mL water + 1 ml saturated $NaHCO_3$ solution). The aqueous layer was washed with EtOAc (20 mL), and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resultant crude material was purified by flash chromatography (silica gel; 40-50% EtOAc/hexanes) to afford ketoamide 146c as a faint-yellow foam (1.465g). ^1H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 8.90 (d, J = 2.3, 1H), 8.30 (dd, J = 8.5, 2.4, 1H), 8.01-8.07 (m, 1H), 7.90 (d, J = 8.3, 1H), 4.6 (m, 1H), 4.64 (dd, J = 19.1, 5.5, 1H); 4.19 (m, 1H), 3.39 (m, 1H), 3.32-3.26 (m, 1H), 2.20-2.01 (m, 1H), 1.95-1.70 (m, 3H),1.40/1.35 (two app s, 9H).

LC (Cond. 1): RT = 1.91 min

LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{17}H_{22}BrN_3NaO_4$: 434.07; found 433.96.

Example 146, Step d



146d

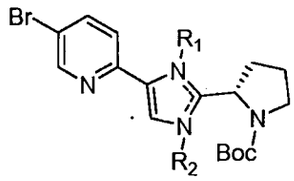
A mixture of ketoamide 146c (782.2 mg, 1.897 mmol) and NH_4OAc (800 mg, 10.4 mmol) in xylenes was heated with a microwave (140 °C) for 90 min. The volatile component was removed *in vacuo* and the residue was carefully partitioned between CH_2Cl_2 and water, where enough saturated $NaHCO_3$ solution was added to neutralize it. The aqueous phase was extracted with CH_2Cl_2 (2x), and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resultant crude material was purified by flash chromatography (silica gel; 50% CH_2Cl_2/EtOAc) to afford imidazole 146d as an off-white solid (552.8 mg). ^1H NMR (DMSO, δ = 2.5

ppm; 400 MHz): 12.49/12.39/12.15/12.06 (br s, 1H), 8.62 (app br s, 0.2H), 8.56 (d, J = 2, 0.8H), 8.02 (br d, J = 8.5, 0.2H), 7.97 (br d, J = 7.8, 0.8H), 7.77 (d, J = 8.6, 0.8H), 7.72 (d, J = 8.6, 0.2H), 7.61-7.49 (m, 1H), 4.93-4.72 (m, 1H), 3.53 (m, 1H), 3.41-3.32 (m, 1H), 2.33-1.77 (m, 4H), 1.39/1.14 (app br s, 3.7H+5.3H).

LC (Cond. 1): RT = 1.67 min; >95% homogeneity index

LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{17}H_{21}BrN_4NaO_2$: 415.08; found 415.12

Example 146, Step e



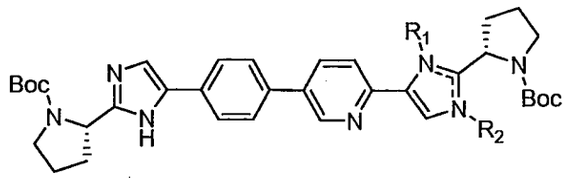
146e (R_1 = H, R_2 = SEM) or (R_1 = SEM, R_2 = H)

NaH (60%; 11.6 mg, 0.29 mmol) was added in one batch to a heterogeneous mixture of imidazole 146d (80 mg, 0.203 mmol) and DMF (1.5 mL), and stirred at ambient condition for 30 min. SEM-Cl (40 μL, 0.226 mmol) was added drop-wise over 2 min to the above reaction mixture, and stirring was continued for 14 hr. The volatile component was removed *in vacuo* and the residue was partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by a flash chromatography (silica gel; 20% EtOAc/hexanes) to afford 146e as a colorless viscous oil (87.5 mg). The exact regiochemistry of 146e was not determined. ^{1}H NMR ($CDCl_3$, δ = 7.4 ppm; 400 MHz): 8.53 (d, J = 2.2, 1H), 7.90-7.72 (m, 2H), 7.52 (s, 1H), 5.87 (m, 0.46H), 5.41 (m, 0.54H), 5.16 (d, J = 10.8, 1H), 5.03-4.85 (m, 1H), 3.76-3.42 (m, 4H), 2.54-1.84 (m, 4H), 1.38/1.19 (br s, 4.3H + 4.7H), 0.97-0.81 (m, 2H), -0.03 (s, 9H).

LC (Cond. 1): RT = 2.1 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{23}H_{36}BrN_4O_3Si$: 523.17; found 523.24

Example 146, Step f



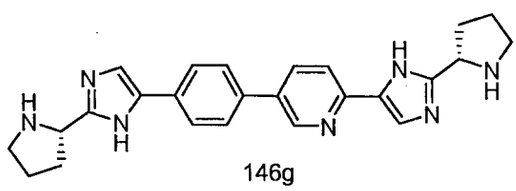
146f: (R_1 = H, R_2 = SEM) or (R_1 = SEM, R_2 = H)

$Pd(Ph_3P)_4$ (24.4 mg, 0.021 mmol) was added to a mixture of imidazole 146e (280 mg, 0.535 mmol), 1c (241.5 mg, 0.55 mmol) and $NaHCO_3$ (148.6 mg, 1.769 mmol) in 1,2-dimethoxyethane (4.8 mL) and water (1.6 mL). The reaction mixture was flushed with nitrogen, heated with an oil bath at 80 °C for ~24 hr and then the volatile component was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and water, and the organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by a Biotage system (silica gel; 75-100% EtOAc/hexanes) followed by a reverse phase HPLC (H_2O/MeOH/TFA). The HPLC elute was neutralized with 2M NH_3/MeOH and evaporated *in vacuo*, and the residue was partitioned between water and CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford 146f as a white foam (162 mg).

LC (Cond. 1): RT = 2.1 min

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{58}N_7O_5Si$: 756.43; found 756.55

Example 146, Step g



146g

Carbamate 146f (208 mg, 0.275 mmol) was treated with 25% TFA/CH_2Cl_2 (4.0 mL) and stirred at ambient temperature for 10 hr. The volatile component was removed *in vacuo* and the residue was first free-based by MCX (MeOH wash; 2.0 M NH_3/MeOH elution) and then purified by a reverse phase HPLC (H_2O/MeOH/TFA), and the resultant material was free-based again (MCX) to afford pyrrolidine 146g as a film of oil (53.7 mg). ^1H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 1.88 (app br s, 2H), 8.83 (d, J = 2.1, 1H), 8.07 (dd, J = 8.3/2.3, 1H0, 7.87 (d, J = 8.5, 1H), 7.84 (d, J

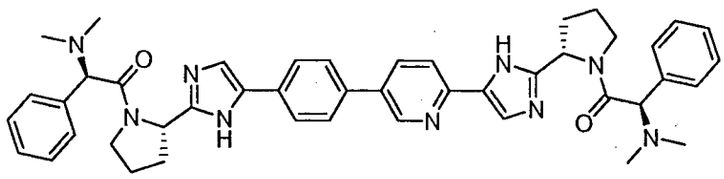
= 8.3, 2H), 7.71 (d, *J* = 8.3, 2H), 7.55 (s, 1H), 7.50 (br s, 1H), 4.18 (m, 2H), 3.00-2.94 (m, 2H), 2.89-2.83 (m, 2H), 2.11-2.02 (m, 2H), 1.95-1.86 (m, 2H), 1.83-1.67 (m, 4H).

LC (Cond. 1): RT = 0.95 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{28}N_7$: 426.24; found 426.27

Example 146

(1R)-2-((2S)-2-(5-(5-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-2-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine



Example 146 (TFA salt) was synthesized from pyrrolidine 146g according to the preparation of Example 132 from intermediate 132e.

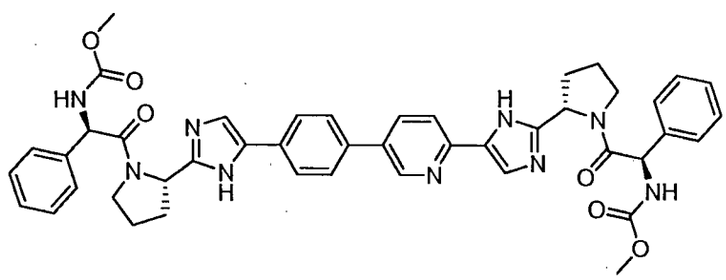
LC (Cond. 1): RT = 1.42 min; 96.5% homogenity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}N_9O_2$: 748.41; found 748.57

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}N_9O_2$: 748.4087; found 748.4100

Example 147

methyl ((1R)-2-((2S)-2-(5-(5-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-2-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate



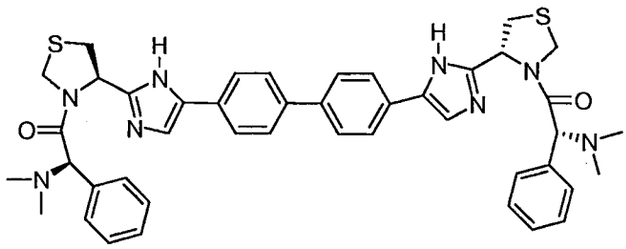
The TFA salt of Example 147 was prepared similarly from intermediate 146g by using *Cap*-4.

LC (Cond. 1): RT = 1.66 min; 95% homogenity index

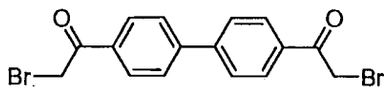
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{46}N_9O_6$: 808.36; found 808.55

Example 148

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(4R)-1,3-thiazolidine-4,3-diyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)



Example 148, Step a

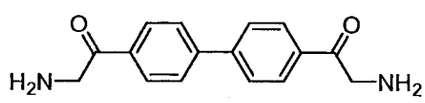


A solution of bromine (1.3mL, 25.0mmol) in 15mL glacial acetic acid was added drop-wise to a solution of 4-4'-diacetylbiphenyl (3.0g, 12.5mmol) in 40mL acetic acid at 50°C. Upon completion of addition the mixture was stirred at room temperature overnight. The precipitated product was filtered off and re-crystallized from chloroform to give 1,1'-(biphenyl-4,4'-diyl)bis(2-bromoethanone) (3.84g, 77.5%) as a white solid.

^{1}H NMR (500 MHz, CHLOROFORM-D) δ ppm 8.09 (4 H, d, *J*=7.93 Hz) 7.75 (4 H, d, *J*=8.24 Hz) 4.47 (4 H, s)

Nominal/LRMS – Anal. Calcd. for 369.07 found; $(M+H)^+$ - 397.33, $(M-H)^-$ - 395.14

Example 148, Step b



.2HCl

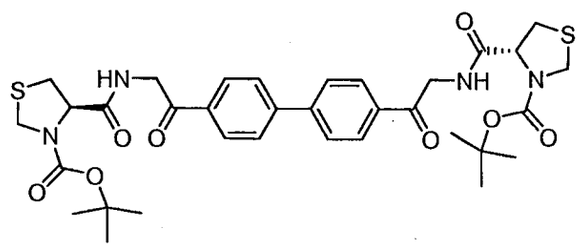
Sodium diformylamide (3.66g, 38.5mmol) was added to a suspension of 1,1'-(biphenyl-4,4'-diyl)bis(2-bromoethanone) (6.1g, 15.4mmol) in 85mL acetonitrile. The mixture was heated at reflux for 4 hours and concentrated under reduced pressure. The residue was suspended in 300mL 5% HCl in ethanol and heated at

reflux for 3.5 hours. Reaction was cooled to room temperature and placed in the freezer for 1 hour. Precipitated solid was collected, washed with 200mL 1:1 ethanol/ether followed by 200mL pentane, and dried under vacuum to give 1,1'-(biphenyl-4,4'-diyl)bis(2-aminoethanone) dihydrochloride (4.85g, 92%). Carried on without further purification.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.47-8.55 (4H, m) 8.11 - 8.17 (4 H, m) 8.00 (4 H, d, *J*=8.42 Hz) 4.59 - 4.67 (4 H, m).

LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, t_R = 0.44 minutes, Anal. Calcd. for $C_{16}H_{16}N_2O_2$ 268.31 found; 269.09 $(M+H)^+$.

Example 148, Step c

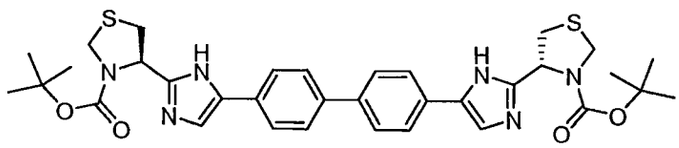


To a stirred solution of 1,1'-(biphenyl-4,4'-diyl)bis(2-aminoethanone) dihydrochloride (0.7g, 2.1mmol), N-(tert-butoxy carbonyl) –L-thioproline (0.96g, 4.2mmol), and HATU(1.68g, 4.4mmol) in 14mL DMF was added diisopropylethyl amine (1.5mL, 8.4mmol) drop-wise over 5 minutes. The resulting clear yellow solution was stirred at room temperature overnight (14 hours) and concentrated under reduced pressure. The residue was partitioned between 20%methanol/chloroform and water. The aqueous phase was washed once with 20%methanol/chloroform. The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was chromatographed on silica gel by gradient elution with 10-50% ethyl acetate/CH_2Cl_2 to give (4S,4'S)-tert-butyl 4,4'-(2,2'-(biphenyl-4,4'-diyl)bis(2-oxoethane-2,1-diyl))bis(azanediyl)bis(oxomethylene)dithiazolidine-3-carboxylate (0.39g, 27%) as an orange foam.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.38 (2 H, s) 8.12 (4 H, d, *J*=8.56 Hz) 7.94 (4 H, d, *J*=8.56 Hz) 4.60 - 4.68 (4 H, m) 4.33 - 4.38 (2 H, m) 3.58 - 3.68 (2 H, m) 3.38 (2 H, s) 3.08 - 3.18 (2 H, m) 1.40 (18 H, s)

LCMS – Water-Sunfire C-18 4.6 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, t_R = 3.69 min., Anal. Calcd. for $C_{34}H_{42}N_4O_8S_2$ 698.85 found; 699.12 $(M+H)^+$.

Example 148, Step d

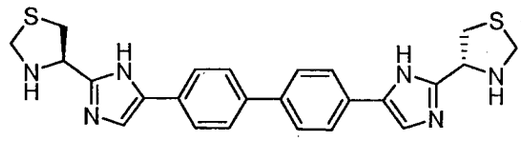


(4S,4'S)-tert-butyl 4,4'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))dithiazolidine-3-carboxylate (0.39g, 0.56mmol) and ammonium acetate (0.43g, 5.6mmol) were suspended in 8mL o-xylene in a microwave reaction vessel. The mixture was heated under standard microwave conditions at 140°C for 70 minutes and concentrated under reduced pressure. The residue was dissolved in 30mL 20% methanol/chloroform and washed with 10% $NaHCO_3$(aq). The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was chromatographed on silica gel by gradient elution with 1-6% methanol/CH_2Cl_2 to give (4S,4'S)-tert-butyl 4,4'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2- diyl))dithiazolidine-3-carboxylate (0.15g, 41%) as a yellow solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.02 (2 H, s) 7.70 - 7.88 (10 H, m) 5.28 - 5.37 (2 H, m) 4.68 (2 H, d, *J*=9.16 Hz) 4.47 - 4.55 (2 H, m) 3.46 (2 H, s) 3.23 (2 H, s) 1.26 – 1.43 (18 H, m)

LCMS - Luna C-18 3.0 x 50mm, 0 to 100% B over 3.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate, t_R = 1.96 min., Anal. Calcd. for $C_{34}H_{40}N_6O_4S_2$ 660.85 found; 661.30 $(M+H)^+$, 659.34 $(M-H)^-$

Example 148, Step e



.4HCl

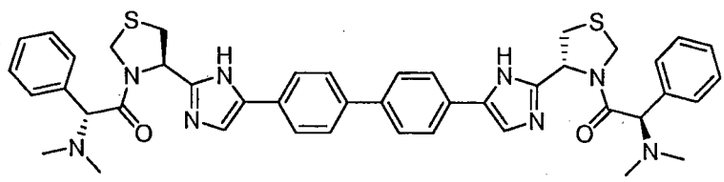
To a solution of (4S,4'S)-tert-butyl 4,4'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2- diyl))dithiazolidine-3-carboxylate in 1mL dioxane was added 0.3mL of a 4.0M solution of HCl in dioxane. The reaction was stirred for 3 hours at room temperature and concentrated under reduced pressure. The resulting tan solid was dried under vacuum to give 4,4'-bis(2-((S)-thiazolidin-4-yl)-1H-imidazol-5-yl)biphenyl tetrahydrochloride (0.12g, 100%) as a yellow solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.09 (2 H, s) 8.01 (4 H, d, *J*=8.55 Hz) 7.90 (4 H, d, *J*=8.55 Hz) 5.08 (2 H, t, *J*=6.10 Hz) 4.38 (2 H, d, *J*=9.16 Hz) 4.23 (2 H, d, *J*=9.46 Hz) 3.48 - 3.54 (2 H, m,) 3.35 - 3.41 (2 H, m)

LCMS - Luna C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate, t_R = 1.70 min., Anal. Calcd. for $C_{24}H_{24}N_6S_2$ 460.62 found; 461.16 $(M+H)^+$, 459.31 $(M-H)^-$

Example 148

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(4R)-1,3-thiazolidine-4,3-diyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)



To a stirred solution of (4,4'-bis(2-((S)-thiazolidin-4-yl)-1H-imidazol-5-yl)biphenyl tetrahydrochloride (0.028g, 0.046mmol), (R)-2-(dimethylamino)-2-phenylacetic acid (*Cap*-1, 0.017g, 0.0.10mmol), and HATU (0.039g, 0.10mmol) in 2mL DMF was added diisopropylethyl amine (0.05mL, 0.28mmol).The reaction was stirred at room temperature overnight (16 hours) and concentrated under reduced pressure. The crude product was purified by reverse-phase preparative HPLC to provide (2R,2'R)-1,1'-((4S,4'S)-4,4'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-

diyl))bis(thiazolidine-4,3-diyl))bis(2-(dimethylamino)-2-phenylethanone), TFA salt (0.012g, 21%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.59 - 7.91 (20 H, m) 5.62 (2 H, dd, *J*=6.56, 2.59 Hz) 4.99 (2 H, d, *J*=8.85 Hz) 4.82/4.35 (2 H, s) 4.22 (2 H, s) 3.42 (2 H, s) 3.25 (2 H, s) 2.35-2.61 (12H, m)

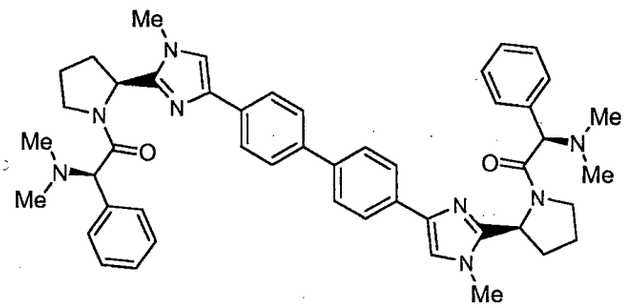
LCMS - Luna C-18 3.0 x 50mm, 0 to 100% B over 7.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate mobile phase t_R = 3.128 min.

Nominal/LRMS – Calcd. for $C_{44}H_{46}N_8O_2S_2$ 783.03; found 783.28 $(M+H)^+$

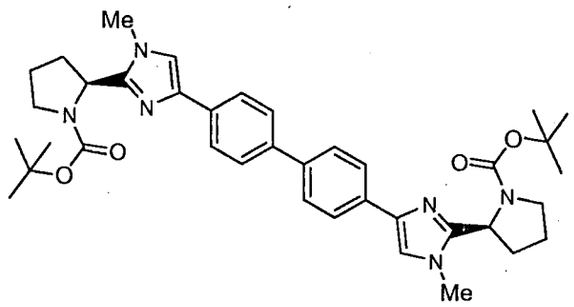
Accurate/HRMS – Calcd. for $C_{44}H_{47}N_8O_2S_2$ 783.3263; 783.3246 $(M+H)^+$

Example 151

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis((1-methyl-1H-imidazole-4,2-diyl)(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)



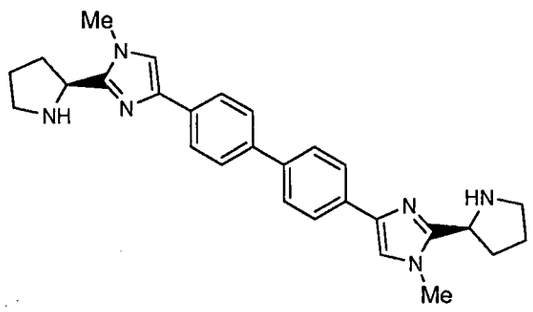
Example 151, Step a



To a stirred solution of 1d, (2S,2'S)-tert-butyl 2,2'-(4,4'-(biphenyl-4,4'-diyl)bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate (100 mg, 0.16 mmole) and iodomethane (40 µL, 0.16 mmole) in CH_2Cl_2 (2 mL) was added sodium hydride

(40%) (21.2 mg, 0.352 mmole). After five hours at ambient temperature, it was concentrated under reduced pressure. The crude reaction product 151a, (2S,2'S)-tert-butyl 2,2'-(4,4'-(biphenyl-4,4'-diyl)bis(1-methyl-1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate (~ 90 mg) was moved onto next step without further purification (purity ~ 85%) LCMS: Anal. Calcd. for: $C_{38}H_{48}N_6O_4$ 652.83; Found: 653.51 $(M+H)^+$. It should be recognized that multiple methylation isomers are possible in this reaction and no attempt to assign these was made.

Example 151, Step b



151a, (2S,2'S)-tert-butyl 2,2'-(4,4'-(biphenyl-4,4'-diyl)bis(1-methyl-1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate (100 mg, 0.153 mmole) treated with 4 M HCl/dioxane (20 mL). After three hours at ambient temperature, it was concentrated under reduced pressure. The crude reaction product, 4,4'-bis(1-methyl-2-((S)-pyrrolidin-2-yl)-1H-imidazol-4-yl)biphenyl(~110 mg, HCl salt) was moved onto the next step without further purification (purity ~ 85%) LCMS: Anal. Calcd. for: $C_{28}H_{32}N_6$ 452.59; Found: 453.38 $(M+H)^+$. Multiple imidazole isomers were present and carried forward.

Example 151

HATU (58.9 mg, 0.150 mmol) was added to a mixture of 151b, 4,4'-bis(1-methyl-2-((S)-pyrrolidin-2-yl)-1H-imidazol-4-yl)biphenyl (45.0 mg, 0.075 mmol), (*i*-Pr)$_2$EtN (78 µL, 0.451 mmol) and *Cap*-1, (*R*)-2-(dimethylamino)-2-phenylacetic acid (0.026 mg 0.150mmol) in DMF (1.0 mL). The resultant mixture was stirred at ambient temperature until the coupling was complete as determined by LC/MS analysis. Purification was accomplished by reverse-phase preparative HPLC (Waters-Sunfire 30 X 100mm S5, detection at 220 nm, flow rate 30 mL/min, 0 to

90% B over 14 min; A = 90% water, 10 % ACN, 0.1% TFA, B = 10% water, 90 % ACN, 0.1% TFA) to provide two isomer of 151, (2R,2'R)-1,1'-((2S,2'S)-2,2'-(4,4'-(biphenyl-4,4'-diyl)bis(1-methyl-1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(2-(dimethylamino)-2-phenylethanone), TFA salts.

Isomer 1: *(1R,1'R)-2,2'-(4,4'-biphenyldiylbis((1-methyl-1H-imidazole-4,2-diyl)(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)*

(8 mg, 8.6%) as a colorless wax.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.84 - 2.25 (m, 8 H) 2.32 - 2.90 (m, 12 H) 3.67 - 3.92 (m, 8 H) 4.07 (s, 2 H) 5.23 (s, 2 H) 5.51 (s, 2 H) 7.51 - 7.91 (m, 20 H)

HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minutes hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid, RT = 2.74 min, 98%.

LCMS: Anal. Calcd. for: $C_{48}H_{54}N_8O_2$ 775.02; Found: 775.50 $(M+H)^+$.

Isomer 2: *(1R,1'R)-2,2'-(4,4'-biphenyldiylbis((1-methyl-1H-imidazole-4,2-diyl)(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)*

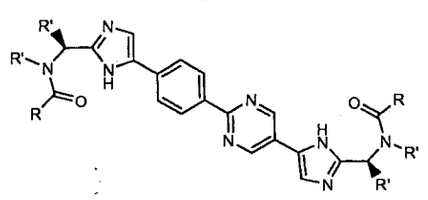
(10.2 mg, 11%) as a colorless wax.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.83 - 2.26 (m, 8 H) 2.30 - 2.92 (m, 12 H) 3.68 - 3.94 (m, 8 H) 4.06 (s, 2 H) 5.25 (d, *J*=2.14 Hz, 2 H) 5.50 (s, 2 H) 7.52 - 7.91 (m, 20 H).

HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minutes hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid, RT = 2.75 min, 90%.

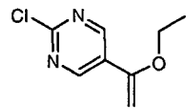
LCMS: Anal. Calcd. for: $C_{48}H_{54}N_8O_2$ 775.02; Found: 775.52 $(M+H)^+$.

Example 152



Example 152a-1 step a.

2-Chloro-5-(1-ethoxyvinyl)pyrimidine



To a solution of 5-bromo-2-chloropyrimidine (12.5 g, 64.62 mmol) in dry DMF (175 mL) under N_2 was added tributyl(1-ethoxyvinyl)tin (21.8 mL, 64.62 mmol) and dichlorobis(triphenylphosphine)palladium (II) (2.27 g, 3.23 mmol). The mixture was heated at 100°C for 3h before being allowed to stir at room temperature for 16 hr.. The mixture was then diluted with ether (200 mL) and treated with aqueous KF soln (55 g of potassium fluoride in 33 mL of water). The two phase mixture was stirred vigorously for 1h at room temperature before being filtered through diatomaceous earth (Celite®). The fitrate was washed with sat'd $NaHCO_3$ soln and brine prior to drying (Na_2SO_4). The original aqueous phase was extracted with ether (2x) and the organic phase was treated as above. Repetition on 13.5 g of 5-bromo-2-chloropyrimidine and combined purification by Biotage™ flash chromatography on silica gel (gradient elution on a 65M column using 3% ethyl acetate in hexanes to 25% ethyl acetate in hexanes with 3.0 L) afforded the title compound as a white, crystalline solid (18.2 g, 73%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.97 (s, 2H), 5.08 (d, *J*=3.7 Hz, 1H), 4.56 (d, *J*=3.4 Hz, 1H), 3.94 (q, *J*=7.0 Hz, 2H), 1.35 (t, *J*=7.0 Hz, 3H)..

LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 2.53 min, 98.8% homogeneity index.

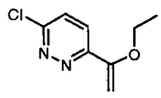
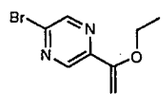
LCMS: Anal. Calcd. for $C_8H_{10}ClN_2O$ 185.05; found: 185.04 $(M+H)^+$.

HRMS: Anal. Calcd. for $C_8H_{10}ClN_2O$ 185.0482; found: 185.0490 $(M+H)^+$.

The same method was used for the preparation of Examples 152a-2 & 152a-3:

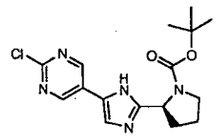
LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

Condition 2: Phenomenex LUNA C-18 4.6 × 50 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, 220nm, 5 μL injection volume.

Example 152a-2	 from dichloropyridazine	t_R = 2.24 min 96.4%, condition 1 LRMS: Anal. Calcd. for $C_8H_{10}ClN_2O$ 185.05; found: 185.06 $(M+H)^+$. HRMS: Anal. Calcd. for $C_8H_{10}ClN_2O$ 185.0482; found: 185.0476 $(M+H)^+$.
Example 152a-3	 from dibromopyrazine	t_R = 2.82 min (52.7%, inseparable with 2,5-dibrompyrazine (t_R =1.99 min, 43.2%)); condition 1 LRMS: Anal. Calcd. for $C_8H_{10}BrN_2O$ 229.00; found: 228.93 $(M+H)^+$.

Example 152b-1, step b.

(S)-tert-Butyl 2-(5-(2-chloropyrimidin-5-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate or (S)-2-[5-(2-Chloro-pyrimidin-5-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester



NBS (16.1 g, 90.7 mmol) was added in one portion to a stirred solution of 2-chloro-5-(1-ethoxyvinyl)pyrimidine (152a-1, 18.2 g, 98.6 mmol) in THF (267 mL) and H_2O (88 mL) at 0°C under N_2. The mixture was stirred for 1h at 0°C before it was diluted with more H_2O and extracted with ethyl acetate (2x). The combined extracts were washed with sat'd $NaHCO_3$ soln and brine prior to drying (Na_2SO_4), filtration, and solvent evaporation. LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 1.52 min (unsymmetrical peak). LCMS: Anal. Calcd. for $C_6H_{14}BrClN_2O$ 235.92; found: 236.85 $(M+H)^+$.

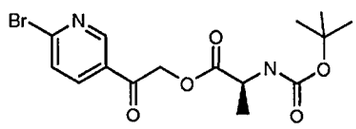
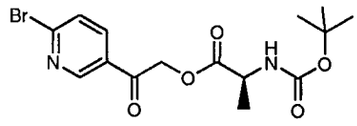
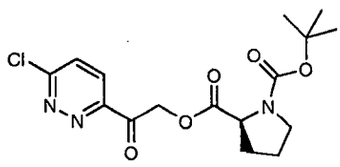
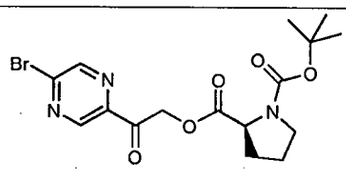
Example 152c-1, step c.

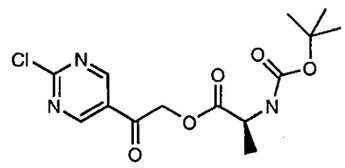
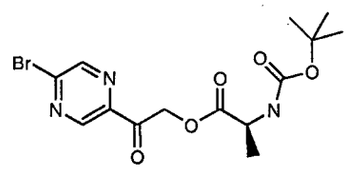
Half of the crude residue (2-bromo-1-(2-chloropyrimidin-5-yl)ethanone, ~14.5g) was dissolved into anhydrous acetonitrile (150 mL) and treated directly with N-Boc-L-proline (9.76 g, 45.35 mmol) and diisopropylethylamine (7.9 mL, 45.35 mmol). After being stirred for 3h, the solvent was removed *in vacuo* and the residue was partitioned into ethyl acetate and water. The organic phase was washed with 0.1N hydrochloric acid, sat'd $NaHCO_3$ soln and brine prior to drying (Na_2SO_4), filtration, and concentration. LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 2.66 min.

The same method was used to prepare Examples 152c-2 through 152c-6.

LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

Condition 2: Phenomenex LUNA C-18 4.6 × 50 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, 220nm, 5 μL injection volume.

Example 152c-2		t_R = 1.81 min (condition 2, ~95 %) LRMS: Anal. Calcd. for $C_{15}H_{19}BrN_4O_2$ 386.05 found: 387.07 $(M+H)^+$.
Example 152c-3		t_R = 1.84 min (condition 2, 94%) LRMS: Anal. Calcd. for $C_{15}H_{19}BrN_2O_5$ 386.05; found: 387.07 $(M+H)^+$.
Example 152c-3a		t_R = 2.65 min; condition 1 LCMS: Anal. Calcd. for $C_{16}H_{20}ClN_3O_5$ 369.11 found: 391.89 $(M+Na)^+$.
Example 152c-4		t_R = 1.94 min, (condition 2) LCMS: Anal. Calcd. for

		$C_{16}H_{21}BrN_3O_5$ 414.07 found: 414.11 $(M+H)^+$.
Example 152c-5		t_R = 2.22 min; condition 1 LCMS: Anal. Calcd. for $C_{14}H_{18}ClN_3O_5$ 343.09 found: undetermined.
Example 152c-6		t_R = 2.41 min, condition 1 LCMS: Anal. Calcd. for $C_{14}H_{18}{}^{37}BrN_3O_5$ 389.04 found: 412.03 $(M+Na)^+$.

Example 152d-1, step d.

This residue ((S)-1-tert-butyl 2-(2-(2-chloropyrimidin-5-yl)-2-oxoethyl) pyrrolidine-1,2-dicarboxylate) was taken up in xylenes (200 mL) and treated to NH_4OAc (17.5 g, 0.23 mol). The mixture was heated at 140°C for 2 hr in a thick-walled, screw-top flask before it was cooled to ambient temperature and suction-filtered. The filtrate was then concentrated, partitioned into ethyl acetate and sat'd $NaHCO_3$ soln and washed with brine prior to drying (Na_2SO_4), filtration, and concentration The original precipitate was partitioned into aqueous $NaHCO_3$ soln and ethyl acetate and sonicated for 2 min before being suction-filtered. The filtrate was washed with brine, dried over (Na_2SO_4), filtered, and concentrated to dryness. Purification of the combined residues by Biotage™ flash chromatography on silica gel (65M column, preequilibration with 2%B for 900mL followed by gradient elution with 2%B to 2%B for 450 ml followed by 2%B to 40%B for 3000mL where B=methanol and A=dichloromethane) afforded the title compound (7.0 g, 44% yield, 2 steps, pure fraction) as an yellowish orange foam. The mixed fractions were

subjected to a second Biotage™ chromatography on silica gel (40M column, preequilibration with 1%B for 600mL followed by gradient elution with 1%B to 1%B for 150 ml followed by 1%B to 10%B for 1500mL where B=MeOH and A=CH_2Cl_2) afforded additional title compound (2.8 g, 18%) as a brownish-orange foam. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.24-12.16 (m, 1H), 9.05 (s, 2H), 7.84-7.73 (m, 1H), 4.90-4.73 (m, 1H), 3.59-3.46 (m, 1H), 3.41-3.31 (m, 1H), 2.32-2.12 (m, 1H), 2.03-1.77 (m, 3H), 1.39 and 1.15 (2s, 9H)..

LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 1.92 min, 94.7% homogeneity index.

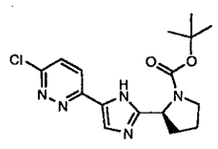
LRMS: Anal. Calcd. for $C_{16}H_{21}ClN_5O_2$ 350.14; found: 350.23 $(M+H)^+$.

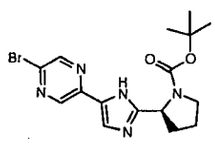
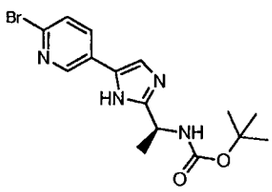
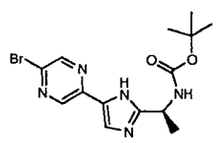
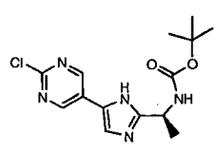
HRMS: Anal. Calcd. for $C_{16}H_{21}ClN_5O_2$ 350.1384; found: 350.1398 $(M+H)^+$.

The same method was used to prepare Examples 152d-2 through 152d-6.

LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

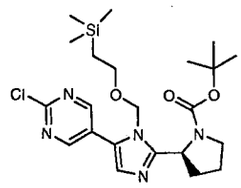
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

Example 152d-2	 from 152c-3a	t_R = 1.92 min (86.5%); condition 1 LRMS: Anal. Calcd. for $C_{16}H_{21}ClN_5O_2$ 350.14; found: 350.23 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{16}H_{21}ClN_5O_2$ 350.1384; found: 350.1393 $(M+H)^+$.

Example 152d-3	 from 152c-4	t_R = 1.90min (>95%); condition 1 LRMS: Anal. Calcd. for $C_{16}H_{21}BrN_5O_2$ 394.09; found: 393.82 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{16}H_{21}BrN_5O_2$ 394.0879; found: 394.0884 $(M+H)^+$.
Example 152d-4	 from 152c-3	t_R = 1.45 min (condition 2, 100%) LRMS: Anal. Calcd. for $C_{15}H_{19}BrN_4O_2$ 366.07 found: 367.07 $(M+H)^+$.
Example 152d-5	 from 152c-6	t_R = 1.88 min (>95%); condition 1 LRMS: Anal. Calcd. for $C_{14}H_{18}BrN_5O_2$ 367.06; found: 368.10 $(M+H)^+$.
Example 152d-6	 from 152c-5	t_R = 1.66 min (85%); condition 1 LRMS: Anal. Calcd. for $C_{14}H_{18}ClN_5O_2$ 323.11; found: 324.15 $(M+H)^+$.

Example 152e-1, step e.

Example 152e-1: (S)-tert-Butyl 2-(5-(2-chloropyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate



Sodium hydride (60% dispersion in mineral oil , 0.23 g, 5.72 mmol) was added in one portion to a stirred solution of (S)-tert-butyl 2-(5-(2-chloropyrimidin-5-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (152d-1, 2.0 g, 5.72 mmol) in dry DMF (45 mL) at ambient temperature under N_2. The mixture was stirred for 5 min. before SEM chloride (1.01 mL, 5.72 mmol) was added in approx. 0.1 mL increments. The mixture was stirred for 3h before being quenched with sat'd NH_4Cl soln and diluted with ethyl acetate. The organic phase was washed with sat'd $NaHCO_3$ soln and brine, dried over (Na_2SO_4), filtered, and concentrated. The original aqueous phase was extracted twice more and the combined residue was purified by Biotage™ flash chromatography (40M column, 50 mL/min, preequilibration with 5%B for 750mL, followed by step gradient elution with 5%B to 5%B for 150 mL, 5%B to 75%B for 1500 mL, then 75%B to 100%B for 750 mL where solvent B is ethyl acetate and solvent A is hexanes). Concentration of the eluant furnished the title compound as a pale yellow foam (2.35 g, 85%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.04 (s, 2H), 7.98-7.95 (m, 1H), 5.70-5.31 (3m, 2H), 5.02-4.91 (m, 1H), 3.59-3.49 (m, 3H), 3.45-3.35 (m, 1H), 2.30-2.08 (m, 2H), 1.99-1.83 (m, 2H), 1.36 and 1.12 (2s, 9H), 0.93-0.82 (m, 2H), -0.02 (s, 9H).

LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 2 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 2.38 min, 95% homogeneity index.

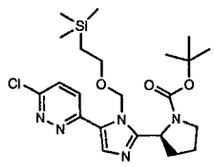
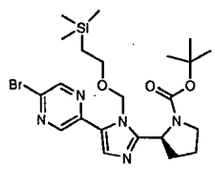
LRMS: Anal. Calcd. for $C_{22}H_{35}ClN_5O_3Si$ 480.22; found: 480.23 $(M+H)^+$.

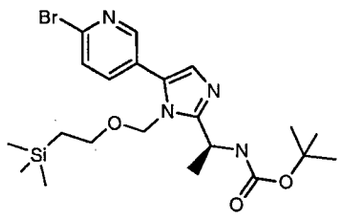
HRMS: Anal. Calcd. for $C_{22}H_{35}ClN_5O_3Si$ 480.2198; found: 480.2194 $(M+H)^+$.

The same method was used to prepare 152e-2 through 152e-4

LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

Condition 2: Phenomenex LUNA C-18 4.6 × 50 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, 220nm, 5 μL injection volume.

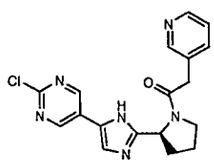
Example 152e-2	 from 152d-2	t_R = 2.34 min (85.7%); condition 1 LCMS: Anal. Calcd. for $C_{22}H_{35}ClN_5O_3Si$ 480.22; found: 480.22 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{35}ClN_5O_3Si$ 480.2198 found: 480.2198 $(M+H)^+$.
Example 152e-3	 from 152d-3	t_R = 3.18 min (>95%); condition 1 LCMS: Anal. Calcd. for $C_{22}H_{35}{}^{37}BrN_5O_3Si$ 526.17; found: 525.99 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{35}{}^{37}BrN_5O_3Si$ 526.1692; found: 526.1674 $(M+H)^+$.

Example 152e-4	 from 152d-4	t_R = 2.14 min (condition 2, 96%) LRMS: Anal. Calcd. For $C_{21}H_{33}BrN_4O_3Si$ 496.15 found: 497.13 $(M+H)^+$.

Examples 152f-1 to 152f-2

Example 152f-1

(S)-1-(2-(5-(2-chloropyrimidin-5-yl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-2-(pyridin-3-yl)ethanone



Cold (0°C) 4 *N* HCl in dioxanes (5 mL) was added *via* syringe to (S)-tert-butyl 2-(5-(2-chloropyrimidin-5-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (152d-1, 0.50 g, 1.43 mmol) in a 100 mL pear-shaped flask followed by MeOH (1.0 mL). The suspension was stirred at room temperature for 4h before it was concentrated down to dryness and placed under high vacuum for 1h. There was isolated intermediate (S)-2-chloro-5-(2-(pyrrolidin-2-yl)-1*H*-imidazol-5-yl)pyrimidine trihydrochloride as a pale yellow solid (with an orange tint) which was used without further purification.

HATU (0.60 g, 1.57 mmol) was added in one portion to a stirred solution of intermediate (S)-2-chloro-5-(2-(pyrrolidin-2-yl)-1H-imidazol-5-yl)pyrimidine trihydrochloride (0.46 g, 1.43 mmol, theoretical amount), 2-(pyridin-3-yl)acetic acid (0.25 g, 1.43 mmol) and DIEA (1.0 mL, 5.72 mmol) in anhydrous DMF (10 mL) at ambient temperature. The mixture was stirred at room temperature for 2h before the DMF was removed *in vacuo*. The residue was taken up in CH_2Cl_2 and subjected to Biotage™ flash chromatography on silica gel (40M column, preequilibration with 0%B for 600mL followed by step gradient elution with 0%B to 0%B for 150 mL

followed by 0%B to 15%B for 1500mL followed by 15%B to 25% B for 999 mL where B= MeOH and A= CH_2Cl_2). There was isolated the title compound (0.131 g, 25%, 2 steps) as a yellow solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.10-9.08 (2s, 2H), 8.72-8.55 (series of m, 2H), 8.21-8.20 and 8.11-8.10 (2m, 1H), 8.00 and 7.93 (2s, 1H), 7.84-7.77 (series of m, 1H), 5.43-5.41 and 5.17-5.15 (2m, 1H), 4.02-3.94 (3m, 2H), 3.90-3.58 (3m, 2H), 2.37-2.26 (m, 1H), 2.16-1.85 (2m, 3H).

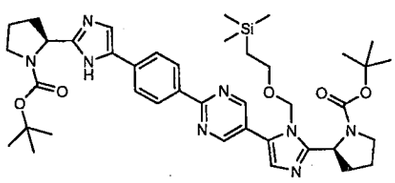
LCRMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 0.92 min, 95.1 % homogeneity index.

LRMS: Anal. Calcd. for $C_{18}H_{18}ClN_6O$ 369.12; found: 369.11 $(M+H)^+$.

HRMS: Anal. Calcd. for $C_{18}H_{18}ClN_6O$ 369.1231; found: 369.1246 $(M+H)^+$.

Examples 152g-1 to 152g-17

Example 152g-1 from 1c and 152e-1. (S)-2-[5-(2-{4-[2-((S)-1-tert-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-phenyl}-pyrimidin-5-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester



Pd $(Ph_3)_4$ (0.12 g, 0.103 mmol) was added in one portion to a stirred suspension of (S)-tert-butyl 2-(5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (1c, 1.00 g, 2.27 mmol), (S)-tert-butyl 2-(5-(2-chloropyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (152c-1, 0.99 g, 2.06 mmol) and $NaHCO_3$ (0.87 g, 10.3 mmol) in a solution of DME (20 mL) and H_2O (6 mL) at room temperature under N_2. The vessel was sealed and the mixture was placed into a preheated (80°C) oil bath and stirred at 80°C for 16h before additional catalyst (0.12 g) was added. After heating the mixture for an additional 12h at 80°C, the mixture was cooled to ambient temperature, diluted with ethyl acetate and washed with sat'd $NaHCO_3$ soln and brine prior to drying over anhydrous sodium sulfate and solvent

concentration. Purification of the residue by Biotage™ flash chromatography on silica gel using a 40M column (preequilibrated with 40% B followed by step gradient elution with 40%B to 40%B for 150mL, 40%B to 100%B for 1500mL, 100%B to 100%B for 1000mL where B=ethyl acetate and A=hexanes) furnished the title compound as a yellow foam (1.533 g, 98%). A small amount of the yellow foam was further purified for characterization purposes by pHPLC (Phenomenex GEMINI, 30 × 100 mm, S10, 10 to 100% B over 13 minutes, 3 minute hold time, 40 mL/min, A = 95% water, 5% acetonitrile, 10mM NH_4OAc, B = 10% water, 90% acetonitrile, 10mM NH_4OAc) to yield 95% pure title compound as a white solid.

^1H NMR (500 MHz, DMSO-d_6) δ 12.30-11.88 (3m, 1H), 9.17-9.16 (m, 2H), 8.43-8.31 (m, 2H), 7.99-7.35 (series of m, 4H), 5.72-5.30 (3m, 2H), 5.03-4.76 (2m, 2H), 3.64-3.50 (m, 4H), 3.48-3.31 (m, 2H), 2.36-2.07 (m, 2H), 2.05-1.80 (m, 4H), 1.46-1.08 (2m, 18H), 0.95-0.84 (m, 2H), -0.01 (s, 9H).

HPLC Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 2.91 min, 95% homogeneity index.

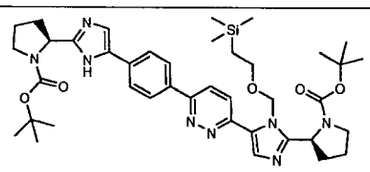
LRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.42; found: 757.42 $(M+H)^+$.

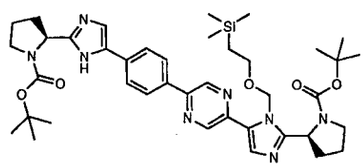
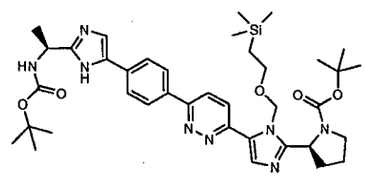
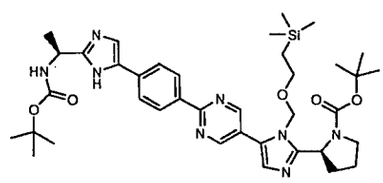
HRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.4221; found: 757.4191 $(M+H)^+$.

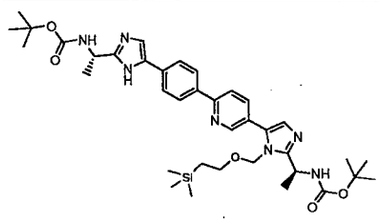
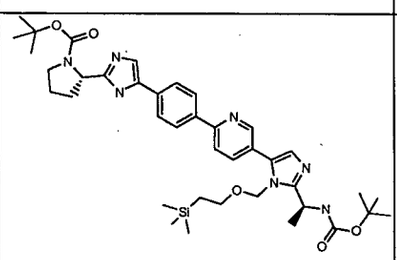
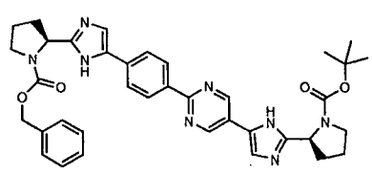
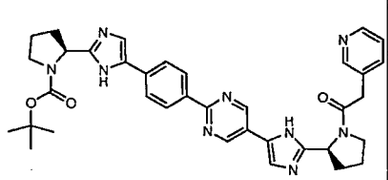
The same procedure was used to prepare Examples 152g-2 through 152g-17:

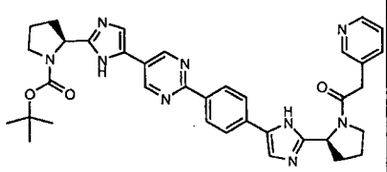
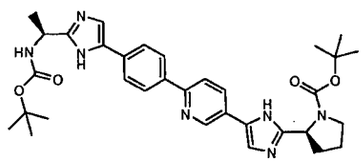
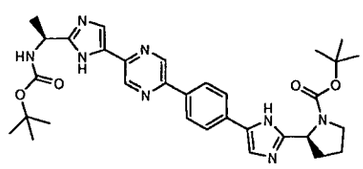
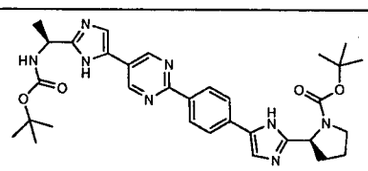
LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

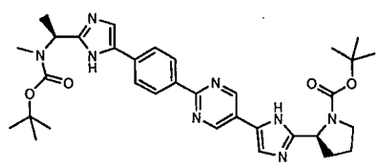
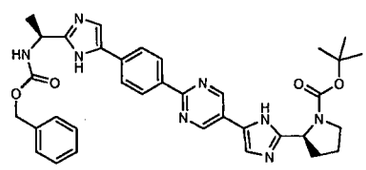
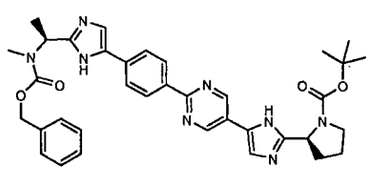
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

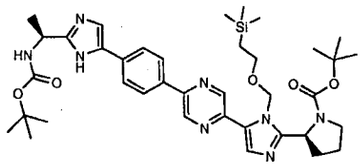
Example 152g-2	 Prepared from 1c and 152e-2	t_R = 2.81 min (79%); Condition 1 LRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.42; found: 758.05 $(M+H)^+$.

		HRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.4221; found: 757.4196 $(M+H)^+$.
Example 152g-3	 Prepared from 1c and 152e-3	t_R = 2.89 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.42; found: 757.35 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.4221; found: 757.4191 $(M+H)^+$.
Example 152g-4	 Prepared from 1-6c and 152e-2	t_R = 2.87 min (97%); Condition 1 LRMS: Anal. Calcd. for $C_{38}H_{55}N_8O_5Si$ 731.41; found: 731.26 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{55}N_8O_5Si$ 731.4065; found: 731.4070 $(M+H)^+$.
Example 152g-5	 Prepared from 1-6c and 152e-1	t_R = 2.94 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{38}H_{55}N_8O_5Si$ 731.41; found: 731.26 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{55}N_8O_5Si$ 731.4065; found: 731.4046 $(M+H)^+$.

Example 152g-6	 Prepared from 1-6c and 152e-4	t_R = 1.99 min (condition 2, 96%) LRMS: Anal. Calcd. for $C_{37}H_{53}N_7O_2Si$ 703.39; found: 704.34 $(M+H)^+$.
Example 152g-7	 Prepared from 1c and 152e-4	t_R = 1.99 min (condition 2, 96%) LRMS: Anal. Calcd. for $C_{39}H_{55}N_7O_5Si$ 729.40 found: 730.42 $(M+H)^+$.
Example 152g-8	 Prepared from 1-5c and 152d-1	t_R = 2.15 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{37}H_{41}N_8O_4$ 661.33; found: 661.39 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{37}H_{41}N_8O_4$ 661.3251; found: 661.3268 $(M+H)^+$.
Example 152g-9	 Prepared from 1c and 152f-1	t_R = 1.71 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{36}H_{40}N_9O_3$ 646.76; found: 646.47 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{40}N_9O_3$ not done found: not done $(M+H)^+$.

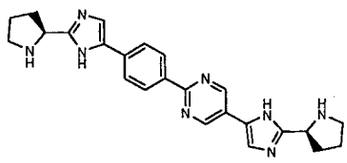
Example 152g-10	 Prepared from 152d-1 and 1-10c	t_R = 1.71 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{36}H_{40}N_9O_3$ 646.33; found: 646.37 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{40}N_9O_3$ 646.3254; found: 646.3240 $(M+H)^+$.
Example 152g-11	 Prepared from 1-6c and 152e-4	t_R = 2.12 min (>93.9%); Condition 1 LRMS: Anal. Calcd. for $C_{33}H_{42}N_7O_4$ 600.33; found: 600.11 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{33}H_{42}N_7O_4$ 600.3298; found: 600.3312 $(M+H)^+$.
Example 152g-12	 Prepared from 1c and 152d-5	t_R = 2.13 min (97.3%); Condition 1 LRMS: Anal. Calcd. for $C_{32}H_{41}N_8O_4$ 601.33; found: 601.36 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{32}H_{41}N_8O_4$ 601.3251; found: 601.3253 $(M+H)^+$.
Example 152g-13		t_R = 2.11 min (98.5%); Condition 1 LRMS: Anal. Calcd. for $C_{32}H_{41}N_8O_4$ 601.33; found: 601.36

	Prepared from 1c and 152d-6	$(M+H)^+$. HRMS: Anal. Calcd. for $C_{32}H_{41}N_8O_4$ 601.3251; found: 601.3253 $(M+H)^+$.
Example 152g-14	 Prepared from 1-8c and 152d-1	t_R = 2.18 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{33}H_{43}N_8O_4$ 615.34; found: 615.38 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{33}H_{43}N_8O_4$ 615.3407; found: 615.3433 $(M+H)^+$.
Example 152g-15	 Prepared from 1c and 152d-1	t_R = 2.20 min (97.7%); Condition 1 LRMS: Anal. Calcd. for $C_{35}H_{39}N_8O_4$ 635.31; found: 635.36 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{35}H_{39}N_8O_4$ 635.3094; found: 635.3119 $(M+H)^+$.
Example 152g-16	 Prepared from 1-9c and 152d-1	t_R = 2.26 min (>95%); Condition 1 LRMS: Anal. Calcd $C_{36}H_{41}N_8O_4$ 649.33; found: 649.39 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{41}N_8O_4$ 649.3251; found: 649.3276 $(M+H)^+$.

Example 152g-17	 Prepared from 1-6c and 152e-3	t_R = 2.98 min (98.5%); Condition 1 LRMS: Anal. Calcd. for $C_{38}H_{54}N_8O_5Si$ 730.39; found: 731.40 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{54}N_8O_5Si$ 731.4065; found: 731.4045 $(M+H)^+$.

Example 152h-1-152h-7

Example 152h-1 from 152g-1. 5-((S)-2-Pyrrolidin-2-yl-3H-imidazol-4-yl)-2-[4-((S)-2-pyrrolidin-2-yl-3H-imidazol-4-yl)-phenyl]-pyrimidine



TFA (8 mL) was added in one portion to a stirred solution of (S)-2-[5-(2-{4-[2-((S)-1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-3*H*-imidazol-4-yl]-phenyl}-pyrimidin-5-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.50 g, 1.98 mmol) in dry CH_2Cl_2 (30 mL) at room temperature. The flask was sealed and the mixture was stirred at room temperature for 16h before the solvent(s) were removed *in vacuo*. The residue was taken up in methanol, filtered through a PVDF syringe filter (13mm x 0.45μm), distributed to 8 pHPLC vials and chromatographed by HPLC (gradient elution from 10%B to 100%B over 13 min on a Phenomenex C18 column, 30 x 100mm, 10μm, where A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA). After concentration of the selected test tubes by speed vacuum evaporation, the product was dissolved in methanol and neutralized by passing the solution through an UCT CHQAX 110M75 anion exchange cartridge. There was isolated the title compound as a yellow mustard-colored solid (306.7 mg, 36% yield) upon concentration of the eluant.

^{1}H NMR (500 MHz, DMSO-d_6) μ 12.50-11.80 (br m, 2H), 9.18 (s, 2H), 8.36 (d, *J*=8.5 Hz, 2H), 7.89 (d, *J*=8.2 Hz, 2H), 7.77 (s, 1H), 7.61 (s, 1H), 4.34-4.24 (m, 2H), 3.09-2.89 (m, 4H), 2.18-2.07 (m, 2H), 2.02-1.89 (m, 2H), 1.88-1.72 (m, 4H).

LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 1.33 min, >95% homogeneity index.

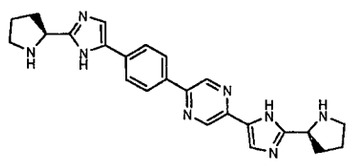
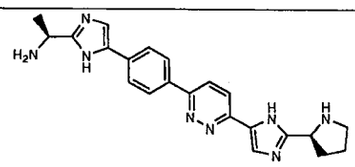
LRMS: Anal. Calcd. for $C_{24}H_{27}N_8$ 427.24; found: 427.01 $(M+H)^+$.

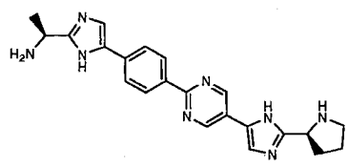
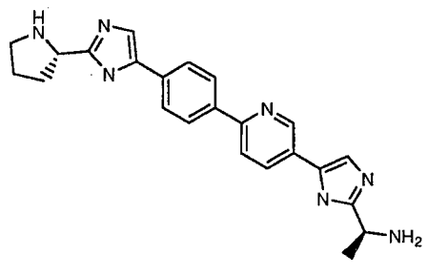
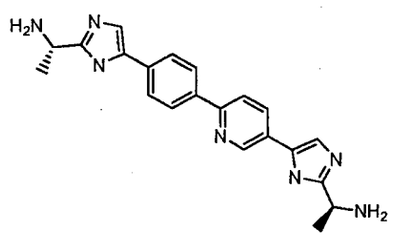
HRMS: Anal. Calcd. for $C_{24}H_{27}N_8$ 427.2359; found: 427.2363 $(M+H)^+$.

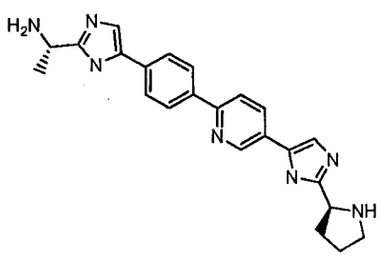
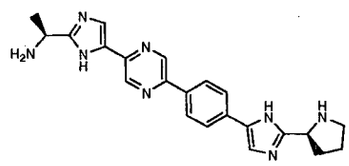
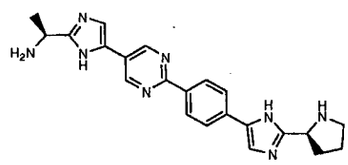
The same conditions were used to prepare Examples 152h-2 through 152h-14.

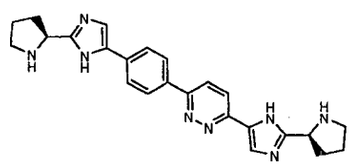
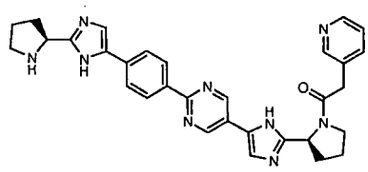
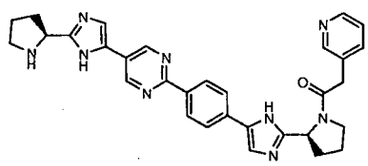
LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

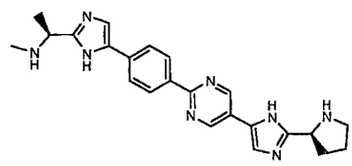
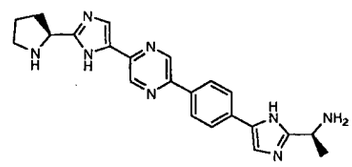
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

Example 152h-2	 Prepared from 152g-3	t_R = 1.36 min (98%); Condition 1 LRMS: Anal. Calcd. for $C_{24}H_{27}N_8$ 427.24; found: 427.48 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{24}H_{27}N_8$ 427.2359; found: 427.2339 $(M+H)^+$.
Example 152h-3	 Preapared from 152g-4	t_R = 1.17 min (>95%); Condition 1 LRMS: Anal. Calcd.

		for $C_{22}H_{25}N_8$ 401.22; found: 401.16 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.2202; found: 401.2193 $(M+H)^+$.
Example 152h-4	 Prepared from 152g-5	t_R = 1.28 min (89.3%); Condition 1 LRMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.22; found: 401.16 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.2202; found: 401.2201 $(M+H)^+$.
Example 152h-5	 Prepared from 152g-7	t_R = 0.93 min; Condition 2 LRMS: Anal. Calcd. for $C_{23}H_{25}N_7$ 399; found: 400 $(M+H)^+$.
Example 152h-6	 Prepared from 152g-6	t_R = 0.81 min; Condition 2 LRMS: Anal. Calcd. for $C_{21}H_{23}N_7$ 373; found: 374 $(M+H)^+$.

Example 152h-7	 Prepared from 152g-11	t_R = 1.14 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{23}H_{26}N_7$ 400.23; found: 400.14 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{23}H_{26}N_7$ 400.2250; found: 400.2234 $(M+H)^+$.
Example 152h-8	 Prepared from 152g-12	t_R = 1.29 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.22; found: 401.21 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.2202; found: 401.2204 $(M+H)^+$.
Example 152h-9	 Prepared from 152g-13	t_R = 1.29 min (97.6%); Condition 1 LRMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.22; found: 401.21 $(M+H)^+$. HRMS: Anal. Calcd.

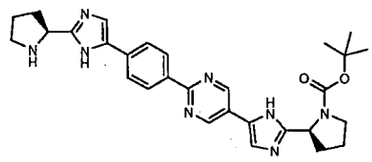
		for $C_{22}H_{25}N_8$ 401.2202; found: 401.2220 $(M+H)^+$.
Example 152h-10	 Prepared from 152g-2	t_R = 1.26 min (86.4%); Condition 1 LRMS: Anal. Calcd. for $C_{24}H_{27}N_8$ 427.24; found: 427.48 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{24}H_{27}N_8$ 427.2359; found: 427.2339 $(M+H)^+$.
Example 152h-11	 Prepared from 152g-9	t_R = 1.26 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{31}H_{32}N_9O$ 546.27; found: 546.28 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{31}H_{32}N_9O$ 546.2730 found: 546.2739 $(M+H)^+$.
Example 152h-12	 Prepared from 152g-10	t_R = 1.39 min (95%); Condition 1 LRMS: Anal. Calcd. for $C_{31}H_{32}N_9O$ 546.27; found: 546.32 $(M+H)^+$.

		HRMS: Anal. Calcd. for $C_{31}H_{32}N_9O$ 546.2730; found: 546.2719 $(M+H)^+$.
Example 152h-13	 Prepared from 152g-14	t_R = 1.42 min; Condition 1 LRMS: Anal. Calcd. for $C_{23}H_{26}N_8$ 414.24; found: 415.27 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{23}H_{26}N_8$ 415.2359; found: 415.2371 $(M+H)^+$.
Example 152h-14	 Prepared from 152g-17	t_R = 1.30 min; Condition 1 LRMS: Anal. Calcd. for $C_{22}H_{24}N_8$ 400.21; found: 401.24 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{24}N_8$ 401.2202; found: 401.2198 $(M+H)^+$.

5

Example 152i-1 to 152i-3

Example 152i-1 from 152g-8. (S)-2-(5-{2-[4-((S)-2-Pyrrolidin-2-yl-3H-imidazol-4-yl)-phenyl]-pyrimidin-5-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carboxylic acid tert-butyl ester



A solution of (S)-2-[5-(2-{4-[2-((S)-1-Benzyloxycarbonyl-pyrrolidin-2-yl)-3*H*-imidazol-4-yl]-phenyl}-pyrimidin-5-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (317.1 mg, 0.48 mmol) in MeOH (1 mL) was added to a stirred suspension of 10% palladium on carbon (60 mg) and K_2CO_3 (70 mg) in a solution of MeOH (5 mL) and H_2O (0.1 mL) at room temperature under N_2. The flask was charged and evacuated three times with H_2 and stirred for 3h at atmosphere pressure. Additional catalyst (20 mg) was then added and the reaction mixture was stirred further for 3h before it was suction-filtered through diatomaceous earth (Celite®) and concentrated. The residue was diluted with MeOH, filtered through a PVDF syringe filter (13mm x 0.45μm), distributed into 4 pHPLC vials and chromatographed (gradient elution from 20%B to 100%B over 10 min on a Phenomenex-Gemini C18 column (30 x 100mm, 10μm) where A = 95% water, 5% acetonitrile, 10mM NH_4OAc, B = 10% water, 90% acetonitrile, 10mM NH_4OAc). After concentration of the selected test tubes by speed vacuum evaporation, there was isolated the title compound as a yellow solid (142.5 mg, 56% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.35-12.09 (br m, 1H), 9.17 (s, 2H), 8.35 (d, *J*=8.3Hz, 2H), 7.87 (d, *J*=8.3Hz, 2H), 7.80-7.72 (m, 1H), 7.56 (s, 1H), 4.92-4.77 (m, 1H), 4.21-4.13 (m, 1H), 3.61-3.05 (2m, 4H), 3.02-2.80 (2m, 2H), 2.37-1.67 (series of m, 6H), 1.41 and 1.17 (2s, 9H).

LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 1.77 min, >95 % homogeneity index.

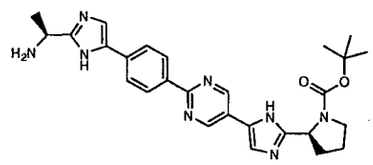
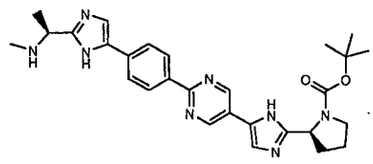
LRMS: Anal. Calcd. for $C_{29}H_{35}N_8O_2$ 527.29; found: 527.34 $(M+H)^+$.

HRMS: Anal. Calcd. for $C_{29}H_{35}N_8O_2$ 527.2883; found: 527.2874 $(M+H)^+$.

The same procedure was used to prepare Examples 152i-2 through 152i-3.

LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

Condition 2: Phenomenex LUNA C-18 4.6 × 50 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, 220nm, 5 μL injection volume.

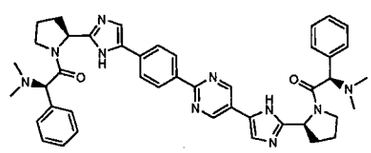
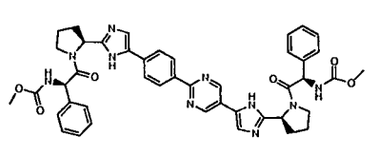
Example 152i-2	 Prepared from 152g-15	t_R = 1.70 min (95.7%); Condition 1 LRMS: Anal. Calcd. for $C_{27}H_{33}N_8O_2$ 501.27; found: 501.35 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{27}H_{33}N_8O_2$ 501.2726 found: 501.2709 $(M+H)^+$.
Example 152i-3	 Prepared from 152g-16	t_R = 1.77 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{28}H_{35}N_8O_2$ 515.29; found: 515.37 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{28}H_{35}N_8O_2$ 515.2883 found: 515.2869 $(M+H)^+$.

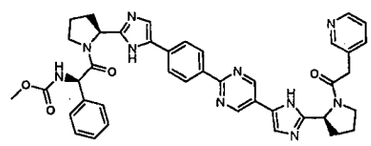
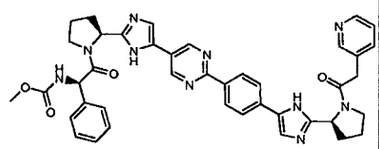
Examples 152j-1 to 152j-28

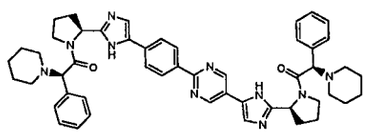
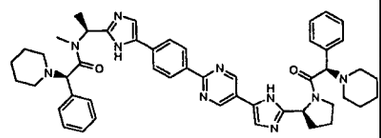
Examples 152j were isolated as TFA or AcOH salts prepared using the procedure to convert Example 148e to 148.

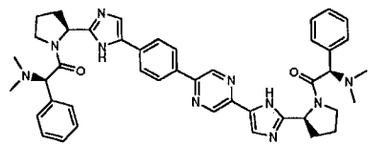
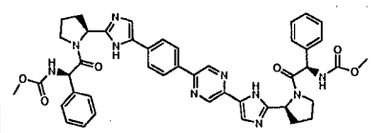
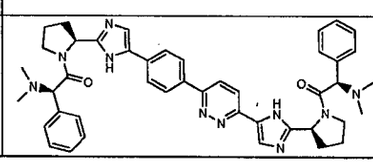
LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

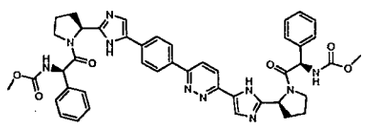
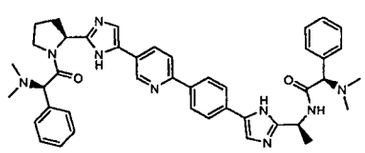
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

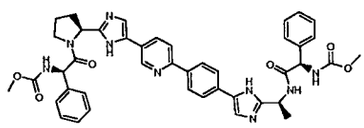
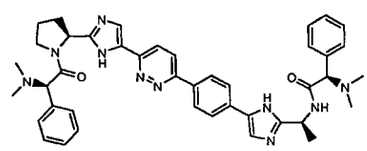
Example	*Compound Name*	*Structure*	*Data*
Example 152j-1	(1R)-2-((2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine	 Prepared from 152h-1 and *Cap*-1.	t_R = 1.61 min; (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{44}H_{49}N_{10}O_2$ 749.40 found: 749.32 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{44}H_{49}N_{10}O_2$ 749.4040 found: 749.4042 $(M+H)^+$
Example 152j-2	methyl ((1R)-2-((2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-	 Prepared from 152h-1 and *Cap*-4	t_R = 1.99 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.35 found: 809.17 $(M+H)^+$

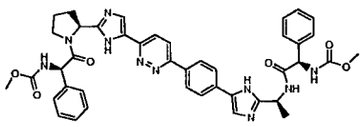
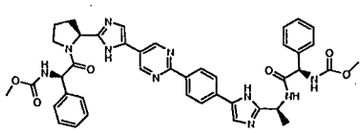
	imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		HRMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.3524 found: 809.3505 $(M+H)^+$
Example 152j-3	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4-(5-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate	 Prepared from 152h-11 and *Cap-4*	t_R = 1.65 min (92.3%); Condition 1 LRMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_2$ 737.33 found: 737.49 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_4$ 737.3312 found: 737.3342 $(M+H)^+$
Example 152j-4	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(2-(4-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate	 Prepared from 152h-12 and *Cap-4*	t_R = 1.64 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_4$ 737.33 found: 737.75 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_4$

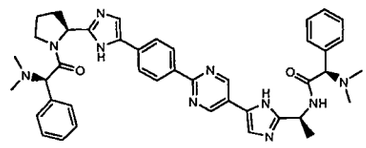
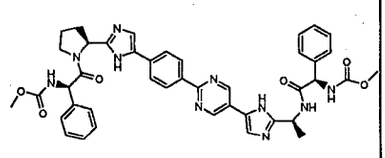
			737.3312 found: 737.3284 $(M+H)^+$
Example 152j-5	5-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-(4-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)phenyl)pyrimidine	 Prepared from 152h-1 and *Cap*-14	t_R = 1.70 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{50}H_{57}N_{10}O_2$ 829.47 found: 829.39 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{50}H_{57}N_{10}O_2$ 829.4666 found: 829.4658 $(M+H)^+$
Example 152j-6	(2R)-N-methyl-2-phenyl-N-((1S)-1-(4-(4-(5-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)ethyl)-2-(1-piperidinyl)acetamide	 Prepared from 152h-13 and *Cap*-14	t_R = 1.66 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{49}H_{57}N_{10}O_2$ 817.47 found: 817.44 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{49}H_{57}N_{10}O_2$ 817.4666 found: 817.4673 $(M+H)^+$

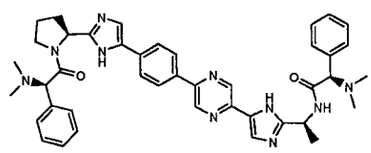
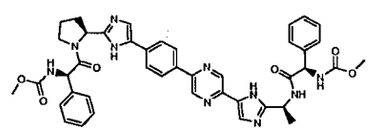
Example 152j-7	(1R)-2-((2S)-2-(5-(5-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-2-pyrazinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine	 Prepared from 152h-2 and *Cap*-1	t_R = 1.60 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{41}H_{49}N_{10}O_2$ 749.40 found: 749.31 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{44}H_{49}N_{10}O_2$ 749.4040 found: 749.4031 $(M+H)^+$
Example 152j-8	methyl ((1R)-2-((2S)-2-(5-(5-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-2-pyrazinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from 152h-2 and *Cap*-4	t_R = 2.01 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.35 found: 809.24 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.3523 found: 809.3493 $(M+H)^+$
Example 152j-9	(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-		t_R = 1.76 min (>95%); Condition 1

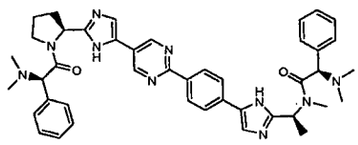
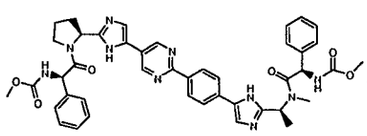
	phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridazinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine	Prepared from 152h-10 and *Cap*-1	LRMS: Anal. Calcd. for $C_{44}H_{49}N_{10}O_2$ 749.40 found: not obsd $(M+H)^+$ HRMS: Anal. Calcd. for $C_{44}H_{49}N_{10}O_2$ 749.4040 found: 749.4056 $(M+H)^+$
Example 152j-10	methyl ((1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridazinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from 152h-10 and *Cap*-4	t_R = 2.17 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.35 found: 809.59 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.3524 found: 809.3499 $(M+H)^+$
Example 152j-11	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(4-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-	 Prepared from 152h-7 and *Cap*-1	t_R = 1.56 min (>95%); Condition 1 LRMS: Anal. Calcd. for

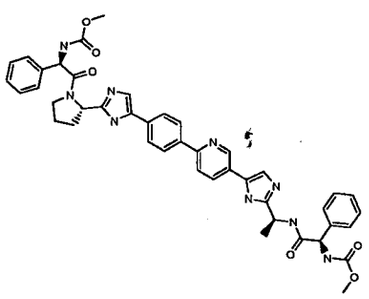
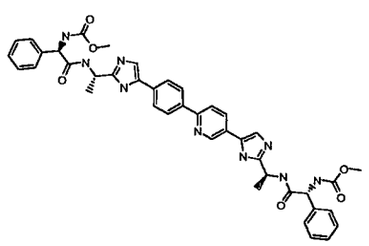
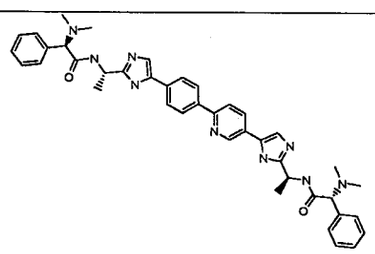
	pyrrolidinyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)ethyl)-2-phenylacetamide		$C_{43}H_{48}N_9O_2$ 722.39 found: 722.89 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{43}H_{48}N_9O_2$ 722.3931 found: 722.3930 $(M+H)^+$
Example 152j-12	methyl ((1R)-2-((2S)-2-(5-(6-(4-(2-((1S)-1-(((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)amino)ethyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from 152h-7 and *Cap*-4	t_R = 1.95 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{43}H_{44}N_9O_6$ 782.34 found: 782.93 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{43}H_{44}N_9O_6$ 782.3415 found: 782.3398 $(M+H)^+$
Example 152j-13	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(4-(6-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-pyridazinyl)phenyl)-	 Prepared from 152h-3 and *Cap*-1	t_R = 1.55 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$ 723.39 found: 723.88 $(M+H)^+$

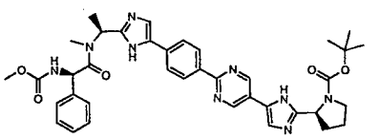
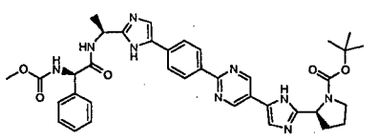
	1H-imidazol-2-yl)ethyl)-2-phenylacetamide		HRMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$ 723.3883 found: 723.3903 $(M+H)^+$
Example 152j-14	methyl ((1R)-2-((2S)-2-(5-(6-(4-(2-((1S)-1-(((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)amino)ethyl)-1H-imidazol-5-yl)phenyl)-3-pyridazinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from 152h-3 and *Cap*-4	t_R = 1.95 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.34 found: 783.95 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.3367 found: 783.3337 $(M+H)^+$
Example 152j-15	methyl ((1R)-2-((2S)-2-(5-(2-(4-(2-((1S)-1-(((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)amino)ethyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-	 Prepared from 152h-4 and *Cap*-4	t_R = 1.97 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.34 found: 783.97 $(M+H)^+$ HRMS: Anal. Calcd. for

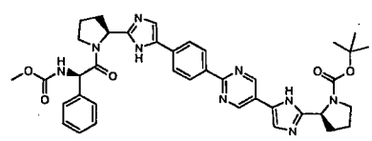
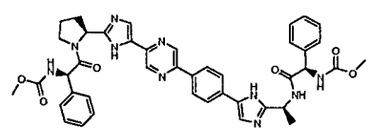
	phenylethyl)carbamate		$C_{42}H_{43}N_{10}O_6$ 783.3367 found: 783.3357 $(M+H)^+$
Example 152j-16	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(2-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)ethyl)-2-phenylacetamide	 Prepared from 152h-9 and *Cap*-1	t_R = 1.61 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$ 723.39 found: 723.52 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$ 723.3883 found: 723.3893 $(M+H)^+$
Example 152j-17	methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((1S)-1-(((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)amino)ethyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from 152h-9 and *Cap*-4	t_R = 1.99 min (95.6%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.34 found: 783.44 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.3367 found: 783.3328 $(M+H)^+$

Example 152j-18	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(5-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-2-pyrazinyl)-1H-imidazol-2-yl)ethyl)-2-phenylacetamide	 Prepared from 152h-8 and *Cap*-1	t_R = 1.60 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$ 723.39 found: 723.47 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{47}N_{10}O_2$ 723.3883 found: 723.3861 $(M+H)^+$
Example 152j-19	methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((1S)-1-(((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)amino)ethyl)-1H-imidazol-5-yl)-2-pyrazinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from 152h-8 and *Cap*-4	t_R = 1.97 min (94.7%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.34 found: 783.69 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.3367 found: 783.3345 $(M+H)^+$

Example 152j-20	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(4-(5-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)ethyl)-N-methyl-2-phenylacetamide	 Prepared from 152h-13 and *Cap*-1	t_R = 1.54 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{43}H_{49}N_{10}O_2$ 737.40 found: 737.54 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{43}H_{49}N_{10}O_2$ 737.4040 found: 7374066 $(M+H)^+$
Example 152j-21	methyl ((1R)-2-((2S)-2-(5-(2-(4-(2-((1S)-1-(((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)(methyl)amino)ethyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from 152h-13 and *Cap*-4	t_R = 2.00 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{43}H_{45}N_{10}O_6$ 797.35 found: 797.38 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{43}H_{45}N_{10}O_6$ 797.3524 found: 797.3528 $(M+H)^+$

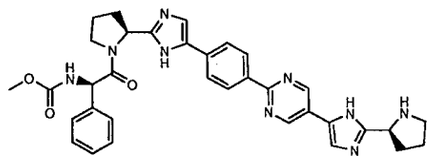
Example 152j-22	methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((1S)-1-(((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)amino)ethyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from 152h-5 and *Cap*-4	t_R = 1.46 min (condition 2, 98%) LRMS: Anal. Calcd. for $C_{43}H_{43}N_9O_6$ 781.33; found: 782.34 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{43}H_{44}N_9O_6$ 782.3415 found: 782.3417 $(M+H)^+$
Example 152j-23	methyl ((1R)-2-(((1S)-1-(5-(6-(4-(2-((1S)-1-(((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)amino)ethyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)ethyl)amino)-2-oxo-1-phenylethyl)carbamate	 Prepared from 152h-6 and *Cap*-4	t_R = 1.44 min condition 2, 90%) LRMS: Anal. Calcd. for $C_{41}H_{41}N_9O_6$ 755.32; found: 756.35 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{42}N_9O_6$ 756.3258 found: 756.3239 $(M+H)^+$.
Example 152j-24	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(6-(4-(2-((1S)-1-(((2R)-2-(dimethylamino)-2-		t_R = 1.18 min (condition 2, 91%) LRMS: Anal. Calcd. for

	phenylacetyl)amino)ethyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)ethyl)-2-phenylacetamide	Prepared from 152h-6 and Cap1	$C_{41}H_{45}N_9O_2$ 695.37; found: 696.37 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{46}N_9O_2$ 696.3774 found: 696.3806 $(M+H)^+$.
Example 152j-25		 Prepared from 152i-3 and *Cap*-4	t_R = 2.08 min (95.8 %); Condition 1 LRMS: Anal. Calcd. for $C_{38}H_{44}N_9O_5$ 706.35; found: 706.53 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{44}N_9O_5$ 706.3465; found: 706.3492 $(M+H)^+$.
Example 152j-26		 Prepared from 152i-2 and *Cap*-4	t_R = 2.04 min (96.4 %); Condition 1 LRMS: Anal. Calcd. for $C_{37}H_{42}N_9O_5$ 692.33; found: 692.49 $(M+H)^+$. HRMS: Anal.

			Calcd. for $C_{37}H_{42}N_9O_5$ 692.3309; found: 692.3322 $(M+H)^+$.
Example 152j-27		 Prepared from 152i-1 and *Cap*-4	t_R = 2.04 min (>95 %); Condition 1 LRMS: Anal. Calcd. for $C_{39}H_{44}N_9O_5$ 718.35; found: 718.49 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{39}H_{44}N_9O_5$ 718.3465; found: 718.3483 $(M+H)^+$.
Example 152j-28	methyl ((1R)-2-((2S)-2-(5-(5-(4-(2-((1S)-1-(((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)amino)ethyl)-1H-imidazol-5-yl)phenyl)-2-pyrazinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from 152h-14 and *Cap*-4	t_R = 2.00 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.34 found: 783.96 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.3367 found: 783.3375 $(M+H)^+$

Examples 152k-1 to 152k-

Example 152k-1 from 152j-27. {(R)-2-Oxo-1-phenyl-2-[(S)-2-(5-{4-[5-((S)-2-pyrrolidin-2-yl-3H-imidazol-4-yl)-pyrimidin-2-yl]-phenyl}-1H-imidazol-2-yl)-pyrrolidin-1-yl]-ethyl}-carbamic acid methyl ester



Cold (0°C) 4 *N* HCl in dioxanes (4 mL) was added *via* syringe to (S)-2-{5-[2-(4-{2-[(S)-1-((R)-2-methoxycarbonylamino-2-phenyl-acetyl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-phenyl)-pyrimidin-5-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (104.6 mg, 0.146 mmol) in a 100 mL pear-shaped flask followed by MeOH (0.5 mL). The homogeneous mixture was stirred at room temperature for 15 min before a precipitate was observed. After stirring further for 1.75h, the suspension was diluted with ether and hexanes. Suction-filtration of a small portion of the suspension yielded the title compound as a yellow solid which was used for characterization purposes. The balance of the suspension was concentrated down to dryness and placed under high vacuum for 16h. There was isolated the rest of the title compound also as a yellow solid (137.7 mg, 123%) which was used without further purification.

^{1}H NMR (500 MHz, DMSO-d_6) δ 15.20 and 14.66 (2m, 1H), 10,29 (br s, 0.7H), 9.38-9.36 (m, 2H), 8.55-8.00 (series of m, 4H), 7.42-7.28 (2m, 3H), 5.53-4.00 (series of m, 7H), 3.99-3.13 (series of m, 4H), 3.57 and 3.52 (2s, 3H), 2.50-1.84 (series of m, 8H) .

LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 1.79 min, >95 % homogeneity index.

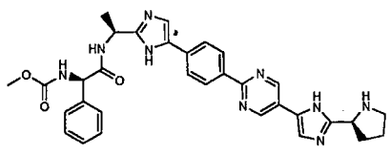
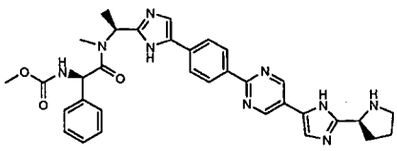
LRMS: Anal. Calcd. for $C_{34}H_{36}N_9O_3$ 618.29; found: 618.42 $(M+H)^+$.

HRMS: Anal. Calcd. for $C_{34}H_{36}N_9O_3$ 618.2921; found: 618.2958 $(M+H)^+$.

The same procedure was used to prepare Examples 152k-2 through 152k-3.

LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

Condition 2: Phenomenex LUNA C-18 4.6 × 50 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, 220nm, 5 μL injection volume.

Example	*Compound Name*	*Structure*	*Data*
Example 152k-2		 Prepared from 152j-26	t_R = 1.74 min (>95 %); Condition 1 LRMS: Anal. Calcd. for $C_{32}H_{34}N_9O_3$ 592.28; found: 592.41 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{32}H_{34}N_9O_3$ 592.2785; found: 592.2775 $(M+H)^+$.
Example 152k-3		 Prepared from 152j-25	t_R = 1.79 min (>95 %); Condition 1 LRMS: Anal. Calcd. for $C_{33}H_{36}N_9O_3$ 606.29; found:

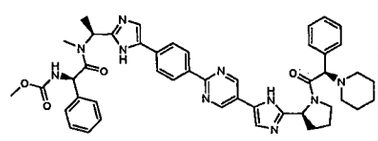
			606.43 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{33}H_{36}N_9O_3$ 606.2941; found: 606.2925 $(M+H)^+$.

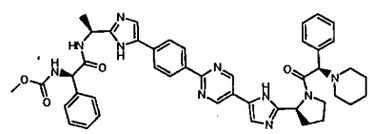
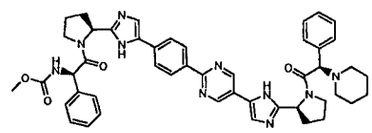
Examples 152l-1 to 152l-3

Examples 152l-1 through 152l-3 were isolated as TFA or AcOH salts prepared using the same procedure to convert Example 148e to 148.

LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

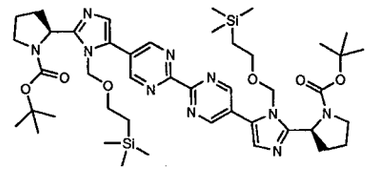
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

Example	*Compound Name*	*Structure*	*Data*
Example 152l-1	methyl ((1R)-2-(methyl((1S)-1-(4-(4-(5-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)ethyl)amino)-2-oxo-1-phenylethyl)carbamate	 Prepared from 152k-3 and *Cap*-14	t_R = 1.87 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{46}H_{51}N_{10}O_4$ 807.41 found: 807.57 $(M+H)^+$ HRMS: Anal. Calcd. for

			$C_{46}H_{51}N_{10}O_4$ 807.4095 found: 807.4128 $(M+H)^+$
Example 152l-2	methyl ((1R)-2-oxo-1-phenyl-2-(((1S)-1-(4-(4-(5-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)ethyl)amino)ethyl)carbamate	 Prepared from 152k-2 and *Cap*-14	t_R = 1.83 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{45}H_{49}N_{10}O_4$ 793.39 found: 793.52 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{45}H_{49}N_{10}O_4$ 793.3938 found: 793.3934 $(M+H)^+$
Example 152l-3	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4-(5-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate	 Prepared from 152k-1 and *Cap*-14	t_R = 1.87 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{47}H_{51}N_{10}O_4$ 819.41 found: 819.50 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{47}H_{51}N_{10}O_4$ 819.4095 found: 819.4127 $(M+H)^+$

Examples 153a-1 through 153a-4.

Example 153a-1 prepared from 152e-1. (S)-2-[5-{5'-[2-((S)-1-tert-Butoxycarbonyl-pyrrolidin-2-yl)-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-[2,2']bipyrimidinyl-5-yl}-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester



To a stirred solution of (S)-tert-butyl 2-(5-(2-chloropyrimidin-5-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (1.0 g, 2.08 mmol) and dichlorobis(benzonitrile) palladium (40 mg, 0.104 mmol) in dry DMF (10 mL) at room temperature under argon was added neat tetrakis(dimethylamino)ethylene (1.0 mL, 4.16 mmol). The mixture was heated to 60°C for 15h before it was diluted with ethyl acetate and suction-filtered through diatomaceous earth (Celite®). The filtrate was washed with sat'd $NaHCO_3$ soln and brine prior to drying over Na_2SO_4 and solvent evaporation. Purification of the residue by Biotage™ flash chromatography on silica gel (step gradient elution with 15%B to 15%B for 150 mL, 15%B to 75%B for 1500 mL, 75%B to 100%B for 1000 mL, 100%B to 100%B for 1000 mL where B=ethyl acetate and A=hexane followed by a second gradient elution with 10%B to 100%B for 700 mL where B=methanol and A=ethyl acetate) furnished the title compound as a caramel-colored, viscous oil (487.8 mg, 26% yield).

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.27 (s, 4H), 8.09-8.06 (m, 2H), 5.73-5.66 and 5.50-5.44 (2m, 2H), 5.06-4.93 (m, 2H), 3.60-3.39 (2m, 8H), 2.32-2.08 (3m, 4H), 2.00-1.85 (m, 4H), 1.37 and 1.14 (2s, 18H), 0.95-0.84 (m, 4H), -0.01 (s, 18H).

LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 3.37min, >95% homogeneity index.

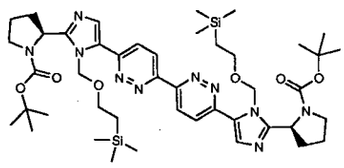
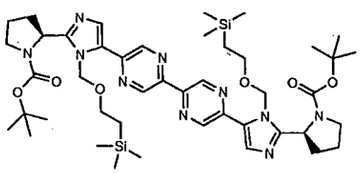
LRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.49; found: 889.57 $(M+H)^+$.

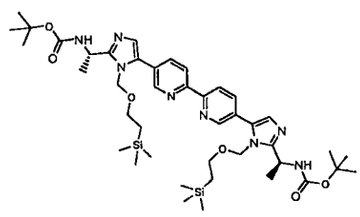
HRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.4940; found: 889.4920 $(M+H)^+$.

The same procedure was used to prepare Examples 153a-2 through 153a-4.

LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Condition 2: Phenomenex LUNA C-18 4.6 × 50 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, 220nm, 5 µL injection volume.

Example	*Compound Name*	*Structure*	*Data*
Example 153a-2		 Prepared from 152e-2	t_R = 3.37 min (89.6%); Condition 1 LRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.49; found: 889.56 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.494; found: 889.4951 $(M+H)^+$.
Example 153a-3		 Prepared from 152e-3	t_R = 3.37 min (95%); Condition 1 LRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.49; found: 889.51 $(M+H)^+$.

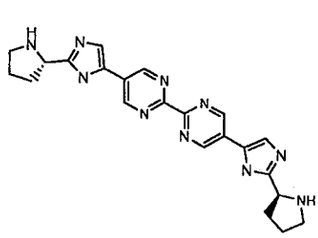
			HRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.4940; found: 889.4915 $(M+H)^+$.
Example 153a-4		 Prepared from 152e-4	t_R = 2.3 min (condition 2) LRMS: Anal. Calcd. for $C_{42}H_{66}N_8Si_2$ 834; found: 835 $(M+H)^+$.

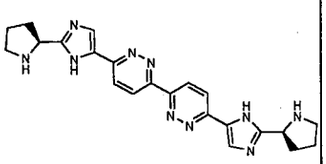
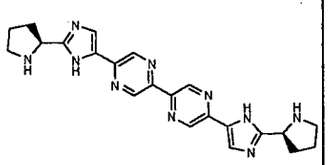
Example 153b-1-153b-3

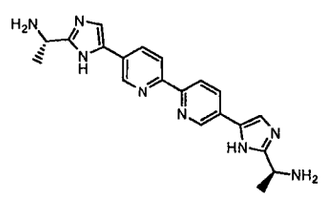
The hydrolysis reactions was performed as above for Example 152h.

LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Condition 2: Phenomenex LUNA C-18 4.6 × 50 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, 220nm, 5 µL injection volume.

Example	*Compound Name*	*Structure*	*Data*
Example 153b-1		 Prepared from 153a-1	t_R = 1.18 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{22}H_{25}N_{10}$ 429.23; found: 429.01 $(M+H)^+$.

			HRMS: Anal. Calcd. for $C_{22}H_{25}N_{10}$ 429.2264; found: 429.2259 $(M+H)^+$.
Example 153b-2		 Prepared from 153a-2	t_R = 1.26 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_2$ 737.33 found: 737.49 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_4$ 737.3312 found: 737.3342 $(M+H)^+$
Example 153b-3		 Prepared from 153a-3	t_R = 1.40 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{22}H_{25}N_{10}$ 429.23; found: 429.20 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{25}N_{10}$: 429.2264; Found:

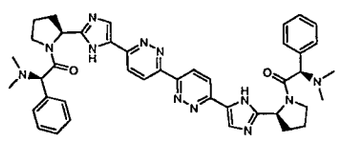
			429.2254 $(M+H)^+$
Example 153b-4		 Prepared from 153a-4	t_R = 0.85 min (condition 1) LCMS: Anal. Calcd. for $C_{20}H_{22}N_8$ 374; found: 375 $(M+H)^+$.

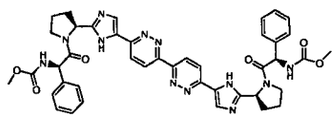
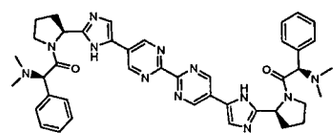
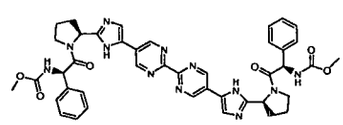
Examples 153c-1 to 153c-7

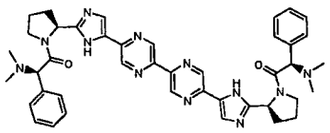
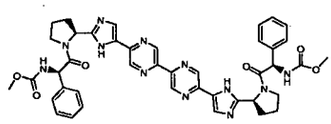
Examples 153c-1 through 153c-7 were isolated as TFA or AcOH salts using the procedure used to convert Example 148e to 148.

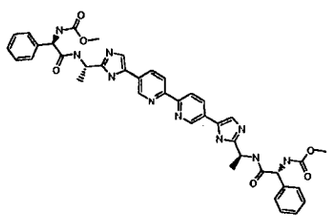
LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Condition 2: Phenomenex LUNA C-18 4.6 × 50 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, 220nm, 5 µL injection volume.

Example	*Compound Name*	*Structure*	*Data*
Example 153c-1	(1R,1'R)-2,2'-(3,3'-bipyridazine-6,6'-diylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)	 Prepared from 153b-2 and *Cap*-1	t_R = 1.55 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.39 found: 751.64 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.3945 found:

			751.3936 $(M+H)^+$
Example 153c-2	dimethyl (3,3'-bipyridazine-6,6'-diylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 Prepared from 153b-2 and *Cap*-4	t_R = 1.95 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.34 found: 811.22 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.3429 found: 811.3406 $(M+H)^+$
Example 153c-3	(1R,1'R)-2,2'-(2,2'-bipyrimidine-5,5'-diylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)	 Prepared from 153b-1 and *Cap*-1	t_R = 1.51 min (>90%*); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.39 found: 751.21 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.3945 found: 751.3921 $(M+H)^+$
Example 153c-4	dimethyl (2,2'-bipyrimidine-5,5'-diylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarba	 Prepared from 153b-1 and *Cap*-4	t_R = 1.88 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.34 found: 811.10 $(M+H)^+$

	mate		HRMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.3429 found: 811.3401 $(M+H)^+$
Example 153c-5	(1R,1'R)-2,2'-(2,2'-bipyrazine-5,5'-diylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)	 Prepared from 153b-3 and *Cap*-1	t_R = 1.61 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.39 found: 751.30 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{47}N_{12}O_2$ 751.3945 found: 751.3943 $(M+H)^+$
Example 153c-6	dimethyl (2,2'-bipyrazine-5,5'-diylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 Prepared from 153b-3 and *Cap*-4	t_R = 2.00 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.34 found: 811.23 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{43}N_{12}O_6$ 811.3429 found: 811.3407 $(M+H)^+$

Example 153c-7	dimethyl (2,2'-bipyridine-5,5'-diylbis(1H-imidazole-5,2-diyl(1S)-1,1-ethanediylimino((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 Prepared from 153b-4 and *Cap*-4	t_R = 1.42 min (condition 2, 94%) LRMS: Anal. Calcd. for $C_{40}H_{40}N_{10}O_6$ 756.31; found: 757.34 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{41}N_{10}O_6$ 757.3211 found: 757.3180 $(M+H)^+$.

Section F LC Conditions for determining retention time

Condition 7

Column: Phenomenex C18 10u 4.6 X 30 mm

Start % B = 0

Final % B = 100

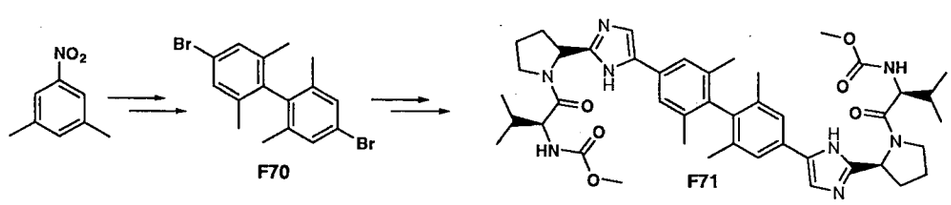
Gradient Time = 3 min

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



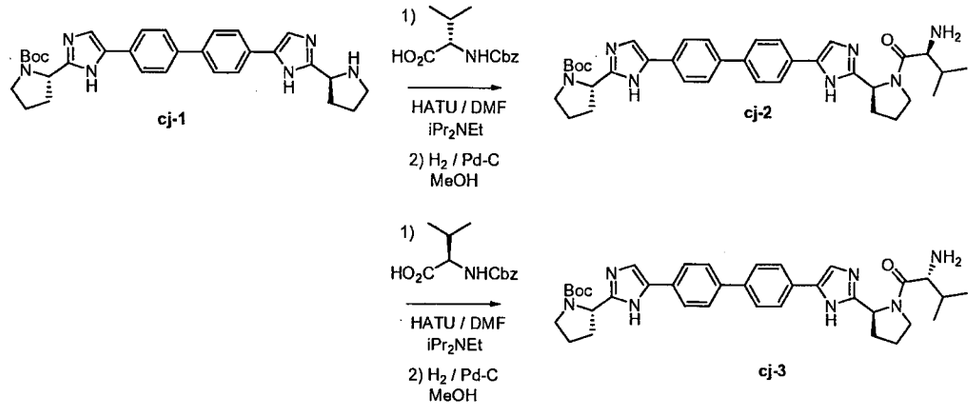
Compound F70 was prepared following the procedure described in Anna Helms et al., *J. Am. Chem. Soc.* 1992 114(15) pp 6227-6238.

Compound F71 was prepared in analogous fashion to the procedure used to sythesize Example 1.

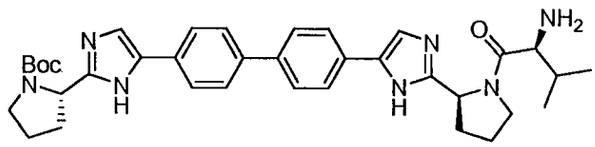
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.69-0.95 (m, 12H) 1.92 (s, 12H) 1.97-2.27 (m, 8H) 2.40 (s, 2H) 3.55 (s, 6H) 3.73-3.97 (m, 4H) 4.12 (t, *J*=7.78 Hz, 2H) 5.14 (t, *J*=7.02 Hz, 2H) 7.34 (d, *J*=8.24 Hz, 2H) 7.49-7.70 (m, 4H) 8.04 (s, 2H) 14.59 (s, 2H) RT = 2.523 minutes (condition 7, 96%); LRMS: Anal. Calcd. for C44H58N8O6 794.45; found: 795.48 $(M+H)^+$.

Section cj: Synthesis of Carbamate Replacements

Example cj-2 and cj-3



Preparation of (*S*)-*tert*-Butyl 2-(5-(4'-(2-((*S*)-1-((*S*)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-2)



To a solution of (*S*)-*tert*-butyl 2-(5-(4'-(2-((*S*)-pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-1) (1.00 g, 1.91 mmol), iPr_2NEt (1.60 mL, 9.19 mmol) and *N*-Z-valine (0.62 g, 2.47 mmol) in DMF (10 mL) was added HATU (0.92 g, 2.42 mmol). The solution was allowed to stir at rt for 1 h and then it was poured into ice water (*ca.* 250 mL) and allowed to stand for 20 min. The mixture was filtered and the solid washed with water and then dried *in*

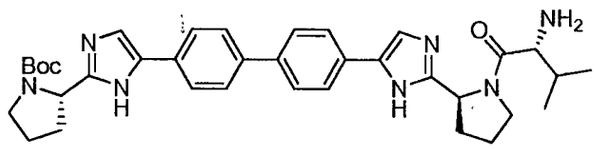
vacuo overnight to afford a colorless solid (1.78 g) which was used as such in the next step. LCMS: Anal. Calcd. for $C_{44}H_{51}N_7O_5$: 757; found: 758 $(M+H)^+$.

A mixture of this material (1.70 g) and 10% Pd-C (0.37 g) in MeOH (100 mL) was hydrogenated (balloon pressure) for 12 h. The mixture was then filtered and the solvent removed *in vacuo*. The residue was purified by silica gel chromatography (Biotage system/ 0-10% MeOH-CH_2Cl_2) to afford the title compound as a light yellow foam (0.90 g, 76%).

^{1}HNMR (400 MHz, DMSO-d_6) δ 12.18 (s, 0.35H), 11.73 (s, 0.65H), 11.89 (s, 0.65H), 11.82 (s, 0.35H), 7.77–7.81 (m, 3H), 7.57–7.71 (m, 5H), 7.50–7.52 (m, 2H), 5.17 (dd, J = 3.6, 6.5 Hz, 0.3H), 5.08 (dd, J = 3.6, 6.5 Hz, 0.7H), 4.84 (m, 0.3H), 4.76 (m, 0.7H), 3.67–3.69 (m, 1H), 3.50-3.62 (m, 1H), 3.34–3.47 (m, 2H), 2.22-2.28 (m, 2H), 2.10-2.17 (m, 2H), 1.74–2.05 (m, 6H), 1.40 (s, 4H), 1.15 (s, 5H), 0.85 – 0.91 (m, 4H), 0.79 (d, J = 6.5 Hz, 2H).

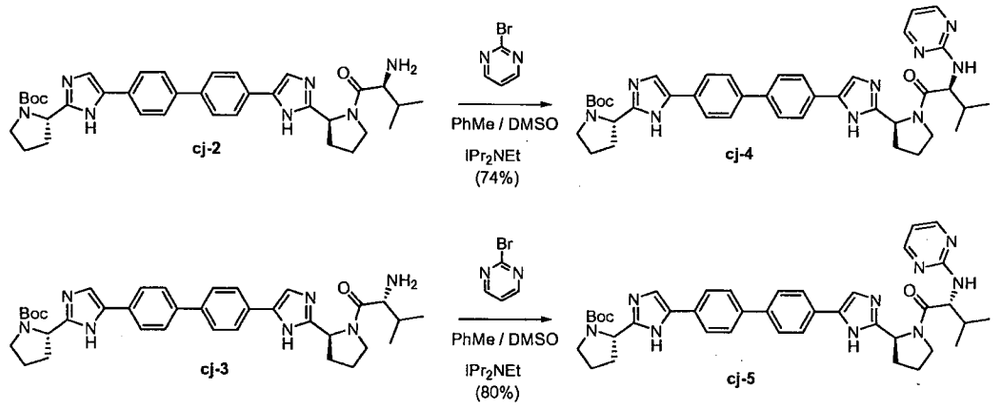
LCMS: Anal. Calcd. for $C_{36}H_{45}N_7O_3$: 623; found: 624 $(M+H)^+$.

Preparation of (*S*)-*tert*-Butyl 2-(5-(4'-(2-((*S*)-1-((*R*)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-3)

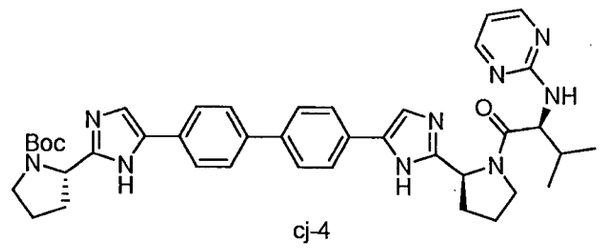


(*S*)-*tert*-Butyl 2-(5-(4'-(2-((*S*)-1-((*R*)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-3) was prepared using the same method used to prepare cj-2 to give a colorless foam (1.15 g, 76%). ^{1}HNMR (400 MHz, DMSO-d_6) δ 12.17 (s, 0.35H), 12.04 (s, 0.65H), 11.89 (s, 0.65H), 11.81 (s, 0.35H), 7.78–7.83 (m, 3H), 7.60–7.71 (m, 5H), 7.43–7.52 (m, 2H), 5.22–5.25 (m, 0.4H), 5.05–5.07 (m, 0.6H), 4.83–4.86 (m, 0.5H), 4.72–4.78 (m, 0.5H), 3.78–3.84 (m, 1H), 3.49-3.64 (m, 2H), 3.35–3.43 (m, 2H), 2.19 -2.32 (m, 1H), 2.04-2.17 (m, 3H), 1.95–2.04 (m, 2H), 1.76–1.90 (m, 3H), 1.40 (s, 4H), 1.15 (s, 5H), 0.85–0.91 (m, 4H), 0.67 (d, J = 6.5 Hz, 1H), 0.35 (d, J = 6.5 Hz, 1H). LCMS: Anal. Calcd. for $C_{36}H_{45}N_7O_3$: 623; found: 624 $(M+H)^+$.

Example cj-4 and cj-5



Preparation of (*S*)-*tert*-Butyl 2-(5-(4'-(2-((*S*)-1-((*S*)-3-methyl-2-(pyrimidin-2-ylamino)butanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-4)



cj-4

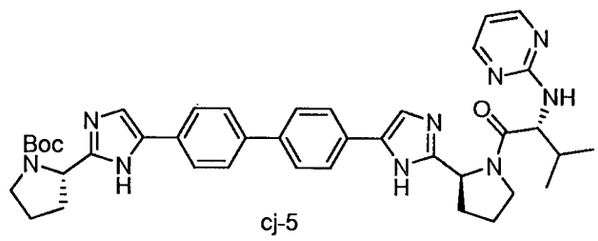
A mixture of (*S*)-*tert*-butyl 2-(5-(4'-(2-((*S*)-1-((*S*)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-2) (0.45 g, 0.72 mmol), 2-bromopyrimidine (0.37 g, 2.34 mmol) and iPr_2NEt (0.20 mL, 1.18 mmol) in toluene-DMSO (4:1, 5 mL) was heated at 90°C overnight. The volatiles were removed *in vacuo* and the residue was purified by preparative HPLC (YMC Pack C-18, 30X100mm/MeCN-H_2O-TFA). The title compound (0.56 g, 74%), as its TFA salt, was obtained as a yellow-orange glass.

^{1}HNMR (400 MHz, DMSO-d_6) δ 14.56 (br s, 2H), 8.28 (d, J = 5.0 Hz, 1H), 8.12 – 8.20 (m, 2H), 7.94 – 7.97 (m, 3H), 7.83 – 7.91 (m, 5H), 7.06 (d, J = 8.1 Hz, 1H), 6.62 (app t, J = 5.0 Hz, 1H), 4.99 – 5.10 (m, 2H), 4.50 (app t, J = 7.7 Hz, 1H), 4.07 – 4.12 (m, 2H), 3.83 – 3.87 (m, 1H), 3.56 – 3.62 (m, 1H), 3.40 – 3.47 (m, 2H), 2.36 –

2.41 (m, 1H), 1.94 – 2.22 (m, 6H), 1.40 (s, 4H), 1.17 (s, 5H), 0.88 (app t, J = 6.5 Hz, 6H).

LCMS: Anal. Calcd. for $C_{40}H_{47}N_9O_3$: 701; found: 702 $(M+H)^+$.

Preparation of (*S*)-tert-Butyl -2-(5-(4'-(2-((*S*)-1-((*R*)-3-methyl-2-(pyrimidin-2-ylamino)butanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-5)



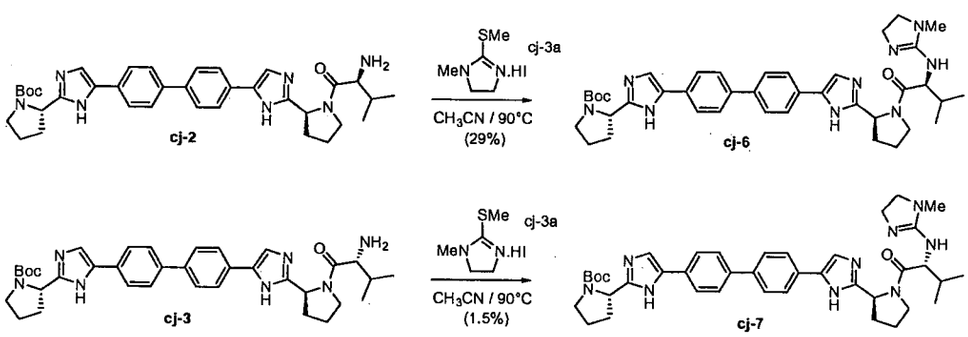
cj-5

The TFA salt of the title compound was prepared following the same method method used to prepare cj-4 to give a light yellow solid (0.375 g, 59%).

^{1}HNMR (400 MHz, DMSO-d_6) δ 14.67 (br s, 2H), 8.30 (d, J = 4.3 Hz, 1H), 8.04 – 8.19 (m, 2H), 7.84 – 7.96 (m, 8H), 6.88 (d, J = 8.6 Hz, 1H), 6.61 (app t, J = 4.5 Hz, 1H), 5.17 (dd, J = 4.4, 8.0 Hz, 1H), 5.00 – 5.07 (m, 1H), 4.67 (dd, J = 7.3, 8.1 Hz, 1H), 3.91 – 3.96 (m, 1H), 3.70-3.75 (m, 1H), 3.56 – 3.62 (m, 1H), 3.42 – 3.45 (m, 1H), 2.39 – 2.43 (m, 2H), 2.04 – 2.16 (m, 5H), 1.94 – 1.97 (m, 2H), 1.40 (s, 4H), 1.17 (s, 5H), 0.95 (d, J = 6.6 Hz, 2.5H), 0.91 (d, J = 6.6 Hz, 2.5H), 0.86 (d, J = 6.6 Hz, 0.5H), 0.81 (d, J = 6.6 Hz, 0.5H).

LCMS: Anal. Calcd. for $C_{40}H_{47}N_9O_3$: 701; found: 702 $(M+H)^+$.

Example cj-6 and cj-7



Preparation of 1-Methyl-2-(methylthio)-4,5-dihydro-1*H*-imidazole hydroiodide



cj-3a

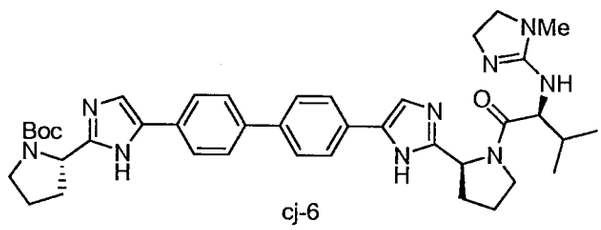
The title compound was prepared according to : Kister, J.; Assef, G.; Dou, H. J.-M.; Metzger, J. *Tetrahedron* 1976, *32*, 1395. Thus, a solution of *N*-methylethylenediamine (10.8 g, 146 mmol) in EtOH-H_2O (1:1, 90 mL) was preheated to 60°C and CS_2 (9.0 mL, 150 mmol) was added dropwise. The resulting mixture was heated at 60°C for 3 h and then conc. HCl (4.7 mL) was slowly added. The temperature was raised to 90°C and stirring was continued for 6 h. After the cooled mixture had been stored at -20°C, it was filtered and the resulting solid dried *in vacuo* to afford 1-methylimidazolidine-2-thione (8.43g, 50%) as a beige solid.

^{1}HNMR (400 MHz, $CDCl_3$) δ 5.15 (s, br, 1H), 3.67 – 3.70 (m, 2H), 3.53 – 3.58 (m, 2H), 3.11 (s, 3H).

To a suspension of 1-methylimidazolidine-2-thione (5.17 g, 44.5 mmol) in acetone (50 mL) was added MeI (2.9 mL, 46.6 mmol). The solution was allowed to stir at room temperature for 4 h and the resulting solid was quickly filtered and then dried *in vacuo* to give 1-methyl-2-(methylthio)-4,5-dihydro-1*H*-imidazole hydroiodide (8.79 g, 77%) as beige solid.

^{1}HNMR (400 MHz, $CDCl_3$) δ 9.83 (s, br, 1H), 3.99 – 4.12 (m, 4H), 3.10 (s, 3H), 2.99 (s, 3H).

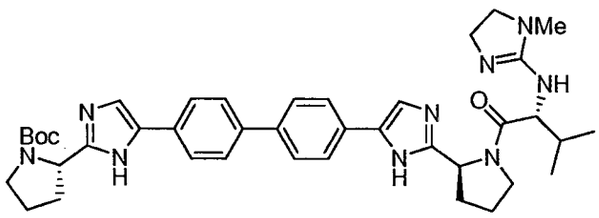
Preparation of (*S*)-*tert*-Butyl 2-(5-(4'-(2-((*S*)-1-((*S*)-3-methyl-2-(1-methyl-4-5-dihydroimidazol-2-ylamino)butanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-6)



cj-6

A mixture of (*S*)-*tert*-butyl 2-(5-(4'-(2-((*S*)-1-((*S*)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)-pyrrolidine-1-carboxylate (cj-2) (0.280 g, 0.448 mmol) and 1-methyl-2-(methylthio)-4,5-dihydro-1*H*-imidazole hydroiodide (cj-3a) (0.121 g, 0.468 mmol) in CH_3CN (5 mL) was heated at 90°C for 12 h. Another 0.030 g of 1-methyl-2-(methylthio)-4,5-dihydro-1*H*-imidazole hydroiodide (cj-3a) was added and heating continued for a further 12 h. The crude reaction mixture was directly purified by prep HPLC (Luna C-18/MeCN-H_2O-TFA) to give the TFA salt of the title compound (0.089 g) as a light yellow solid which was used as such in the subsequent steps.
LCMS: Anal. Calcd. for $C_{40}H_{51}N_9O_3$: 705; found: 706 $(M+H)^+$.

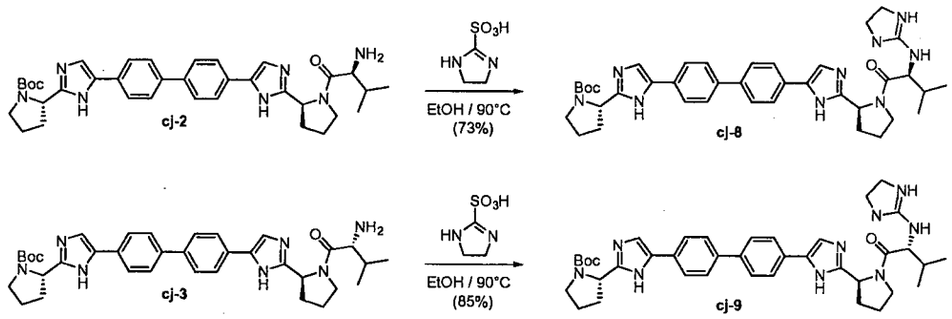
Preparation of (S)-*tert*-Butyl 2-(5-(4'-(2-((*S*)-1-((*R*)-3-methyl-2-(1-methyl-4-5-dihydroimidazol-2-ylamino)butanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-7)



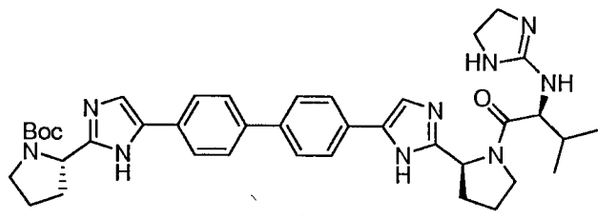
cj-7

The title compound was prepared from cj-3 according to the method described for the synthesis of cj-6, except that the reaction mixture was initially purified by prep HPLC (YMC-Pack 25X250mm/MeCN-H_2O-NH_4OAc) and then repurified by prep HPLC (Luna Phenyl-hexyl//MeCN-H_2O-NH_4OAc). This gave the desired product (0.005 g) as a foam which was used as such in the subsequent steps.
LCMS: Anal. Calcd. for $C_{40}H_{51}N_9O_3$: 705; found: 706 $(M+H)^+$.

Example cj-8 and cj-9



Preparation of (*S*)-*tert*-Butyl 2-(5-(4'-(2-((*S*)-1-((*S*)-3-methyl-2-(3,4-dihydroimidazol-2-ylamino)butanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-8)



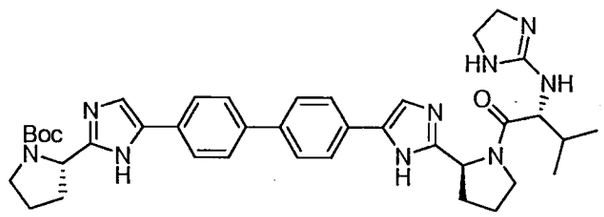
cj-8

A mixture of (*S*)-*tert*-butyl 2-(5-(4'-(2-((*S*)-1-((*S*)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-2) (0.298 g, 0.480 mmol), 4,5-dihydro-1*H*-imidazole-2-sulfonic acid (AstaTech) (0.090 g, 0.60 mmol) and iPr_2NEt (0.083 mL, 0.48 mmol) in EtOH (4 mL) was heated at 100°C for 12 h. The cooled mixture was evaporated to dryness and the residue was purified by prep HPLC (Luna 5u C18/MeCN-H_2O-TFA, x2) to afford the TFA salt of the title compound (0.390 g, 73%) as a light yellow solid.

^{1}HNMR (400 MHz, DMSO-d_6) δ 14.66 (br s, 2H), 8.51 (br s, 1H), 8.20 (d, J = 10.1 Hz, 2H), 8.10 (br s, 1H), 7.82 – 7.91 (m, 7H), 7.30 (br s, 1H), 5.12 (t, J = 7.1 Hz, 1H), 4.97 – 5.05 (m, 2H), 4.37 (dd, J = 4.3, 10.1 Hz, 2H), 3.82 – 3.86 (m, 2H), 3.73 – 3.77 (m, 2H), 3.59 (s, 4H), 3.39 – 3.48 (m, 2H), 2.15 – 2.25 (m, 2H), 1.93 – 2.07 (m, 5H), 1.40 (s, 4H), 1.17 (s, 5H), 0.93 (d, J = 6.6 Hz, 3H), 0.69 (br s, 3H).

LCMS: Anal. Calcd. for $C_{39}H_{49}N_9O_3$: 691; found: 692 $(M+H)^+$.

Preparation of (*S*)-*tert*-Butyl 2-(5-(4'-(2-((*S*)-1-((*R*)-3-methyl-2-(3,4-dihydroimidazol-2-ylamino)butanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-9)



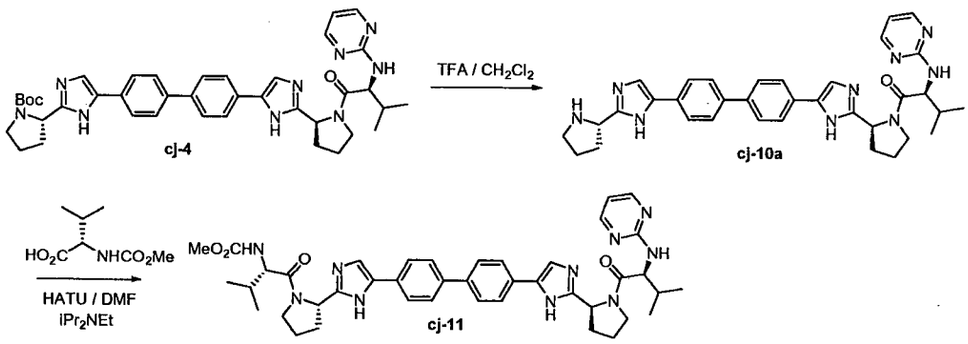
cj-9

The title compound was prepared from cj-3 according to the same method used to prepare cj-8 to afford the TFA salt (0.199 g, 57%) as a yellow glass.

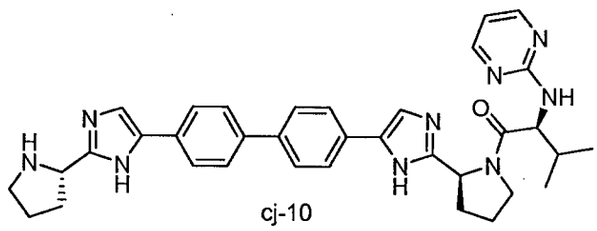
^{1}HNMR (400 MHz, DMSO-d_6) δ 14.58 (br s, 4H), 8.23 (d, J = 9.6 Hz, 1H), 8.11 (s, 1H), 7.87 – 7.89 (m, 6H), 7.25 (br s, 1H), 5.17 – 5.20 (m, 1H), 4.96 – 5.04 (m, 1H), 4.37 (dd, J = 5.5, 9.6 Hz, 1H), 3.91-3.95 (m, 2H), 3.37 – 3.46 (m, partially obscured by H_2O, 4H), 2.39 – 2.42 (m, partially obscured by solvent, 2H), 2.01 – 2.09 (m, 4H), 1.94 – 1.98 (m, 2H), 1.40 (s, 3H), 1.17 (s, 6H), 0.95 (d, J = 6.5 Hz, 2.5H), 0.85 (d, J = 6.5 Hz, 2.5H), 0.66 (d, J = 7.0 Hz, 0.5H), 0.54 (d, J = 6.5 Hz, 0.5H).

LCMS: Anal. Calcd. for $C_{39}H_{49}N_9O_3$: 691; found: 692 $(M+H)^+$.

Example cj-11



Preparation of (*S*)-3-Methyl-2-(pyrimidin-2-ylamino)-1-((*S*)-2-(5-(4'-(2-((*S*)-pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)butan-1-one (cj-10a).



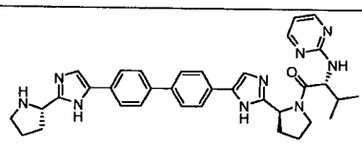
cj-10

Step 1: A solution of the TFA salt of (*S*)-*tert*-butyl 2-(5-(4'-(2-((*S*)-1-((*S*)-3-methyl-2-(pyrimidin-2-ylamino)butanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-4) (0.208 g, 0.199 mmol) in a mixture CH_2Cl_2 (4 mL) and TFA (3 mL) was stirred at room temperature for 1.5 h. The solvents were then removed *in vacuo* and the residue was purified by prep HPLC (Luna 5u C18/MeCN-H_2O-TFA) to give the TFA salt of the title compound (0.391 g) as an orange gum.

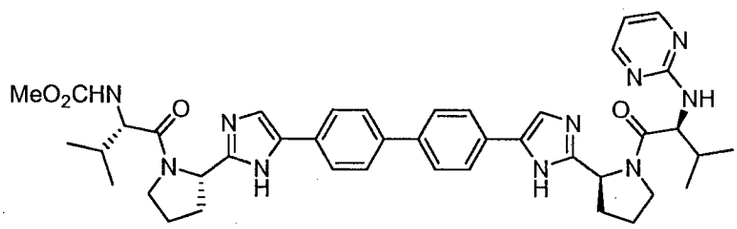
^{1}HNMR (400 MHz, DMSO-d_6) δ 14.53 (br s, 3H), 9.52 – 9.57 (m, 2H), 8.98 – 9.04 (m, 2H), 8.28 (d, J = 4.6 Hz, 2H), 8.13 (br s, 1H), 7.79 – 7.91 (m, 7H), 7.07 (d, J = 8.1 Hz, 1H), 6.62 (app t, J = 4.8 Hz, 1H), 5.07 (t, J = 7.1 Hz, 1H), 4.72 – 4.78 (m, 2H), 4.48 – 4.51 (m, 1H), 4.08-4.12 (m, 2H), 3.28 – 3.36 (m, 2H), 2.37 – 2.42 (m, 2H), 1.97 – 2.22 (m, 6H), 0.88 (app t, J = 4.5 Hz, 6H).

LCMS: Anal. Calcd. for $C_{35}H_{39}N_9O$: 601; found: 602 $(M+H)^+$.

Similarly, the following example was prepared according to the representative method above;

Example	*Structure*	*LCMS*
cj-10a (from cj-3)		LCMS: Anal. Calcd. for $C_{35}H_{39}N_9O$: 601; found: 602 $(M+H)^+$.

Preparation of *methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate* (cj-11)



cj-11

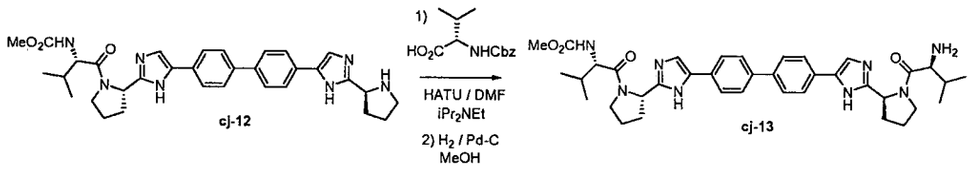
methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate

Step 2: To a solution of the TFA salt of (*S*)-3-methyl-2-(pyrimidin-2-ylamino)-1-((*S*)-2-(5-(4'-(2-((*S*)-pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)butan-1-one (cj-10) (0.208 g, 0.197 mmol) in DMF (4 mL) was added iPr_2NEt (0.20 mL, 1.15 mmol), (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.049 g, 0.28 mmol) and HATU (0.105 g, 0.276 mmol). The solution was stirred for 1.5 h at room temperature, diluted with MeOH (2 mL) and purified directly by prep HPLC (Luna 5u C18/MeCN-H_2O-NH_4OAc). This material was repurified by flash chromatography (SiO_2/2-10% MeOH-CH_2Cl_2) to give a solid which was lyophilized from CH_3CN-H_2O to give the title compound (48.6 mg, 32%) as a colourless solid.

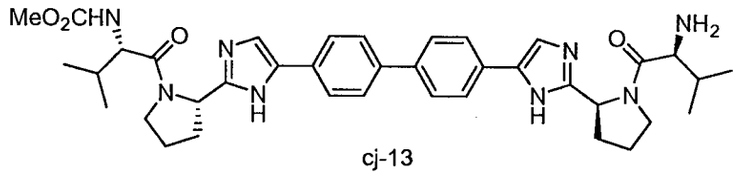
^{1}HNMR (400 MHz, DMSO-d_6) δ 11.78 (br s, 1H), 8.28 (d, *J* = 4.5 Hz, 1H), 7.76 – 7.79 (m, 4H), 7.66 – 7.69 (m, 4H), 7.48-7.51 (m, 2H), 7.29 (d, *J* = 8.6 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.60 (app t, *J* = 4.5 Hz, 1H), 5.03 – 5.09 (m, 2H), 4.48 (t. *J* = 8.1 Hz, 1H), 3.99 – 4.08 (m, 2H), 3.78 – 3.85 (m, 2H) 3.53 (s, 3H), 2.12 – 2.21 (m, 4H), 1.87 – 2.05 (m, 7H), 0.83 – 0.97 (m, 12H).

LCMS: Anal. Calcd. for $C_{42}H_{50}N_{10}O_4$:758; found: 759 $(M+H)^+$.

Example-cj-13



Preparation of Methyl (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-13)



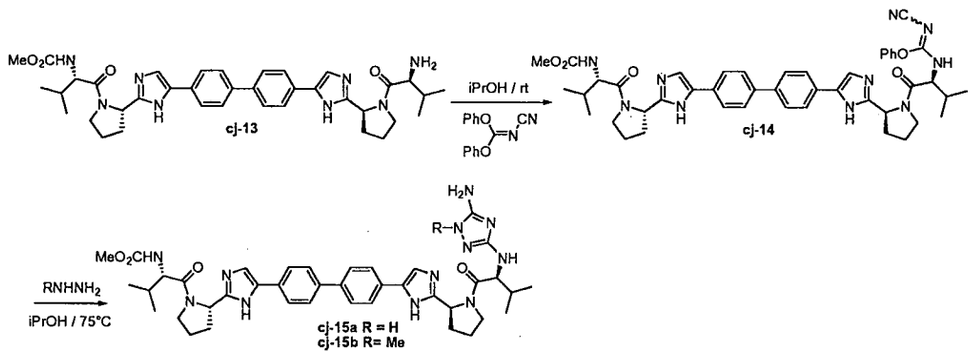
cj-13

To a solution of methyl (*S*)-3-methyl-1-oxo-1-((*S*)-2-(5-(4'-(2-((*S*)-pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)butan-2-ylcarbamate (cj-12) (1.16 g, 1.99 mmol), Z-Val-OH (0.712 g, 2.83 mmol) and iPr_2NEt (0.70 mL, 5.42 mmol) in DMF (40 mL) was added HATU (1.10 g, 2.89 mmol) portionwise. The mixture was allowed to stir at room temperature for 1 h and was then poured into ice-water (400 mL) and allowed to stand for 20 min. The mixture was filtered and the solid washed with cold water and allowed to air dry overnight to give the Z-protected intermediate. LCMS: Anal. Calcd. for $C_{46}H_{54}N_8O_6$: 814; found: 815 $(M+H)^+$.

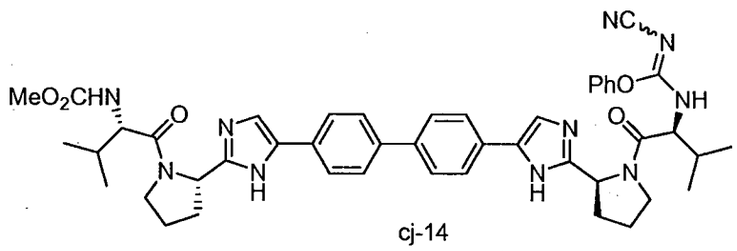
The obtained solid was dissolved in MeOH (80 mL), 10% Pd-C (1.0 g) was added and the mixture was hydrogenated at room temperature and atmospheric pressure for 3 h. The mixture was then filtered and the filtrate concentrated *in vacuo*. The resulting residue was purified by flash chromatography (SiO_2/ 5-20% MeOH-CH_2Cl_2) to afford the title compound (1.05 g, 77%) as a colorless foam. ^{1}HNMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1H), 7.75 – 7.79 (m, 3H), 7.61 – 7.67 (m, 5H), 7.49 (s, 1H), 7.26 – 7.28 (m, 1H), 5.05 – 5.09 (m, 2H), 4.03 – 4.09 (m, 2H), 3.77 – 3.80 (m, 1H), 3.66 – 3.70 (m, 1H), 3.52 (s, 3H), 3.40 – 3.47 (m, 2H), 2.21 – 2.26 (m, 1H), 2.10 – 2.17 (m, 3H), 1.81 – 2.02 (m, 6H), 0.77 – 0.92 (m, 12H).

LCMS: Anal. Calcd. for $C_{38}H_{48}N_8O_4$: 680; found: 681 $(M+H)^+$.

Example cj-15



Preparation of Methyl (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-((*Z*/*E*)-(cyanoimino)(phenoxy)methylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-14)

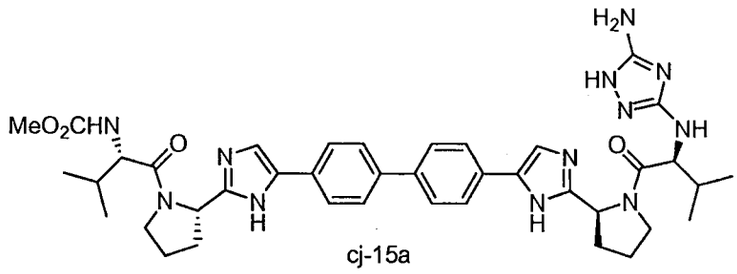


cj-14

A mixture of methyl (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-13) (0.329 g, 0.527 mmol) and diphenyl cyanocarbonimidate (0.128 g, 0.537 mmol) in iPrOH (10 mL) was stirred at room temperature for 12 h. The resulting solid was filtered and air-dried to give the title compound (0.187 g, 43%) as a cream-colored solid. This material was used as such in the next step without further purification.

LCMS: Anal. Calcd. for $C_{46}H_{52}N_{10}O_5$: 824; found: 825 $(M+H)^+$.

Preparation of *methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(5-amino-1-methyl-1H-1,2,4-triazol-3-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate* (cj-15a, R=H)



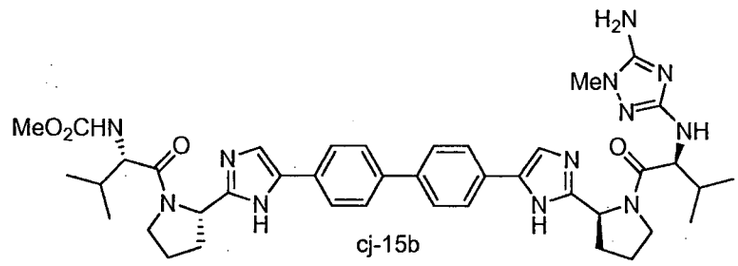
cj-15a

A solution of methyl (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-((*Z/E*)-(cyanoimino)(phenoxy)methylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-14) (0.074 g, 0.090 mmol) and hydrazine hydrate (0.05 mL, 0.88 mmol) in iPrOH (2 mL) was heated at 75°C for 7 h. The solvent was then removed *in vacuo* and the residue was purified by prep HPLC (Luna 5u C18/MeCN-H_2O-NH_4OAc) to give foam which was lyophilized from CH_3CN-H_2O to give the title compound (0.032 g, 46%) as a colorless solid.

^{1}HNMR (400 MHz, DMSO-d_6) δ 12.17 (s, 1H), 11.75 (m, 2H), 10.66 – 10.84 (m, 2H), 7.76 – 7.79 (m, 3H), 7.62 – 7.74 (m, 4H), 7.49 – 7.51 (m, 1H), 7.24 – 7.29 (m, 2H), 5.28 – 5.32 (m, 1H), 5.05 – 5.08 (m, 2H), 4.04 – 4.09 (m, 3H), 3.87 – 3.94 (m, 2H), 3.72 – 3.81 (m, 2H), 3.53 (s, 3H), 2.09 – 2.17 (m, 2H), 1.90 – 2.02 (m, 6H), 0.81 – 0.99 (m, 12H).

LCMS: Anal. Calcd. for $C_{40}H_{50}N_{12}O_4$: 762; found: 763 $(M+H)^+$.

Preparation of Methyl (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-(5-amino-1-methyl-1*H*-1,2,4-triazol-3-ylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-15b, R= Me)



cj-15b

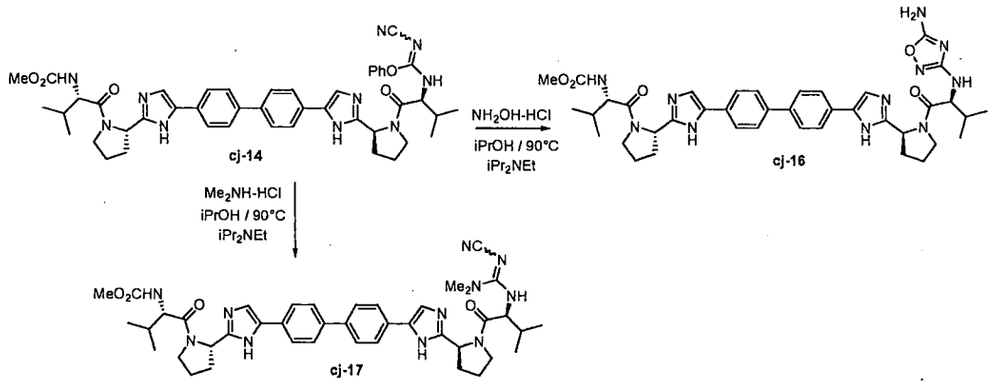
A solution of methyl (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-((*Z/E*)-(cyanoimino)(phenoxy)methylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-14) (0.105 g, 0.128 mmol) and N-methylhydrazine (0.010 mL, 0.188 mmol) in iPrOH (2 mL) was heated at 75°C for 3 h. A second portion of N-methylhydrazine (0.010 mL, 0.188 mmol) was added and heating was continued for 7 h. The volatiles were then removed *in vacuo* and the residue was purified by prep HPLC (Luna 5u C18/MeCN-H_2O-NH_4OAc) to give a foam which was further purified by flash chromatography (SiO_2/0-20% MeOH-CH_2Cl_2). The resulting material was lyophilized from CH_3CN-H_2O to give the title compound (0.029 g, 29%) as a colorless solid.

^{1}HNMR (400 MHz, DMSO-d_6) δ 13.79 (s, 0.4H), 12.19 (s, 1H), 11.76 (m, 1.6H), 7.77 – 7.85 (m, 4H), 7.62 – 7.71 (m, 4H), 7.49 – 7.51 (m, 1H), 7.24 – 7.29 (m, 1H), 6.31 (d, *J* = 9.1 Hz, 0.5H), 6.09 (d, *J* = 9.1 Hz, 1.5H), 5.87 (s, 1H), 5.34 – 5.36 (m, 1H), 5.04 – 5.08 (m, 2H), 4.89 (s, 1H), 4.75 (s, 2H), 3.53 (s, 3H), 2.10 – 2.17 (s, 3H), 1.94 – 2.02 (m, 6H), 0.81 – 0.98 (m, 12H).

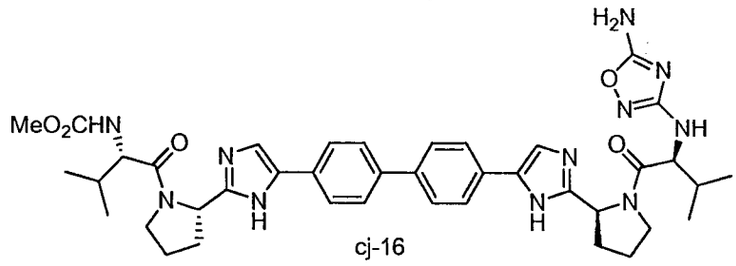
LCMS: Anal. Calcd. for $C_{41}H_{52}N_{12}O_4$: 776; found: 777 $(M+H)^+$.

HRMS: Anal. Calcd. for $C_{41}H_{52}N_{12}O_4$: 776.4234; found: 777.4305 $(M+H)^+$.

Example cj-16 and cj-17



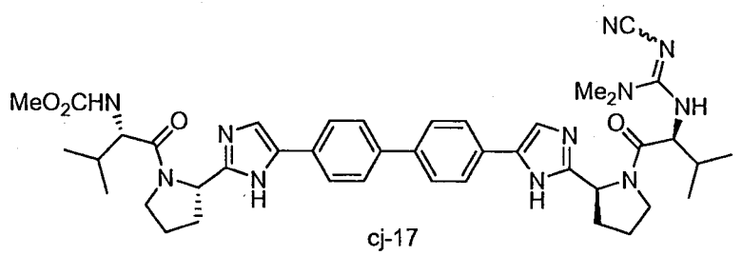
Preparation of methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(5-amino-1,2,4-oxadiazol-3-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (cj-16)



A solution of methyl (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-((*Z/E*)-(cyanoimino)(phenoxy)methylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-14) (0.120 g, 0.205 mmol) and hydroxylamine hydrochloride (0.0213 g, 0.307 mmol) in iPrOH (5 mL) was heated at 75°C for 3 h. A second portion of hydroxylamine hydrochloride (0.0213 g, 0.307 mmol) was added and heating continued for 7 h. The volatiles were then removed *in vacuo* and the residue was purified by prep HPLC (Luna 5u C18/MeCN-H_2O-NH_4OAc) to give a foam which was further purified by flash chromatography (SiO_2/5% MeOH-CH_2Cl_2). The resulting colorless wax was lyophilized from CH_3CN-H_2O to give the title compound (0.0344 g, 22%) as a colorless solid.

^{1}HNMR (400 MHz, DMSO-d_6) δ 12.18 – 12.22 (m, 1H), 11.80 (s, 1H), 11.75 (s, 1h), 8.03 – 8.06 (m, 1H), 7.77 (app d, J = 8.1 Hz, 2H), 7.62 – 7.73 (m, 4H), 7.50 (dd, J = 2.0, 5.5 Hz, 1H), 7.24 – 7.29 (m, 2H), 5.69 (s, 1H), 5.06 – 5.11 (m, 2H), 4.14 (t, J = 8.6 Hz, 1H), 4.06 (unresolved dd, J = 8.0, 8.6Hz, 1H), 3.78 – 3.90 (m, 3H), 3.53 (s, 3H), 3.01 (br s, 2H), 2.10 – 2.19 (m, 3H), 1.90 – 2.04 (m, 5H), 0.81 – 0.96 (m, 12H). LCMS: Anal. Calcd. for $C_{40}H_{49}N_{11}O_5$: 763; found: 764 $(M+H)^+$.

Preparation of methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(cyano(dimethyl)carbamimidoyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (cj-17)



cj-17

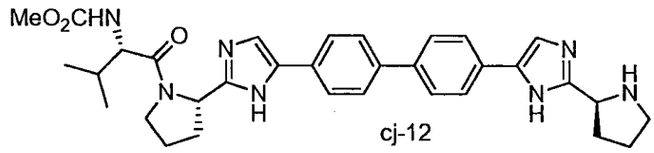
A solution of methyl (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-((*Z/E*)-(cyanoimino)(phenoxy)methylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-14) (0.115 g, 0.198 mmol) and dimethylamine hydrochloride (0.0257 g, 0.315 mmol) in iPrOH (5 mL) was heated at 90°C for 12 h. A second portion of dimethylamine hydrochloride (0.0257 g, 0.315 mmol) was added and heating was continued for 48 h. The volatiles were then removed *in vacuo* and the residue was purified by prep HPLC (Luna 5u C18/MeCN-H_2O-NH_4OAc) and then repurified by flash chromatography (SiO_2/5% MeOH-CH_2Cl_2). The resulting colorless wax was lyophilized from CH_3CN-H_2O to give the title compound (0.0318 g, 21%) as a colorless solid.

^{1}HNMR (400 MHz, DMSO-d_6) δ 12.22 (m, 0.6H), 11.81 (s, 1H), 11.75 (s, 1H), 12.17 – 12.22 (m, 0.5H), 11.99 – 12.04 (m, 0.5H), 11.75-11.81 (m, 1H), 7.76 – 7.79 (m, 3H), 7.62 – 7.73 (m, 5H), 7.50 (t, J = 2.0 Hz, 1H), 7.23 – 7.29 (m, 1H), 6.64 (d, J =

8.1 Hz, 1H), 5.06 – 5.08 (m, 2H), 4.47 (t, J = 8.1 Hz, 2H), 4.06 (unresolved dd, J = 8.0, 8.6 Hz, 1H), 3.84 – 3.90 (m, 2H), 3.76 – 3.82 (m, 3H), 3.53 (s, 3H), 3.00 (s, 6H), 2.11 – 2.20 (m, 3H), 1.90 – 2.04 (m, 5H), 0.97 (d, J = 6.5 Hz, 3H), 0.89 – 0.91 (m, 6H), 0.84 (d, J = 6.5 Hz, 3H).

LCMS: Anal. Calcd. for $C_{42}H_{53}N_{11}O_4$: 775; found: 776 $(M+H)^+$

Preparation of Methyl (*S*)-3-methyl-1-oxo-1-((*S*)-2-(5-(4'-(2-((*S*)-pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)butan-2-ylcarbamate (cj-12)



cj-12

Synthesized from Intermediate-28d and *Cap*-51 as in Example 28e, followed by Boc removal with TFA/CH_2Cl_2 and free base formation with MCX resin.

^{1}HNMR (400 MHz, MeOH-d_4) δ 7.79 – 7.82 (m, 3H), 7.65 – 7.75 (m, 5H), 7.48 (s, 1H), 7.32 (s, 1H), 5.19 (dd, J = 5.5, 5.7 Hz, 1H), 4.75 (t, J = 7.8 Hz, 1H), 4.25 (d, J = 7.3 Hz, 1H), 3.88 – 4.04 (m, 2H), 3.67 (s, 3H), 3.35 – 3.51 (m, 3H), 2.43 – 2.51 (m, 1H), 2.02-2.38 (m, 7H), 0.97 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H).

LCMS: Anal. Calcd. for $C_{33}H_{39}N_7O_3$: 581; found: 582 $(M+H)^+$.

Section OL LC Conditions:

Condition 1: Solvent A: 5% acetonitrile / 95% water / 10mmol ammonium acetate; Solvent B: 95% acetonitrile / 5% water / 10mmol ammonium acetate; Column: Phenomenex GEMINI 5u C18 4.6 x 5.0mm; Wavelength: 220nM; Flow rate: 4 ml / min; 0%B to 100% B over 3 min with a 1 min hold time.

Condition 2: Solvent A: 5% acetonitrile / 95% water / 10mmol ammonium acetate; Solvent B: 95% acetonitrile / 5% water / 10mmol ammonium acetate; Column: Phenomenex GEMINI 5u C18 4.6 x 5.0mm; Wavelength: 220nM; Flow rate: 4 ml / min; 0%B to 100% B over 2 min with a 1 min hold time

Condition 3: Solvent A: 5% acetonitrile / 95% water / 10mmol ammonium acetate; Solvent B: 95% acetonitrile / 5% water / 10mmol ammonium acetate; Column: Phenomenex GEMINI 5u C18 4.6 x 5.0mm; Wavelength: 220nM; Flow rate: 4 ml / min; 0%B to 100% B over 4 min with a 1 min hold time

Condition 4: Solvent A: 10%MeOH / 90% water / 0.1% TFA; Solvent B: 90% MeOH / 10% water / 0.1% TFA; Column: Phenomenex 10u C18 3.0 x 5.0mm; Wavelength: 220nM; Flow rate: 4ml / min; 0%B to 100% B over 4 min with a 1min hold time

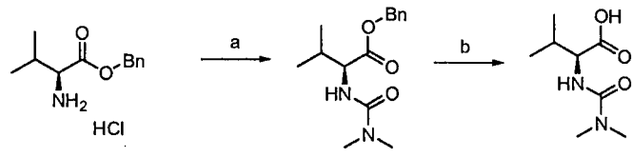
Condition 5: Solvent A: 5% acetonitrile / 95% water / 10mmol ammonium acetate; Solvent B: 95% acetonitrile / 5% water / 10mmol ammonium acetate; Column: Phenomenex GEMINI 5u C18 4.6 x 5.0mm; Wavelength: 220nM; Flow rate: 4 ml / min; 0%B to 100% B over 9 min with a 1 min hold time

Condition 6: Solvent A: 10%MeOH / 90% water / 0.2% H_3PO_4; Solvent B: 90% MeOH / 10% water / 0.2% H_3PO_4; Column: Phenomenex 5u C-18 4.6 x 50mm; Wavelength: 220nM; Flow rate: 1.5ml / min; 0%B to 100% B over 14 min with a 3min hold time

Condition 7: Solvent A: 10%MeOH / 90% water / 0.1% TFA; Solvent B: 90% MeOH / 10% water / 0.1% TFA; Column: Phenomenex 10u C18 3.0 x 5.0mm; Wavelength: 220nM; Flow rate: 4ml / min; 0%B to 100% B over 3 min with a 1min hold time

Condition 8: Solvent A: 10%MeOH / 90% water / 0.1% TFA; Solvent B: 90% MeOH / 10% water / 0.1% TFA; Column: Phenomenex 10u C18 3.0 x 5.0mm; Wavelength: 220nM; Flow rate: 4ml / min; 0%B to 100% B over 2 min with a 1min hold time

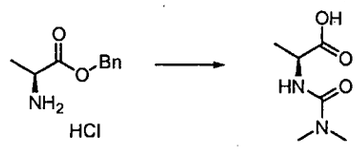
Experimentals Caps:



Intermediate Cap OL-1 Cap OL-2

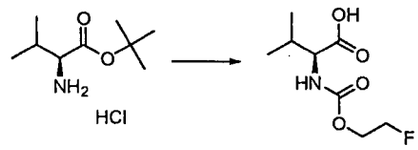
Step a: Dimethylcarbamoyl chloride (0.92 mL, 10 mmol) was added slowly to a solution of (S)-benzyl 2-amino-3-methylbutanoate hydrochloride (2.44 g; 10 mmol) and Hunig's base (3.67 mL, 21 mmol) in THF (50 mL). The resulting white suspension was stirred at room temperature overnight (16 hours) and concentrated 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 Intermediate Cap OL-1 as a 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 Intermediate Cap OL-1 (2.35 g; 8.45 mmol) in 50 ml MeOH 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 OL-2 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 $[M+H]^+$ $C_8H_{17}N_2O_3$: 1898.12; found 189.04.



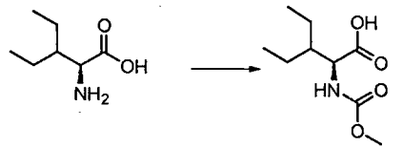
Cap OL-3

Cap OL-3 was prepared from (S)-benzyl 2-aminopropanoate hydrochloride according to the method described for Cap OL-2. ^{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.



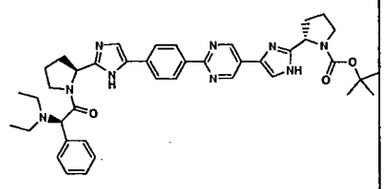
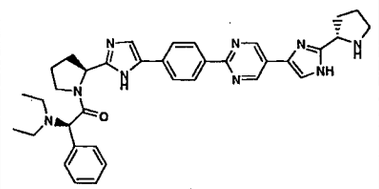
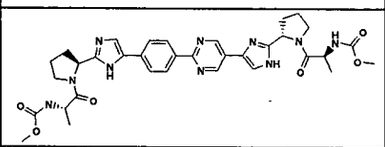
Cap OL-4

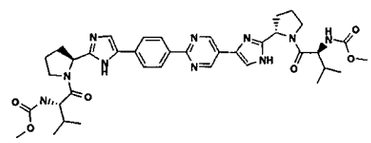
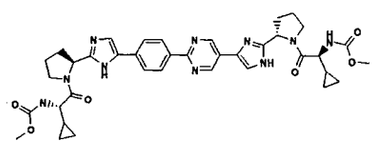
Cap OL-4 was prepared from (S)-tert-butyl 2-amino-3-methylbutanoate hydrochloride and 2-fluoroethyl chloroformate according to the method described for *Cap*-47. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.87 (t, *J*=6.71 Hz, 6H) 1.97-2.10 (m, 1H) 3.83 (dd, *J*=8.39, 5.95 Hz, 1H) 4.14-4.18 (m, 1H) 4.20-4.25 (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)

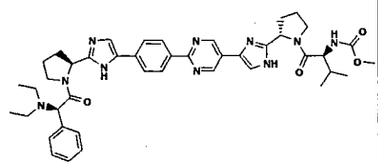
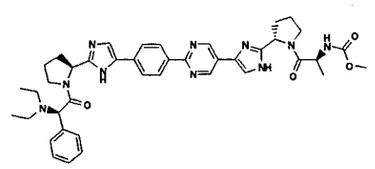


Cap OL-5

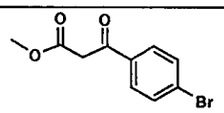
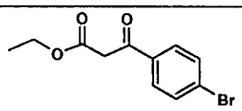
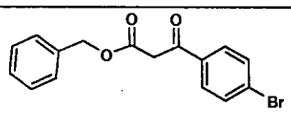
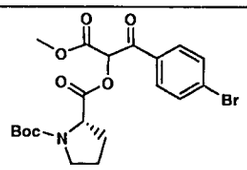
Cap OL-5 was prepared from (S)-diethyl alanine and methyl chloroformate according to the method described for *Cap*-51. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.72-0.89 (m, 6H) 1.15-1.38 (m, 4H) 1.54-1.66 (m, 1H) 3.46-3.63 (m, 3H) 4.09 (dd, *J*=8.85, 5.19 Hz, 1H) 7.24 (d, *J*=8.85 Hz, 1H) 12.55 (s, 1H). LC (Cond. 2): RT = 0.66 min; MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{18}NO_4$:204.12; found 204.02.

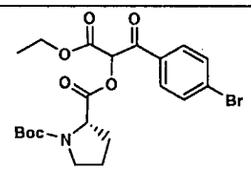
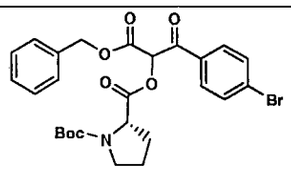
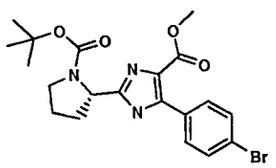
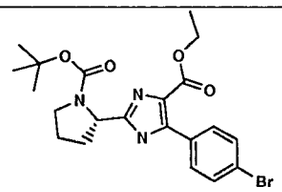
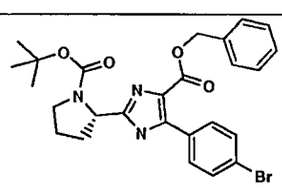
Example Number	*Compound Name*	*Heterocycles with New Caps*	*Analytical Data (Cond 1: 3 min gradient, 4 min run; Cond 2: 2 min gradient, 3 min run)*
D71	tert-butyl (2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from 152i-1 (in lieu of 148e) and *Cap*-2 using experimental conditions outlined in Example 148	t_R = 1.82 min, (97.7%), (Cond 1) LRMS: Anal. Calcd. for $C_{41}H_{50}N_9O_3$ 716.40; found: 716.44 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{50}N_9O_3$ 716.4037; found: 716.4056 $(M+H)^+$.
D72	(1R)-N,N-diethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4-(5-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine	 Prepared from entry 71 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-l.	t_R = 1.56 min, (~95.3%, has shoulder), (Cond 1) LRMS: Anal. Calcd. for $C_{36}H_{42}N_9O$ 616.35; found: 616.37 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{42}N_9O$ 616.3512; found: 616.3540 $(M+H)^+$.
D73	methyl ((1S)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-(N-		t_R = 1.52 min, (96.2%), (Cond 1)

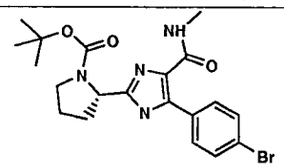
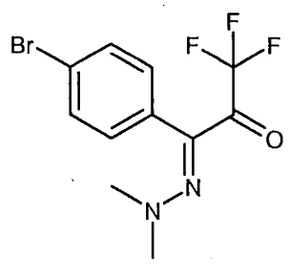
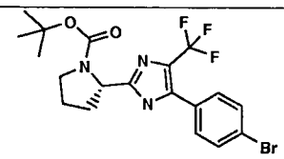
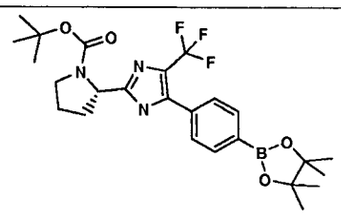
	(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	Prepared from 152h-1 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148	LRMS: Anal. Calcd. for $C_{34}H_{41}N_{10}O_6$ 685.32; found: 685.21 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{34}H_{41}N_{10}O_6$ 685.3211; found: 685.3196 $(M+H)^+$.
D74	methyl ((1S)-1-(((2S)-2-(5-(2-(4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from 152h-1 (in lieu of 148e) and *Cap*-51 using experimental conditions outlined in Example 148	t_R = 2.09 min, (95%), (Cond 1) LRMS: Anal. Calcd. for $C_{38}H_{49}N_{10}O_6$ 741.38; found: 741.26 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{49}N_{10}O_6$ 741.3837; found: 741.3824 $(M+H)^+$.
D75	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(2-(4-(2-((2S)-1-((2S)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-	 Prepared from 152h-1 (in lieu of 148e) and *Cap*-54b using experimental conditions outlined in Example 148	t_R = 1.98 min, (95%), (Cond 1) LRMS: Anal. Calcd. for $C_{38}H_{45}N_{10}O_6$ 737.35; found: 737.22 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{45}N_{10}O_6$ 737.3524; found:

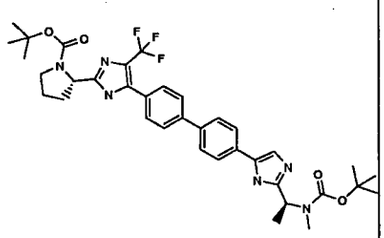
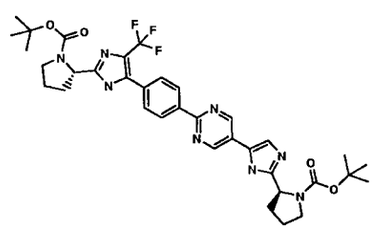
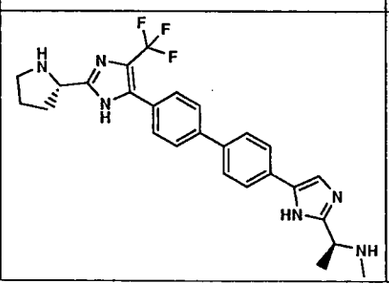
	imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		737.3555 $(M+H)^+$.
D76	methyl ((1S)-1-(((2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry D72 (in lieu of 148e) and *Cap*-51 using experimental conditions outlined in Example 148	t_R = 1.69 min, (95%), (Cond 1) LRMS: Anal. Calcd. for $C_{43}H_{53}N_{10}O_4$ 773.43; found: 773.30 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{43}H_{53}N_{10}O_4$ 773.4251; found: 773.4280 $(M+H)^+$.
D77	methyl ((1S)-2-((2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 Prepared from entry D72 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148	t_R = 1.81 min, (97.5%), (Cond 1) LRMS: Anal. Calcd. for $C_{41}H_{49}N_{10}O_4$ 745.39; found: 745.27 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{49}N_{10}O_4$ 745.3938; found: 745.3939 $(M+H)^+$.

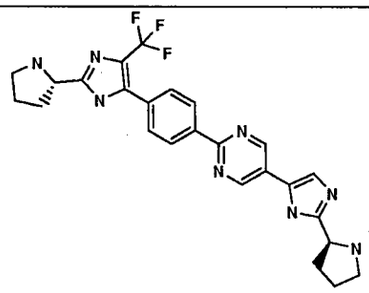
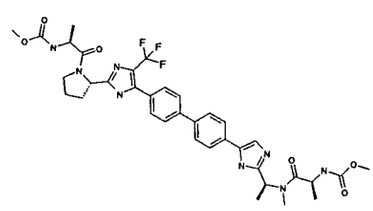
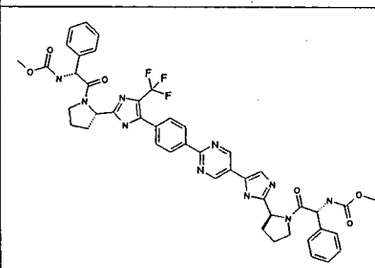
Section J

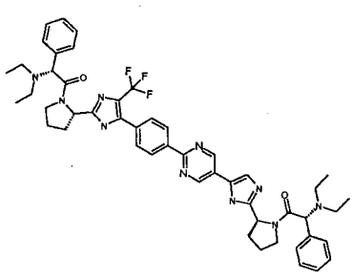
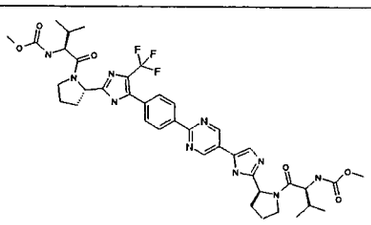
Example Number	*Compound Name*	*Structure*	*Analytical Data*
J.1a		 Prepared from 4-bromoacetophenone and dimethylcarbonate from Bioorg.Med.Chem.Lett (2001)11, 641	t_R = 1.7 min, (Cond 2); LCMS: $C_{10}H_9BrO_3$ found: 257 $(M+H)^+$.
J.1b		 Prepared from 4-bromoacetophenone and diethylcarbonate from Bioorg.Med.Chem.Lett (2001)11, 641.	t_R = 1.9 min, (Cond 2); LCMS: $C_{11}H_{11}BrO_3$ found: 271 $(M+H)^+$.
J.1c		 Prepared from 4-bromoacetophenone and dibenzylcarbonate from Bioorg.Med.Chem.Lett (2001)11, 641.	t_R = 2.1min, (Cond 2); LCMS: $C_{16}H_{13}BrO_3$ found: 332 $(M+H)^+$.
J1		 Prepared from entry J.1a (in lieu of J.1b) and proline using experimental conditions in Example J2.	t_R = 2.2min, (Cond 2); LCMS: $C_{20}H_{24}BrNO_7$ found: 470 $(M+H)^+$.

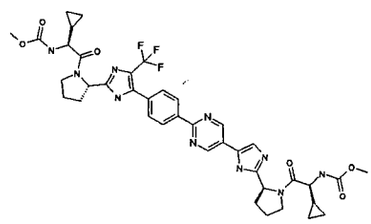
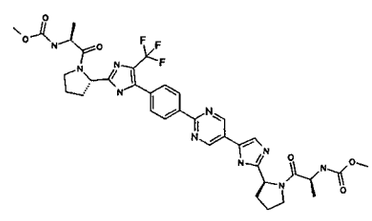
J2		 Prepared from entry J.1b and proline using experimental conditions in Example J2.	t_R = 2.2min, (Cond 2); LCMS: $C_{21}H_{26}BrNO_7$ found: 484 $(M+H)^+$.
J3		 Prepared from entry J.1c (in lieu of J.1b) and proline using experimental conditions in Example J2.	t_R = 2.3min, (Cond 2); LCMS: $C_{26}H_{28}BrNO_7$ found: 546 $(M+H)^+$.
J4		 Prepared from entry J.1 and (in lieu of J.2) using experimental conditions in Example J2.	t_R = 1.84 min, (100%) (Cond 2); LRMS: Anal. Calcd. for $C_{20}H_{24}BrN_3O_4$; 450.10; found: 450.13 and 452.13 $(M+H)^+$.
J5		 Prepared from entry J2 using experimental conditions in J5.	t_R = 1.93 min, (99%) (Cond 2); Reported in J5.
J6		 Prepared from entry J3 (in lieu of	t_R = 2.1 min, (93%) (Cond 2); LRMS: Anal. Calcd. for $C_{26}H_{29}BrN_3O_4$

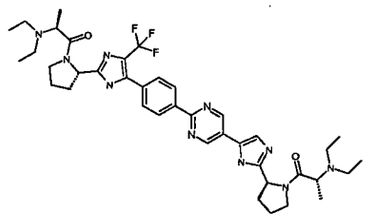
		entry J1) using experimental conditions in J5.	526.13; found: 526.16 and 528.16 $(M+H)^+$.
J7		 Prepared from entry J5 using experimental in J7.	t_R = 1.7 min, (100%) (Cond 2); Reported in J7.
J32		 Prepared from 4-bromobenzaldehyde according to procedure described in J.Org.Chem. (1988), 53, 129.	t_R = 1.96 min, (96%) (Cond 2); LRMS: Anal. Calcd. for $C_{11}H_{11}BrF_3N_2O$ 323.00; found: 323.05 and 325.05 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 7.58 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 3.06 (s, 6H).
J32.a		 Prepared from entry J32 using experimental conditions in J32.a	t_R = 2.19 min, (96%) (Cond 2); Reported in J32.a
J32.b		 Prepared from entry J32.a (in lieu	t_R = 2.3 min, (73%) (Cond 2); LCMS: $C_{25}H_{34}BF_3N_3O_4$ found: 508 $(M+H)^+$.

		of 1b) using experimental conditions outlined in Example 1 step c.	
J33.a	tert-butyl (2S)-2-(5-(4'-(2-((1S)-1-((tert-butoxycarbonyl)(methyl)amino)ethyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry J32.a (in lieu of 152e-1) and 1-8c using experimental conditions outlined in Example 152g-1.	t_R = 1.97 min, (97%) (Cond 2); LRMS: Anal. Calcd. for $C_{36}H_{44}F_3N_6O_4$ 681.34; found: 681.31 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{44}F_3N_6O_4$ 681.3376; found: 681.3383 $(M+H)^+$.
J34.a	tert-butyl (2S)-2-(5-(4-(5-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry J32.b (in lieu of 152e-1) and 152d-1 using experimental conditions outlined in Example 152g-1.	t_R = 1.97 min, (93%) (Cond 2); LRMS: Anal. Calcd. for $C_{35}H_{42}F_3N_8O_4$ 695.33; found: 695.28 $(M+H)^+$.
J35.a			LCMS: $C_{26}H_{28}F_3N_6$ found: 481 $(M+H)^+$.

		Prepared from entry J33.a (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	
J36.a		 Prepared from entry J34.a (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.45 min, (Cond 2); LCMS: $C_{25}H_{26}F_3N_8$ found: 495 $(M+H)^+$.
J42.a	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((1S)-1-((N-(methoxycarbonyl)-L-alanyl)(methyl)amino)ethyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 Prepared from entry J35.a (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148.	t_R = 1.69 min, (100%) (Cond 2); LRMS: Anal. Calcd. for $C_{36}H_{42}F_3N_8O_6$ 739.32; found: 739.31 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{42}F_3N_8O_6$ 739.3179; found: 739.3195 $(M+H)^+$.
J46	methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-		t_R = 1.82 min, (98%) (Cond 2); LRMS: Anal. Calcd. for $C_{45}H_{44}F_3N_{10}O_6$ 877.34; found:

	pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	Prepared from entry J34.a (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148	877.29 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{45}H_{44}F_3N_{10}O_6$ 877.3397; found: 877.3403 $(M+H)^+$.
J47	(1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine	 Prepared from entry J34.a (in lieu of 148e) and *Cap*-2 using experimental conditions outlined in Example 148	t_R = 1.58 min, (97%) (Cond 2); LRMS: Anal. Calcd. for $C_{49}H_{56}F_3N_{10}O_2$ 873.44; found: 873.40 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{49}H_{56}F_3N_{10}O_2$ 873.4540; found: 873.4536 $(M+H)^+$.
J48	methyl ((1S)-1-(((2S)-2-(5-(2-(4-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-4-(trifluoromethyl)-1H-imidazol-5-yl)phenyl)-5-	 Prepared from entry J34.a (in lieu of 148e) and *Cap*-51 using experimental conditions outlined in Example 148	t_R = 1.85 min, (99%) (Cond 2); LRMS: Anal. Calcd. for $C_{39}H_{48}F_3N_{10}O_6$ 809.37; found: 809.37 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{39}H_{48}F_3N_{10}O_6$

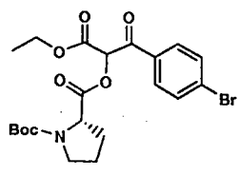
	pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		809.3710; found: 809.3683 $(M+H)^+$.
J49	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2S)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 Prepared from entry J34.a (in lieu of 148e) and *Cap*-54b using experimental conditions outlined in Example 148	t_R = 1.75 min, (100%) (Cond 2); LRMS: Anal. Calcd. for $C_{39}H_{44}F_3N_{10}O_6$ 805.34; found: 805.34 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{39}H_{44}F_3N_{10}O_6$ 805.3397; found: 805.3384 $(M+H)^+$.
J50	methyl ((1S)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 Prepared from entry J34.a (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148	t_R = 1.61 min, (94%) (Cond 2); LRMS: Anal. Calcd. for $C_{35}H_{40}F_3N_{10}O_6$ 753.31; found: 753.31 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{35}H_{40}F_3N_{10}O_6$ 753.3084; found: 753.3099 $(M+H)^+$.

J51	(2R)-1-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-(diethylamino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-1-oxo-2-propanamine	 Prepared from entry J34.a (in lieu of 148e) and *Cap*-70b using experimental conditions outlined in Example 148	t_R = 1.41 min, (92%) (Cond 2); LRMS: Anal. Calcd. for $C_{39}H_{52}F_3N_{10}O_2$ 749.42; found: 749.37 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{39}H_{52}F_3N_{10}O_2$ 749.4227; found: 749.4223 $(M+H)^+$.

Cond 1: LCMS conditions: Phenomenex-Luna 4.6 x 50 mm S10, 0 to 100%B over 3 min, 4 min stop time, 4 mL/min, 220nm, A: 10% MeOH-90%H2O - 0.1% TFA; B: 90% MeOH-10%H2O-0.1% TFA

Cond 2: LCMS conditions: Phenomenex-Luna 4.6 x 50 mm S10, 0 to 100%B over 2 min, 3 min stop time, 4 mL/min, 220nm, A: 10% MeOH-90%H2O - 0.1% TFA; B: 90% MeOH-10%H2O-0.1% TFA

Example J2. (2S)-2-(1-(4-bromophenyl)-3-ethoxy-1,3-dioxopropan-2-yl) 1-tert-butyl pyrrolidine-1,2-dicarboxylate



J2

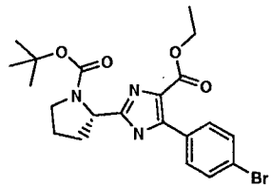
The ethyl 3-(4-bromophenyl)-3-oxopropanoate (15 g, 55 mmol) was dissolved in CH_2Cl_2 (600 mL) and freshly recrystallized NBS (9.8 g, 55 mmol) was added and the solution stirred 18 hr. The reaction mixture was washed with $NaHCO_3$ solution, brine, and dried ($MgSO_4$), filtered, and concentrated to give a residue which was not

purified. Ethyl 2-bromo-3-(4-bromophenyl)-3-oxopropanoate (16.5 g, 48 mmol) and N-Boc-L-proline (10 g, 48 mmol) were taken up in acetonitrile (450 mL) and Hunig's base (16 mL, 95 mmol) was added and the solution stirred 18 hr. The solvent was removed by rotorary evaporation and the residue taken up in ethyl acetate, washed with 0.1 N HCl, and brine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.95 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 6.68-6.65 (m, 1H), 4.39-4.30 (m, 1H), 4.21-4.12 (m, 2H), 2.27-2.21 (m, 1H), 2.0-1.95 (m, 1H), 1.90-1.76 (m, 2H), 1.39 (s, 2H), 1.31 (s, 9H), 1.11 (t, J = 7.3Hz, 3H).

LRMS: Anal. Calcd. for $C_{21}H_{26}BrNO_7$ 484.09; found: 410.08 $(M+H)^+$.

Example J5.

(S)-ethyl 5-(4-bromophenyl)-2-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazole-4-carboxylate

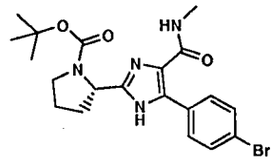


J5

A 1L pressure bottle was charged with (2S)-2-(1-(4-bromophenyl)-3-ethoxy-1,3-dioxopropan-2-yl) 1-tert-butyl pyrrolidine-1,2-dicarboxylate J2 (7 g, 35 mmol) and 11 g of NH_4OAc in 125 mL of Xylene, and the reaction was heated at 140°C for 3.5 hr. After being cooled, the solution was partition between ethyl actate and water. The organic layer was concentrated and the resultant residue applied to a Biotage 40 m silica gel cartridge and eluted by 20 -100% gradient, ethyl acetate/ Hex to give 3g (45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.75 (br. s, 7.82), (br. s, 2H), 7.50 (d, J = 8.4 Hz, 2H), 4.96-4.92 (m, 1H), 4.23 (q, J = 6.6 Hz, 2H), 3.68-3.50 (m, 1H), 3.40-3.32 (m, 1H), 2.19-2.15 (m, 1H), 1.99-1.89 (m, 3H), 1.48/1.13 (s, 9H), 1.23 (t, J = 7.3Hz, 3H). LRMS: Anal. Calcd. for $C_{21}H_{26}BrN_3O_4$ 464.12; found: 464.15 and 466.15 $(M+H)^+$.

Example J7.

(S)-tert-butyl 2-(5-(4-bromophenyl)-4-(methylcarbamoyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate



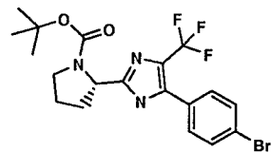
J7

(S)-ethyl 5-(4-bromophenyl)-2-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazole-4-carboxylate (1g, 2.1 mmol) was dissolved in 2M methylamine in MeOH (35 mL) and heated in a pressure vessel at 70°C for 48 h. The reaction mixture was concentrated and the residue applied to a Biotage 25 m silica gel cartridge and eluted by 10 -100% gradient, ethyl acetate/ Hex to give 556 mg (57%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.5 (br.s, 1H), 7.86-7.82 (m, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.7 Hz, 2H), 4.83-4.70 (m, 1H), 3.69-3.52 (br.s, 1H), 3.42-3.32 (m, 1H), 2.71 (d, 4.8 Hz, 3H), 2.30-1.78 (m, 4H), 1.19-1.14 (m, 9H).

LRMS: Anal. Calcd. for $C_{20}H_{26}BrN_4O_3$ 449.12; found: 449.15 and 451.14 $(M+H)^+$.

Example J32.a.

(S)-tert-butyl 2-(5-(4-bromophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

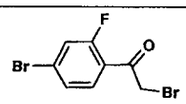
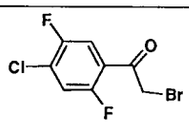
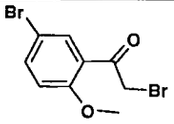


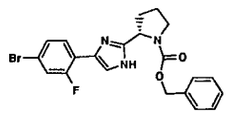
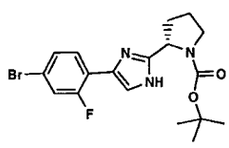
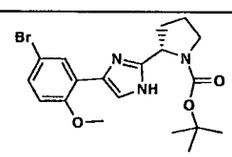
J32.a

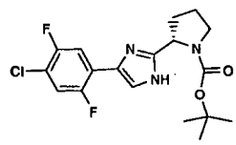
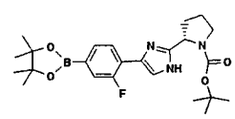
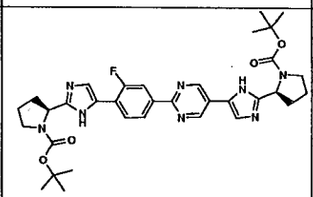
3-(4-bromophenyl)-3-(2,2-dimethylhydrazono)-1,1,1-trifluoropropan-2-one (2.0g, 6.2 mmol) was suspended in 5N sulfuric acid (60 mL) and heated at 45°C for 6 h. The temperature was raised to 85°C for 2 h, and upon cooling a precipitate formed. This material which was isolated by filtration to give 1-(4-bromophenyl)-3,3,3-trifluoropropane-1,2-dione 1.6g (92%) as a yellow solid. The dione (1.6g, 5.7 mmol) was taken up in methanol (30 mL), N-(tert-butoxycarbonyl)-L-prolinal (1g, 5.0 mmol) was added, followed by addition of 28% ammonium hydroxide solution (10

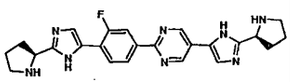
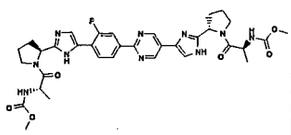
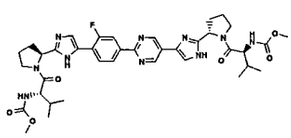
mL). The reaction was stirred at room temperature for 18 h, poured onto dichloromethane (200 mL), washed with water and dried with $MgSO_4$. Filtration, concentration and application to a 40 M Biotage cartridge, gradient elution with 5% - 30% ethyl acetate/Hexanes, gave J32.a 1.3g (50%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.88 (br.s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 4.84-4.70 (m, 1H), 3.57-3.49 (m, 1H), 3.39-3.29 (m, 1H), 2.31-2.20 (m, 1H), 1.98-1.78 (m, 3H), 1.39/1.13 (m, 9H). LRMS: Anal. Calcd. for $C_{19}H_{20}BrF_3N_3O_2$ 458.07; found: 458.06 and 460.06 $(M-H)^-$. HRMS: Anal. Calcd. for $C_{19}H_{22}BrF_3N_3O_2$ 460.0847; found: 460.0866 and 462.0840 $(M+H)^+$.

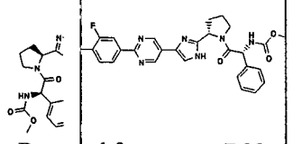
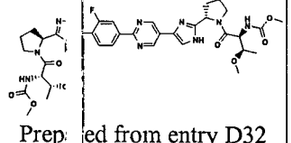
Section D

Entry	*Compound Name*	*Structure*	***Data*
D1		 Prepared from 1-(4-bromo-2-fluorophenyl)ethanone (Vendor: Marshalton 50043) using bromination conditions outlined in D5.	t_R = 2.65 min, (86.7%) LCMS: Anal. Calcd. for $C_8H_{15}BrFO$ 296.88; found: 296.91 $(M+H)^+$.
D2		 Prepared from 1-(4-chloro-2,5-difluorophenyl)ethanone (Vendor: Oakwood products, 001626) using bromination conditions outlined in D5.	t_R = 2.66 min, (80%) LCMS: Anal. Calcd. for $C_8H_4BrClFO$ 270.92; found: ND $(M+H)^+$.
D3			t_R = 2.57 min, (95%) LCMS: Anal. Calcd. for

		Prepared from 2-bromo-1-(5-bromo-2-methoxyphenyl)ethanone (Andersh et al., Synth. Comm. 2000, 30 (12), 2091-98) using bromination conditions outlined in D5.	$C_9H_9BrO_2$ 228.99; found: 229.00 $(M+H)^+$.
D4		 Prepared from entry D1 and CBz-L-proline (in lieu of Boc-L-proline) using experimental conditions outlined in D5.	t_R = 2.38 min, (95.0%) LRMS: Anal. Calcd. for $C_{19}H_{20}{}^{79}BrFN_3O_2$ 444.07; found: 444.04 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{19}H_{20}{}^{79}BrFN_3O_2$ 444.0721; found: 444.0736 $(M+H)^+$
D5		 Experimental conditions in D5	t_R = 2.27min, (95%) LRMS: Anal. Calcd. for $C_{18}H_{22}BrFN_3O_2$ 410.09 and 412.08; found: 410.08 and 412.08 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{18}H_{22}{}^{79}BrFN_3O_2$ 410.0879; found: 410.0893 $(M+H)^+$.
D6		 Prepared from entry D3 (in lieu of entry D1) using experimental	t_R = 2.26 min, (95%) LRMS: Anal. Calcd. for $C_{19}H_{25}BrN_3O_3$ 422.11 and 424.11; found: 422.10 and 424.10 $(M+H)^+$.

		conditions outlined in D5.	HRMS: Anal. Calcd. for $C_{19}H_{25}{}^{79}BrN_3O_3$ 422.1079; found: 422.1089 $(M+H)^+$.
D7		 Prepared from entry D2 (in lieu of entry D1) using experimental conditions outlined in enclosed experiment.	t_R = 2.28 min, (95%) LRMS: Anal. Calcd. for $C_{18}H_{21}ClF_2N_3O_2$ 384.13; found: 384.13 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{18}H_{21}ClF_2N_3O_2$ 384.1290; found: 384.1301 $(M+H)^+$.
D8		 Prepared from entry D5 (in lieu of 1b) using experimental conditions outlined in Example 1, Step c.	t_R = 2.62 min, (~50%) and 1.95 min (~50%, boronic acid) LRMS: Anal. Calcd. for $C_{24}H_{34}BFN_3O_4$ 458.26; found: 458.23 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{24}H_{34}BFN_3O_4$ 458.2626; found: 458.2610 $(M+H)^+$.
D13	tert-butyl (2S)-2-(5-(2-(4-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-3-fluorophenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-	 Prepared from entry D8 (in lieu of 1c) and 152b-1 using experimental	t_R = 2.27min, (95%) LRMS: Anal. Calcd. for $C_{34}H_{42}FN_8O_4$ 645.33; found: 645.34 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{34}H_{42}FN_8O_4$

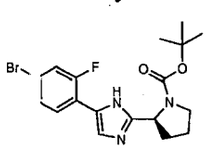
	pyrrolidinecarboxylate	conditions outlined in Example 152g-1.	645.3313; found: 645.3323 $(M+H)^+$.
D32	2-(3-fluoro-4-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)pyrimidine	 Prepared from entry D13 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.63 min, (95%) LRMS: Anal. Calcd. for $C_{24}H_{26}FN_8$ 445.23; found: 445.23 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{24}H_{26}FN_8$ 445.2264; found: 445.2268 $(M+H)^+$.
D67	methyl ((1S)-2-((2S)-2-(5-(2-fluoro-4-(5-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 Prepared from entry D32 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148.	t_R = 1.58 min, (91.1%) LRMS: Anal. Calcd. for $C_{34}H_{40}FN_{10}O_6$ 703.31; found: 703.27 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{34}H_{40}FN_{10}O_6$ 703.3116; found: 703.3101 $(M+H)^+$.
D68	methyl ((1S)-1-(((2S)-2-(5-(2-fluoro-4-(5-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-	 Prepared from entry D32 (in lieu of 148e) and *Cap*-51 using experimental conditions outlined in Example 148.	t_R = 1.95 min, (99.3%) LRMS: Anal. Calcd. for $C_{38}H_{48}FN_{10}O_6$ 759.37; found: 759.30 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{48}FN_{10}O_6$ 759.3742; found: 759.3715 $(M+H)^+$.

	1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate			
D69	methyl ((1R)-2-((2S)-2-(5-(2-(3-fluoro-4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		Prep (in lie 4 u con | ed from entry D32 of 148e) and *Cap*-ng experimental itions outlined in xample 148.	t_R = 2.05 min, (99.3%) LRMS: Anal. Calcd. for $C_{44}H_{44}FN_{10}O_6$ 827.34; found: 827.27 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{44}H_{44}FN_{10}O_6$ 827.3429; found: 827.3407 $(M+H)^+$.
D70	methyl ((1S,2R)-1-(((2S)-2-(5-(2-fluoro-4-(5-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate		Prep (in lie 86 u con | ed from entry D32 of 148e) and *Cap*-ing experimental itions outlined in xample 148.	t_R = 1.79 min, (93.0%) LRMS: Anal. Calcd. for $C_{38}H_{48}FN_{10}O_8$ 791.36; found: 791.31 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{48}FN_{10}O_8$ 791.3641; found: 791.3636 $(M+H)^+$.

**LCMS conditions: Phenomenex-Luna 4.6 x 50 mm S10, 0 to 100%B over 3 min, 4 min stop time, 4 mL/min, 220nm, A: 10% MeOH-90%H2O - 0.1% TFA; B: 90% MeOH-10%H2O-0.1% TFA

Example D5.

(S)-tert-butyl 2-(5-(4-bromo-2-fluorophenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate



D5

Bromine (0.54 mL, 10.6 mmol) was added dropwise to a cold (0 °C) solution of 4-bromo-2-fluoroacetophenone (2.30 g, 10.6 mmol) in dioxane (80 mL) and tetrahydrofuran (80 mL). The mixture was stirred for 1h at 0°C and warmed to RT for 15h. The mixture was diluted with ethyl acetate, washed with saturated $NaHCO_3$ solution, 5% sodium thiosulfate solution and brine prior to drying (Na_2SO_4). 2-Bromo-1-(4-bromo-2-fluorophenyl)ethanone (D1) was isolated as a colorless film which solidified upon further concentration under high vacuum. This solid was dissolved into anhydrous acetonitrile (50 mL) and treated with N-Boc-L-proline (2.28 g, 10.6 mmol) and diisopropylethylamine (1.85 mL, 10.6 mmol). After being stirred for 3h at RT, the solvent was removed *in vacuo* and the residue was partitioned into ethyl acetate and water. The organic phase was washed with 0.1N hydrochloric acid, saturated $NaHCO_3$ solution and brine prior to drying (Na_2SO_4), filtration, and concentration. This residue was taken up in xylenes (50 mL) and treated to solid NH_4OAc (4.1 g, 53.0 mmol). The mixture was heated at 140°C for 2 hr in a thick-walled, screw-top flask before it was cooled to ambient temperature, diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution and brine prior to drying (Na_2SO_4) and concentration. Purification of the residue by Biotage™ flash chromatography on silica gel (65M column, preequilibration with 16%B for 1800 mL followed by gradient elution with 16%B to 16%B for 450 mL, 16%B to 50%B for 2199 ml and finally 50%B to 100%B for 2199 mL) afforded title compound (D5) (3.61 g, 83%) as a brownish/caramel-colored oil. A small portion (40 mg) of the title compound was further purified by preparative HPLC (20%B to 100%B over 14 min

where B is 10mM NH_4OAc in 10:90 H_2O/ACN and A is 10 mM NH_4OAc in 95:5 H_2O/CAN using a Phenomenex-Gemini 30 x 100 mm S10 column flowing at 40 mL/min) to afford pure title compound (31.8 mg) as a white solid.

^1H NMR (500 MHz, DMSO-d_6) δ 12.13-11.95 (m, 1H), 7.94 (br s, 1H), 7.54 (d, J = 10.7 Hz, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.36-7.34 (m, 1H), 4.86-4.77 (2m, 1H), 3.54 (m, 1H), 3.38-3.32 (m, 1H), 2.28-2.14 (2m, 1H), 2.05-1.78 (2m, 3H), 1.39 and 1.14 (2s, 9H).

HPLC Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 2.27 min, 95% homogeneity index.

LRMS: Anal. Calcd. for $C_{18}H_{22}BrFN_3O_2$ 410.09 and 412.09; found: 410.08 and 412.08 $(M+H)^+$.

HRMS: Anal. Calcd. for $C_{18}H_{22}BrFN_3O_2$ 410.0879; found: 410.0893 $(M+H)^+$.

Section M: LC Conditions were as follows:

Condition 1

Column	= Phenomenex-Luna 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
Slovent A	= 0.1% TFA in 10% methanol/90%H_2O
Solvent B	= 0.1% TFA in 90% methanol/10% H_2O

Condition 2

Column	= Phenomenex-Luna 4.6X50 mm S10
Start %B	= 0
Final %B	= 100
Gradient time	= 2 min
Stop time	= 3 min
Flow Rate	= 5 mL/min

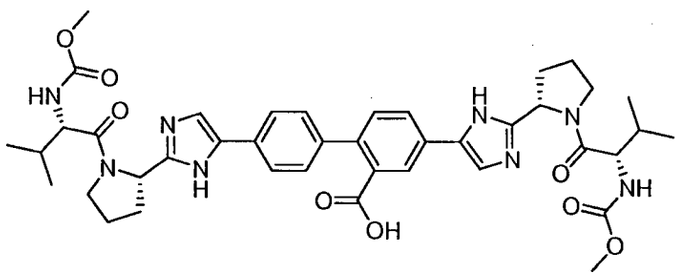
Wavelength = 220 nm
Slovent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition 3
Column = HPLC 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
Slovent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

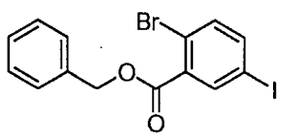
Condition M1
Column: Luna 4.6X 50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 3 min
Stop time = 4 min
Flow rate = 4 mL/min
Solvent A: = 95% H_20: 5% CH_3CN, 10 mm Ammonium acetate
Solvent B: = 5% H_2O : 95% CH_3CN; 10 mm Ammonium acetate

Example M114

4,4'-bis(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-biphenylcarboxylic acid

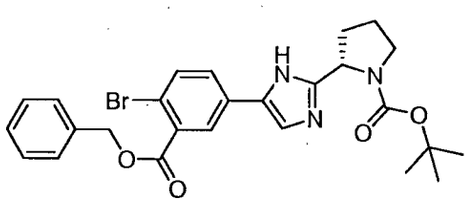


Example M114, Step a



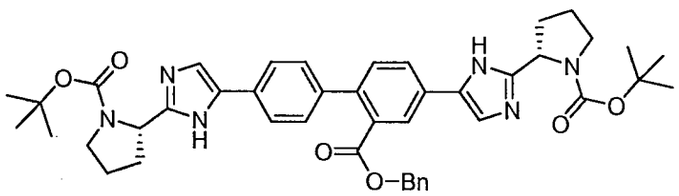
DMF (20 mL) was added to mixture of $KHCO_3$ (1.84g, 18.4 mmol) and 2-bromo-5-iodobenzoic acid (4.99 g, 15.3 mmol) and the resulting mixture was stirred for 15 min. Benzyl bromide (2.4 mL, 20.2 mmol) was added drop-wise over 5 min and stirring was continued at ambient condition for ~20 hr. Most of the volatile component was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 (50 mL) and water (50 mL), and the organic layer was washed with water (50 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting crude material was purified with flash chromatography (7% EtOAc/hexanes) to afford ester M114a as a colorless viscous oil (6.01 g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 8.07 (d, J = 2.0, 1H), 7.81 (dd, J = 8.4, 2.1, 1H), 7.53 (d, J = 8.4, 1H), 7.48 (m, 2H), 7.43-7.34 (m, 3H), 5.34 (s, 2H). LC (Cond. 1): RT = 2.1 min; LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{14}H_{10}BrINaO_2$: 438.88; found 438.83.

Example M114, Step b-d



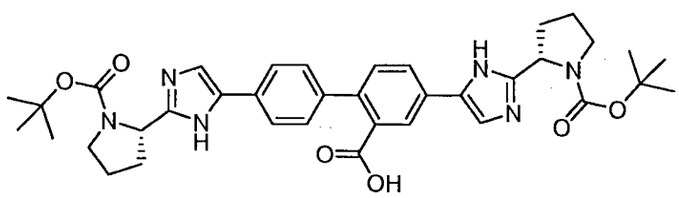
Ester M114a was elaborated to ester M114d by employing a three step protocol employed in the synthesis of bromide 121c from 1-bromo-4-iodo-2-methylbenzene. M114d: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.04/11.97 (br s, 1H), 8.12 (d, *J* = 2.0, 0.92H), 7.99 (app br s, 0.08H), 7.81 (dd, *J* = 8.3, 2.0, 0.92H), 7.74-7.62 (m, 2.08H), 7.50 (app br d, *J* = 7.0, 2H), 7.44-7.35 (m, 3H), 5.38 (s, 2H), 4.79 (m, 1H), 3.52 (app br s, 1H), 3.36 (m, 1H), 2.24-1.79 (m, 4H), 1.39/5.11 (two s, 9H). LC (Cond. 1): RT = 1.66 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{29}BrN_3O_4$: 526.13; found 526.16.

Example M114, Step e



Ester M114e was prepared from bromide M114d and boronate 1c according to the preparation of dimer 1d. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.18/12.00/11.91/11.83 (four br s, 2H), 8.11-7.03 (m, 14H), 5.10 (s, 2H), 4.85-4.78 (m, 2H), 3.55 (app br s, 2H), 3.37 (m, 2H), 2.29-1.80 (m, 8H), 1.41/1.16 (two s, 18H). LC (Cond. 1): RT = 1.54 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{51}N_6O_6$: 759.39; found 759.63.

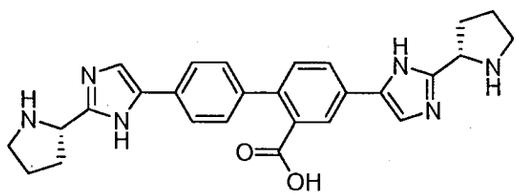
Example M114, Step f



A mixture of benzyl ester M114e (1.005 g, 1.325 mmol) and 10% Pd/C (236 mg) in MeOH (20 mL) was stirred under a balloon of H_2 for 5 hr. The reaction mixture was then treated with a 1:1 mixture of MeOH and CH_2Cl_2, filtered through a pad of diatomaceous earth (Celite®-521), and the filtrate was rotervaped to afford acid M114f (840 mg), contaminated with Ph_3PO which was a carryover from the Suzuki coupling step. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ

12.17/11.98/11.89/11.81 (four app br s, 2H), 8.04-7.31 (m, 9H), 4.85-4.78 (m, 2H), 3.55 (app br s, 2H), ~3.37 (m, 2H, overlaped with water signal) 2.27-1.84 (m, 8H), 1.41/1.16 (two s, 18H). LC (Cond. 1): RT = 1.37 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{45}N_6O_6$: 669.34; found 669.53.

Example M114, Step g



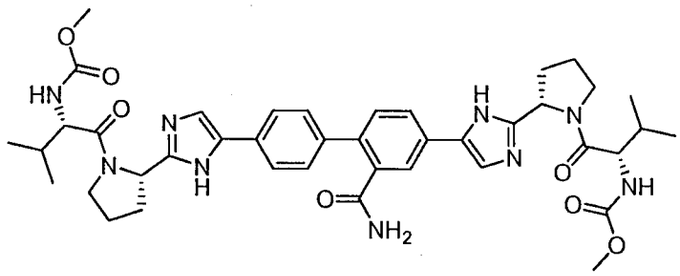
4N HCl/dioxane (8.0 mL) and CH_2Cl_2 (2.0 mL) were sequentially added to carbamate M114f (417 mg, 0.623 mmol), the mixture was vigorously stirred 5.5 hr, and then the volatile component was removed *in vacuo* to afford the HCl (.4x) salt of pyrrolidine M114g (487 mg), contaminated with Ph_3PO impurity. ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz) after D_2O exchange: δ 8.23 (d, J = 1.7, 1H), 8.09-8.04 (m, 3H), 7.92 (d, J = 8.3, 2H), 7.53 (d, J = 8.1, 1H), 7.48 (d, J = 8.3, 2H), 5.00 (app br t, J = 8.3, 1H), 4.90 (app br t, J = 8.4, 1H), 3.6-3.3 (m, 4H), 2.5-1.99 (m, 8H). LC (Cond. 1): RT = 0.92 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{29}N_6O_2$: 469.24; found 469.31.

Example M114

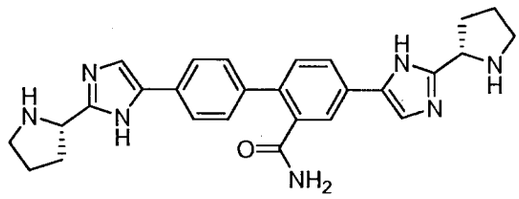
HATU (79.9 mg, 0.21 mmol) was added to a DMF (3.0 mL) solution of pyrrolidine M114g.4HCl (80 mg, 0.13 mmol), *Cap*-51 (92.4 mg, 0.527 mmol) and *i*-Pr_2EtN (160 µL, 0.919 mmol), and the reaction mixture was stirred at ambient condition for 2 hr. The volatile component was removed *in vacuo* and the residue was purified with a combination of MCX (MeOH wash; 2.0 M NH_3/MeOH elution) and a reverse phase HPLC ($CH_3CN/H_2O/$ NH_4OAc) to afford the acetic acid salt of Example M114. LC (Cond. 1): RT = 1.20 min; >98 homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{51}N_8O_8$: 783.38; found 783.34. HRMS Calcd. for $[M+H]^+$ $C_{41}H_{51}N_8O_8$: 783.3830; found 783.3793.

Example M118

methyl ((1S)-1-(((2S)-2-(5-(2'-carbamoyl-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate



Example M118, Step a



Et_3N (300 μL, 2.15 mmol) was added to a mixture of acid M114f (198.3 mg, 0.297 mmol), HOBt (94.2 mg, 0.697 mmol), EDCI (0.66 mmol), NH_4Cl (101 mg, 1.89 mmol) in DMF (8.0 mL) and stirred for 17 hr at ambient condition. The reaction mixture was filtered through 0.45 μm filter, the volatile component was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and water. The organic layer was concentrated and the resulting crude material was purified with a reverse phase HPLC ($MeOH/H_2O$/TFA).

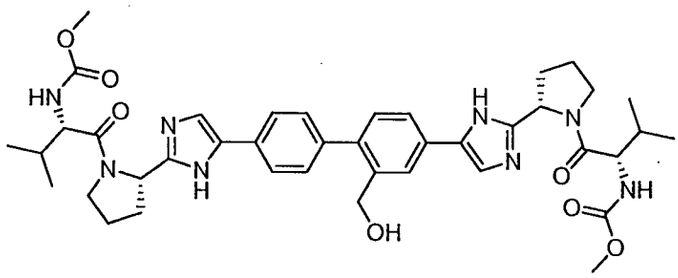
The above product was treated with 25% TFA/CH_2Cl_2 (4.0 mL) and the reaction mixture was stirred for 2.5 hr at ambient condition. The volatile component was removed *in vacuo* and the residue was free-based (MCX; MeOH wash; 2.0 M NH_3/MeOH elution) to afford amide M118a (67.2 mg). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 11.83 (br s, 2H), 7.81-7.80 (m, 2H), 7.73 (d, *J* = 8.3, 2H), 7.65 (br s, 1H), 7.52 (br S, 1H), 7.44 (br s, 1H), 7.41 (d, *J* = 8.3, 2H), 7.36 (d, *J* = 8.3, 1H), 7.31 (br s, 1H), 4.16 (app t, *J* = 7.2, 2H), 3.00-2.94 (m, 2H), 2.88-2.82 (m, 2H), 2.10-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.83-1.66 (m, 4H). LC (Cond. 1): RT = 0.89 min; >95 homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{30}N_7O$: 468.25; found 468.24.

Example M118

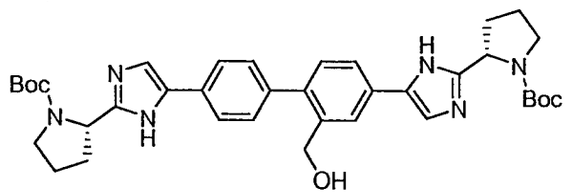
The TFA salt of Example M118 was prepared from intermediate M118a and *Cap*-51 according to the procedure described for Example 1. LC (Cond. 1): RT = 1.16 min; 97% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{52}N_9O_7$: 782.40; found 782.40. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{52}N_9O_7$: 782.3990; found 782.3979.

Example M119

methyl ((1S)-1-(((2S)-2-(5-(2-(hydroxymethyl)-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate



Example M119, step a



DIBAL-H (8.0 mL of 1.0 M/CH_2Cl_2, 8.0 mmol) was added drop-wise to an ice-water cooled CH_2Cl_2 (20 mL) solution of benzyl ester M114e (1.216 g, 1.60 mmol), and the reaction mixture was stirred for 1 hr and an additional DIBAL-H (0.5 mL of 1.0 M/CH_2Cl_2, 0.5 mmol) was added and stirring was continued for ~2.5 hr. The reaction was quenched with excess saturated NH_4Cl solution and the mixture was diluted with water and extracted with CH_2Cl_2 (3x). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified with a Biotage (100 g silica gel; 2-6% MeOH/EtOAc) to afford alcohol M119a as an off-white foam (610 mg). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.23 (br s, 0.19 H), 12.17 (br s, 0.19H), 11.89 (br s, 0.81H), 11.82 (br s,

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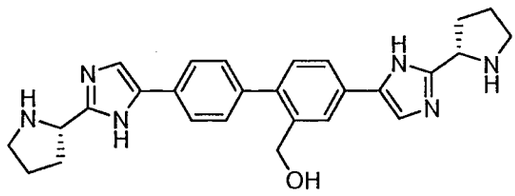
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TOMO: 2/3

0.81H), 7.97 (s, 0.81H), 7.84 (s, 0.19H), 7.78 (d, J = 8.1, 1.62H), 7.69-7.20 (m, 6.38H), 5.21-5.15 (m, 1H), 4.86-4.78 (m, 2H), 4.49-4.45 (m, 2H), ~3.54 (m, 2H), 3.40-3.34 (m, 2H), 2.30-1.80 (m, 8H), 1.41/1.17 (two s, 18H). LC (Cond. 1): RT = 1.36 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{47}N_6O_5$: 655.36; found 655.34.

Example M119, Step b



25% TFA/CH_2Cl_2 (3.0 mL) was added to carbamate M119a (105 mg, 0.160 mmol) and the mixture was stirred at ambient condition for 4.5 hr. The volatile component was removed *in vacuo* and the residue was free-based (MCX; MeOH wash; 2.0 M NH3/MeOH elution) to afford pyrrolidine M119b, contaminated with its trifluoroacetylated derivative of unknown regiochemistry. The sample was dissolved in MeOH (1.5 mL) and treated with 1.0 M NaOH/H_2O (300 μL, 0.3 mmol) and the mixture was stirred for 2.75 hr. It was then directly submitted to MCX purification (MeOH wash; 2.0 M NH_3/MeOH elution) to afford M119b as a film of white solid (63.8 mg). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 11.82 (br s, 2H), 7.96 (s, 1H), 7.77 (d, J = 8.0, 2H), 7.66 (d, J= 8.0, 1H), 7.46 (br s, 1H), 7.42 (br s, 1H), 7.36 (d, J = 8.0, 2H), 7.21 (d, J = 8.0, 1H), 5.16 (app br s, 1H), 4.46 (s, 2H), 4.16 (app t, J = 7.1, 2H), 3.00-2.82 (two m, 4H; there is a broad base line signal in this region from the pyrrolidine NH that was not included in the integration), 2.10-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.83-1.67 (m, 4H). LC (Cond.1): RT = 0.78 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{31}N_6O$: 455.26; found 455.27.

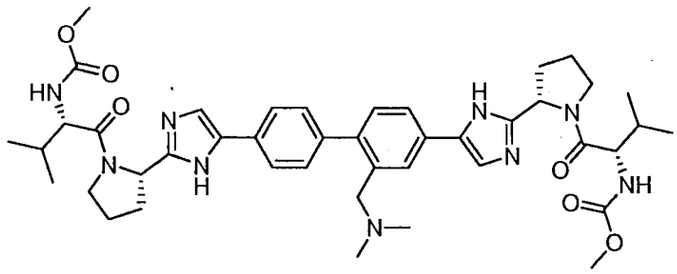
Example M119

Example M119 was prepared from M119b and *Cap*-51 according to the procedure described for Example 1, with the exception that a reverse phase HPLC with ACN/H_2O/NH_4OAC solvent system was employed for the purification step. LC (Cond. 1): RT = 1.15 min; 98% homogeneity index. LC/MS: Anal. Calcd. for

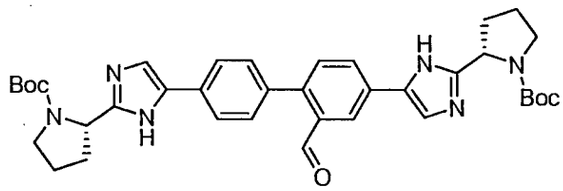
$[M+H]^+$ $C_{41}H_{53}N_8O_7$: 769.40; found 769.40. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{53}N_8O_7$: 769.4037; found 769.4023.

Example M120

methyl ((1S)-1-(((2S)-2-(5-(2-((dimethylamino)methyl)-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

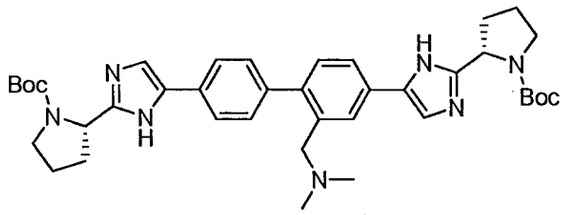


Example M120, step a



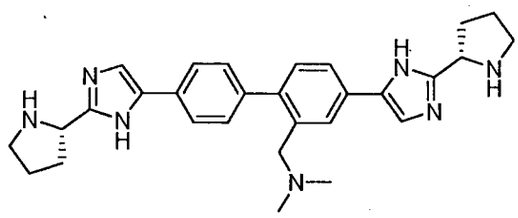
CH_2Cl_2 (6.0 mL) was added to a mixture alcohol M119a (501 mg, 0.765 mmol), TPAP (29.1, 0.083 mmol) and 4-methylmorpholine *N*-oxide (135.8 mg, 1.159 mmol), and the resultant heterogeneous mixture was vigorously stirred at ambient condition for 14.5 hr. Additional TPAP (11.0 mg, 0.031 mmol) and 4-methylmorpholine *N*-oxide (39 mg, 0.33 mmol) were added and stirring was continued for an additional 24 hr. The mixture was filtered through diatomaceous earth (Celite®), the filtrate was rotervaped and the resulting crude material was purified with a Biotage (2% MeOH/EtOAc) to afford aldehyde M120a as a yellow viscous oil (195.6 mg). LC (Cond. 1): RT = 1.37 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{45}N_6O_5$: 653.35; found 653.40.

Example M120, Step b



$NaCNBH_3$ (33 mg, 0.50 mmol) was added in one batch to a MeOH (3.0 mL) solution of aldehyde M120a (195.6 mg, 0.30 mmol) and Me_2NH (200 μL of 40% solution in H_2O), and the reaction mixture was stirred for 4 hr. The volatile component was removed *in vacuo* and the residue was purified with a flash chromatography (sample was loaded as a silica gel mesh; 3-15% MeOH/CH_2Cl_2) to afford amine M120b as an off-white foam (120 mg). LC (Cond. 1): RT = 1.32 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{52}N_7O_4$: 682.41; found 682.42.

Example M120, Step c



Carbamate M120b was converted to M120c by employing the protocol described for the preparation of 1e from 1d. ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 11.82 (br s, 2H), 7.87 (s, 1H), 7.77 (d, *J* = 8.0, 2H), 7.65 (d, *J* = 7.8, 1H), 7.45/7.43 (overlapping two br s, 2H), 7.37 (d, *J* = 7.8, 2H), 7.21 (d, *J* = 7.8, 1H), 4.87 (m, 0.1H), 4.17 (m, 1.90H), ~3.3 (signal of Me_2NCH_2 overlapped with that of water), 3.01-2.94 (m, 2H), 2.89-2.83 (m, 2H), 2.10 (s, 6H), 2.10-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.81-1.67 (m, 4H). LC (Cond. 1): RT = 0.79 min. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{29}H_{36}N_7$: 482.30; found 482.35.

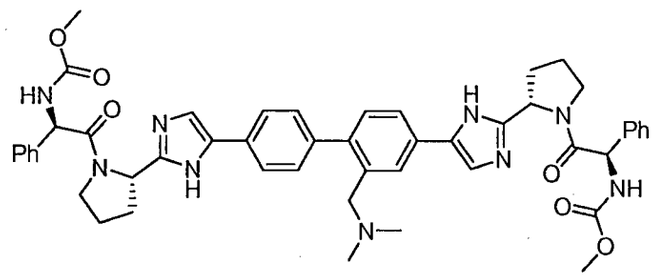
Example M120

The TFA salt of Example M120 was prepared from pyrrolidine M120c and *Cap*-51 according to the procedure described for Example 1. LC (Cond. 1): RT = 1.06 min; 96% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{58}N_9O_6$:

796.45; found 796.48. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{58}N_9O_6$: 796.4510; found 796.4515.

Example M121

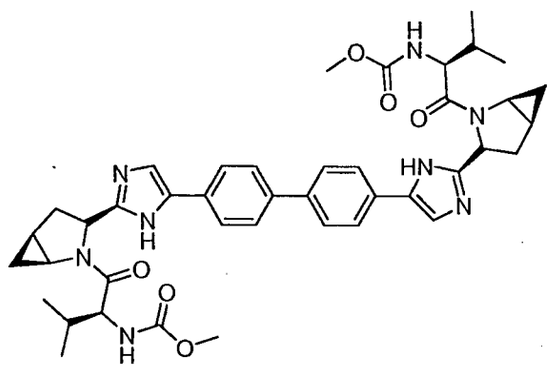
dimethyl ((2-((dimethylamino)methyl)-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate



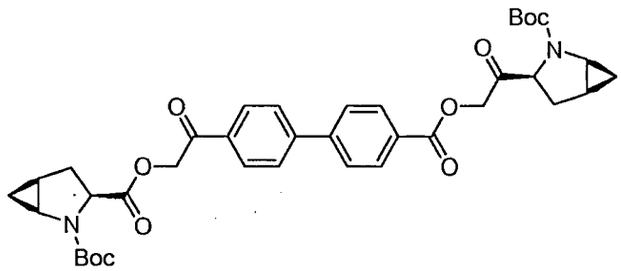
The TFA salt of Example M121 was prepared from M120c and *Cap*-4 according to the procedure described for Example 1. LC (Cond. 1): RT = 1.15 min; >98% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{49}H_{54}N_9O_6$: 796.45; found 864.46. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{49}H_{54}N_9O_6$: 864.4197; found 864.4222.

Example M122

methyl ((1S)-1-(((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate

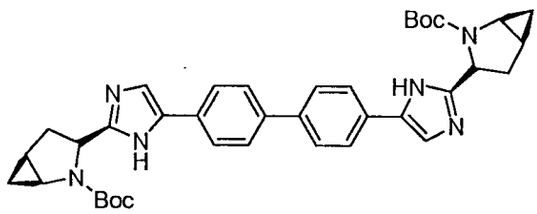


Example M122, step a



Diisopropyl ethylamine (1.81 mL, 10.4 mmol) was slowly added to acetonitrile (20 mL) solution of (1S,3S,5S)-2-(tert-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (2.36 g, 10.4 mmol) and (2-(4'-(2-bromoacetyl)biphenyl-4-yl)-2-oxoethyl)bromonium (2.0 g, 5.05 mmol), and the reaction mixture was stirred at ambient conditions for 16 hr. The solvent was evaporated and the residue was partitioned between ethyl acetate and water (1:1, 40 mL each). The organic layer was washed with Sat. $NaHCO_3$ (2 x 10 mL), brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford ketoester M122a (3.58 g) as a viscous amber oil, which solidified upon storage in a refrigerator. ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 8.20 (m, 4H), 7.97 (d, J = 8.5, 4H), 5.71-5.48 (m, 4H), 4.69 (m, 2H), 3.44 (m, 2H), 3.3 (m, 2H), 2.76-2.67 (m, 2 H), 2.27 (m, 2H), 1.60 (m, 2H), 1.44/1.38 (two s, 18H), 0.78 (m, 2H), 0.70 (m, 2H). LC (Cond. 1): RT = 1.70 min; LC/MS: the molecular ion was not picked up.

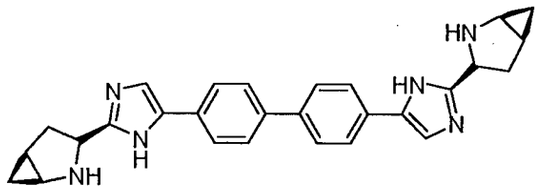
Example M122, Step b



Ammonium acetate (2.89 g, 37.5 mmol) was added to a toluene (20 mL) solution of ketoester M122a (2.58 g, 3.75 mmol), and the resulting mixture was heated at 120 °C for 4.5 hr, while azaetroping the water that is formed with a Dean-Stark set-up. The reaction mixture was cooled to room temperature and the volatile component was removed *in vacuo*. Sat. $NaHCO_3$ solution (10 mL) was added to the solid and the mixture was stirred for 30 min, and the solid was filtered, dried *in vacuo*

and submitted to a Biotage purification (28-100% EtOAc/hexanes) to afford imidazole M122b as light yellow solid (0.6 g). LC (Cond. 1): RT = 1.52 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{45}N_6O_4$: 649.35; found 649.78.

Example M122, Step c



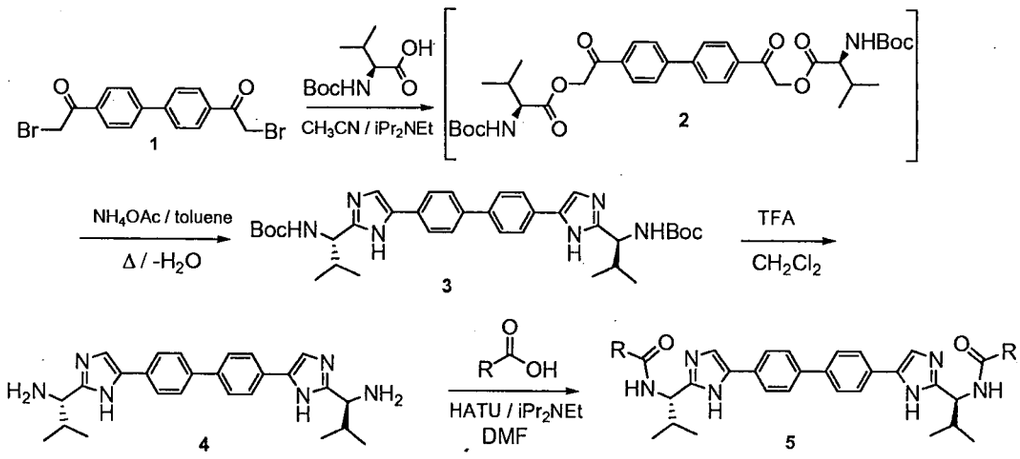
4 N HCl in dioxane (5 mL) was added to a ice-water cooled dioxane (16 mL) solution of carbamate M122b (0.8 g, 1.2 mmol), the ice-water bath was removed and the mixture was stirred at ambient condition for 4 hr. Big chunks of solid that formed during the reaction were broken up with a spatula. Removal of the volatile component *in vacuo* afforded pyrrolidine M122c (.4 HCl) as yellow solid (0.73 g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 7.90 (d, J = 8.3, 4H), 7.84 (br s, 2H), 7.79 (d, J = 8.3, 4H), 5.24 (m, 2H), 3.38 (m, 2H), 2.71 (m, 2H), ~2.50 (2H, overlapped with solvent signal), 1.93 (m, 2H), 1.38 (m, 2H), 0.96 (m, 2H). LC (Cond. 1): RT = 1.03 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{28}H_{29}N_6$: 449.25; found 449.59.

Example M122

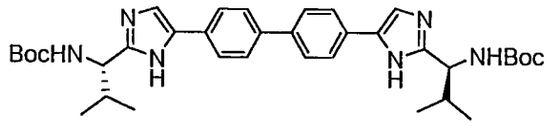
The TFA salt of Example M122 was prepared from M122c and *Cap*-51 according to the procedure described for Example 1. LC (Cond. 1): RT = 1.34 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{51}N_8O_6$: 763.39; found 763.73.

Section R

Scheme 1

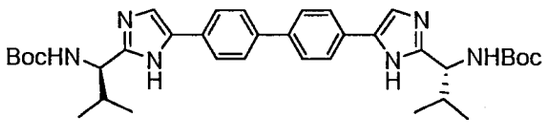


Example R1. tert-butyl (1S,1'S)-1,1'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(2-methylpropane-1,1-diyl)dicarbamate (3).



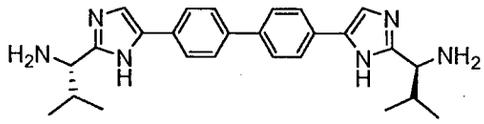
A solution of 1,1'-(biphenyl-4,4'-diyl)bis(2-bromoethanone) (1) (5.14 g, 18.4 mmol) and N-Boc-L-Valine (8.00 g, 36.8 mmol) in dry CH_3CN (40 mL) was treated with iPr_2NEt (7.05 mL, 40.5 mmol) and the solution was allowed to stir at rt overnight. The solvent was removed in vacuo and the resulting slurry was partitioned between EtOAc and H_2O. The layers were separated and the aq phase was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was suspended in toluene (100 mL) and NH_4OAc (14.2 g, 184.2 mmol) was added. The mixture was heated reflux for 16 h with azeotropic removal of H_2O (Dean-Stark). The mixture was cooled to rt and concentrated to dryness in vacuo. The residue was purified column chromatography (biotage) eluting with 0 to 40% CH_3CN in CH_2Cl_2 and then 10% MeOH in CH_2Cl_2 to afford the title compound (5.77 g, 50%) as a yellow foam. ^{1}HNMR (500 MHz, DMSO-d_6) δ 11.77 – 11.93 (m, 2H), 7.80 (s, br, 4H), 7.66 – 7.68 (m, 4H), 7.53 (s, br, 2H), 6.89 (d, J = 7.7 Hz, 2H), 4.43 (app t, J = 8.2 Hz, 2H), 2.05 – 2.11 (m, 2H), 1.38 (s, 18H), 0.90 (d, J = 6.6 Hz, 6H), 0.78 (d, J = 6.6 Hz, 6H). LCMS: Anal. Calcd. for $C_{36}H_{48}N_6O_4$: 628; found: 629 $(M+H)^+$.

Example R2. tert-butyl (1R,1'R)-1,1'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(2-methylpropane-1,1-diyl)dicarbamate.



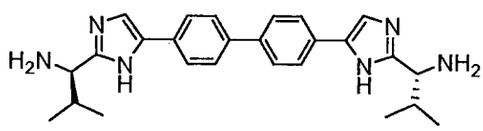
The title compound was prepared according to the method in Example R1 starting with 1,1'-(biphenyl-4,4'-diyl)bis(2-bromoethanone) (1) and N-Boc-D-Valine. LCMS: Anal. Calcd. for $C_{36}H_{48}N_6O_4$: 628; found: 629 $(M+H)^+$.

Example R3. (1S,1'S)-1,1'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(2-methylpropan-1-amine).



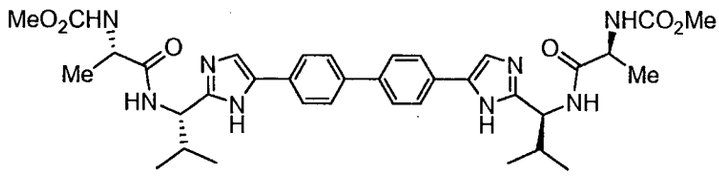
A solution of tert-butyl (1R,1'R)-1,1'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(2-methylpropane-1,1-diyl)dicarbamate (1.00 g, 1.59 mmol) in CH_2Cl_2 (30 mL) was added TFA (20 mL) and the solution was allowed to stir at rt for 5 h. The solvents were removed in vacuo, the residue was dissolved in CH_2Cl_2 : MeOH (1:1) (ca. 10 mL) and absorbed onto an MCX cation exchange cartridge (Oasis). The resin was washed with MeOH and the desired material was released by elution with NH_3 in MeOH (2M). The solvents were removed in vacuo to afford the title compound (0.622 g, 91%) as a yellow foam which was sufficiently pure for use in subsequent steps. ^{1}HNMR (300 MHz, CD_3OD) δ 7.76 (app d, J = 8.4 Hz, 4H), 7.68 (app d, J = 8.4 Hz, 4H), 7.38 (s, 2H), 3.77 (d, J = 7.3 Hz, 2H), 2.07 (sept, J = 7.0 Hz, 2H), 1.03 (d, J = 7.0 Hz, 6H), 0.88 (d, J = 7.0 Hz, 6H). LCMS: Anal. Calcd. for $C_{26}H_{32}N_6$: 428; found: 429 $(M+H)^+$.

Example R4. (1R,1'R)-1,1'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(2-methylpropan-1-amine).



The title compound was prepared according to the method given in Example R3 starting with tert-butyl (1R,1'R)-1,1'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(2-methylpropane-1,1-diyl)dicarbamate. LCMS: Anal. Calcd. for $C_{26}H_{32}N_6$: 428; found: 429 $(M+H)^+$.

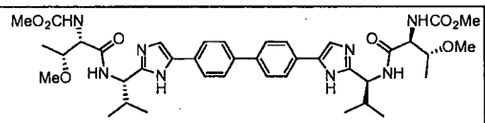
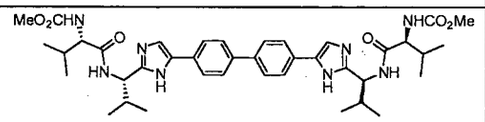
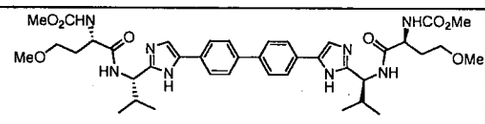
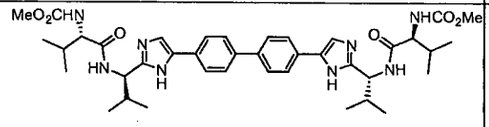
Example R5: *dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1S)-2-methyl-1,1-propanediyl)imino((2S)-1-oxo-1,2-propanediyl)))biscarbamate*

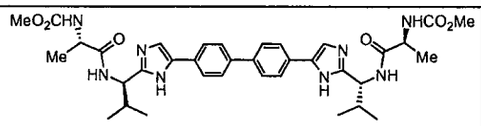
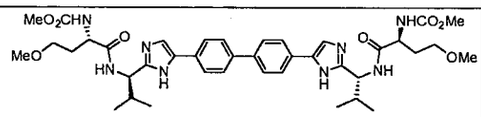
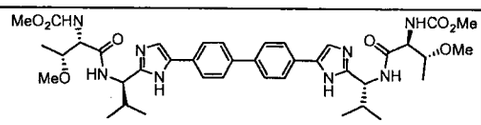


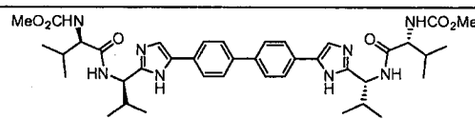
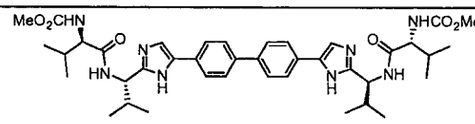
A solution of (1S,1'S)-1,1'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(2-methylpropan-1-amine) (120 mg, 0.280 mmol), (S)-2-(methoxycarbonylamino)propanoic acid (124 mg, 0.840 mmol) and iPr_2NEt (0.489 mL, 2.80 mmol) in DMF (5 mL) was treated with HATU (426 mg, 1.12 mmol) and the reaction mixture was stirred at rt for 2h. The reaction mixture was partitioned between H_2O and EtOAc, the layers separated and the aq phase was extracted with EtOAc. The combined organic layers were concentrated in vacuo and purified by column chromatography (Biotage, 25S eluting with 0 to 40% CH_3CN in CH_2Cl_2 and then 10% MeOH in CH_2Cl_2. The appropriate fractions were concentrated in vacuo and the residue was purified by prep HPLC (CH_3CN- H_2O-TFA). Two subsequent purifications by prep HPLC (CH_3CN- H_2O-NH_4OAc) followed by a final prep HPLC (CH_3CN- H_2O-TFA) afforded the TFA salt of the title compound (4.9 mg, 2%) as a colorless solid. ^{1}HNMR (300 MHz, CD_3OD) δ 7.89 (s, 2H), 7.86 (s, 8H), 4.87 (d, J = 8.5 Hz, 2H), 4.19 (q, J = 7.0 Hz, 2H), 3.65 (s, 6H), 1.33 (d, J = 7.0 Hz, 6H), 1.14 (d, J = 7.0 Hz, 6H), 0.96 (d, J = 7.0 Hz, 6H). LCMS: Anal. Calcd. for $C_{36}H_{46}N_8O_6$: 686; found: 687 $(M+H)^+$.

Table 1A. The following were prepared similary starting with the appropriate amine and substitute amino acid.

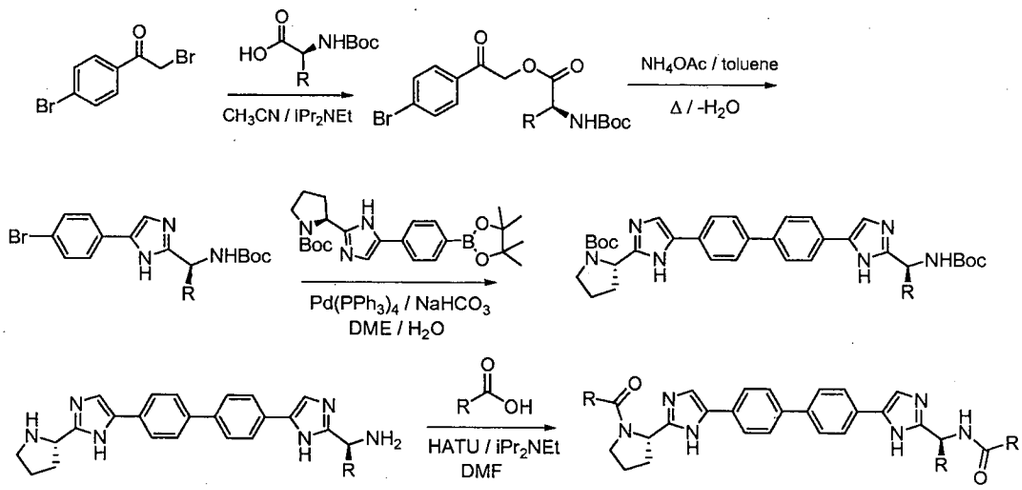
Example	*Compound Name*	*Structure*	*Analytical Data*

Example R6	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1S)-2-methyl-1,1-propanediyl)imino((2S,3R)-3-methoxy-1-oxo-1,2-butanediyl)))biscarbamate		LCMS: Anal. Calcd. for $C_{40}H_{54}N_8O_8$: 774; found: 775 $(M+H)^+$.
Example R7	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1S)-2-methyl-1,1-propanediyl)imino((2S)-3-methyl-1-oxo-1,2-butanediyl)))biscarbamate		LCMS: Anal. Calcd. for $C_{40}H_{54}N_8O_6$: 742; found: 743 $(M+H)^+$.
Example R8	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1S)-2-methyl-1,1-propanediyl)imino((2S)-4-methoxy-1-oxo-1,2-butanediyl)))biscarbamate		LCMS: Anal. Calcd. for $C_{40}H_{54}N_8O_8$: 774; found: 775 $(M+H)^+$.
Example R9	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1R)-2-methyl-1,1-		LCMS: Anal. Calcd. for $C_{40}H_{54}N_8O_6$: 742; found: 743 $(M+H)^+$.

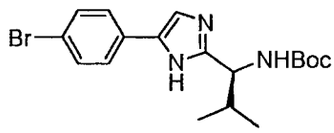
	propanediyl)imino((2S)-3-methyl-1-oxo-1,2-butanediyl)))biscarbamate		
Example R10	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1R)-2-methyl-1,1-propanediyl)imino((2S)-1-oxo-1,2-propanediyl)))biscarbamate		LCMS: Anal. Calcd. for $C_{36}H_{46}N_8O_6$: 686; found: 687 $(M+H)^+$.
Example R11	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1R)-2-methyl-1,1-propanediyl)imino((2S)-4-methoxy-1-oxo-1,2-butanediyl)))biscarbamate		LCMS: Anal. Calcd. for $C_{40}H_{54}N_8O_8$: 774; found: 775 $(M+H)^+$.
Example R12	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1R)-2-methyl-1,1-propanediyl)imino((2S,3R)-3-methoxy-1-oxo-1,2-butanediyl)))biscarbamate		LCMS: Anal. Calcd. for $C_{40}H_{54}N_8O_8$: 774; found: 775 $(M+H)^+$.

Example R13	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1R)-2-methyl-1,1-propanediyl)imino((2R)-3-methyl-1-oxo-1,2-butanediyl)))biscarbamate		Anal. Calcd. for $C_{40}H_{54}N_8O_6$: 742; found: 743 $(M+H)^+$.
Example R14	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1S)-2-methyl-1,1-propanediyl)imino((2R)-3-methyl-1-oxo-1,2-butanediyl)))biscarbamate		Anal. Calcd. for $C_{40}H_{54}N_8O_6$: 742; found: 743 $(M+H)^+$.

Scheme 2

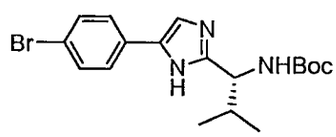


Example R15. (S)-tert-butyl 1-(5-(4-bromophenyl)-1H-imidazol-2-yl)-2-methylpropylcarbamate.



A solution of 2-bromo-1-(4-bromophenyl)ethanone (6.23 g, 22.3 mmol) and N-Boc-L-Valine (5.00 g, 23.0 mmol) in dry CH_3CN (30 mL) was treated with iPr_2NEt (4.40 mL, 25.3 mmol) and the solution was allowed to stir at rt overnight. The solvent was removed in vacuo and the resulting slurry was partitioned between EtOAc and H_2O. The layers were separated and the aq phase was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to give a yellow oil. LCMS: Anal. Calcd. for $C_{18}H_{24}BrNO_5$: 413, 415; found: 412, 414 $(M-H)^-$. The residue was suspended in toluene (60 mL) and NH_4OAc (8.61 g, 111.7 mmol) was added. The mixture was heated reflux for 16 h with azeotropic removal of H_2O (Dean-Stark). The mixture was cooled to rt and concentrated to dryness in vacuo. The residue was purified column chromatography (biotage) eluting with 10% MeOH in CH_2Cl_2 to afford the title compound (8.55 g, 94%) as a yellow foam. ^{1}HNMR (500 MHz, CD_3OD) δ 7.84 (s, 1H), 7.66 (app d, J = 8.9 Hz, 2H), 7.64 (app d, J = 8.9 Hz, 2H), 4.65 (d, J = 7.7 Hz, 1H), 2.23 – 2.27 (m, 1H), 1.42 (s, 9H), 1.07 (d, J = 6.5 Hz, 3H), 0.93 (d, J = 6.5 Hz, 3H). LCMS: Anal. Calcd. for $C_{18}H_{24}BrN_3O_2$: 393, 395; found: 394, 396 $(M+H)^+$.

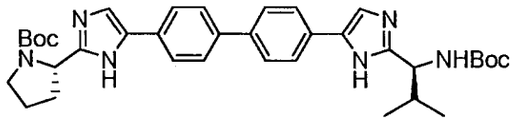
Example R16. (R)-tert-butyl 1-(5-(4-bromophenyl)-1H-imidazol-2-yl)-2-methylpropylcarbamate.



The title compound was prepared starting from 2-bromo-1-(4-bromophenyl)ethanone and N-Boc-D-Valine using the method given in Example 15. ^{1}HNMR (500 MHz, CD_3OD) δ 7.83 (s, 1H), 7.68 (app d, J = 8.7 Hz, 2H), 7.64 (app d, J = 8.7 Hz, 2H), 4.65 (d, J = 7.3 Hz, 1H), 2.22 – 2.26 (m, 1H), 1.42 (s, 9H), 1.08

(d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H). LCMS: Anal. Calcd. for $C_{18}H_{24}BrN_3O_2$: 393, 395; found: 394, 396 $(M+H)^+$.

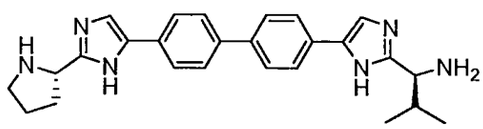
Example R17. (S)-tert-butyl 2-(5-(4'-(2-((S)-1-(tert-butoxycarbonylamino)-2-methylpropyl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate.



A solution of (S)-tert-butyl 1-(5-(4-bromophenyl)-1H-imidazol-2-yl)-2-methylpropylcarbamate (2.00 g, 5.07 mmol), (S)-tert-butyl 2-(5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (2.23 g, 5.07 mmol) and $NaHCO_3$ (1.49 g, 17.8 mmol) in DME (50 mL) and Water (15 mL) was degassed by evacuating and backfilling with N_2.

Tetrakis(triphenylphosphine)palladium(0) (0.293 g, 0.254 mmol) was added and the the reaction mixture was heated overnight at 100°C. The mixture was cooled to rt and the DME was removed in vacuo. The residue was partitioned between H_2O and EtOAc and the layers separated. The aq phase was extracted with EtOAc and the combined organic layers were concentrated to dryness in vacuo and purified purified by column chromatography (Biotage) eluting with a gradient of 0 to 40% CH_3CN in CH_2Cl_2 and then 0 to 10% MeOH in CH_2Cl_2. The title compound (2.05 g, 65 % yield) was obtained as a brown foam. This material was used as is in subsequent steps. LCMS: Anal. Calcd. for $C_{36}H_{46}N_6O_4$:626; found: 627 $(M+H)^+$.

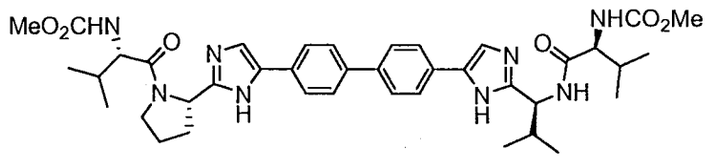
Example R17A. (S)-2-methyl-1-(5-(4'-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)propan-1-amine.



To a solution of (S)-tert-butyl 2-(5-(4'-(2-((S)-1-(tert-butoxycarbonylamino)-2-methylpropyl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (2.05 g, 3.27 mmol) in CH_2Cl_2 (20 mL) was added TFA (5 mL, 64.9 mmol) and the solution was allowed to stir for 2h. The solvents were removed in

vacuo, the residue was dissolved in CH_2Cl_2 : MeOH (1:1) (ca. 10 mL) and absorbed onto an MCX cation exchange cartridge (Oasis). The resin was washed with MeOH and the desired material was released by elution with NH_3 in MeOH (2M). The solvents were removed in vacuo to afford the title compound (0.622 g, 91%) as a yellow foam which was sufficiently pure for use in subsequent steps. ^{1}HNMR (500 MHz, CD_3OD) δ 7.85 – 7.88 (m, 4H), 7.75 (m, app d, J = 8.2 Hz, 4H), 7.70 (app d, J = 5.8 Hz, 2H), 4.96 (t, J = 8.2 Hz, 1H), 4.30 (d, J = 8.5 Hz, 1H), 3.54 – 3.57 (m, 1H), 3.47 – 3.52 (m, 1H), 2.55 – 2.62 (m, 1H), 2.38 – 2.46 (m, 1H), 2.28 – 2.36 (m, 1H), 2.15 – 2.24 (m, 1H), 1.17 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H). LCMS: Anal. Calcd. for $C_{26}H_{30}N_6$: 426; found: 427 $(M+H)^+$.

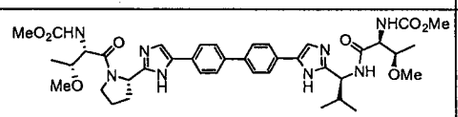
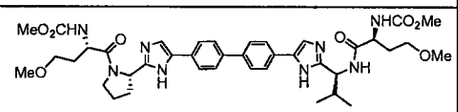
Example R18. *N^2-(methoxycarbonyl)-N-((1S)-1-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-methylpropyl)-L-valinamide*

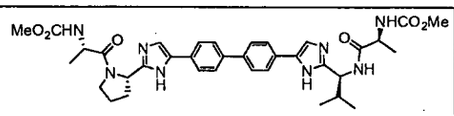
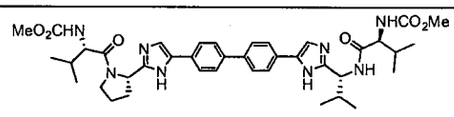
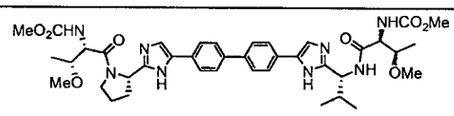


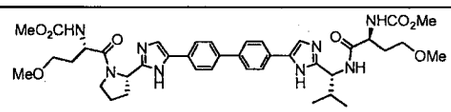
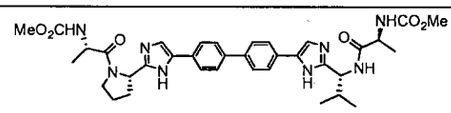
A single neck 50 mL flask equipped with a magnetic stirrer was charged with (S)-2-methyl-1-(5-(4'-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)propan-1-amine (80 mg, 0.188 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (99 mg, 0.563 mmol) in DMF (5 mL) and DIEA (0.328 mL, 1.875 mmol) was added. To this solution was added HATU (285 mg, 0.750 mmol) added and the reaction was allowed to stir for 4h rt. The reaction mixture was partitioned between H_2O and EtOAc, the layers separated and the aq phase was extracted with EtOAc. The combined organic layers were concentrated in vacuo and purified by column chromatography (Biotage, 25S) eluting with 0 to 40% CH_3CN in CH_2Cl_2 and then 10% MeOH in CH_2Cl_2. The appropriate fractions were concentrated in vacuo and the residue was purified by prep HPLC (CH_3CN-H_2O-TFA) and then a subsequent purification by prep HPLC (CH_3CN-H_2O-NH_4OAc) gave the title compound (31.8 mg, 23%) as a colorless solid. ^{1}HNMR (500 MHz, CD_3OD) δ 7.71 (m, 4H), 7.64 – 7.67 (m, 4H), 7.35 (s, 1H), 7.32 (s, 1H), 5.33 – 5.34 (m, 0.2H), 5.17 (dd, J = 7.6, 5.5 Hz, 0.8H), 4.77 (d, J = 9.2 Hz, 1H), 4.22 and

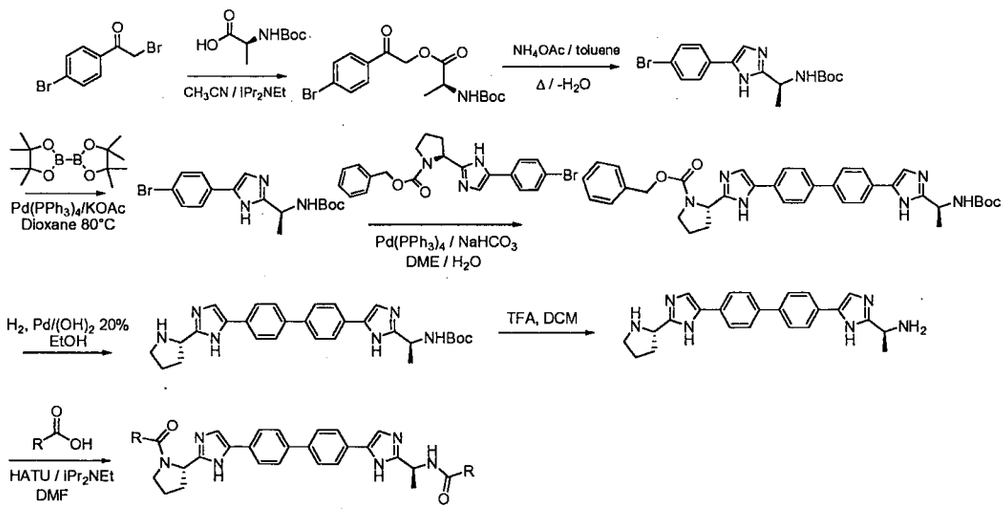
4.10 (d, J = 7.6 Hz, 1H, rotamers 4:1 ratio), 3.97 – 4.01 (m, 1H), 3.94 (d, J = 7.0 Hz, 1H), 3.84 – 3.89 (m, 1H), 3.64 (s, 6H), 2.28 – 2.35 (m, 1H), 2.18 – 2.27 (m, 3H), 1.98 – 2.08 (m, 3H), 1.05 (d, J = 6.7 Hz, 3H), 0.98 and 0.94 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 6.7 Hz, 6H), 0.88 (d, J = 6.7 Hz, 3H), 0.86 (d, J = 6.7 Hz, 3H). LCMS: Anal. Calcd. for $C_{40}H_{52}N_8O_6$: 740; found: 741 $(M+H)^+$.

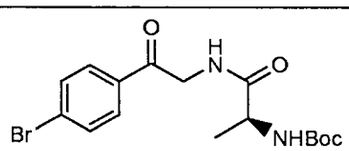
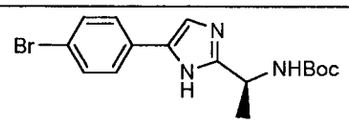
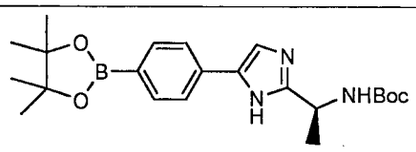
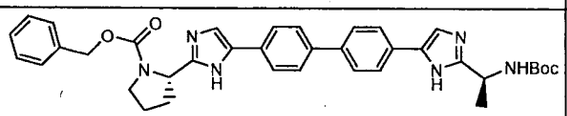
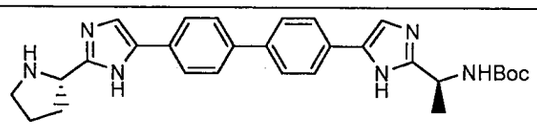
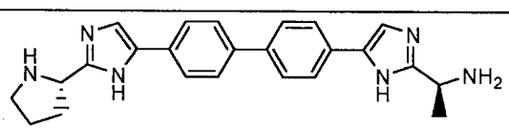
Table 2A. The following were prepared similary starting with the appropriate amine and substitute amino acid.

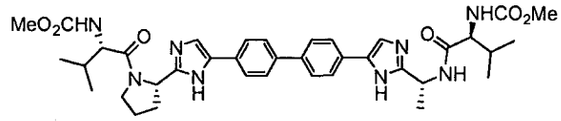
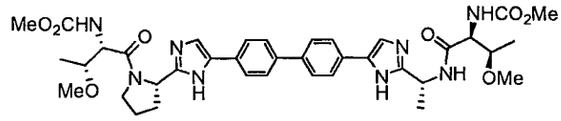
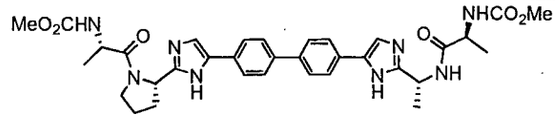
Example	*Compound Name*	*Structure*	*Analytical Data*
Example R19	methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(4-(4'-(2-((1S)-1-((N-(methoxycarbonyl)-O-methyl-L-threonyl)amino)-2-methylpropyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		LCMS: Anal. Calcd. for $C_{40}H_{52}N_8O8$: 772 found: 773 $(M+H)^+$.
Example R20	methyl ((1S)-3-methoxy-1-(((2S)-2-(4-(4'-(2-((1S)-1-((N-(methoxycarbonyl)-O-methyl-L-homoseryl)amino)-2-methylpropyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		LCMS: Anal. Calcd. for $C_{40}H_{52}N_8O8$: 772 found: 773 $(M+H)^+$.

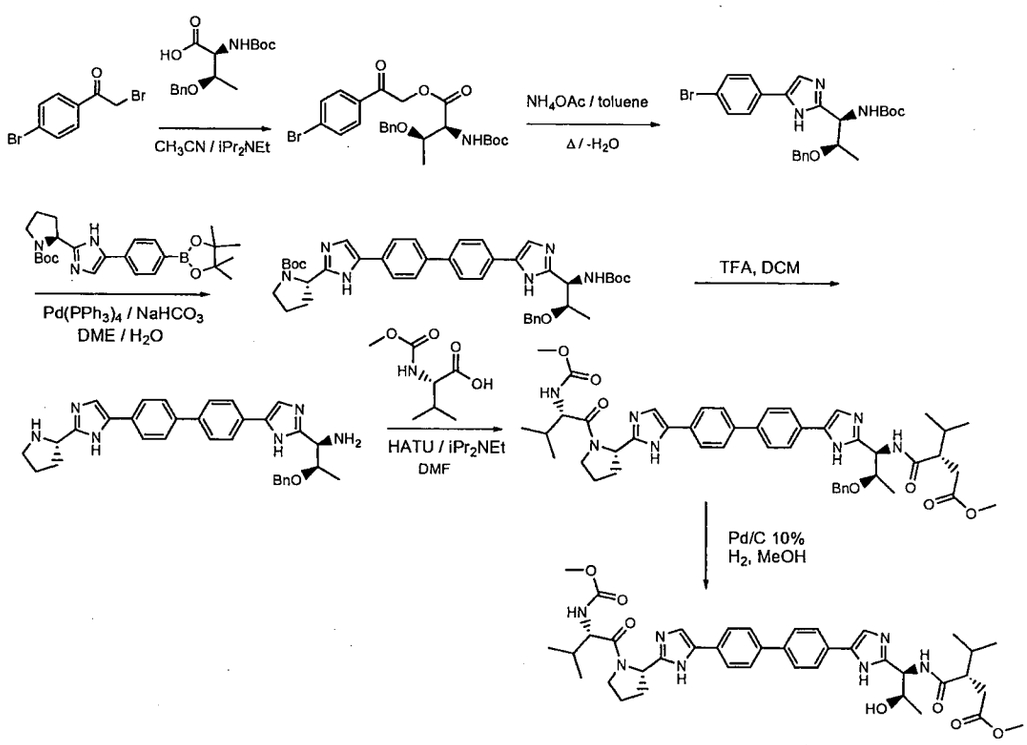
Example R21	methyl ((1S)-2-((2S)-2-(4-(4'-(2-((1S)-1-((N-(methoxycarbonyl)-L-alanyl)amino)-2-methylpropyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{36}H_{44}N_8O_6$: 684; found: 685 $(M+H)^+$.
Example R22	N^2-(methoxycarbonyl)-N-((1R)-1-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-methylpropyl)-L-valinamide		LCMS: Anal. Calcd. for $C_{40}H_{52}N_8O_6$: 740; found: 741 $(M+H)^+$.
Example R23	methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(4-(4'-(2-((1R)-1-((N-(methoxycarbonyl)-O-methyl-L-threonyl)amino)-2-methylpropyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		LCMS: Anal. Calcd. for $C_{40}H_{52}N_8O_8$: 772 found: 773 $(M+H)^+$.

Example R24	methyl ((1S)-3-methoxy-1-(((2S)-2-(4-(4'-(2-((1R)-1-((N-(methoxycarbonyl)-O-methyl-L-homoseryl)amino)-2-methylpropyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		LCMS: Anal. Calcd. for $C_{40}H_{52}N_8O_8$: 772; found: 773 $(M+H)^+$.
Example R25	methyl ((1S)-2-((2S)-2-(4-(4'-(2-((1R)-1-((N-(methoxycarbonyl)-L-alanyl)amino)-2-methylpropyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{36}H_{44}N_8O_6$: 684; found: 685 $(M+H)^+$.

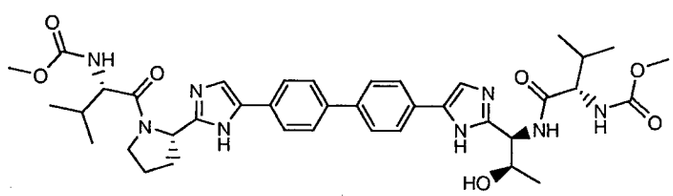


Example	*Structure*	*Analytical Data*
Example A		LCMS: Anal. Calcd. for $C_{16}H_{21}BrN_2O_4$: 385 found: 386(M+H)$^+$.
Example B		LCMS: Anal. Calcd. for $C_{16}H_{21}BrN_3O_2$: 366 found: 367 (M+H)$^+$.
Example C		LCMS: Anal. Calcd. for $C_{22}H_{32}BN_3O_4$: 413; found: 414 (M+H)$^+$.
Example D		LCMS: Anal. Calcd. for $C_{37}H_{40}N_6O_4$: 632; found: 633 (M+H)$^+$.
Example E		LCMS: Anal. Calcd. for $C_{29}H_{34}N_6O_2$: 498 found: 499 (M+H)$^+$.
Example F		LCMS: Anal. Calcd. for $C_{24}H_{26}N_6$: 398; found: 399 (M+H)$^+$.

Example R26		LCMS: Anal. Calcd. for $C_{38}H_{48}N_8O_6$: 712; found: 713 $(M+H)^+$.
Example R27		LCMS: Anal. Calcd. for $C_{38}H_{48}N_8O_8$: 744; found: 745 $(M+H)^+$.
Example R28		LCMS: Anal. Calcd. for $C_{34}H_{40}N_8O_6$: 756; found: 757 $(M+H)^+$.

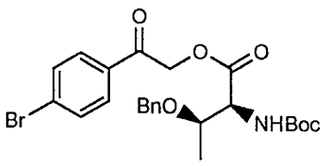
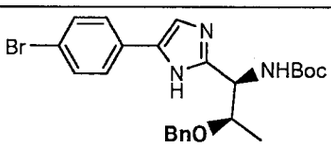
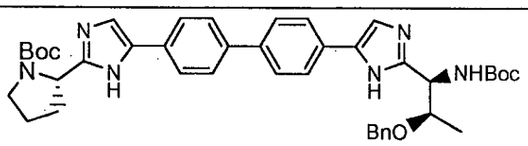
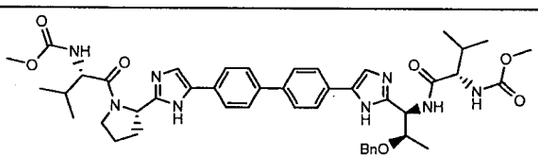
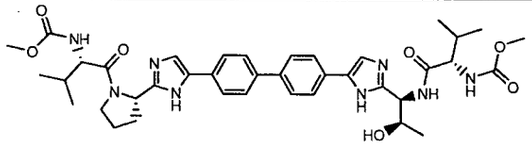


Example R29.

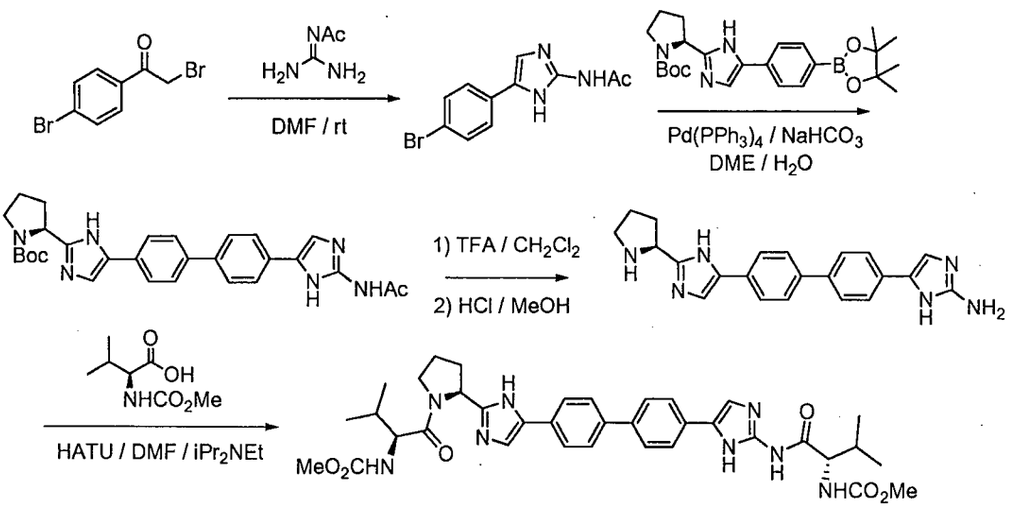


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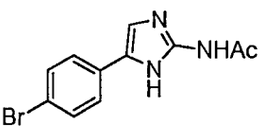
A single neck 50 mL flask equipped with a magnetic stirrer was charged with a compound from, Example E (150 mg, 180 mmol) in Methanol (5 mL). To this solution was added a slurry of Palladium on carbon 10% (100 mg) in Methanol (2mL). The mixture was purged with 60 psi of Hydrogen. The mixture was shaked on a Parr overnight at room temperature. The contain of the reactor was analyzed by LC-MS and showed a 20% completion. A slurry of Palladium Hydroxide on carbon 20 % (100 mg) in Acetic acid (2 mL) was added. The mixture was purged with hydrogen and shake on a Parr shaker with 60 psi of Hydrogen over the weekend. The reaction was filtered through a pad of Celite and the filtrate was evaporated in vavuo. The residue was purified by prep HPLC (CH_3CN-H_2O-TFA) to give the compound (Example 29) 32 mg 23 % yield as a white solid. LCMS: Anal. Calcd. for $C_{39}H_{50}N_8O_7$: 742; found: 743 $(M+H)^+$

Example	*Structure*	*Analytical Data*
Example G		LCMS: Anal. Calcd. for $C_{24}H_{28}BrNO_6$: 506 found: No ionization $(M+H)^+$.
Example H		LCMS: Anal. Calcd. for $C_{24}H_{28}BrN_3O_3$: 486 found: 487 $(M+H)^+$.
Example I		LCMS: Anal. Calcd. for $C_{42}H_{50}BN_6O_5$: 718 found: 719 $(M+H)^+$.
Example J		LCMS: Anal. Calcd. for $C_{46}H_{56}N_8O_7$: 832; found: 833 $(M+H)^+$.
Example R29		LCMS: Anal. Calcd. for $C_{46}H_{56}N_8O_7$: 742 found: 743 $(M+H)^+$.

Scheme 3

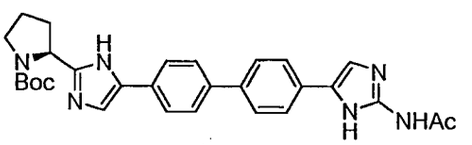


Example R30. N-(5-(4-bromophenyl)-1H-imidazol-2-yl)acetamide.



A mixture of 2-bromo-1-(4-bromophenyl)ethanone (2.00 g, 7.20 mmol) and acetylguanidine (2.18 g, 21.6 mmol) in DMF (40 mL) was stirred at rt for 48 h. The solution was concentrated to dryness in vacuo and the resulting brown solid was of sufficient purity for use in the next step. LCMS: Anal. Calcd. for $C_{11}H_{10}BrN_3O$: 279, 281; found: 280, 282 $(M+H)^+$.

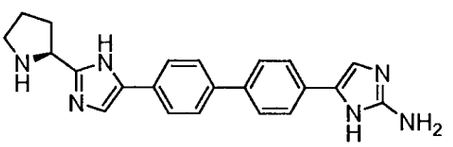
Example R31. (S)-tert-butyl 2-(5-(4'-(2-acetamido-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate



A mixture of N-(5-(4-bromophenyl)-1H-imidazol-2-yl)acetamide (0.604 g, 2.16 mmol), (S)-tert-butyl 2-(5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (0.950 g, 2.16 mmol), $NaHCO_3$ (0.636 g, 7.57 mmol) in DME (20 mL) and H_2O (5 mL) was degassed by evacuating and back-filling with N_2 (X3). To this solution $Pd(PPh_3)_4$ (0.125 g, 0.11

mmol) was added and the suspension heated at 125°C for 24h. The mixture was evaporated to dryness in vacuo and the residue was purified by column chromatography (Biotage) eluting with a gradient of 0 to 10% MeOH in CH_2Cl_2. The material was then purified by prep HPLC (CH_3CN-H_2O-NH_4OAc) to afford the title compound as a colorless solid. 7.76 (app dd, J = 8.4, 2.2 Hz, 4H), 7.69 (app d, J = 8.4 Hz, 2H), 7.66 (app d, J = 8.4 Hz, 2H), 7.45 (s, 1H), 7.23 (s, 1H), 3.66 – 3.72 (m, 1H), 3.48 – 3.53 (s, 1H), 2.34 – 2.46 (m, 1H), 2.18 (s, 3H), 1.96 – 2.10 (m, 3H), 1.46, 1.25 (s, 9H, rotamers, 1:2 ratio). LCMS: Anal. Calcd. for $C_{29}H_{32}N_6O_3$: 512; found: 513, 282 $(M+H)^+$.

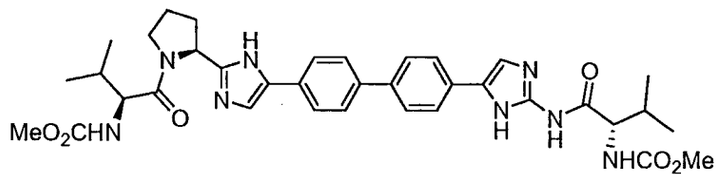
Example R32. (S)-5-(4'-(2-(pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-amine.



Step 1. A solution of (S)-tert-butyl 2-(5-(4'-(2-acetamido-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (55.0 mg, 0.11 mmol) in CH_2Cl_2 (5 mL) and TFA (1 mL) was allowed to stir at rt for 3 h. The reaction mixture was concentrated in vacuo to give the TFA salt of the title compound (55.0 mg) which was carried directly to the next step. LCMS: Anal. Calcd. for $C_{24}H_{24}N_6O$: 412; found: 413 $(M+H)^+$.

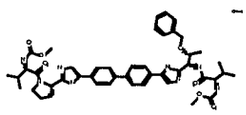
Step 2. The brown oil from Step 1 was suspended in 25% conc. HCl in MeOH (10 mL) and heated at reflux for 3h. The volatiles were removed under reduced pressure and the residue was purified by prep HPLC (CH_3CN-H_2O-TFA) to give the TFA salt of the title compound (20 mg, 42%). LCMS: Anal. Calcd. for $C_{22}H_{22}N_6$: 370; found: 371 $(M+H)^+$.

Example R33. (S)-2-methoxycarbonylamino-N-(5-(4'-(2-((S)-1-((S)-2-methoxycarbonylamino-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)-3-methylbutanamide

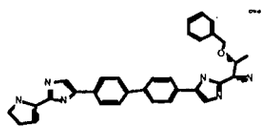


To a solution of (S)-5-(4'-(2-(pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-amine trifluoroacetic acid salt (20 mg, 0.04 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (25 mg, 0.14 mmol) and iPr_2NEt (0.09 mL, 0.53 mmol) in DMF (5 mL) was added HATU (54 mg, 0.14 mmol). The solution was allowed to stir for 3h and then poured into H_2O. The mixture was concentrated to dryness in vacuo and the residue was purified by prep HPLC (CH_3CN-H_2O-TFA) affording the title compound and recovered starting material. The recovered starting material was resubjected to the reaction conditions and purified as above. The two lots of product were then purified by prep HPLC (CH_3CN-H_2O-NH_4OAc) to give the title compound as a tan solid (18 mg, 76%). ^{1}HNMR (400 MHz, CD_3OD) δ 7.80 – 7.88 (m, 9H), 7.56 (s, 1H), 5.24 (app t, J = 7.6 Hz, 1H), 4.23 (d, J = 7.1 Hz, 1H), 4.18 (d, J = 6.6 Hz, 1H), 4.08 – 4.13 (m, 1H), 3.83 – 3.90 (m, 1H), 3.68 (s, 3H), 3.65 (s, 3H), 2.54 – 2.63 (m, 1H), 2.17 – 2.30 (m, 4H), 2.01 – 2.09 (m, 1H). LCMS: Anal. Calcd. for $C_{36}H_{44}N_8O_6$: 684; found: 685 $(M+H)^+$.

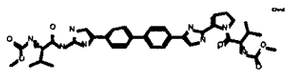
The following Examples were prepared as described in the above examples using the appropriate starting materials:



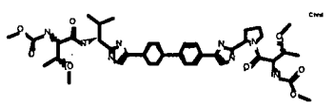
Example R34



Example R35



Example R36



Example R37

BIOLOGICAL ACTIVITY

An HCV Replion 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.

HCV 1b-377-neo replicon cells were used to test the currently described compound series as well as cells resistant to compound A due to a Y2065H mutation in NS5A (described in application PCT/US2006/022197). The compounds tested

were determined to have more than 10-fold less inhibitory activity on cells resistant to compound A than wild-type cells indicating a related mechanism of action between the two compound series. Thus, the compounds of the present disclosure can be effective to inhibit 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 EC50 values of representative compounds of the present disclosure against the HCV 1b genotype. In one embodiment compounds of the present disclosure are active against the 1a, 1b, 2a, 2b, 3a, 4a, and 5a genotypes. EC50 ranges against HCV 1b are as follows: A = 1-10 μM; B = 100-999 nM; C = 1-99 nM; and D = 1-999 pM.

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.

Table 2

Example	Range
1	D
24-4e	C
24-4f	B
24-4g	A
25-1	D
25-2	D
25-3	D
25-4	D
25-5	D
25-6	C
25-7	C
25-8	D
24-4h	D
120-9	D
120	D
120-5	C
120-6	C
120-7	D
120-8	C
103-3	D
103-4	D
103-1	D
103-2	D
103-5	D
103-6	C
103-8	D
103-7	D
151 isomer 1	C
151 isomer 2	B
152j-9	C
152j-10	C
152j-1	C
152j-2	D
153c-5	C
153c-6	C
153c-2	C
153c-1	C
152j-7	C
152j-8	D
153c-3	A
153c-4	A
152j-11	D
152j-12	D
152j-15	D
152j-28	D
152j-13	C
152j-14	C
152j-19	D
152j-16	D

Example	Range
152j-3	D
152j-20	C
152j-17	D
152j-18	D
152j-3	D
152j-5	D
152j-6	D
152l-2	D
152l-1	D
152j-24	D
152j-23	D
153c-7	C
152j-22	D
24-18-2	D
24-18-1	D
24-18-4	D
24-18-5	D
24-18-6	D
24-18-3	D
152j-21	D
152l-3	D
131.1-2	D
131.1-1	D
24-4a	D
120-1	D
120-2	D
120-3	D
120-4	D
24-10	D
24-9	D
24-8	D
24-11	C
24-12	C
11	C
24-16	D
24-18	D
24-17	D
24-15	C
24-13	B
24-14	C
24-4b	C
24-4c	D
24-4d	D
148	C
149	D
150	C
24-5	D
24-6	D
24-7	D

Example	Range
24-1	D
24-2	D
24-3	D
28-1	D
28-2	D
28-3	D
28-4	D
28-5	D
84-1	D
84-2	D
84-3	D
84-4	D
84-7	C
84-10	C
84-12	D
84-14	C
84-15	C
84-17	D
84-18	C
84-19	C
84-20	C
84-24	D
84-26	D
84-27	D
84-28	D
84-32	D
84-33	D
84-34	C
84-35	D
84-36	D
84-38	D
84-39	D
84-40	D
84-44	D
84-46	D
84-47	D
84-48	D
84-49	D
84-50	D
84-51	D
84-52	D
84-53	D
84-54	D
84-55	D
84-56	D
84-57	D
84-58	D
84-59	D
84-60	D

Example	Range
84-61	D
84-62	D
84-63	D
84-64	D
84-65	C-D
84-66	C-D
84-67	D
84-68	C
84-69	D
84-70	C
84-71	C
84-72	C
84-73	C
84-74	D
84-75	C
84-76	D
84-77	D
84-78	D
84-79	D
84-80	D
84-81	D
84-82	D
84-83	D
84-84	D
84-85	D
84-86	D
84-87	D
94-1	D
94-2	C
94-3	D
94-6	C-D
94-9	D
94-10	D
94-12	C
94-13	D
94-17	D
94-19	D
94-20	C
94-24	D
94-25	D
94-26	D
94-27	C
94-30	D
94-32	C
94-33	C
94-34	C
94-36	D
94-37	C
94-38	D
94-42	D

Example	Range
94-44	D
94-45	D
94-46	D
94-47	D
94-48	D
94-49	D
94-50	D
94-51	D
94-52	D
94-53	D
94-54	D
94-55	D
94-56	D
107-1	D
107-2	D
107-3	D
107-4	D
107-5	D
107-6	D
107-7	D
107-8	D
107-9	D
107-10	D
107-11	D
107-12	D
107-13	D
107-14	D
107-15	D
107-16	D
107-17	D
107-18	D
107-19	D
107-20	D
107-21	D
107-22	D
107-23	D
107-24	D
107-25	D
107-26	D
107-27	D
107-28	D
107-29	D
107-30	D
107-31	D
107-32	D
107-33	D
107-34	D
107-35	D
107-36	D
107-37	D

Example	Range
107-38	D
107-39	D
107-40	D
107-41	D
107-42	D
107-43	D
107-44	D
2	D
3	D
4	D
5	C
6	C
7	D
8	D
24-23	D
9	C
10	C
11	C
12	C
13	C
14	B
15	C
16	C
17	D
18	D
19	D
20	C
21	D
22	D
23	D
24	C
25	D
26	C
27	C
28	C
29	D
30	C
31	D
32	C
33	D
34	D
35	D
36	D
37	D
38	D
39	D
40	D
41	D
42	D
43	D

44	D
45	D
46	D
47	D
48	D
49	D
50	B
51	D
52	D
53	D
54	D
55	D
56	D
57	D
58	D
59	D
60	D
61	D
62	D
63	D
64	D
65	C
67	D
68	D
69	D
70	C
71	D
72	C
73	D
74	D
75	D
76	D
77	D

78	D
79	D
80	D
81	D
82	D
83	D
84	D
85	D
86	D
87	D
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90	D
91	D
92	D
93	D
94	D
95	D
96	D
97	D
98	D
99	D
100	D
101	D
102	D
103	D
104	D
105	D
106	D
107	D
108	D
109	C
110	D
111	D

112	D
113	D
114	D
115	D
116	D
117	D
118	D
119	D
120	D
121	D
122	D
123	D
124	D
125	D
126	D
127	D
128	D
129	D
130	D
131	D
132	D
133	C
134	D
135	D
136	D
138	D
139	D
140	D
141	D
142	C
143	D
144	D
145	D

146	D
147	D
LS2	C
LS3	C
LS4	C
LS16	C
LS6	B
LS11	A
LS14	D
LS20	D
LS21	D
LS22	D
LS23	D
LS24	D
LS25	D
LS26	D

LS27 D'mer 1	D
LS27 D'mer 2	D
LS36	D
LS37	D
F5	D
F6	D
F7	D
F8	D
F14	D
F15	D
F16	D
F17	D
F20	B
F21	B

F22	B
F25	D
F26	C
F27	C
F28	C
F29	C
F30	C
F32	B
F33	B
F34	C
F35	B
F37	B
F38	D
F39 Diastereomers	D

F41	D
F43	D
F48	D
F49	C
F51	D
F52	D
F53	D
F54	D
F55	D
F56	D
F57	D
F58	D
F60	D
F61	C
F62	C
F63	D
F64	C
F65	B
F66	C
F67	C
F69	B
F70	B
F71	D
cj-48	B
cj-49	C
cj-50	D
cj-51	D
cj-52	D
cj-53	D
cj-54	D
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cj-68	D
cj-69	D
cj-70	D
cj-71	D
cj-72	D
cj-73	D
cj-74	C
cj-75	D

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cj-120	D
cj-121	D
cj-122	D
cj-45	D
cj-41	D
cj-47	C
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cj-38	D
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cj-35	C
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cj-137	C
cj-138	A
cj-139	C
cj-140	B
cj-141	A
cj-142	A
cj-143	A
cj-144	D
cj-145	C
cj-146	B
cj-147	C
cj-148	C
cj-149	C
cj-150	C
cj-151	C
cj-152	C
cj-153	D
cj-154	D
cj-155	C
cj-156	D
cj-126	D
cj-127	C
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cj-129	D
cj-130	D
cj-131	C
cj-132	B
cj-133	C
cj-134	C
cj-135	C
cj-125	C
cj-15c	D
cj-20c	D
cj-20b	D
cj-20a	D
cj-17	D
cj-16	D
cj-20d	D

cj-20	D
cj-15a	D
cj-15	D
cj-15d	D
cj-11n	C
cj-11o	C
cj-11p	D
cj-11m	C
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cj-11i	D
cj-11j	D
cj-11k	D
cj-11e	A
cj-11f	C
cj-11g	C
cj-11d	D
cj-11b	D
cj-11	D
cj-11a	D
cj-11c	D
JG-3	D
JG-4	C
JG-5	D
JG-6	C
JG-7	D
JG-8	D
JG-9	D
JG-10	C
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JG-17	D
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J17	D
J18	D
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J21	D
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J24	D
J25	D
J26	D
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J28	C
J29	D
J30	C
J31	D
J37	D
J38	D
J39	D
J40	D
J41	D
J42	D
J42.a	D
J45	D
J46	D
J47	D
J48	D
J49	D
J50	D
J51	C
D33	D
D34	D
D35	D
D36	D

D37	D
D38	D
D39	D
D40	D
D41	D
D42	D
D43	D
D44	D
D45	D
D46	D
D47	D
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D49	D
D50	D
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D52	D
D53	D
D54	D
D55	D
D56	D
D57	D
D58	D
D59	D
D60	D
D61	D
D62	D
D63	D
D64	D
D65	D
D66	D
D67	D
D68	D
D69	D
D70	D
M1	>A
M2	C
M3	C
M4	B
M5	A
M6	A
M7	>A
M8	A
M9	B
M10	>A
M11	C
M12	C
M13	B
M14	B
M15	B
M16	A
M17	B

M18	A
M19	>A
M21	C
M22	A
M23	C
M24	C
M25	C
M26	B
M27	C
M28	A
M28-2	B
M29	>A
M30	C
M31	C
M32	B
M33	C
M34	C
M35	C
M36	C
M37	C
M38	C
M39	C
M40	C
M41	C
M42	C
M43	C
M44	B
M45	C
M46	C
M47	C
M48	C
M49	C
M50	C
M51	C
M52	C
M53	C
M54	C
M55	C
M56	C
M57	C

M58	C
M59	C
M60	C
M61	C
M62	C
M63	C
M64	C
M65	C
M66a	B
M66b	B
M66x	C
M67a	B
M67b	B
M68	B
M69	B
M70	C
M71	C
M72	C
M73	B
M74	C
M75	C
M76	C
M77	C
M78	C
M79	C
M80	C
M81	B
M82	C
M83	C
M84	C
M85	C
M86	C
M87	C
M88	C
M89	C
M90	A
M91	C
M91x	C
M91y	B
M92	A

M93	C
M94	C
M95	C
M96	B
M97	C
M98	C
M99	C
M100	C
M101	B
M102	C
M103	B
M104	B
M105	C
M106	C
M107	C
M108	C
M109	C
M110	C
M111	A
M112	C
M113	C
M114	>A
M115	>A
M116	>A
M117	>A
M118	>A
M119	B
M120	B
M121	B
M122	C
M123	A
M124	C
M125	C
M126	C
M127	C
M128	C
M129	A
M130	C

R26	D
R27	D
R28	D
R34	D
R35	B
R29	D

R36	D
R20	D
R37	D
R33	C

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.

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. Compounds of the present disclosure may inhibit multiple genotypes of HCV.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound selected from

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1S)-2-methyl-1,1-propanediyl)imino((2S)-1-oxo-1,2-propanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1S)-2-methyl-1,1-propanediyl)imino((2S,3R)-3-methoxy-1-oxo-1,2-butanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1S)-2-methyl-1,1-propanediyl)imino((2S)-3-methyl-1-oxo-1,2-butanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1S)-2-methyl-1,1-propanediyl)imino((2S)-4-methoxy-1-oxo-1,2-butanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1R)-2-methyl-1,1-propanediyl)imino((2S)-3-methyl-1-oxo-1,2-butanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1R)-2-methyl-1,1-propanediyl)imino((2S)-1-oxo-1,2-propanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1R)-2-methyl-1,1-propanediyl)imino((2S)-4-methoxy-1-oxo-1,2-butanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1R)-2-methyl-1,1-propanediyl)imino((2S,3R)-3-methoxy-1-oxo-1,2-butanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1R)-2-methyl-1,1-propanediyl)imino((2R)-3-methyl-1-oxo-1,2-butanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1S)-2-methyl-1,1-propanediyl)imino((2R)-3-methyl-1-oxo-1,2-butanediyl)))biscarbamate;

N^2-(methoxycarbonyl)-N-((1S)-1-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-methylpropyl)-L-valinamide;

methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(4-(4'-(2-((1S)-1-((N-(methoxycarbonyl)-O-methyl-L-threonyl)amino)-2-methylpropyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-3-methoxy-1-(((2S)-2-(4-(4'-(2-((1S)-1-((N-(methoxycarbonyl)-O-methyl-L-homoseryl)amino)-2-methylpropyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-2-((2S)-2-(4-(4'-(2-((1S)-1-((N-(methoxycarbonyl)-L-alanyl)amino)-2-methylpropyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

N^2-(methoxycarbonyl)-N-((1R)-1-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-methylpropyl)-L-valinamide;

methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(4-(4'-(2-((1R)-1-((N-(methoxycarbonyl)-O-methyl-L-threonyl)amino)-2-methylpropyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-3-methoxy-1-(((2S)-2-(4-(4'-(2-((1R)-1-((N-(methoxycarbonyl)-O-methyl-L-homoseryl)amino)-2-methylpropyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-2-((2S)-2-(4-(4'-(2-((1R)-1-((N-(methoxycarbonyl)-L-alanyl)amino)-2-methylpropyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1S)-2-methyl-1,1-propanediyl)imino((2S)-1-oxo-1,2-propanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1S)-2-methyl-1,1-propanediyl)imino((2S,3R)-3-methoxy-1-oxo-1,2-butanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1S)-2-methyl-1,1-propanediyl)imino((2S)-3-methyl-1-oxo-1,2-butanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1S)-2-methyl-1,1-propanediyl)imino((2S)-4-methoxy-1-oxo-1,2-butanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1R)-2-methyl-1,1-propanediyl)imino((2S)-3-methyl-1-oxo-1,2-butanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1R)-2-methyl-1,1-propanediyl)imino((2S)-1-oxo-1,2-propanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1R)-2-methyl-1,1-propanediyl)imino((2S)-4-methoxy-1-oxo-1,2-butanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1R)-2-methyl-1,1-propanediyl)imino((2S,3R)-3-methoxy-1-oxo-1,2-butanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1R)-2-methyl-1,1-propanediyl)imino((2R)-3-methyl-1-oxo-1,2-butanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((1S)-2-methyl-1,1-propanediyl)imino((2R)-3-methyl-1-oxo-1,2-butanediyl)))biscarbamate;

N^2-(methoxycarbonyl)-N-((1S)-1-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-methylpropyl)-L-valinamide;

methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(4-(4'-(2-((1S)-1-((N-(methoxycarbonyl)-O-methyl-L-threonyl)amino)-2-methylpropyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-3-methoxy-1-(((2S)-2-(4-(4'-(2-((1S)-1-((N-(methoxycarbonyl)-O-methyl-L-homoseryl)amino)-2-methylpropyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-2-((2S)-2-(4-(4'-(2-((1S)-1-((N-(methoxycarbonyl)-L-alanyl)amino)-2-methylpropyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

N^2-(methoxycarbonyl)-N-((1R)-1-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-methylpropyl)-L-valinamide;

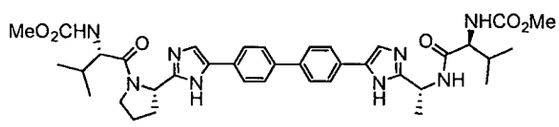
methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(4-(4'-(2-((1R)-1-((N-(methoxycarbonyl)-O-methyl-L-threonyl)amino)-2-methylpropyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-3-methoxy-1-(((2S)-2-(4-(4'-(2-((1R)-1-((N-(methoxycarbonyl)-O-methyl-L-homoseryl)amino)-2-methylpropyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate; and

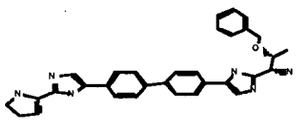
methyl ((1S)-2-((2S)-2-(4-(4'-(2-((1R)-1-((N-(methoxycarbonyl)-L-alanyl)amino)-2-methylpropyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

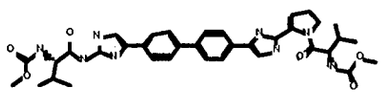
or a pharmaceutically acceptable salt thereof.

2. A compound selected from

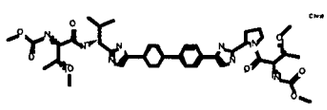


;





; and



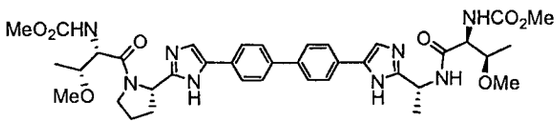
;

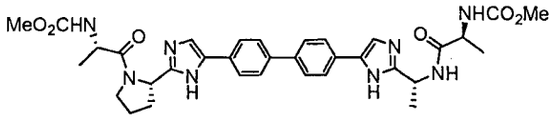
or a pharmaceutically acceptable salt thereof.

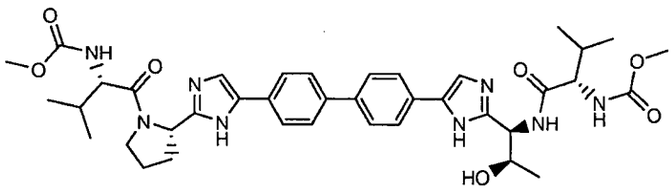
3. A composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

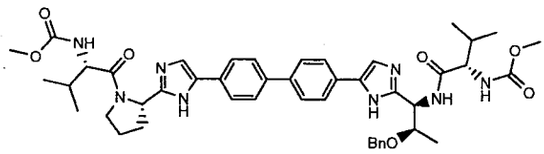
4. The composition of claim 3 further comprising one or two additional compounds having anti-HCV activity.

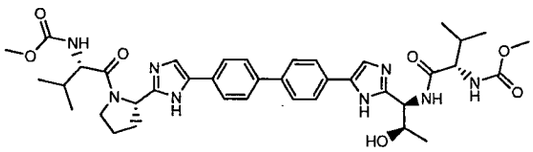
5. The composition of claim 4 wherein at least one of the additional compounds is an interferon or a ribavirin.

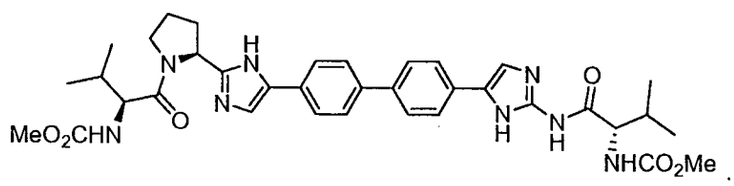

MeO2CHN
MeO
NHCO2Me
OMe
;

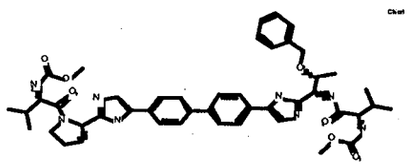

MeO2CHN
NHCO2Me
;


HO
;


BnO
;


HO
;


MeO2CHN
NHCO2Me
;


;

6. The composition of claim 5 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

7. The composition of claim 4 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.

8. The composition of claim 4 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.

9. A composition comprising a compound of claim 2, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

10. The composition of claim 9 further comprising one or two additional compounds having anti-HCV activity.

11. The composition of claim 10 wherein at least one of the additional compounds is an interferon or a ribavirin.

12. The composition of claim 11 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

13. The composition of claim 10 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.

14. The composition of claim 10 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.

15. 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.

16. The method of claim 15 further comprising administering one or two additional compounds having anti-HCV activity prior to, after or simultaneously with the compound of claim 1, or a pharmaceutically acceptable salt thereof.

17. The method of claim 16 wherein at least one of the additional compounds is an interferon or a ribavirin.

18. The method of claim 17 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

19. The method of claim 16 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.

20. The method of claim 16 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 portein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of

an HCV infection.

21. A method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of claim 2, or a pharmaceutically acceptable salt thereof.

22. The method of claim 21 further comprising administering one or two additional compounds having anti-HCV activity prior to, after or simultaneously with the compound of claim 2, or a pharmaceutically acceptable salt thereof.

23. The method of claim 22 wherein at least one of the additional compounds is an interferon or a ribavirin.

24. The method of claim 23 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

25. The method of claim 22 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.

26. The method of claim 22 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 portein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

000317

INHIBIDORES DE VIRUS DE LA HEPATITIS C

Descripción de la Invención

La presente invención está dirigida generalmente a compuestos antivirales, y más específicamente dirigida a compuestos que pueden inhibir la función de la proteína NS5A codificada por virus de la hepatitis C (HCV, por sus siglas en inglés), a composiciones que comprenden estos compuestos y a métodos para inhibir la función de la proteína NS5A.

HCV es un gran patógeno humano, que infecta a un estimado de 170 millones de personas a nivel mundial - casi cinco veces el número infectado por el virus de la inmunodeficiencia humana tipo 1. Una fracción sustancial de estos individuos infectados por HCV desarrolla seria enfermedad hepática progresiva, incluyendo cirrosis y carcinoma hepatocelular.

Actualmente, la terapia contra HCV más efectiva emplea una combinación de alfa-interferón y ribavirina, llevando a eficacia prolongada en 40% de los pacientes. Resultados clínicos recientes demuestran que alfa-interferón pegilado es superior al alfa-interferón no modificado como monoterapia. Sin embargo, incluso con regímenes terapéuticos experimentales que incluyen combinaciones de alfa-interferón pegilado y ribavirina, una fracción sustancial de pacientes no tienen una reducción prolongada en la carga viral. Así,

existe una clara y larga necesidad por desarrollar terapéuticos efectivos para el tratamiento de infección por HCV.

HCV es un virus de ARN de hebra positiva. Con base en una comparación de la secuencia de aminoácidos deducida y la extensa similitud en la región no traducida 5', HCV ha sido clasificado como un género separado de la familia de Flaviviridae. Todos los miembros de la familia Flaviviridae tienen viriones encapsidados que contienen un genoma de ARN de hebra positiva que codifica para todas las proteínas específicas del virus por medio de la traducción de un solo marco de lectura abierto no interrumpido.

Considerable heterogeneidad se encuentra dentro de la secuencia de nucleótidos y aminoácidos codificada a lo largo del genoma de HCV. Por lo menos seis genotipos principales han sido caracterizados, y más de 50 subtipos han sido descritos. Los principales genotipos de HCV difieren en su distribución a nivel mundial, y el significado clínico de la heterogeneidad genética del HCV sigue siendo elusivo a pesar de numerosos estudios del posible efecto de genotipos en patogénesis y terapia.

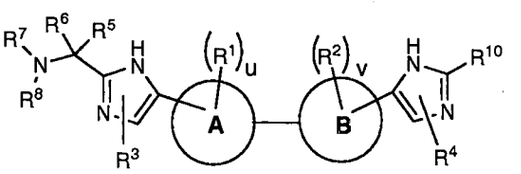
El genoma del ARN de HCV de una sola hebra tiene aproximadamente 9,500 nucleótidos de largo y tiene un solo marco de lectura abierta (ORF, por sus siglas en inglés) que codifica para una sola poliproteína grande de aproximadamente

3,000 aminoácidos. En células infectadas, esta poliproteína es cortada en varios sitios por proteasas celulares y virales para producir las proteínas estructurales y no estructurales (NS, por sus siglas en inglés). En el caso de HCV, la generación de proteínas no estructurales maduras (NS2, NS3, NS4A, NS4B, NS5A y NS5B) se lleva a cabo por dos proteasas virales. Se cree que la primera es una metaloproteasa y corta en la unión NS2-NS3; la segunda es una serina proteasa contenida dentro de la región N-terminal de NS5 (también referida en la presente como proteasa NS3) y media todos los cortes subsecuentes hacia el extremo 3' de NS3; tanto en cis, en el sitio de corte NS3-NS4A, como en trans, para los restantes sitios NS4A-NS4B, NS4B-NS5A, NS5A-NS5B. La proteína NS4A parece tener varias funciones, actuando como un cofactor para la proteasa NS3 y posiblemente ayudando en la ubicación en membrana de NS3 y otros componentes de replicasa virales. La compleja formación de la proteína NS3 con NS4A parece necesaria para los eventos de procesamiento, incrementando la eficiencia proteolítica en todos los sitios. La proteína NS3 también exhibe actividades nucleósido trifosfatasa y ARN helicasa. NS5B (también referido en la presente como HCV polimerasa) es una ARN polimerasa dependiente de ARN que está implicada en la replicación de HCV.

Se desean compuestos útiles para tratar pacientes infectados por HCV los cuales inhiban selectivamente la

replicación del virus HCV. En particular, se desean compuestos que sean efectivos para inhibir la función de la proteína NS5A. La proteína NS5A de HCV se describe, por ejemplo, en Tan, S.-L., Katzel, M.G. *Virology* 2001, *284*, 1-12; y en Park, K.-J.; Choi, S.-H, *J. Biological Chemistry* 2003.

En su primer aspecto la presente invención proporciona un compuesto de la fórmula (I)



(I),

o una sal farmacéuticamente aceptable del mismo, en donde

u y v son independientemente 0, 1, 2 ó 3;

A y B se seleccionan independientemente de fenilo y un anillo heteroaromático de seis miembros que contiene uno, dos o tres átomos de nitrógeno;

cada R^1 y R^2 se seleccionan independientemente de alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, arialcoxicarbonilo, carboxi, formilo, halo, haloalquilo, hidroxi, hidroxialquilo, $-NR^aR^b$, (NR^aR^b)alquilo y (NR^aR^b)carbonilo;

R^3 y R^4 se seleccionan cada uno independientemente de hidrógeno, alcoxicarbonilo, alquilo, arilalcoxicarbonilo, carboxi, haloalquilo, (NR^aR^b)carbonilo, y

trialquilsililalcoxialquilo;

R^5 y R^6 se seleccionan cada uno independientemente de hidrógeno, alquenilo, alcoxialquilo, alquilo, haloalquilo y (NR^aR^b)alquilo; o,

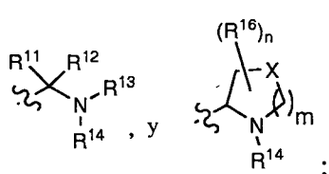
R^5 y R^6, junto con el átomo de carbono al cual están unidos, forman un anillo saturado de cinco o seis miembros que contiene opcionalmente uno o dos heteroátomos seleccionados de NR^z, O y S; en donde R^z se selecciona de hidrógeno y alquilo;

R^7 se selecciona de hidrógeno, R^9-C(O)- y R^9-C(S)-;

R^8 se selecciona de hidrógeno y alquilo;

R^9 se selecciona independientemente de alcoxi, alcoxialquilo, alcoxicarbonilo, alcoxicarbonilalquilo, alquilo, alquilcarbonilalquilo, ario, arilalquenilo, arilalcoxi, arilalquilo, ariloxialquilo, ciclaolquilo, (cicloalquil)alquenilo, (cicloalquil)alquilo, cicloalquiloxialquilo, haloalqulo, heterociclilo, heterociclilaquenilo, heterociclilalcoxi, heterociclilalquilo, heterocicliloxialquilo, hidroxialquilo, $-NR^cR^d$, (NR^cR^d)alquenilo, (NR^cR^d)alquilo y (NR^cR^d)carbonilo;

R^{10} se selecciona de



; en donde

R^{11} y R^{12} son cada uno independientemente

seleccionados de hidrógeno, alquenilo, alcoxialquilo, alquilo, haloalquilo y (NR^aR^b)alquilo; o,

R^{11} y R^{12}, junto con el átomo de carbono al cual están unidos, forman un anillo saturado de cinco o seis miembros que contiene opcionalmente uno o dos heteroátomos seleccionados de NR^z, O y S; en donde R^z se selecciona de hidrógeno y alquilo;

R^{13} se selecciona de hidrógeno y alquilo;

R^{14} se selecciona de hidrógeno, R^{15}-C(O)-, y R^{15}-C(S)-;

R^{15} se selecciona independientemente de alcoxi, alcoxialquilo, alcoxicarbonilo, alcoxicarbonilalquilo, alquilo, alquilcarbonilalquilo, arilo, arilalquenilo, arilalcoxi, arilalquilo, ariloxialquilo, cicloalquilo, (cicloalquil)alquenilo, (cicloalquil)alquilo, cicloalquiloxialquilo, haloalquilo, heterociclilo, heterociclilalquenilo, heterociclilalcoxi, heterociclilalquilo, heterocicliloxialquilo, hidroxialquilo, $-NR^cR^d$, (NR^cR^d)alquenilo, (NR^cR^d)alquilo y (NR^cR^d)carbonilo;

m es 0, 1 ó 2;

n es 0, 1, 2, 3 ó 4;

X se selecciona de O, S, S(O), SO_2, CH_2, CHR^{16} y $C(R^{16})_2$;

siempre que cuando m sea 0, X se seleccione de CH_2, CHR^{16} y $C(R^{16})_2$;

cada R^{16} se selecciona independientemente de alcoxi, alquilo, arilo, halo, haloalquilo, hidroxi y $-NR^aR^b$, en donde el alquilo puede formar opcionalmente un anillo de tres a seis miembros fusionado con un átomo de carbono adyacente, en donde el anillo de tres a seis miembros es sustituido opcionalmente con uno o dos grupos alquilo.

En una primera modalidad del primer aspecto m es 0.

En una segunda modalidad el primer aspecto u y v son cada uno independientemente 0 ó 1; y cada R^1 y R^2 se selecciona independientemente de alquilo y halo.

En una tercera modalidad del primer aspecto u y v son cada uno 0.

En una cuarta modalidad del primer aspecto X se selecciona de CH_2 y CHR^{16}.

En una quinta modalidad del primer aspecto X es CH_2.

En una sexta modalidad del primer aspecto R^3 y R^4 son cada uno independientemente seleccionados de hidrógeno, haloalquilo y trialquilsilalcoxialquilo. En una séptima modalidad R^3 y R^4 se seleccionan cada uno independientemente de hidrógeno y haloalquilo.

En una octava modalidad del primer aspecto n es 0, 1 ó 2; y, cuando está presente, cada R^{16} es halo. En una novena modalidad n es 0.

En una décima modalidad del primer aspecto R^5 y R^6

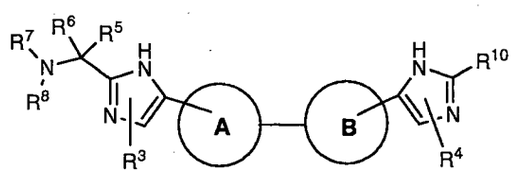
se selecciona independientemente de hidrógeno y alquilo.

En una onceava modalidad del primer aspecto, R^{11} y R^{12} se seleccionan independientemente de hidrógeno y alquilo.

En una doceava modalidad del primer aspecto por lo menos uno de R^7 y R^{14} es hidrógeno.

En una treceava modalidad del primer aspecto R^7 es R^9-C(O)-; y R^{14} y R^{15}-C(O)-. En una catorceava modalidad R^9 y R^{15} se selecciona cada uno independientemente de alcoxi, alcoxiaqluilo, alquilo, alquilcarbonilalquilo, arilo, arilalquenilo, arilalcoxi, arilalquilo, ariloxialquilo, cicloalquilo, (cicloalquil)alquilo, cicloalquiloxialquilo, heterociclilo, heterociclilalquilo, hidroxialquilo, $-NR^cR^d$, (NR^cR^d)alquenilo, (NR^cR^d)alquilo y (NR^cR^d)carbonilo. En una quinceava modalidad R^9 y R^{15} se seleccionan cada uno independientemente de alcoxi, arilalcoxi, arilalquilo y (NR^cR^d)alquilo.

En un segundo aspecto la presente invención proporciona un compuesto de la fórmula (II)



(II),

o una sal farmacéuticamente aceptable del mismo, en donde

A y B se seleccionan independientemente de fenilo y un anillo heteroaromático de seis miembros que contiene uno,

dos o tres átomos de nitrógeno;

R^3 y R^4 se seleccionan cada uno independientemente de hidrógeno, haloalquilo y trialquilsililacoxialquilo;

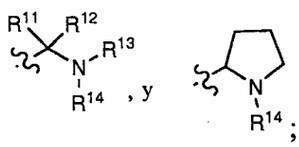
R^5 y R^6 se seleccionan cada uno independientemente de hidrógeno y alquilo;

R^7 se selecciona de hidrógeno y R^9-C(O)-;

R^8 se selecciona de hidrógeno y alquilo;

R^9 se selecciona independientemente de alcoxi, arilalcoxi, arilalquilo y (NR^cR^d)alquilo;

R^{10} se selecciona de



; en donde

R^{11} y R^{12} se seleccionan cada uno independientemente de hidrógeno y alquilo;

R^{13} se selecciona de hidrógeno y alquilo;

R^{14} se selecciona de hidrógeno y R^{15}-C(O)-; y

R^{15} se selecciona independientemente de alcoxi, arilalcoxi, arilalquilo y (NR^cR^d)alquilo.

En un tercer aspecto la presente invención proporciona una composición que comprende un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, y un portador farmacéuticamente aceptable. En una primera modalidad del tercer aspecto, la composición comprende uno o dos compuestos adicionales que tienen actividad anti-HCV. En

una segunda modalidad del tercer aspecto por lo menos uno de los compuestos adicionales es un interferón o una ribavirina. En una tercera modalidad del tercer aspecto el interferón se selecciona de interferón alfa 2B, interferón alga pegilado, interferón de consenso, interferón alfa 2A, e interferón linfoblastoide tau.

En una cuarta modalidad del tercer aspecto la presente invención proporciona una composición que comprende un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, un portador farmacéuticamente aceptable y uno o dos compuestos adicionales que tienen actividad anti-HCV, en donde al menos uno de los compuestos adicionales se selecciona de interleucina 2, interleucina 6, interleucina 12, un compuesto que incrementa el desarrollo de una respuesta a células T auxiliares tipo 1, ARN de interferencia, ARN anti-sentido, imiquimod, ribavirina, un inhibidor de inosín 5'-monofosfato deshidrogenasa, amantadina y rimantadina.

En una quinta modalidad del tercer aspecto la presente invención proporciona una composición que comprende un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, un portador farmacéuticamente aceptable, y uno o dos compuestos adicionales que tienen actividad anti-HCV, en donde al menos uno de los compuestos adicionales es efectivo para inhibir la función de un objetivo seleccionado

de metaloproteasa de HCV, serina proteasa de HCV, polimerasa de HCV, helicasa de HCV, proteína NS4B de HCV, entrada a HCV, ensamble de HCV, salida de HCV, proteína NS5A de HCV e IMPDH para el tratamiento de una infección por HCV.

En un cuarto aspecto la presente invención proporciona un método para tratar una infección por HCV en un paciente, que comprende administrar al paciente una cantidad terapéuticamente efectiva de un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo. En una primera modalidad del cuarto aspecto el método comprende además administrar uno o dos compuestos adicionales que tengan actividad anti-HCV antes de, después o simultáneamente con el compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo. En una segunda modalidad del cuarto aspecto por lo menos uno de los compuestos adicionales es un interferón o una ribavirina. En una tercera modalidad del cuarto aspecto el interferón se selecciona de interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A, e interferón linfoblastoide tau.

En una cuarta modalidad del cuarto aspecto de la presente invención proporciona un método para tratar una infección por HCV en un paciente, que comprende administrar al paciente una cantidad terapéuticamente efectiva de un compuesto de la fórmula (I), o una sal farmacéuticamente

aceptable del mismo y administrar uno o dos compuestos adicionales que tengan actividad anti-HCV antes de, después o simultáneamente con el compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde por lo menos uno de los compuestos adicionales se selecciona de interleucina 2, interleucina 6, interleucina 12, un compuesto que incrementa el desarrollo de una respuesta a células T auxiliares tipo 1, ARN de interferencia, ARN antisentido, imiquimod, ribavirina, un inhibidor de inosín 5'-monofosfato deshidrogenasa, amantadina y rimantadina.

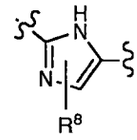
En una quinta modalidad del cuarto aspecto la presente invención proporciona un método para tratar una infección por HCV en un paciente, que comprende administrar al paciente una cantidad terapéuticamente efectiva de un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo y administrar uno o dos compuestos adicionales que tengan actividad anti-HCV antes de, después o simultáneamente con el compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde al menos uno de los compuestos adicionales es efectivo para inhibir la función de un objetivo seleccionado de metaloproteasa de HCV, serina proteasa de HCV, polimerasa de HCV, helicasa de HCV, proteína NS4B de HCV, entrada HCV, ensamble de HCV, salida de HCV, proteína NS5A de HCV e IMPDH para el tratamiento de una infección por HCV.

Otras modalidades de la presente invención pueden comprender combinaciones adecuadas de dos o más de las modalidades y/o aspectos descritos en la presente.

Otras modalidades y aspectos más de la invención se harán evidentes de acuerdo con la descripción proporcionada abajo.

Los compuestos de la presente invención existen también como tautómeros; por lo tanto la presente invención abarca también todas las formas tautoméricas.

La descripción de la presente invención debe considerarse aquí en congruencia con las leyes y principios de enlace químico. En algunos casos puede ser necesario remover un átomo de hidrógeno para de esta manera recibir un sustituyente en cualquier lugar dado. Por ejemplo, en la estructura mostrada abajo



R^8 puede ser unido ya sea al átomo de carbono en el anillo de imidazol o, alternativamente,

R^8 puede tener el lugar del átomo de hidrógeno en el anillo de nitrógeno para formar un imidazol N-sustituido.

Se debe entender que los compuestos abarcados por la presente invención son aquellos que son adecuadamente estables para usarse como un agente farmacéutico.

Se intenta que la definición de cualquier sustituyente o variable (por ejemplo, R^1, R^2, R^5, R^6, etc.) en un lugar particular en una molécula sea independiente de sus definiciones en cualquier lado en esa molécula. Por ejemplo, cuando u es 2, cada uno de los dos grupos R^1 pueden ser iguales o diferentes.

Todas las patentes, solicitudes de patente y referencias a la literatura citadas en la descripción se incorporan en la presente a manera de referencia en su totalidad. En el caso de inconsistencias, la presente invención, incluyendo las definiciones, prevalecerán.

Según se usa en la presente descripción, los siguientes términos tienen los significados indicados:

Según se usa en la presente, las formas singulares "un", "uno", "una" y "el", "la" incluyen referencias plurales a menos que el contexto claramente dicte lo contrario.

A menos que se indique lo contrario, todos los grupos arilo, cicloalquilo y heterociclilo de la presente invención pueden ser sustituidos como se describe en cada una de sus definiciones respectivas. Por ejemplo, la parte arilo de un grupo arilalquilo puede ser sustituida como se describe en la definición del término "arilo".

El término "alquenilo", según se usa en la presente, se refiere a un grupo de cadena recta o ramificada de dos a seis átomos de carbono que contiene al menos un

doble enlace carbono-carbono.

El término "alqueniloxi", según se usa en la presente, se refiere a un grupo alquenilo unido a la porción molecular de origen a través de un átomo de oxígeno.

El término "alqueniloxicarbonilo" según se usa en la presente, se refiere a un grupo alqueniloxi unido en la porción molecular de origen a través de un grupo carbonilo.

El término "alcoxi", según se usa en la presente, se refiere a un grupo alquilo unido a la porción molecular de origen a través de un átomo de oxígeno.

El término "alcoxialquilo", según se usa en la presente, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos alcoxi.

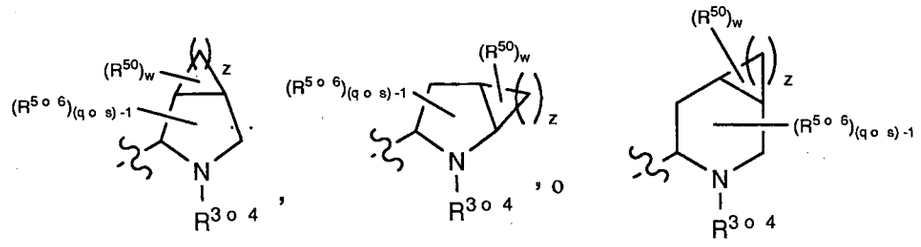
El término "alcoxialquilcarbonilo", según se usa en la presente, se refiere a un grupo alcoxialquilo unido a la porción molecular de origen a través de un grupo carbonilo.

El término "alcoxicarbonilo", según se usa en la presente, se refiere a un grupo alcoxi unido a la porción molecular de origen a través de un grupo carbonilo.

El término "alcoxicarbonilalquilo", según se usa en la presente, se refiere a un grupo alquilo sustituido con uno, dos, o tres grupos alcoxicarbonilo.

El término "alquilo" según se usa en la presente, se refiere a un grupo derivado de un hidrocarburo saturado de cadena recta o ramificada que contiene de uno a seis átomos

de carbono. En los compuestos de la presente invención, cuando m y/o n es 1 ó 2; X y/o Y es CHR^5 y/o CHR^6, respectivamente, y R^5 y/o R^6 es alquilo, cada alquilo puede formar opcionalmente un anillo de tres a seis miembros fusionado con un átomo de carbono adyacente para proporcionar una de las estructuras mostradas a continuación:



en donde z es 1, 2, 3 ó 4, w es 0, 1 ó 2 y R^{50} es alquilo. Cuando w es 2, los dos grupos alquilo R^{50} pueden ser iguales o diferentes.

El término "alquilcarbonilo", según se usa en la presente, se refiere a un grupo alquilo unido a la porción molecular de origen a través de un grupo carbonilo.

El término "alquilcarbonilalquilo", según se usa en la presente, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos alquilcarbonilo.

El término "alquilcarboniloxi", según se usa en la presente, se refiere a un grupo alquilcarbonilo unido a la porción molecular de origen a través de un átomo de oxígeno.

El término "alquilsulfanilo", según se usa en la presente, se refiere a un grupo alquilo unido a la porción molecular de origen a través de un átomo de azufre.

El término "alquilsulfonilo", según se usa en la presente, se refiere a un grupo alquilo unido a la porción molecular de origen a través de un grupo sulfonilo.

El término "arilo", según se usa en la presente, se refiere a un grupo fenilo, o a un sistema de anillo fusionado bicíclico en el que uno o ambos de los anillos es un grupo fenilo. Los sistemas de anillo fusionado bicíclico consisten en un grupo fenilo fusionado a un anillo carbocíclico aromático o no aromático de cuatro a seis miembros. Los grupos arilo de la presente invención pueden ser unidos a la porción molecular de origen a través de cualquier átomo de carbono sustituible en el grupo. Ejemplos representativos de grupos arilo incluyen, pero no están limitados a, indanilo, indenilo, naftilo, fenilo y tetrahidronaftilo. Los grupos arilo de la presente invención son sustituidos opcionalmente con uno, dos, tres, cuatro o cinco sustituyentes seleccionados independientemente de alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, alquilcarbonilo, un segundo grupo arilo, arilalcoxi, arilalquilo, arilcarbonilo, ciano, halo, haloalcoxi, haloalquilo, heterociclilo, heterocicloalquilo, heterociclilcarbonilo, hidroxi, hidroxialquilo, nitro, $-NR^XR^Y$, (NR^XR^Y)alquilo, oxo y $-P(O)OR_2$, en donde cada R se selecciona independientemente de hidrógeno y alquilo; y en donde la parte alquilo del arilalquilo y el heterociclilalquilo es sustituida y en donde el segundo grupo arilo, la parte arilo

del arilalquilo, la parte arilo del arilcarbonilo, el heterociclilo y la parte heterociclilo del heterociclilalquilo y el heterociclilcarbonilo son además sustituidos opcionalmente con uno, dos o tres sustituyentes seleccionados independientemente de alcoxi, alquilo, ciano, halo, haloalcoxi, haloalquilo y nitro.

El término "arilalquenilo", según se usa en la presente, se refiere a un grupo alquenilo sustituido con uno, dos o tres grupos arilo.

El término "arilalcoxi", según se usa en la presente, se refiere a un grupo arilo unido a la porción molecular de origen a través de un grupo alcoxi.

El término "arilalcoxialquilo", según se usa en la presente, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos arilalcoxi.

El término "arilalcoxialquilcarbonilo", según se usa en la presente, se refiere a un grupo arilalcoxialquilo unido a la porción molecular de origen a través de un grupo carbonilo.

El término "arilalcoxicarbonilo", según se usa en la presente, se refiere a un grupo arilalcoxi unido a la porción molecular de origen a través de un grupo carbonilo.

El término "arilalquilo", según se usa en la presente, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos arilo. La parte alquilo del arilalquilo es

además sustituido opcionalmente con uno o dos grupos adicionales seleccionados independientemente de alcoxi, alquilcarboniloxi, halo, haloalcoxi, haloalquilo, heterociclilo, hidroxi y $-NR^cR^d$, en donde el heterociclilo es además sustituido opcionalmente con uno o dos sustituyentes seleccionados independientemente de alcoxi, alquilo, arilo no sustituido, arilalcoxi no sustituido, arilalcoxicarbonilo no sustituido, halo, haloalcoxi, haloalquilo, hidroxi y $-NR^xR^y$.

El término "arilalquilcarbonilo", según se usa en la presente, se refiere a un grupo arilalquilo unido a la porción molecular de origen a través de un grupo carbonilo.

El término "arilcarbonilo", según se usa en la presente, se refiere a un grupo arilo unido a la porción molecular de origen a través de un grupo carbonilo.

El término "ariloxi", según se usa en la presente, se refiere a un grupo arilo unido a la porción molecular de origen a través de un átomo de oxígeno.

El término "ariloxialquilo", según se usa en la presente, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos ariloxi.

El término "ariloxicarbonilo", según se usa en la presente, se refiere a un grupo ariloxi unido a la porción molecular de origen a través de un grupo carbonilo.

El término "arilsulfonilo", según se usa en la presente, se refiere a un grupo arilo unido a la porción

molecular de origen a través de un grupo sulfonilo.

Los términos "Extremo" y "extremo" según se usa en la presente, se refieren al grupo que está puesto en el átomo de nitrógeno del anillo que contiene nitrógeno terminal, es decir, los anillos de pirrolidina del compuesto 1e. Debe entenderse que "Extremo" o "extremo" se puede referir al reactivo usado para anexar el grupo al anillo que contiene nitrógeno terminal o al fragmento en el producto final, es decir, "Extremo-51" o "el fragmento Extremo-51 encontrado en LS-19".

El término "carbonilo", según se usa en la presente, se refiere a -C(O)-.

El término "carboxi", según se usa en la presente, se refiere a $-CO_2H$.

El término "ciano", según se usa en la presente, se refiere a -CN.

El término "cicloalquilo", según se usa en la presente, se refiere a un sistema de anillo hidrocarburo monocíclico saturado que tiene tres a siete átomos de carbono y cero heteroátomos. Ejemplos representativos de grupos cicloalquilo incluyen, pero no están limitados a, ciclopropilo, ciclopentilo y ciclohexilo. Los grupos cicloalquilo de la presente invención son sustituidos opcionalmente con uno, dos, tres, cuatro o cinco sustituyentes seleccionados independientemente de alcoxi,

alquilo, arilo, ciano, halo, haloalcoxi, haloalquilo, heterociclilo, hidroxi, hidroxialquilo, nitro y $-NR^xR^y$, en donde el arilo y el heterociclilo son además sustituidos opcionalmente con uno, dos o tres sustituyentes seleccionados independientemente de alcoxi, alquilo, ciano, halo, haloalcoxi, haloalquilo, hidroxi y nitro.

El término "(cicloalquil)alquenilo", según se usa en la presente, se refiere a un grupo alquenilo sustituido con uno, dos o tres grupos cicloalquilo.

El término "(cicloalquil)alquilo", según se usa en la presente, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos cicloalquilo. La parte alquilo del (cicloalquil)alquilo es además sustituido opcionalmente con uno o dos grupos seleccionados independientemente de hidroxi y $-NR^cR^d$.

El término "cicloalquiloxi", según se usa en la presente, se refiere a un grupo cicloalquilo unido a la porción molecular de origen a través de un átomo de oxígeno.

El término "cicloalquiloxialquio", según se usa en la presente, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos cicloalquiloxi.

El término "cicloalquilsulfonilo", según se usa en la presente, se refiere a un grupo cicloalquilo unido a la porción molecular de origen a través de un grupo sulfonilo.

El término "formilo", según se usa en la presente,

se refiere a -CHO.

Los términos "halo" y "halógeno", según se usan en la presente, se refieren a F, Cl, Br o I.

El término "haloalcoxi", según se usa en la presente, se refiere a un grupo haloalquilo unido a la porción molecular de origen a través de un átomo de oxígeno.

El término "haloalcoxicarbonilo", según se usa en la presente, se refiere a un grupo haloalcoxi unido a la porción molecular de origen a través de un grupo carbonilo.

El término "haloalquilo", según se usa en la presente, se refiere a un grupo alquilo sustituido por uno, dos, tres o cuatro átomos de halógeno.

El término "heterociclilo", según se usa en la presente, se refiere a un anillo de cuatro, cinco, seis o siete miembros que contiene uno, dos, tres o cuatro heteroátomos seleccionados independientemente de nitrógeno, oxígeno y azufre. El anillo de cuatro miembros tiene cero dobles enlaces, el anillo de cinco miembros tiene cero a dos dobles enlaces, y los anillos de seis y siete miembros tienen cero a tres dobles enlaces. El término "heterociclilo" también incluyen grupos bicíclicos en los cuales el anillo heterociclilo está fusionado a otro grupo heterociclilo monocíclico, o un anillo carbocíclico aromático o no aromático de cuatro a seis miembros, así como grupos bicíclicos puenteados tales como 7-azabiciclo[2.2.1]hept-7-

ilo, 2-azabiciclo[2.2.2]oct-2-tilo y 2-azabiciclo[2.2.2]oc-3-tilo. Los grupos heterociclilo de la presente invención pueden ser unidos a la porción molecular de origen a través de cualquier átomo de carbono o átomo de nitrógeno en el grupo. Ejemplos de grupos heterociclilo incluyen, pero no están limitados a, benzotienilo, furilo, imidazolilo, indolinilo, indolilo, isotiazolilo, isoxazolilo, morfolinilo, oxazolilo, piperazinilo, piperidinilo, pirazolilo, piridinilo, pirrolidinilo, pirrolopiridinilo, pirrolilo, tiazolilo, tienilo, tiomorfolinilo, 7-azabiciclo[2.2.1]hept-7-ilo, 2-azabiciclo[2.2.2]oc-2-tilo y 2-azabiciclo[2.2.2]oc-3-tilo. Los grupos heterociclilo de la presente invención son sustituidos opcionalmente con uno, dos, tres, cuatro o cinco sustituyentes seleccionados independientemente de alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, alquilcarbonilo, arilo, arilalquilo, arilcarbonilo, ciano, halo, haloalcoxi, haloalquilo, un segundo grupo heterociclilo, heterociclilalquilo, heterociclilcarbonilo, hidroxi, hidroxialquilo, nitro, $-NR^XR^Y$, (NR^XR^Y)alquilo y oxo, en donde la parte alquilo del arilalquilo y el heterociclilalquilo es no sustituida y en donde el arilo, la parte arilo del arilalquilo, la parte arilo del arilcarbonilo, el segundo grupo heterociclilo y la parte heterociclilo del heterociclilalquilo y el heterociclilcarbonilo son además sustituidos opcionalmente

con uno, dos o tres sustituyentes seleccionados independientemente de alcoxi, alquilo, ciano, halo, haloalcoxi, haloalquilo y nitro.

El término "heterociclilalquenilo", según se usa en la presente, se refiere a un grupo alquenilo sustituido con uno, dos o tres grupos heterociclilo.

El término "heterociclilalcoxi", según se usa en la presente, se refiere a un grupo heterociclilo unido a la porción molecular de origen a través de un grupo alcoxi.

El término "heterociclilalcoxicarbonilo", según se usa en la presente, se refiere a un grupo heterociclialcoxi unido a la porción molecular de origen a través de un grupo carbonilo.

El término "heterociclilalquilo", según se usa en la presente, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos heterociclilo. La parte alquilo del heterociclilalquilo es además sustituido opcionalmente con uno o dos grupos adicionales seleccionados independientemente de alcoxi, alquilcarboniloxi, arilo, halo, haloalcoxi, haloalquilo, hidroxi y $-NR^cR^d$, en donde el arilo es además sustituido opcionalmente con uno a dos sustituyentes seleccionados independientemente de alcoxi, alquilo, arilo no sustituido, arilalcoxi no sustituido, arilalcoxicarbonilo no sustituido, halo, haloalcoxi, haloalquilo, hidroxi y $-NR^xR^y$.

El término "heterociclilalquilcarbonilo", según se

usa en la presente, se refiere a un grupo heterociclilalquilo unido a la porción molecular de origen a través de un grupo carbonilo.

El término "heterociclilcarbonilo", según se usa en la presente, se refiere a un grupo heterociclilo unido a la porción molecular de origen a través de un grupo carbonilo.

El término "heterocicliloxi", según se usa en la presente, se refiere a un grupo heterociclilo unido a la porción molecular de origen a través de un átomo de oxígeno.

El término "heterocicliloxialquilo", según se usa en la presente, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos heterocicliloxi.

El término "heterocicliloxicarbonilo", según se usa en la presente, se refiere a un grupo heterocicliloxi unido a la porción molecular de origen a través de un grupo carbonilo.

El término "hidroxi", según se usa en la presente, se refiere a -OH.

El término "hidroxialquilo", según se usa en la presente, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos hidroxi.

El término "hidroxialquilcarbonilo", según se usa en la presente, se refiere a un grupo hidroxialquilo unido a la porción molecular de origen a través de un grupo carbonilo.

El término "nitro", según se usa en la presente, se refiere a $-NO_2$.

El término "$-NR^aR^b$", según se usa en la presente, se refiere a dos grupos, R^a y R^b, los cuales están unidos a la porción molecular de origen a través de un átomo de nitrógeno. R^a y R^b se seleccionan independientemente de hidrógeno, alquenilo y alquilo.

El término "(NR^aR^b)alquilo", según se usa en la presente, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos $-NR^aR^b$.

El término "(NR^aR^b)carbonilo", según se usa en la presente, se refiere a un grupo $-NR^aR^b$ unido a la porción molecular de origen a través de un grupo carbonilo.

El término "$-NR^cR^b$", según se usa en la presente, se refiere a dos grupos R^c y R^d, los cuales están unidos a la porción molecular de origen a través de un átomo de nitrógeno. R^c y R^d se seleccionan independientemente de hidrógeno, alqueniloxicarbonilo, alcoxialquilcarbonilo, alcoxicarbonilo, alquilo, alquilcarbonilo, alquilsulfonilo, arilo, arilalcoxicarbonilo, arilalquilo, arilalquilcarbonilo, arilcarbonilo, alquilsulfonilo, arilo, arilalcoxicarbonilo, arilalquilo, arilalquilcarbonilo, arilcarbonilo, ariloxicarbonilo, arilsulfonilo, cicloalquilo, cicloalquilsulfonilo, formilo, haloalcoxicarbonilo, heterociclilo, heterocicilalcoxicarbonilo, heterociclilalquilo, heterociclilalquilcarbonilo, heterociclilcarbonilo,

heterocicliloxicarbonilo, hidroxialquilcarbonilo, (NR^eR^f)alquilo, (NR^eR^f)alquilcarbonilo, (NR^eR^f)carbonilo, (NR^eR^f)sulfonilo, -C(NCN)OR', y $-C(NCN)NR^xR^y$, en donde R' se selecciona de alquilo y fenilo no sustituido, y en donde la parte alquilo del arilalquilo, el arilalquilcarbonilo, el heterociclilalquilo, y el heterociclilalquilcarbonilo es sustituido opcionalmente además con un grupo $-NR^eR^f$; y en donde el arilo, la parte arilo del arilalcoxicarbonilo, el arilalquilo, el arilalquilcarbonilo, el arilcarbonilo, el ariloxicarbonilo y el arilsulfonilo, el heterociclilo y la parte heterociclilo del heterociclilalcoxicarbonilo, el heterociclilalquilo, el heterociclilalquilcarbonilo, el heterociclilcarbonilo, y el heterocicliloxicarbonilo es sustituido opcionalmente además con uno, dos o tres sustituyentes seleccionados independientemente de alcoxi, alquilo, ciano, halo, haloalcoxi, haloalquilo y nitro.

El término "(NR^cR^d)alquenilo", según se usa en la presente, se refiere a un grupo alquenilo sustituido con uno, dos o tres grupos $-NR^cR^d$.

El término "(NR^cR^d)alquilo", según se usa en la presente, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos $-NR^cR^d$. La parte alquilo del (NR^cR^d)alquilo es además sustituido opcionalmente con uno o dos grupos adicionales seleccionados de alcoxi, alcoxialquilcarbonilo, alcoxicarbonilo, alquilsulfanilo, arilalcoxialquilcarbonilo,

carboxi, heterociclilo, heterociclilcarbonilo, hidroxi y (NR^eR^f)carbonilo; en donde el heterociclilo es además sustituido opcionalmente con uno, dos, tres, cuatro o cinco sustituyentes seleccionados independientemente de alcoxi, alquilo, ciano, halo, haloalcoxi, haloalquilo y nitro.

El término "(NR^cR^d)carbonilo", según se usa en la presente, se refiere a un grupo $-NR^cR^d$, unido a la porción molecular de origen a través de un grupo carbonilo.

El término "$-NR^eR^f$", según se usa en la presente, se refiere a dos grupos, R^e y R^f, los cuales están unidos a la porción molecular de origen a través de un átomo de nitrógeno. R^e y R^f se seleccionan independientemente de hidrógeno, alquilo, arilo no sustituido, arilalquilo no sustituido, cicloalquilo no sustituido, (cicloalquil)aquilo no sustituido, heterociclilo no sustituido, heterociclilalquilo no sustituido, (NR^xR^y)alquilo y (NR^xR^y)carbonilo.

El término "(NR^eR^f)alquilo", según se usa en la presente, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos $-NR^eR^f$.

El término "(NR^eR^f)alquilcarbonilo", según se usa en la presente, se refiere a un grupo (NR^eR^f)alquilo unido a la porción molecular de origen a través de un grupo carbonilo.

El término "(NR^eR^f)carbonilo", según se usa en la presente, se refiere a un grupo $-NR^eR^f$ unido a la porción

molecular de origen a través de un grupo carbonilo.

El término "(NR^eR^f)sulfonilo", según se usa en la presente, se refiere a un grupo $-NR^eR^f$ unido a la porción molecular de origen a través de un grupo sulfonilo.

El término "NR^xR^y", según se usa en la presente, se refiere a dos grupos, R^x y R^y, los cuales están unidos a la porción molecular de origen a través de un átomo de nitrógeno. R^x y R^y se seleccionan independientemente de hidrógeno, alcoxicarbonilo, alquilo, alquilcarbonilo, arilo no sustituido, arilalcoxicarbonilo no sustituido, arilalquilo no sustituido, cicloalquilo no sustituido, heterociclilo no sustituido, y $(NR^{x'}R^{y'})$carbonilo, en donde $R^{x'}$ y $R^{y'}$ se seleccionan independientemente de hidrógeno y alquilo.

El término "(NR^xR^y)alquilo", según se usa en la presente, se refiere al grupo alquilo sustituido con uno, dos o tres grupos $-NR^xR^y$.

El término "oxo", según se usa en la presente, se refiere a =O.

El término "sulfonilo", según se usa en la presente, se refiere a $-SO_2-$.

El término "trialquilsililo", según se usa en la presente, se refiere a $-SiR_3$, en donde R es alquilo.

Los grupos R pueden ser iguales o diferentes.

El término "trialquilsililalquilo", según se usa en la presente, se refiere a un grupo alquilo sustituido con

uno, dos o tres grupos trialquilsililo.

El término "trialquilsililalcoxi", según se usa en la presente, se refiere a un grupo trialquilsililalquilo unido a la porción molecular de origen a través de un átomo de oxígeno.

El término "trialquilsililacoxialquilo", según se usa en la presente, se refiere a un grupo alquilo sustituido con uno, dos o tres grupos trialquililalcoxi.

Existen centros asimétricos en los compuestos de la presente invención. Estos centros están designados por los símbolos "R" o "S", dependiendo de la configuración de los sustituyentes alrededor del átomo de carbono quiral. Debe entenderse que la invención abarca todas las formas isoméricas estereoquímicas, o mezclas de las mismas, que poseen la capacidad de inhibir NS5A. Estereoisómeros individuales de compuestos pueden prepararse sintéticamente a partir de materiales de partida disponibles comercialmente los cuales contengan centros quirales o mediante la preparación de mezclas de productos enantioméricos seguida por la separación tal como conversión en una mezcla de diastereómeros seguida por separación o recristalización, técnicas cromatográficas o separación directa de enantiómeros en columnas cromatográficas quirales. Los compuestos de partida de estereoquímica particular están ya sea disponibles comercialmente o pueden elaborarse y resolverse mediante

técnicas conocidas en la técnica.

Ciertos compuestos de la presente invención también pueden existir en diferentes formas conformadoras estables las cuales pueden ser separables. La asimetría torsional debido a la rotación restringida alrededor de un solo enlace asimétrico, por ejemplo debido al impedimento estérico o tensión del anillo, puede permitir la separación de diferentes conformadores. La presente invención incluye cada isómero conformador de estos compuestos y mezclas de los mismos.

El término "compuestos de la presente invención", y expresiones equivalentes, intentan abarcar compuestos de la fórmula (I), y enantiómeros, diastereómeros y sales farmacéuticamente aceptables de los mismos. De manera similar, las referencias a intermediarios intentan abarcar sus sales cuando el contexto así lo permita.

Los compuestos de la presente invención pueden existir como sales farmacéuticamente aceptables. El término "sal farmacéuticamente aceptable", según se usa en la presente, representa sales o formas zwitteriónicas de los compuestos de la presente invención las cuales son solubles o dispersables en agua o aceite, y las cuales son, dentro del alcance de juicio médico correcto, adecuadas para usarse en contacto con los tejidos de pacientes sin toxicidad, irritación, respuesta alérgica excesivas u otro problema o

complicación de acuerdo con una relación beneficio/riesgo razonable, y son efectivos para su uso deseado. Las sales pueden prepararse durante el aislamiento y purificación finales de los compuestos o por separado al hacer reaccionar un átomo de nitrógeno adecuado con un ácido adecuado. Las sales de adición con ácido representativas incluyen acetato, adipato, alginato, citrato, aspartato, benzoato, bencensulfonato, bisulfato, butirato, alcanforato, alcanforsulfonato; digluconato, dibromhidrato, diclorhidrato, diyodhidrato, glicerofosfato, hemisulfato, heptanoato, hexanoato, formiato, fumarato, clorhidrato, bromhidrato, yodhidrato, 2-hidroxietansulfonato, lactato, maleato, mesitilensulfonato, metansulfonato, naftilensulfonato, nicotinato, 2-naftalensulfonato, oxalato, palmoato, pectinato, persulfato, 3-fenilpropionato, picrato, pivalato, propionato, succinato, tartrato, tricloroacetato, trifluoroacetato, fosfato, glutamato, bicarbonato, para-toluensulfonato y undecanoato. Ejemplos de ácidos que pueden emplearse para formar sales de adición farmacéuticamente aceptables incluyen ácidos inorgánicos tales como clorhídrico, bromhídrico, sulfúrico y fosfórico, y ácidos orgánicos tales como oxálico, maleico, succínico y cítrico.

Las sales de adición básicas pueden prepararse durante el aislamiento y purificación finales de los compuestos al hacer reaccionar un grupo carboxi con una base

adecuada tal como el hidróxido, carbonato o bicarbonato de un catión metálico o con amoniaco o una amina primaria, segundaria o terciaria orgánica. Los cationes de las sales farmacéuticamente aceptables incluyen litio, sodio, potasio, calcio, magnesio y aluminio, así como cationes de amina cuaternaria no tóxicos tales como amonio, tetrametilamonio, tetraetilamonio, metilamina, dimetilamina, trimetilamina, trietilamina, dietilamina, etilamina, tributilamina, piriina, 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 con bases incluyen etilendiamina, etanolamina, dietanolamina, piperidina y piperazina.

Cuando es posible que, para usarse en terapia, cantidades terapéuticamente efectivas de un compuesto de la fórmula (I); así como sales farmacéuticamente aceptables del mismo, puedan administrarse como el químico crudo, es posible presentar el ingrediente activo como una composición farmacéutica. En consecuencia, la invención proporciona además composiciones farmacéuticas, las cuales incluyen cantidades terapéuticamente efectivas de los compuestos de la fórmula (I) o sales farmacéuticamente aceptables de los mismos, y uno o más portadores, diluyentes o excipientes farmacéuticamente aceptables. El término "cantidad

terapéuticamente efectiva", según se usa en la presente, se refiere a la cantidad total de cada componente activo que es suficiente para mostrar un beneficio significativo para el paciente, por ejemplo, una reducción en la carga viral. Cuando se aplica a un ingrediente 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 ingredientes activos que dan como resultado el efecto terapéutico, cuando se administran en combinación, en serie o simultáneamente. Los compuestos de la fórmula (I) y sales farmacéuticamente aceptables de los mismos son como se describió arriba. Los portadores, diluyentes o excipientes deben ser aceptables en el sentido de ser compatibles con los demás ingredientes de la formulación y no dañinas para el receptor de la misma. De acuerdo con otro aspecto de la presente invención se proporciona también un procedimiento 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 portadores, diluyentes o excipientes farmacéuticamente aceptables. El término "farmacéuticamente aceptable", según se usa en la presente, se refiere a aquellos compuestos, materiales, composiciones y/o formas de dosis las cuales sean, dentro del alcance del juicio médico correcto, adecuados para usarse en contacto con los tejidos

de pacientes, sin toxicidad, irritación, respuesta alérgica excesivas u otro problema o complicación de acuerdo con una relación beneficio/riesgo razonable, y son efectivos para su uso deseado.

Las formulaciones farmacéuticas pueden presentarse en forma de dosis única que contengan una cantidad predeterminada de ingrediente activo por dosis única. Los niveles de dosificación de entre alrededor de 0.01 y aproximadamente 250 miligramos por kilogramo ("mg/kg") de peso corporal al día, de preferencia entre alrededor de 0.05 y aproximadamente 100 mg/kg de peso corporal al día de los compuestos de la presente invención son típicamente en una monoterapia para la prevención y el tratamiento de enfermedades mediadas por HCV. Típicamente, las composiciones farmacéuticas de esta invención se administrarán de alrededor de 1 a aproximadamente 5 veces al día o como alternativa, como una infusión continua. Esta administración se puede usar como una terapia crónica o aguda. La cantidad de ingrediente activo que se puede combinar con los materiales portadores para producir una sola forma de dosis variará dependiendo de la afección que se esté tratando, la severidad de la afección, el tiempo de administración, la ruta de administración, la velocidad de excreción del compuesto empleado, la duración del tratamiento y la edad, género, peso y condición del paciente. Las

formulaciones de dosis única que se prefieren son aquellas que contienen una dosis o sub-dosis diaria, como la definida arriba, o una fracción adecuada de la misma, del ingrediente activo. El tratamiento puede ser iniciado con dosis pequeñas sustancialmente menores que la dosis óptima del compuesto. Posteriormente, la dosis es incrementada en incrementos pequeños hasta que se alcance el efecto óptimo bajo las circunstancias. En general, el compuesto se administra de manera muy deseable a un nivel de concentración que generalmente brindará resultados antiviralmente efectivos sin causar ningún efecto secundario dañino o perjudicial.

Cuando las composiciones de esta invención comprendan una combinación del compuesto de la presente invención y uno o más agentes terapéuticos o profilácticos adicionales, tanto el compuesto como el agente adicional están presentes normalmente a niveles de dosis de entre alrededor de 10 a 150%, muy preferiblemente entre alrededor de 10 y 80% de la dosis normalmente administrada en un régimen de monoterapia.

Las formulaciones farmacéuticas pueden estar adaptadas para administración mediante cualquier ruta adecuada, por ejemplo mediante la ruta oral (incluyendo bucal o sublingual), rectal, nasal, tópica (incluyendo bucal, sublingual, o transdérmica), vaginal o parenteral (incluyendo inyecciones o infusiones subcutáneas, intracutáneas,

intramusculares, intra-articulares, intrasinoviales, intraesternales, intratecales, intralesionales, intravenosas o intradérmicas. Estas formulaciones pueden prepararse mediante cualquier método conocido en la técnica de farmacia, por ejemplo al poner en asociación el ingrediente activo con los portadores o excipientes. Se prefieren la administración oral o la administración por inyección.

Las formulaciones farmacéuticas adaptadas para administración oral pueden presentarse como unidades individuales tales como cápsulas o tabletas; polvos o gránulos; soluciones o suspensiones en líquidos acuosos o no acuosos; espumas o cremas comestibles; o emulsiones líquidas de aceite en agua o emulsiones de agua en aceite.

Por ejemplo, para administración oral en forma de una tableta o cápsula, el componente de fármaco activo se puede combinar con un portador inerte farmacéuticamente aceptable y no tóxico y oral tal como etanol, glicerol, agua y similares. Los polvos se preparan hasta pulverizar el compuesto hasta un tamaño fino adecuado y mezclando con un portador farmacéutico pulverizador similarmente tal como un carbohidrato comestible, tal como, por ejemplo, almidón o manitol. También pueden estar presentes agentes saborizantes, conservadores, de dispersión y colorantes.

Las cápsulas se elaboran al preparar una mezcla en polvo, como la descrita arriba, y rellenando cubiertas de

gelatina formadas. Deslizantes y lubricantes tales como sílice coloidal, talco, estearato de magnesio, estearato de calcio o polietilenglicol sólido pueden añadirse a la mezcla en polvo antes de la operación de relleno. Un agente desintegrante o de solubilización tal como agar-agar, carbonato de calcio o carbonato de sodio también se puede añadir para mejorar la disponibilidad del medicamento cuando la cápsula sea ingerida. Además, cuando se desee o sea necesario, aglutinantes, lubricantes, agentes de desintegración y agentes colorantes adecuados también se pueden incorporar en la mezcla. Los aglutinantes adecuados incluyen almidón, gelatina, azúcares naturales tales como sucrosa o beta-lactosa, edulcorantes de maíz, gomas naturales y sintéticas tales como acacia, tragacanto o alginato de sodio, carboximetilcelulosa, polietilenglicol o similares. Los lubricantes usados en estas formas de dosis incluyen oleato de sodio, cloruro de sodio y similares. Los desintegradores incluyen, sin limitación, almidón, metilcelulosa, agar, bentonita, goma xantano y similares. Las tabletas se formulan, por ejemplo, al preparar una mezcla en polvo, granulando o suspendiendo, añadiendo un lubricante y desintegrante y comprimiendo para crear tabletas. Una mezcla en polvo se prepara al mezclar el compuesto, pulverizarse adecuadamente con un diluyente o base como el descrito arriba, y opcionalmente, con un aglutinante tal como

carboximetilcelulosa, un alginato, gelatina, o polivinilpirrolidona, un retardante de solución tal como parafina, un acelerador de resorción tal como una sal cuaternaria y/o un agente de absorción tal como bentonita, caolín o fosfato dicálcico. La mezcla en polvo puede ser granulada al humedecer con un aglutinante tal como jarabe, pasta de almidón, mucílago de acacia, o soluciones de materiales celulósicos o poliméricos y forzando a través de un tamiz. Como una alternativa a la granulación, la mezcla en polvo se puede pasar a través de la máquina de tableteo y el resultado es trozos imperfectamente formados que se rompen en gránulos. Los gránulos pueden ser lubricados para impedir la adherencia a los troqueles formadores de tableta por medio de la adición de ácido esteárico, una sal estearato, talco o aceite mineral. La mezcla lubricada es luego comprimida en tabletas. Los compuestos de la presente invención también se pueden combinar con un portador inerte de libre flujo y comprimirse en tabletas directamente sin pasar a través de las etapas de granulación o suspensión. Un recubrimiento protector transparente u opaco que consiste en un recubrimiento de sellado de goma laca, un recubrimiento de azúcar o material polimérico y un recubrimiento de barniz de cera pueden ser provistos. Se pueden agregar colorantes a estos recubrimientos para distinguir diferentes dosis únicas.

Fluidos orales tales como soluciones, jarabes y

elíxires pueden prepararse en forma de dosis única de tal manera que una cantidad dada contenga una cantidad predeterminada de compuesto. Los jarabes pueden prepararse al disolver el compuesto en una solución acuosa de sabor adecuado, mientras que los elíxires se preparan a través del uso de un vehículo no tóxico. Los solubilizadores y emulsionantes tales como alcoholes isoestearílicos etoxilados y éteres de polioxietilensorbitol, conservadores, aditivos de sabor tales como aceite de menta o edulcorantes naturales, o sacarina u otros edulcorantes artificiales, y similares también se pueden añadir.

Cuando sea adecuado, las formulaciones de dosis única para administración oral pueden ser microencapsuladas. La formulación también se puede preparar para prolongar o hacer más larga la liberación tal como por ejemplo al recubrir o incrustar un material en partículas en polímeros, cera o similar.

Los compuestos de la fórmula (I), y sales farmcéuticamente aceptables de los mismos, también se pueden administrar en forma de sistemas de suministro de liposomas, tales como vesículas unilaminares pequeñas, 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 sales farmacéuticamente aceptables de los mismos también se pueden suministrar mediante el uso de anticuerpos monoclonales como portadores individuales a los cuales se acoplen las moléculas del compuesto. Los compuestos también se pueden acoplar con polímeros solubles como portadores de fármaco dirigibles. Estos polímeros pueden incluir polivinilpirrolidona, copolímero de pirano, polihidroxipropilmetacrilamida fenol, polihidroxietilaspartamidafenol o polietilenoxidopolilisina sustituido con residuos de palitoilo. Además, los compuestos pueden ser acoplados a una clase de polímeros biodegradables útiles para lograr la liberación controlada de un fármaco, por ejemplo, ácido poliláctico, polepsilón caprolactona, ácido polihidroxibutírico, poliortoésteres, poliacetales, polidihidropiranos, policianoacrilatos y copolímeros de bloques entrelazados o anfifáticos de hidrogeles.

Las formulaciones farmacéuticas adaptadas para administración transdérmica pueden presentarse como parches individuales destinados a permanecer en contacto íntimo con la epidermis del receptor durante un periodo de tiempo prolongado. Por ejemplo, el ingrediente activo puede ser suministrado en el parche mediante iontoforesis como se describe generalmente en *Pharmaceutical Research* 1986, 3(6), 318.

Las formulaciones farmacéuticas adaptadas para

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administración tópica pueden formularse como ungüentos, cremas, suspensiones, lociones, polvos, soluciones, pastas, geles, sprays, geles, aerosoles o aceites.

Las formulaciones farmacéuticas adaptadas para administración rectal pueden presentarse como supositorios o como enemas.

Las formulaciones farmacéuticas adaptadas para administración nasal en las que el portador es un sólido incluyen un polvo grueso que tiene un tamaño de partícula por ejemplo en la escala de 20 a 500 micras el cual se administra en la manera en la cual se toma una inhalación, es decir, mediante inhalación rápida a través del conducto nasal desde un recipiente del polvo mantenido cerca de la nariz. Las formulaciones adecuadas en las que el portador es un líquido, para administración como spray nasal o gotas nasales, incluyen soluciones acuosas o aceitosas del ingrediente activo.

Las formulaciones farmacéuticas adaptadas para su administración por inhalación incluyen polvos o nieblas de partícula fina, los cuales pueden generarse por medio de varios tipos de aerosoles, nebulizadores o insufladores presurizados de dosis medida.

Las formulaciones farmacéuticas adaptadas para administración vaginal pueden presentarse como pesarios,

tampones, cremas, geles, pastas, espumas o formulaciones en spray.

Las formulaciones farmacéuticas adaptadas para administración parenteral incluyen soluciones para inyección estériles acuosas y no acuosas las cuales pueden contener antioxidantes, reguladores de pH, bacteriostatos y solutos que hagan a la formulación isotónica con la sangre del receptor deseado; y suspensiones estériles acuosas y no acuosas las cuales pueden incluir agentes de suspensión y agentes espesantes. Las formulaciones pueden presentarse en recipientes de una sola dosis o de varias dosis, por ejemplo ampolletas selladas y viales, y se pueden almacenar en una condición secada por congelación (liofilizada) que requiera sólo la adición del portador líquido estéril, por ejemplo agua para inyecciones, inmediatamente antes de usar. Soluciones y suspensiones para inyección extemporánea pueden prepararse a partir de polvos, gránulos y tabletas estériles.

Se debe entender que además de los ingredientes mencionados particularmente arriba, las formulaciones pueden incluir otros agentes convencionales en la técnica haciendo referencia al tipo de formulación en cuestión, por ejemplo aquellos adecuados para administración oral pueden incluir

agentes saborizantes.

El término "paciente" incluye tanto humanos como otros mamíferos.

El término "tratar" se refiere a: (i) prevenir que ocurra una enfermedad, trastorno o afección en un paciente que pudiera estar predispuesto a la enfermedad, trastorno y/o afección pero que aún no haya sido diagnosticado como teniéndola; (ii) inhibir la enfermedad, trastorno o afección, es decir, detener su desarrollo y (iii) aliviar la enfermedad, trastorno o afección, es decir, causar regresión de la enfermedad, trastorno y/o afección.

Los compuestos de la presente invención también se pueden administrar con una ciclosporina, por ejemplo, ciclosporina A. La ciclosporina A ha mostrado ser activa contra HCV en pruebas clínicas (*Hepatology* 2003, *38*, 1282; *Biochem. Biophys. Res. Commun.* 2004, *313*, 42; *J. Gastroenterol.* 2003, *38*, 567).

La siguiente tabla 1 lista algunos ejemplos ilustrativos de compuestos que pueden administrarse con los compuestos de esta invención. Los compuestos de la invención pueden administrarse con otros compuestos que tengan actividad anti-HCV en terapia de combinación, ya sea conjuntamente o por separado, o al combinar los compuestos en una composición.

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Tabla 1

Marca	*Clase Fisiológica*	*Tipo de Inhibidor u Objetivo*	*Compañía de Origen*
NIM811		Inhibidor de Ciclofilina	Novartis
Zadaxin		Inmunomodulador	Sciclone
Suvus		Azul de metileno	Bioenvision
Actilon (CPG10101)		Agonista de TLR9	Coley
Batabulin (T67)	Anticancer	inhibidor de β-tubulina	Tularik Inc., South San Francisco, CA
ISIS 14803	Antiviral	antisentido	ISIS Pharmaceuticals Inc., Carlsbad, CA/Elan Pharmaceuticals Inc., New York, NY
Summetrel	Antiviral	antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA

Marca	*Clase Fisiológica*	*Tipo de Inhibidor u Objetivo*	*Compañía de Origen*
GS-9132 (ACH-806)	Antiviral	Inhibidor de HCV	Achillion / Gilead
Compuestos de pirazolo-pirimidina y sales De WO2005047288 26 Mayo 2005	Antiviral	Inhibidores de HCV	Arrow Therapeutics Ltd.
Levovirin	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, Isreal
Telaprevir (VX-950, LY-570310)	Antiviral	Inhibidor de serina proteasa NS3	Vertex Pharmaceuticals Inc., Cambridge, MA/ Eli Lilly and Co. Inc., Indianapolis, IN
HCV-796	Antiviral	Inhibidor de Replicasa NS5B	Wyeth / Viropharma
NM-283	Antiviral	Inhibidor de Replicasa NS5B	Idenix / Novartis
GL-59728	Antiviral	NS5B Replicase Inhibitor	Gene Labs / Novartis
GL-60667	Antiviral	Inhibidor de Replicasa NS5B	Gene Labs / Novartis
2'C MeA	Antiviral	Inhibidor de Replicasa NS5B	Gilead
PSI 6130	Antiviral	Inhibidor de Replicasa NS5B	Roche
R1626	Antiviral	Inhibidor de Replicasa NS5B	Roche
2'C Metil adenosina	Antiviral	Inhibidor de Replicasa NS5B	Merck
JTK-003	Antiviral	Inhibidor de RdRp	Japan Tobacco Inc., Tokio, Japón
Levovirin	Antiviral	ribavirina	ICN Pharmaceuticals, Costa Mesa, CA

Marca	*Clase Fisiológica*	*Tipo de Inhibidor u Objetivo*	*Compañía de Origen*
Ribavirin	Antiviral	ribavirina	Schering-Plough Corporation, Kenilworth, NJ
Viramidine	Antiviral	Profármaco de Ribavirina	Ribapharm Inc., Costa Mesa, CA
Heptazyme	Antiviral	ribozyme	Ribozyme Pharmaceuticals Inc., Boulder, CO
BILN-2061	Antiviral	inhibidor de serina proteasa	Boehringer Ingelheim Pharma KG, Ingelheim, Germany
SCH 503034	Antiviral	inhibidor de serina proteasa	Schering Plough
Zadazim	Inmunomodulador	Inmunomodulador	SciClone Pharmaceuticals Inc., San Mateo, CA
Ceplene	Inmunomodulador	Inmunomodulador	Maxim Pharmaceuticals Inc., San Diego, CA
CellCept	Inmunosupresor	Inmunosupresor de IgG de HCV	F. Hoffmann-La Roche LTD, Basilea, Suiza
Civacir	Inmunosupresor	Inmunosupresor de IgG de HCV	Nabi Biopharmaceuticals Inc., Boca Raton, FL
Albuferon - α	Interferón	albúmina IFN-α2b	Human Genome Sciences Inc., Rockville, MD
Infergen A	Interferón	IFN alfacon-1	InterMune Pharmaceuticals Inc., Brisbane, CA
Omega IFN	Interferón	IFN-ω	Intarcia Therapeutics
IFN-β y EMZ701	Interferón	IFN-β y EMZ701	Transition Therapeutics Inc., Ontario, Canadá

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Marca	*Clase Fisiológica*	*Tipo de Inhibidor u Objetivo*	*Compañía de Origen*
Rebif	Interferón	IFN-β1a	Serono, Ginebra, Suiza
Roferon A	Interferón	IFN-α2a	F. Hoffmann-La Roche LTD, Basilea, Suiza
Intron A	Interferón	IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
Intron A y Zadaxin	Interferón	IFN-α2b/α1-timosina	RegeneRx Biopharmiceuticals Inc., Bethesda, MD/ SciClone Pharmaceuticals Inc, San Mateo, CA
Rebetron	Interferón	IFN-α2b/ribavirina	Schering-Plough Corporation, Kenilworth, NJ
Actimmune	Interferón	INF-γ	InterMune Inc., Brisbane, CA
Interferon-β	Interferón	Interferón-β-1a	Serono
Multiferon	Interferón	IFN de larga duración	Viragen/Valentis
Wellferon	Interferón	IFN-αn1 linfoblastoide	GlaxoSmithKline plc, Uxbridge, UK
Omniferon	Interferon	IFN-α natural	Viragen Inc., Plantation, FL
Pegasys	Interferón	IFN-α2a PEGilado	F. Hoffmann-La Roche LTD, Basilea, Suiza
Pegasys y Ceplene	Interferón	IFN-α2a PEGilado/ inmunomodulador	Maxim Pharmaceuticals Inc., San Diego, CA
Pegasys y Ribavirin	Interferón	IFN-α2a PEGilado/ ribavirina	F. Hoffmann-La Roche LTD, Basilea, Suiza

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Marca	*Clase Fisiológica*	*Tipo de Inhibidor u Objetivo*	*Compañía de Origen*
PEG-Intron	Interferón	IFN-α2b PEGilado	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron / Ribavirin	Interferón	IFN-α2b PEGilado /ribavirina	Schering-Plough Corporation, Kenilworth, NJ
IP-501	Protección del hígado	antifibrótico	Indevus Pharmaceuticals Inc., Lexington, MA
IDN-6556	Protección del hígado	inhibidor de caspasa	Idun Pharmaceuticals Inc., San Diego, CA
ITMN-191 (R-7227)	Antiviral	inhibidor de serina proteasa	InterMune Pharmaceuticals Inc., Brisbane, CA
GL-59728	Antiviral	Inhibidor de Replicasa NS5B	Genelabs
ANA-971	Antiviral	agonista de TLR-7	Anadys

Los compuestos de la presente invención también se pueden usar como reactivos de laboratorio. Los compuestos pueden ser instrumental para proporcionar herramientas de investigación para el diseño de ensayos de replicación viral, validación de sistemas de ensayo con animales y estudios de biología estructural para incrementar más el conocimiento de mecanismos de la enfermedad por HCV. Además, los compuestos de la presente invención son útiles para establecer o determinar el sitio de unión de otros compuestos antivirales, por ejemplo, mediante inhibición competitiva.

Los compuestos de esta invención también se pueden

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usar para tratar o prevenir contaminación viral de materiales y por lo tanto reducen el riesgo de infección viral de personal de laboratorio o médico o pacientes que entren en contacto con estos materiales, por ejemplo, sangre, tejidos, instrumentos y prendas quirúrgicos, instrumentos y prendas de laboratorio, y aparatos y materiales para toma o transfusión de sangre.

Esta invención intenta abarcar compuestos que tienen la fórmula (I) cuando se preparan mediante procedimientos sintéticos o mediante procedimientos metabólicos incluyendo aquellos que ocurren en el cuerpo humano o animal (*in vivo*) o procesos que ocurren *in vitro*.

Las abreviaturas usadas en la presente solicitud, incluyendo particularmente en los esquemas de reacción y ejemplos ilustrativos siguientes, se conocen bien por los expertos en la técnica. Algunas de las abreviaturas usadas son las siguientes: HATU para hexafluorosfosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio; Boc o BOC para *ter*-butoxicarbonilo; NBS para N-bromosuccinimida; tBu o t-Bu para *ter*-butilo; SEM para -(trimetilsilil)etoximetilo; DMSO para sulfóxido de dimetilo; MeOH para metanol; TFA para ácido trifluoroacético; RT para temperatura ambiente o tiempo de retención (lo regirá el contexto);

t_g para tiempo de retención; EDCI para clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida; DMAP para 4-dimetilaminopiridina; THF para tetrahidrofurano; DBU para 1,8-diazabiciclo[5.4.0]undec-7-eno; *t*-Bu; DEA para dietilamina; HMDS para hexametildisilazida; DMF para N,N-dimetilformamida; Bzl para bencilo; EtOH para etanol; iPrOH o i-PrOH para isopropanol; Me_2S para sulfóxido de dimetilo; Et_3N o TEA para trietilamina; Ph para fenilo; OAc para acetato; EtOAc para acetato de etilo; dppf para 1,1'-bis(difenilfosfino)ferroceno; iPr_2EtN o DIPEA para diisopropiletilamina; Cbz para carbobenzoilo; n-BuLi para n-butil-litio; ACN para acetonitriló; h o hr para horas; m o min para minutos; s para segundos; LiHMDS para hexametildisilazida de litio; DIBAL para hidruro de diisobutilaluminio; TBDMSCI para cloruro de *ter*-butildimetilsililo; Me para metilo; ca. para aproximadamente; OAc para acetato; iPr para isopropilo; Et para etilo; Bn para bencilo; y HOAT para 1-hidroxi-7-azabenzotriazol.

Los compuestos y procedimientos de la presente invención se entenderán mejor en relación con los siguientes esquemas de reacción sintéticos que ilustran los métodos mediante los cuales los compuestos de la presente invención pueden

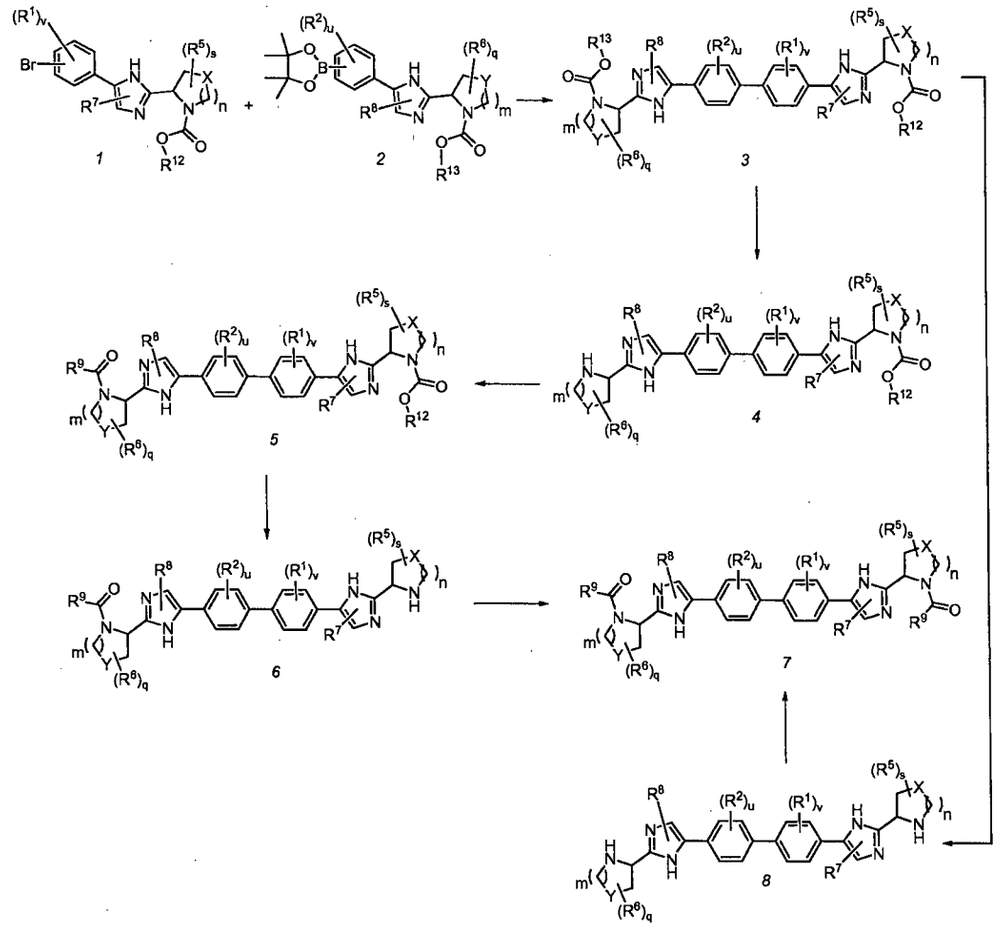
prepararse. Materiales de partida pueden obtenerse de fuentes comerciales o prepararse mediante métodos de literatura bien establecidos conocidos por aquellos de capacidad ordinaria en la técnica. Será fácilmente evidente para alguien de capacidad ordinaria en la técnica que los compuestos definidos arriba pueden sintetizarse mediante sustitución de los reactivos y agentes adecuados en las síntesis mostradas abajo. También será fácilmente evidente para alguien capacitado en la técnica que las etapas de protección y desprotección selectivas, así como el orden de las propias etapas, se pueden llevar a cabo en orden variable, dependiendo de la naturaleza de las variables para completar exitosamente las siguientes síntesis. Las variables son como se definió arriba a menos que se indique lo contrario abajo.

Esquema de reacción 1

Bifenilos simétricos o asimétricos

El haluro de arilo *1* y éster borónico *2* pueden acoplarse para producir el biarilo *3* usando condiciones de acoplamiento de Suzuki-Miayura estándares (*Angew Chem. Int. Ed. Engl* 2001, 40, 4544). Se debe notar que el análogo de ácido borónico de *2* puede ser usado en lugar del éster. La

mono-desprotección de la porción pirrolidina puede lograrse cuando R^{12} y R^{13} sean diferentes. Cuando R^{12} = bencilo, y R^{13} = t-butilo el tratamiento a condiciones hidrogenolíticas produce *4*. Por ejemplo, catalizador de Pd/C en presencia de una base tal como carbonato de potasio puede ser usado. La acilación de *4* puede lograrse usando condiciones de acilación estándares. Un reactivo de acoplamiento tal como HATU en combinación con una base de amina tal como una base de Hunig puede usarse a este respecto. Como alternativa, *4* se puede hacer reaccionar con un cloruro de isocianato carbamoilo para proporcionar compuestos de la fórmula *5* en donde R^9 es una amina. La desprotección adicional de *5* puede lograrse mediante el tratamiento con ácidos fuertes tales como HCl o ácido trifluoroacético. Las condiciones estándares análogas a aquellas usadas para convertir *4* en *5* pueden usar para preparar *7* a partir de *6*. En otra modalidad en donde R^{12}=R^{13}=t-Bu, la conversión directa en *8* puede lograrse mediante tratamiento de *3* con ácido fuerte tal como HCl o ácido trifluoroacético. La conversión de *8* en *7* se logra de manera análoga a los métodos usados para preparar *5* a partir de *4* ó *7* a partir de *6*. Sin embargo, en este caso, los extremos *7* serán idénticos.

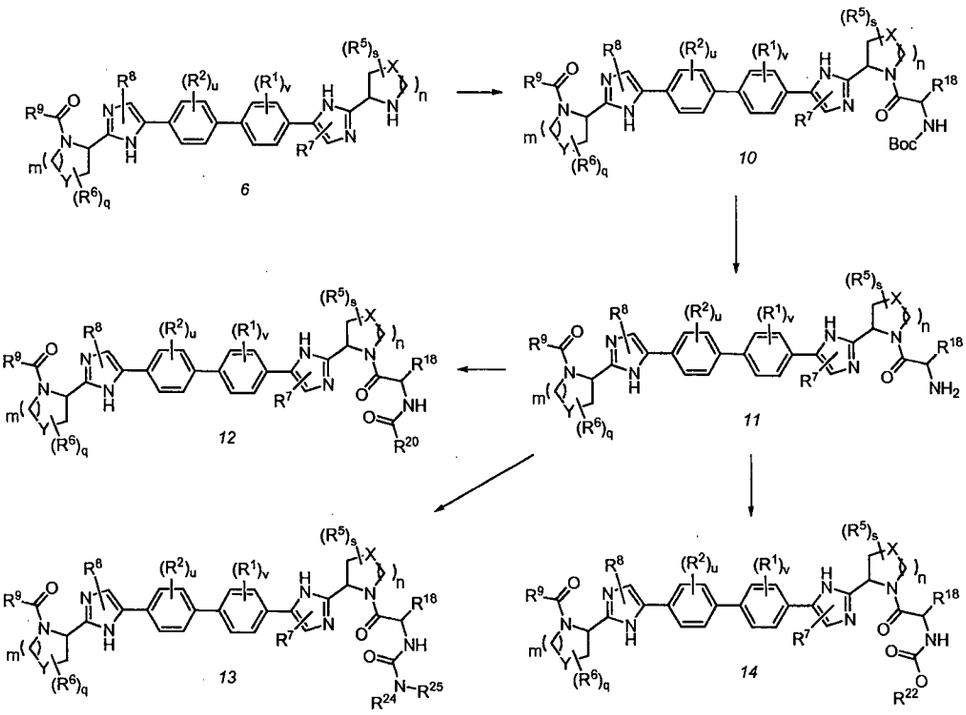


Esquema de reacción 2

Bifenilos con extremos asimétricos

La conversión de *6* (del esquema de reacción 1) en *10* puede usarse usando condiciones de acoplamiento de amina estándares tales como HATU con una base de amina, tal como base de Hunig. La desprotección puede logarse con ácidos fuertes tales como HCl o ácido trifluoroacético dando *11*. El compuesto *11* puede ser luego convertido en *12*, *13* ó *14* usando un cloruro de ácido, un cloruro de

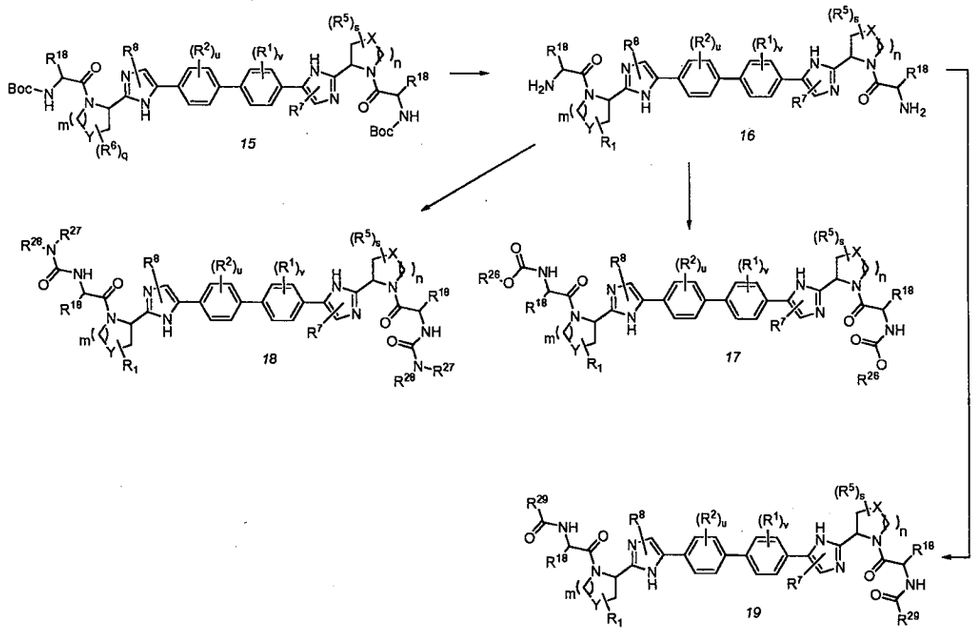
isocianato de carbamoilo, o un cloroformiato respectivamente.



Esquema de reacción 3

Bifenilos elaborados de extremo asimétrico

El compuesto *15* (*15*=*7* (esquema de reacción 1) en donde cada R^9 es $-CH(NHBoc)R^{18}$) puede convertirse en *16* mediante el tratamiento con ácido fuerte tal como HCl o ácido trifluoroacético. Los compuestos *17*, *18* y *19* pueden prepararse a partir de *16* al tratar *16* con un cloroformiato, cloruro de isocianato o carbamoilo adecuado, o un cloruro de ácido respectivamente.

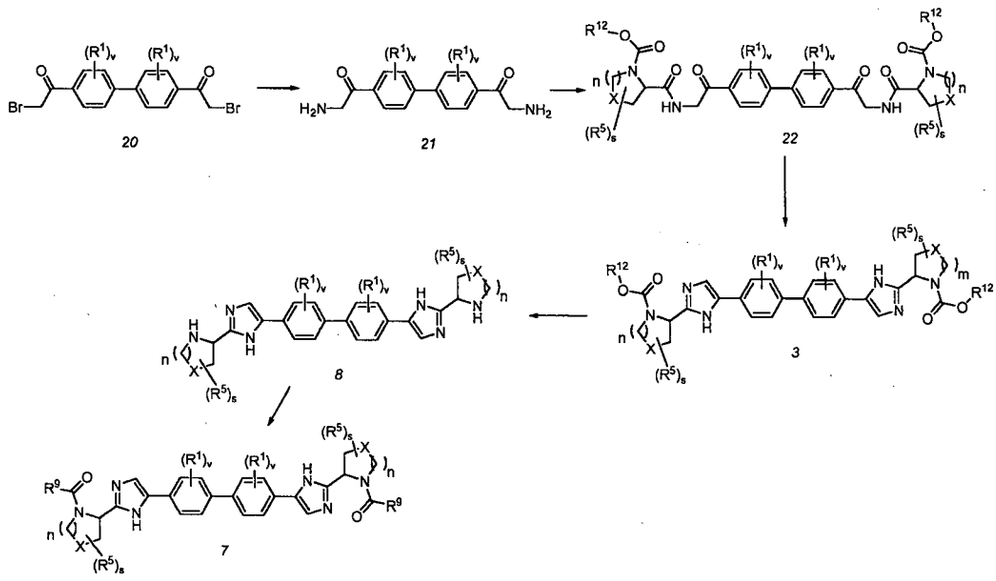


Esquema de reacción 4

Bifenilos simétricos

Análogos de bifenilo simétricos (compuestos de la fórmula 7 en los que ambas mitades de la molécula son equivalentes) pueden sintetizarse iniciando a partir de bromocetona *20*. La aminación por desplazamiento con un nucleófilo tal como azida, ftalimida o de preferencia diformilamida de sodio (Yinglin y Hongwen, *Synthesis* 1990, 122) seguida por desprotección da *21*. La condensación bajo condiciones de aminación estándares tales como HATU y base de Hunig con un aminoácido protegido adecuadamente proporciona *22*. El calentamiento con acetato de amonio bajo condiciones térmicas o de

microondas da como resultado la formación de *3* que puede ser desprotegido con ácido fuerte tal como HCl o ácido trifluoroacético (R^{12}=R^{13}=t-Bu) o mediante hidrogenólisis con gas hidrógeno y un catalizador de metal de transición tal como Pd/C (R^{12} = R^{13} = bencilo). La acilación se puede llevar a cabo con un ácido carboxílico (R^9CO_2H) de una manera similar a la conversión de *21* en *22*. La formación de urea puede lograrse mediante tratamiento con un isocianato adecuado (R^9=$R^{24}R^{25}N$; R^{25}=H) o cloruro de carbamoilo (R^9=$R^{24}R^{25}N$; R^{25} no es hidrógeno).

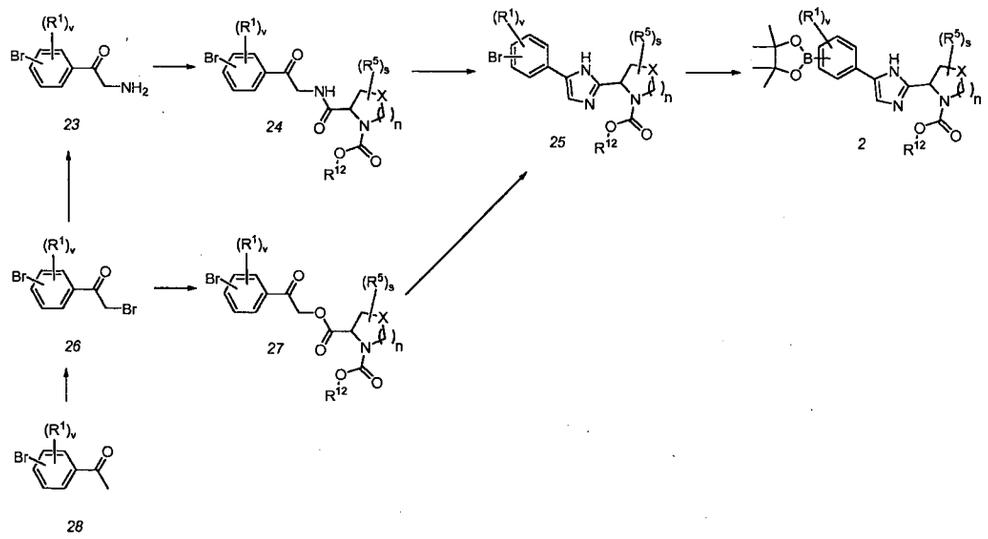


Esquema de reacción 5

Materiales de partida *25* y *2*

El esquema de reacción 5 describe la preparación de algunos de los materiales de partida requeridos para las secuencias sintéticas ilustradas

en los esquemas 1-4. El intermediario clave *25* (análogo a *1* en el esquema de reacción 1) se prepara a partir de la ceto-amida *24* o ceto-éster *27* mediante calentamiento con acetato de amonio bajo condiciones térmicas o de microondas. La ceta-amida *24* puede prepararse a partir de *23* mediante condensación con un aminoácido cíclico o acíclico adecuado bajo condiciones de formación de amida estándares. El bromuro *26* puede dar origen a *23* mediante tratamiento con un nucleófilo tal como azida, ftalimida o diformilamida de sodio (*Synthesis* 1990, 122) seguido por desprotección. El bromuro *26* también se puede convertir en *27* al hacer reaccionar con un aminoácido N-protegido cíclico o acíclico adecuado en presencia de una base tal como carbonato de potasio o bicarbonato de sodio. La bromación de *28* con una fuente de iones de bromonio, tal como bromo, NBS o CBr_4 da como resultado la formación de *26*. El bromuro *25* puede convertirse en éster borónico *2* mediante tratamiento con bis-pinacolatodiboro bajo catálisis con paladio de acuerdo con el método descrito en *Journal of Organic Chemistry* 1995, *60*, 7508, o variaciones del mismo.

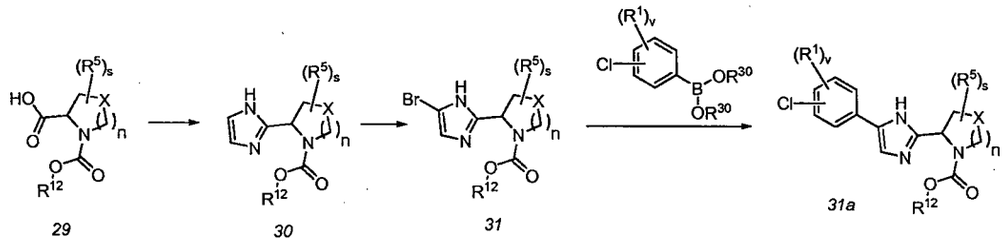


Esquema de reacción 6

Material de partida *31a*

En otra modalidad, materiales de partida tales como *31a* (análogo a *25* en el esquema de reacción 5 y *1* en el esquema de reacción 1) pueden prepararse al hacer reaccionar derivados de bromoimidazol *31* bajo condiciones de acoplamiento tipo Suzuki con una variedad de ácidos arilborónicos cloro-sustituidos los cuales pueden ser ya sea preparados mediante metodologías estándares (véase, por ejemplo, *Organic Letters* 2006, *8*, 305 y referencias citadas en el mismo) o comprarse de proveedores comerciales. El bromoimidazol *31* puede obtenerse al bromar imidazol *30* con una fuente de ión de brominio tal como bromo, CBr_4 o N-bromosuccinimida. El imidazol *30* puede prepararse a partir de aminoácidos N-protegidos los cuales sean sustituidos adecuadamente al hacer reaccionar con glioxal en una solución

metanólica de hidróxido de aminio.



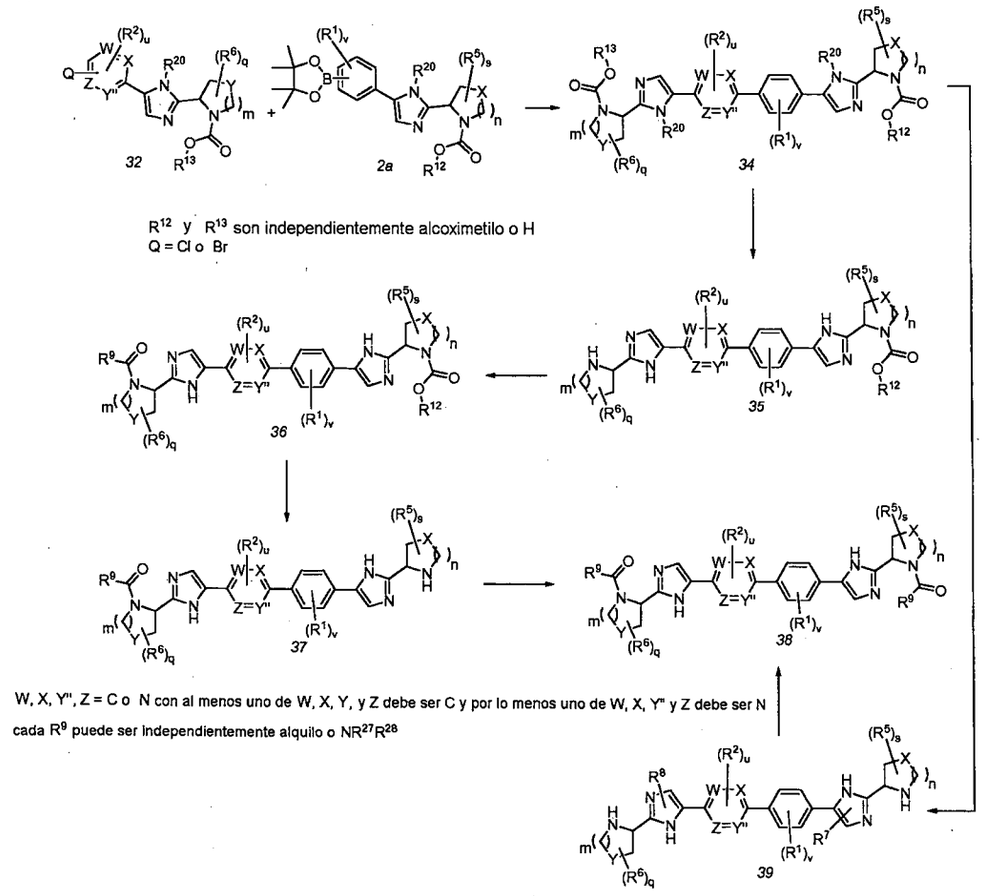
29 30 31 31a

Esquema de reacción 7

Heteroarilos

En otra modalidad más de la presente invención, el haluro de arilo *32* puede acoplarse bajo condiciones catalizadas con paladio de Suzuki-Miyaura para formar el derivado heteroarilo *34*. El compuesto *34* puede elaborarse a *35* mediante tratamiento a condiciones hidrogenolíticas con hidrógeno y un catalizador de metal en transición tal como paladio sobre carbón (R^{13} = bencilo). La acilación de *35* puede lograrse con un cloruro de ácido adecuado (R^9COCl) en presencia de una base tal como trietilamina, con un ácido carboxílico adecuadamente sustituido (R^9CO_2H) en presencia de un reactivo de acoplamiento estándar tal como HATU, o con un isocianato ($R^{27}NCO$ en donde R^9 = $R^{27}R^{28}$-; R^{28} = H) o cloruro de carbamoilo ($R^{27}R^{28}NCOCl$ en donde R^9 = $R^{27}R^{28}N$-). El compuesto *37* puede prepararse a partir de *36* (R^{12} = t-Bu) mediante tratamiento con un ácido fuerte tal como HCl o ácido trifluoroacético. La acilación de la amina resultante en *37* para dar *38* se puede lograr como en la transformación de *35* en *36*. En casos en los que R^{12} = R^{13}, *34* puede transformarse

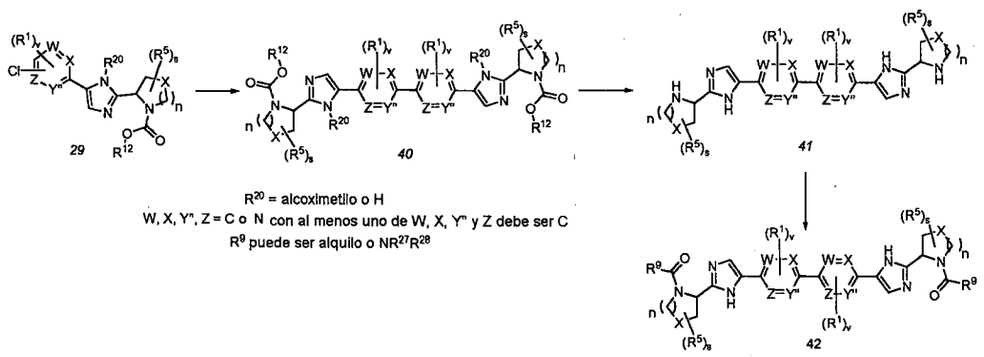
directamente en *39* mediante tratamiento con ácido fuerte tal como HCl o ácido trifluoroacético (R^{12} = R^{13} = t-Bu) o al emplear condiciones hidrogenolíticas con hidrógeno y un catalizador de metal de transición tal como paladio en carbón (R^{12} = R^{13} = bencilo). La acilación de *39* puede lograrse de manera análoga a aquella descrita para la transformación de *35* en *36*.



Esquema de reacción 8

El cloruro de heteroarilo *29* puede convertirse en el análogo asimétrico *40* mediante tratamiento con una fuente

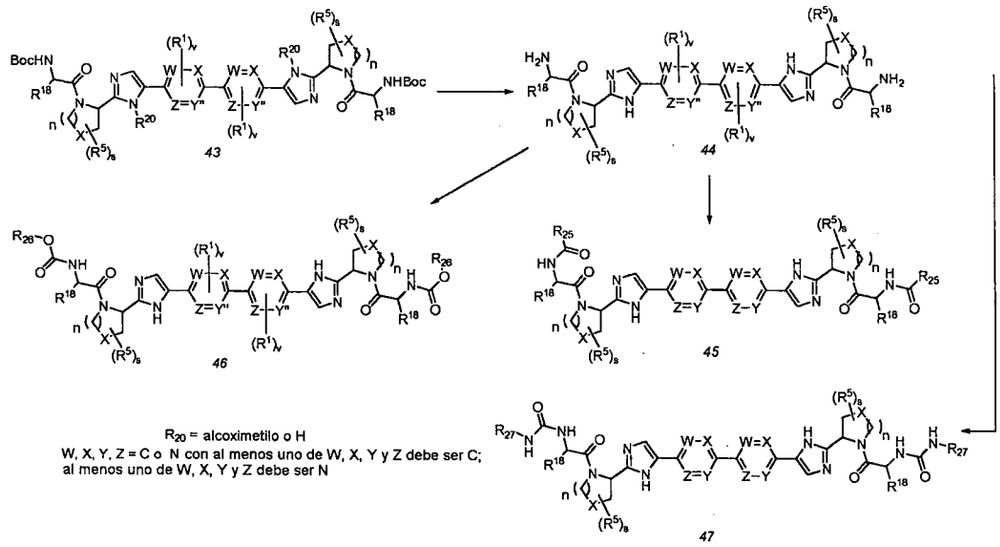
de paladio tal como diclorobis(benzonitrilo)paladio en presencia de tetrakis(dimetilamino)etileno a temperatura elevada. La remoción del éter SEM y Boc carbamatos encontrados en *40* puede lograrse en una etapa mediante tratamiento con un ácido fuerte tal como HCl o ácido trifluoroacético proporcionando *41*. La conversión en *42* puede logarse de forma similar a las condiciones usadas para convertir *38* en *39* en el esquema de reacción 7.



Esquema de reacción 9

Heteroarilos sustituidos con extremo simétrico

El compuesto *43* (análogo a *42* en donde R_{23}=-CH(NHBoc)R_{24}) se puede elaborar en *45*, *46* y *47* mediante metodologías similares a aquellas descritas en el esquema de reacción 3. En casos en los que R_{20}= alcoximetilo (es decir; SEM), la remoción se puede lograr simultáneamente con la remoción del Boc carbamato (véase *43* a *44*) usando ácido fuerte tal como HCl o ácido trifluoroacético.

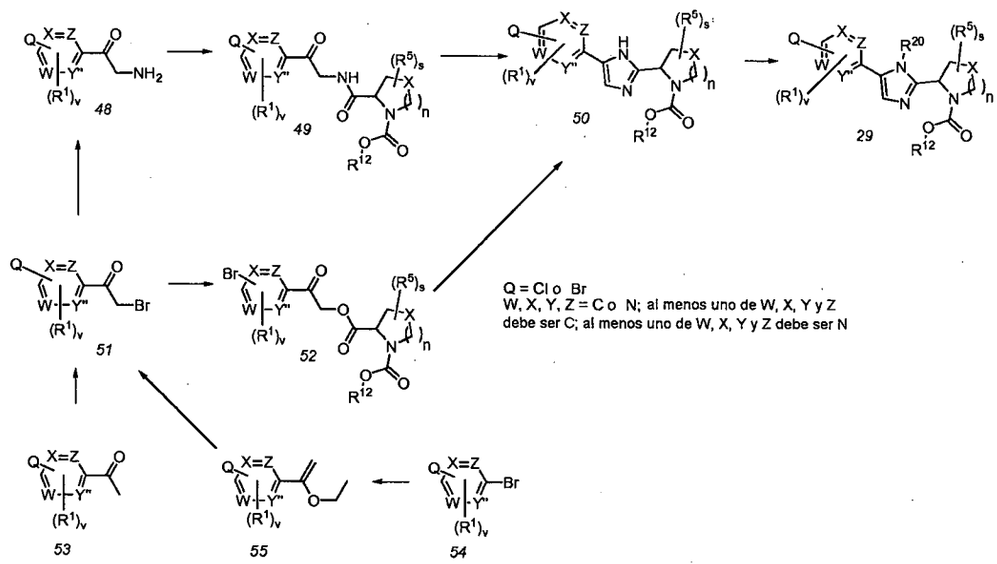


Esquema de reacción 10

Material de partida *29*

Los bromuros de heteroarilo *54* pueden hacerse reaccionar con un estanato de vinilo tal como tributil(1-etoxivinil)estaño en presencia de una fuente de paladio tal como diclorobis(trifenilfosfina)paladio (II) para proporcionar *55* el cual se puede transformar subsecuentemente en la bromocetona *51* mediante tratamiento con una fuente de ión de bromonio tal como bromo, CBr_4 o N-bromosuccinimida. El bromo *51* puede convertirse en la amino cetona *48* mediante adición de azida de sodio, ftalimida de potasio o diformilamida de sodio (*Synthesis* 1990 122) seguido por desprotección. La aminocetona *48* puede ser después acoplada con un aminoácido adecuadamente

sustituido bajo condiciones de formación de amida estándares (es decir, un reactivo de acoplamiento tal como HATU en presencia de una base leve tal como base de Hunig) para proporcionar *49*. El compuesto *49* puede ser después transformado más en imidazol *50* mediante reacción con acetato de amonio bajo condiciones térmicas o de microondas. Como alternativa, *51* se puede hacer reaccionar directamente con un aminoácido sustituido adecuadamente en presencia de una base tal como bicarbonato de sodio o carbonato de potasio proporcionando *52* el cual a su vez puede hacerse reaccionar con acetato de amonio bajo condiciones térmicas o de microondas para proporcionar *50*. El imidazol *50* puede protegerse con un grupo alcoxilmetilo mediante tratamiento con el haluro de alcoximetilo adecuado tal como cloruro de 2-(trimetilisilil)etoximetilo después de haber sido desprotonado primero con una base fuerte tal como hidruro de sodio.



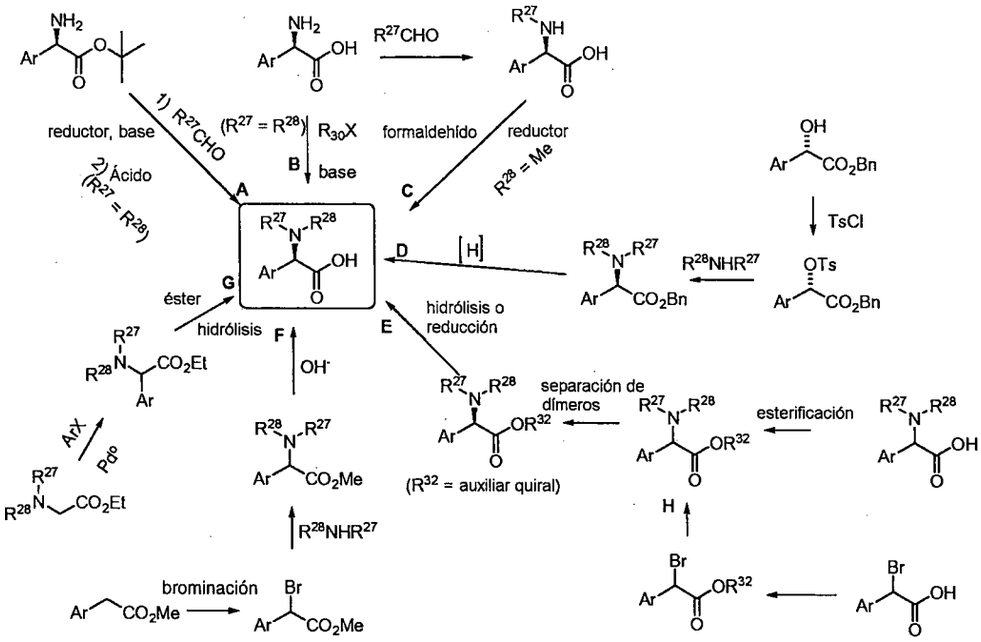
Esquema de reacción 11

Derivados de fenilglicina sustituidos

Los derivados de fenilglicina sustituidos pueden prepararse mediante un número de métodos mostrados abajo. Éster *t*-butílico de fenilglicina puede alquilarse en forma reductora (vía A) con un aldehído adecuado y reductor tal como cianoborohidruro de sodio en medio ácido. La hidrólisis del éster *t*-butílico puede lograrse con ácido fuerte tal como HCl o ácido trifluoroacético. Como alternativa, fenilglicina puede alquilarse con un haluro de alquilo tal como yoduro de etilo y una base tal como bicarbonato de sodio o carbonato de potasio (vía B). La vía C ilustra la alquilación reductora de fenilglicina como en la vía A seguida por una segunda alquilación reductora con un aldehído

alternativo tal como formaldehído en presencia de un agente reductor y ácido. La vía D ilustra la síntesis de fenilglicina sustituidas por medio de los análogos de ácido mandélico correspondientes. La conversión del alcohol secundario en un grupo saliente competente puede lograrse con cloruro de p-toluensulfonilo. El desplazamiento del grupo tosilato con una amina adecuada seguido por la remoción reductora del éster bencílico puede proporcionar derivados de fenilglicina sustituidos. En la vía E un derivado de fenilglicina sustituido racémico es resuelto mediante esterificación con un auxiliar quiral enantiómericamente puro tal como pero no limitado a (+)-1-feniletanol, (-)-1-feniletanol, una oxazolidinona de Evan o pantolactona enantioméricamente pura. La separación de los diastereómeros se logra mediante cromatografía (gel de sílice, HPLC, cristalización, etc.) seguida por la remoción del auxiliar quiral proporcionando derivados de fenilglicina enantioméricamente puros. La vía H ilustra una secuencia sintética que se interseca con la vía E en la cual el auxiliar quiral mencionado arriba es instalado antes de la adición de amina. Como alternativa, un éster de un ácido arilacético puede ser bromado con una fuente de ión de bromonio

tal como bromo, N-bromosuccinimida, o CBr_4. El bromuro bencílico resultante puede ser desplazado con una variedad de aminas mono- o disustituidas en presencia de una base de amina terciaria tal como trietilamin a o base de Hunig. La hidrólisis del éster metílico por medio del tratamiento con hidróxido de litio a baja temperatura o HCl 6N a temperatura elevada proporciona los derivados de fenilglicina sustituidos. Otro método se muestra en la vía G. Los análogos de glicina pueden ser derivados con una variedad de haluros de arilo en presencia de una fuente de paladio (0) tal como bis(tributilfosfina)paladio y base tal como fosfato de potasio. El éster resultante puede ser después hidrolizado mediante tratamiento con base o ácido. Se debe entender que otros métodos bien conocidos para preparar derivados de fenilglicina existen en la técnica y pueden ser enmendados para proporcionar los compuestos deseados en esta invención. También se debe entender que los derivados de fenilglicina finales pueden ser purificados hasta pureza enantiomérica mayor que 98% ee mediante HPLC preparativa.

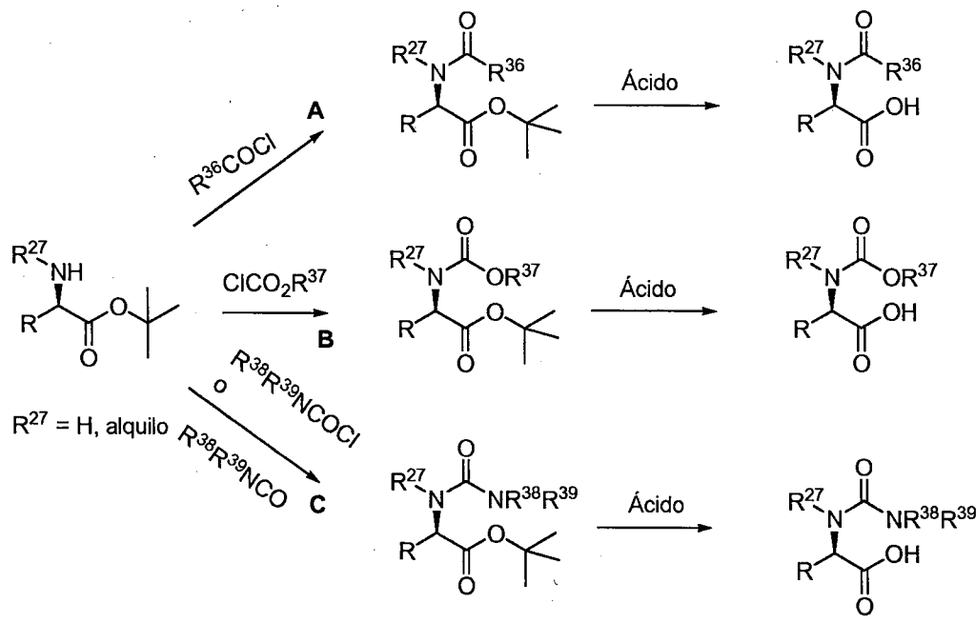


Esquema de reacción 12

Derivados de aminoácido acilados

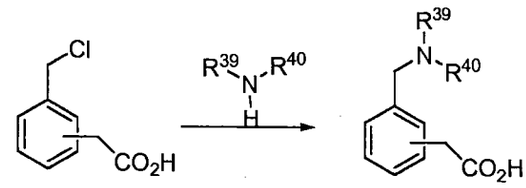
En otra modalidad de la presente invención, derivados de fenilglicina acilados pueden prepararse como se ilustra bajo. Los derivados de fenilglicina en los que el ácido carboxílico es protegido como un éster fácilmente removido, pueden ser acilados con un cloruro de ácido en presencia de una base tal como trietilamina para proporcionar las amidas correspondientes (vía A). La vía B ilustra la acilación del derivado de fenilglicina de partida con un cloroformiato adecuado en tanto que la vía C muestra la reacción con un isocianato o cloruro de carbamoilo adecuado. Cada uno de los tres intermediarios mostrados en las vías A-C puede ser desprotegido mediante métodos conocidos por los expertos

en la técnica (es decir, tratamiento del éster *ter*-butílico con base fuerte tal como HCl o ácido trifluoroacético).



Esquema de reacción 13

Ácidos fenilacéticos amino-sustituidos pueden prepararse mediante tratamiento de un ácido clorometilfenilacético con un exceso de una amina.



Condiciones de análisis de compuestos

La evaluación de la pureza y el análisis de masas de baja resolución se llevaron a cabo en un sistema Shimadzu LC acoplado con un sistema Waters Micromass ZQ MS. Debe notarse que los tiempos de

retención pueden variar ligeramente entre máquinas. Las condiciones LC empleadas para determinar el tiempo de retención (RT) fueron:

Condición 1

Columna = Phenomenex-Luna 3.0X50 mm S10

% B de inicio = 0

% B final = 100

Tiempo gradiente = 2 minutos

Tiempo de detención = 3 minutos

Velocidad de flujo = 4 mL/min

Longitud de onda = 220 nm

Solvente A = 0.1% de TFA en 10% de metanol/90% de H_2O

Solvente B = 0.1% de TFA en 90% de metanol/10% de H_2O

Condición 2

Columna = Phenomenex-Luna 4.6X50 mm S10

% B de inicio = 0

% B final = 100

Tiempo gradiente = 2 minutos

Tiempo de detención = 3 minutos

Velocidad de flujo = 5 mL/min

Longitud de onda = 220 nm

Solvente A = 0.1% de TFA en 10% de metanol/90% de H_2O

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Solvente B = 0.1% de TFA en 90% de metanol/10% de H_2O

Condición 3

Columna = HPLC XTERRA C18 3.0 x 50 mm S7

% B de inicio = 0

% B final = 100

Tiempo gradiente = 3 minutos

Tiempo de detención = 4 minutos

Velocidad de flujo = 4 mL/min

Longitud de onda = 220 nm

Solvente A = 0.1% de TFA en 10% de metanol/90% de H_2O

Solvente B = 0.1% de TFA en 90% de metanol/10% de H_2O

Condición M1

Columna = Luna 4.6X 50 mm S10

% B de inicio = 0

% B final = 100

Tiempo gradiente = 3 minutos

Tiempo de detención = 4 minutos

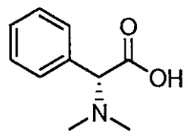
Velocidad de flujo = 4 mL/min

Solvente A = 95% de H_2O: 5% de CH_3CN, 10 mm de acetato de amonio

Solvente B = 5% de H_2O: 95% de CH_3CN; 10 mm de acetato de amonio

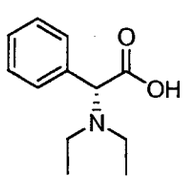
Síntesis de extremos comunes

Extremo-1



Una suspensión de 10% de Pd/C (2.0 g) en metanol (10 mL) se añadió a una mezcla de (R)-2-fenilglicina (10 g, 66.2 mmoles), formaldehído (33 mL de 37% en peso en agua), HCl 1N (30 mL) y metanol (30 mL), y se expuso a H_2 (4.22 kg/cm^2 (60 psi)) durante 3 horas. La mezcla de reacción se filtró a través de tierra diatomácea (Celite®), y el filtrado se concentró al vacío. El material crudo resultante se recristalizó a partir de isopropanol para proporcionar la sal HCl de *Extremo*-1 como una aguja blanca (4.0 g). Rotación óptica: -117.1° [c=9.95 mg/mL en H_2O; λ = 589 nm]. ^1H RMN (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. 1): RT = 0.25; LC/MS: Análisis calculado para $[M+H]^+$ $C_{10}H_{14}NO_2$ 180.10; encontrado 180.17; HRMS: Análisis calculado para $[M+H]^+$ $C_{10}H_{14}NO_2$ 180.1025; encontrado 180.1017.

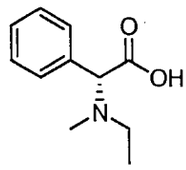
Extremo-2



$NaBH_3CN$ (6.22 g, 94 mmoles) se añadió en porciones

durante pocos minutos a una mezcla enfriada (hielo/agua) de (R)-2-fenilglicina (6.02 g, 39.8 mmoles) y MeOH (100 mL), y se agitó durante 5 min. Se añadió por goteo acetaldehído (10 mL) durante 10 minutos y se continuó agitando a la misma temperatura enfriada durante 45 minutos y a temperatura ambiente durante ~6.5 h. La mezcla de reacción se enfrió de regreso con un baño de hielo-agua, se trató con agua (3 mL) y luego se enfrió rápidamente con una adición por goteo de HCl concentrado durante ~45 minutos hasta que el pH de la mezcla fuera de ~1.5-2.0. Se retiró el baño de enfriamiento y se continuó agitando mientras se añadía HCl concentrado para mantener el pH de la mezcla alrededor de 1.5-2.0. La mezcla de reacción se agitó durante la noche, se filtró para remover la suspensión blanca y el filtrado se concentró al vacío. El material crudo se recristalizó a partir de etanol para dar la sal HCl de *Extremo-2* como un sólido blanco brillante en dos cultivos (cultivo-1: 4.16 g; cultivo-2: 2.19 g). ^{1}H RMN (DMSO-d_6, δ=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). Cultivo-1: $[\alpha]^{25}$-102.21° (c = 0.357, H_2O); cultivo-2: $[\alpha]^{25}$-99.7° (c=0.357, H_2O). LC (Cond. 1): RT = 0.43 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{12}H_{18}NO_2$: 208.13; encontrado 208.26.

Extremo 3

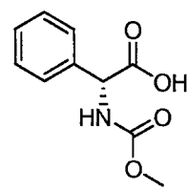


Acetaldehído (5.0 mL, 89.1 mmoles) y una suspensión de 10% de Pd/C (270 mg) en metanol/H_2O (4 mL/1 mL) se añadió secuencialmente a una mezcla enfriada (~15°C) de (R)-2-fenilglicina (3.096 g, 20.48 mmoles), HCl 1N (30 mL) y metanol (40 mL). El baño de enfriamiento se retiró y la mezcla de reacción se agitó bajo un balón de H_2 durante 17 horas. Se añadieron acetaldehído adicional (10 mL, 178.2 mmoles) y se continuó agitando bajo atmósfera de H_2 durante 24 horas. [Nota: el suministro de H_2 fue reabastecido según se requiriera a lo largo de la reacción]. La mezcla de reacción se filtró a través de tierra diatomácea (Celite®), y el filtrado se concentró al vacío. El material crudo resultante se recristalizó a partir de isopropanol para proporcionar la sal HCl de ácido (R)-2-(etilamino)-2-fenilacético como un sólido blanco brillante (2.846 g). ^1H RMN (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. 1): RT = 0.39 min; >95% de índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{10}H_{14}NO_2$: 180.10; encontrado 180.18.

Una suspensión de 10% de Pd/C (536 mg) en

metanol/H_2O (3 mL/1 mL) se añadió a una mezcla de ácido (R)-2-(etilamino)-2-fenilacético/HCl (1.492 g, 6.918 mmoles), 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 balón de H_2 durante ~72 horas, en donde se reabasteció suministro de H_2 según se requiriera. La mezcla de reacción se filtró a través de tierra diatomácea (Celite®) y el filtrado se concentró al vacío. el material crudo resultante se recristalizó a partir de metanol (50 mL) para proporcionar la sal HCl de *Extremo-3* como un sólido blanco (985 mg). ^1H RMN (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. 1): RT=0.39 min; >95% de índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.12; encontrado 194.18; HRMS: Análisis calculado para $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.1180; encontrado 194.1181.

Extremo-4



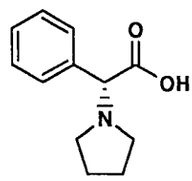
$ClCO_2Me$ (3.2 mL, 41.4 moles) se añadió por goteo a una semi-solución enfriada (hielo/agua) en THF (410 mL) de 2-amino-2-fenilacetato de (R)-*ter*-butilo/HCl (9.877 g, 40.52 mmoles) y diisopropiletilamina (14.2 mL, 81.52 mmoles) durante 6 minutos, y se agitó a temperatura similar durante

5.5 horas. El componente volátil se removió al vacío, y el residuo se dividió entre agua (100 mL) y acetato de etilo (200 m). La capa 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 al vacío. el aceite incoloro resultante se trituró de hexanos, se filtró y se lavó con hexanos (100 mL) para proporcionar 2-(metoxicarbonilamino)-2-fenilacetato de (R)-*ter*-butilo como un sólido blanco (7.7 g). ^1H RMN (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. 1): RT= 1.53 min; ~90% de índice de homogeneidad; LC/MS: Análisis calculado para $[M+Na]^+$ $C_{14}H_{19}NnaO_4$: 288.12; encontrado 288.15.

TFA (16 mL) se añadió por goteo a una solución enfriada (hielo/agua) de 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. Ya que la desprotección aún no se completaba, se añadieron TFA adicional (1.0 mL) y se continuó agitando durante 2 horas más. El componente volátil se removió al vacío, y el residuo aceitoso resultante se trató con éter dietílico (15 mL) y hexanos (12 mL) para proporcionar un precipitado. El precipitado se filtró y se lavó con éter dietílico/hexanos (~1:3 de relación; 30 mL) y se secó al vacío para proporcionar *Extremo-4* como un sólido blanco

esponjoso (5.57 g). Rotación óptica: -176.9° [c = 3.7 mg/mL en H_2O; λ = 589 nm]. ^1H RMN (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. 1): RT = 1.01 min; >95% de índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{10}H_{12}NO_4$ 210.08; encontrado 210.17; HRMS: Análisis calculado para $[M+H]^+$ $C_{10}H_{12}NO_4$ 210.0766; encontrado 210.0756.

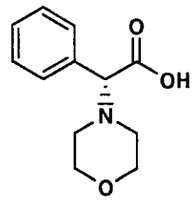
Extremo-5



Una mezcla de (R)-2-fenilglicina (1.0 g, 6.62 mmoles), 1,4-dibromobutano (1.57 g, 7.27 mmoles) y Na_2CO_3 (2.10 g, 19.8 mmoles) en etanol (40 mL) se calentó a 100°C durante 21 horas. La mezcla de reacción se enfrió a la temperatura ambiente y se filtró, y el filtrado se concentró al vacío. El residuo se disolvió en etanol y se acidificó con HCl 1N a pH3-4, y el componente volátil se removió al vacío. El material crudo resultante se purificó mediante un HPLC de fase inversa (agua/metanol/TFA) para proporcionar la sal TFA de *Extremo-5* como una espuma blanca semi-viscosa (1.0 g). ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 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 min (Cond. 1);

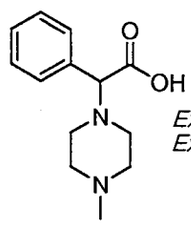
>98% de índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{12}H_{16}NO_2$: 206.12; encontrado 206.25.

Extremo-6



La sal TFA de *Extremo-6* se sintetizó a partir de (R)-2-fenilglicina y 1-bromo-2-(2-bromoetoxi)etano usando el método de preparación de *Extremo-5*. ^1H RMN (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 min (Cond. 1);>98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{12}H_{16}NO_3$: 222.11; encontrado 222.20; HRMS: Análisis calculado para $[M+H]^+$ $C_{12}H_{16}NO_3$: 222.1130; encontrado 222.1121.

Extremo-7



Extremo-7a: enantiómero 1
Extremo-7b: enantiómero 2

Una solución en CH_2Cl_2 (200 mL) de cloruro de p-toluensulfonilo (8.65 g, 45.4 mmoles) se añadió por goteo a una solución enfriada (-5°C) en CH_2Cl_2 (200 mL) de 2-hidroxi-2-fenilacetato de (S)-bencilo (10.0 g, 41.3 mmoles),

trietilamina (5.75 mL, 41.3 mmoles) y 4-dimetilaminopiridina (0.504 g, 4.13 mmoles), mientras se mantenía la temperatura entre -5°C y 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 a la 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 al vacío para proporcionar 2-fenil-2-(tosiloxi)acetato de bencilo como un aceite viscoso que se solidificó después del reposo (16.5 g). La integridad quiral del producto no se verificó y ese producto se usó para la siguiente etapa sin purificación adicional. ^{1}H RMN (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. 3); >90% de índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{22}H_{20}NaO_5S$: 419.09; encontrado 419.04.

Una solución en THF (75 mL) de 2-fenil-2-(tosiloxi)acetato de bencilo (6.0 g, 15.1 mmoles), 1-metilpiperazina (3.36 mL; 30.3 mmoles) y N,N-diisopropiletilamina (13.2 mL, 75.8 mmoles) se calentó a 65°C durante 7 horas. La reacción se dejó enfriar a la temperatura ambiente y el componente volátil se removió al vacío. El residuo se dividió entre acetato de etilo y agua, y la capa orgánica se lavó con agua y salmuera, se secó

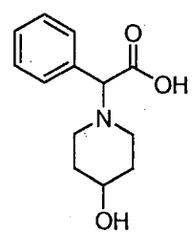
($MgSO_4$), se filtró y se concentró al vacío. El material crudo resultante se purificó mediante cromatografía por vaporización (gel de sílice, acetato de etilo) para proporcionar 2-(4-metilpiperazin-1-il)-2-fenilacetato de bencilo como un aceite viscoso anaranjado-café (4.56 g). El análisis por HPLC 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 llevó a cabo como sigue: el producto se disolvió en 120 mL de etanol/heptano (1:1) y se inyectó (5 mL/inyección) en una columna de HPLC quiral (Chiracel OJ, 5 cm ID x 50 cm L, 20 µm) eluyendo con 85:15 de heptano/etanol a 75 mL/min, y se monitoreó a 220 nm. El enantiómero-1 (1.474 g) y enantiómero-2 (2.2149 g) se retiraron como un aceite viscoso. ^1H RMN ($CDCl_3$, 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 = 1.25, 1H), 4.02 (s, 1H), 2.65-2.38 (app br s, 8H), 2.25 (s, 3H). RT = 2.10 (Cond. 3); >98% de índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{20}H_{25}N_2O_2$: 325.19; encontrado 325.20.

Una solución en metanol (10 mL) ya sea del enantiómero de 2-(4-metilpiperazin-1-il-il)-2-fenilacetato de bencilo (1.0 g, 3.1 mmoles) se añadió a una suspensión de 10% de Pd/C (120 mg) en metanol (5.0 mL). La mezcla de reacción se expuso a un balón de hidrógeno, bajo un monitoreo cuidadoso, durante <50 min. Inmediatamente después de la

conclusión de la reacción, el catalizador se filtró a través de tierra diatomácea (Celite®) y el filtrado se concentró al vacío para proporcionar *Extremo-7*, contaminada con ácido fenilacético como una espuma parda (867.6 mg; la masa está por arriba del rendimiento teórico). El producto se usó para la siguiente etapa sin purificación adicional. ^{1}H RMN (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. bs, 2H), 2.48-2.32 (m, 6H), 2.19 (s, 3H); RT = 0.31 (Cond. 2); >90%de índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235.14; encontrado 235.15; HRMS: Análisis calculado para $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235.1447; encontrado 235.1440.

La síntesis de *Extremo-8* y *Extremo-9* se llevó a cabo de acuerdo con la síntesis de *Extremo-7* usando aminas adecuadas para la etapa de desplazamiento de SN_2 (es decir, 4-hidroxipiperidina para *Extremo-8* y (S)-3-fluoropirrolidina para *Extremo-9*) y condiciones modificadas para la separación de los intermediarios estereoisoméricos respectivos, como se describe abajo.

Extremo-8

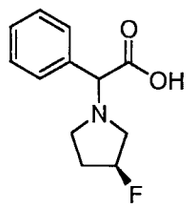


8a: enantiómero 1
8b: enantiómero 2

La separación enantiomérica del intermediario 2-(4-

hidroxipiperidin-1-il)-2-fenilacetato de bencilo se llevó a cabo al emplear las siguientes condiciones: el compuesto (500 mg) se disolvió en etanol/heptano (5 mL/45 mL). La solución resultante se inyectó (5 mL/inyección) en una columna de HPLC quiral (Chiracel OJ, 2 cm ID x 25 cm L, 10 µm) eluyendo con 80:20 de heptano/etanol a 10 mL/min, monitoreada a 220 nm, para proporcionar 186.3 mg de enantiómero-1 y 209.1 mg de enantiómero-2 como aceites viscosos amarillo claro. Este éster bencílico fue hidrogenolizado de acuerdo con la preparación de *Extremo-7* para proporcionar *Extremo-8*. ^{1}H RMN (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. 2); >98% de índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{13}H_{18}NO_3$: 236.13; encontrado 236.07; HRMS: calculado para $[M+H]^+$ $C_{13}H_{18}NO_3$: 236.1287; encontrado 236.1283.

Extremo 9

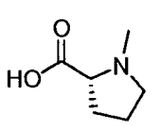


9a: diastereómero 1
9b: diastereómero 2

La separación diastereomérica del intermediario 2-((S)-3-fluoropirrolidin-1-il)-2-fenilacetato de bencilo se llevó a cabo al emplear las siguientes condiciones: el éster (220 mg) se separó en una columna de HPLC quiral (Chiracel

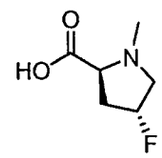
OJ-H, 0.46 cm ID x 25 cm L, 5 µm) eluyendo con 95% de CO_2/5% de metanol con 0.1% de TFA, a presión de 10 bares, 70 mL/min de velocidad de flujo, y una temperatura de 35°C. El eluto de HPLC para los estereoisómeros respectivos fue concentrado, y el residuo se disolvió en CH_2Cl_2 (20 mL) y se lavó con un medio acuoso (10 mL de agua + 1 mL de solución saturada $NaHCO_3$). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró al vacío para proporcionar 92.5 mg de la fracción-1 y 59.6 mg de la fracción-2. Estos ésteres bencílicos fueron hidrogenolizados de acuerdo con la preparación de *Extremo-7* para preparar Caps 9a y 9b. *Extremo-9a* (diastereómero-1; la muestra es una sal TFA como un resultado de purificación en HPLC de fase inversa usando solvente de H_2O/metanol/TFA): ^1H RMN (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 (br s, 1H), 3.84-2.82 (br m, 4H), 2.31-2.09 (m, 2H). RT = 0.42 (Cond. 1); >95% de índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; encontrado 224.14; *Extremo*-9b (diastereómero-2): ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 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). RT = 0.44 (Cond. 1); LC/MS: Análisis calculado para $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; encontrado 224.14.

Extremo-10



A una solución de D-prolina (2.0 g, 17 mmoles) y formaldehído (2.0 mL de 37% en peso en H_2O) en metanol (15 mL) se le añadió una suspensión de 10% de Pd/C (500 mg) en metanol (5 mL). La mezcla se agitó bajo un balón de hidrógeno durante 23 horas. La mezcla de reacción se filtró a través de tierra diatomácea (Celite®) y se concentró al vacío para proporcionar *Extremo-10* como un sólido blanquecino (2.15 g). ^{1}H RMN (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. 2); >98% de índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_6H_{12}NO_2$: 130.09; encontrado 129.96.

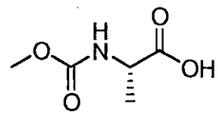
Extremo-11



Una mezcla de ácido (2S,4R)-4-fluoropirrolidin-2-carboxílico (0.50 g, 3.8 mmoles), formaldehído (0.5 mL de 37% en peso en H_2O), HCl 12 N (0.25 mL) y 10% de Pd/C (50 mg) en metanol (20 mL) se agitó bajo un balón de hidrógeno durante 19 horas. La mezcla de reacción se filtró a través de tierra diatomácea (Celite®) y el filtrado se concentró al vacío. El residuo se recristalizó a partir de isopropanol para proporcionar la sal HCl de *Extremo-11* como un sólido blanco

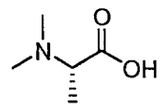
(337.7 mg). ^{1}H RMN (DMSO-d_6, δ = 2.5, 500 MHz): 5.39 (d m, J = 53.7, 1H), 4.30 (m, 1H), 3.90 (ddd, J = 31.5, 13.5, 4.5, 1H), 3.33 (dd, J = 25.6, 13.4, 1H), 2.85 (s, 3H), 2.60-2.51 (m, 1H), 2.39-2.26 (m, 1H), RT = 0.28 (Cond. 2); >98% de índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_6H_{11}FNO_2$: 148.08; encontrado 148.06.

Extremo-12



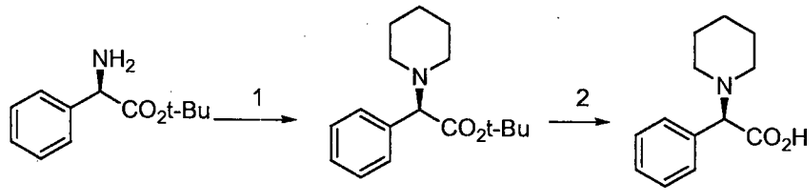
L-alanina (2.0 g, 22.5 mmoles) se disolvió en 10% de solución acuosa de carbonato de sodio (50 mL), y una solución en THF (50 mL) de cloroformiato de metilo (4.0 mL) fue añadida a ésta. La mezcla de reacción se agitó bajo condiciones ambiente bajo 4.5 horas y se concentró al vacío. El sólido blanco resultante 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 combinada se secó (Na_2SO_4), se filtró y se concentró al vacío para proporcionar un aceite incoloro (2.58 g). 500 mg de este material se purificaron mediante una HPLC de fase inversa (H_2O/metanol/TFA) para proporcionar 150 mg de *Extremo-12* como un aceite incoloro. ^{1}H RMN (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).

Extremo-13



Una mezcla de L-alanina (2.5 g, 28 mmoles), formaldehído (8.4 g, 37% en peso), HCl 1N (30 mL) y 10% de Pd/C (500 mg) en metanol (30 mL) se agitó bajo una atmósfera de hidrógeno (3.51 kg/cm^2 (50 psi)) durante 5 horas. La mezcla de reacción se filtró a través de tierra diatomácea (Celite®) y el filtrado se concentró al vacío para proporcionar la sal HCl de *Extremo-13* como un aceite que se solidificó después del reposo al vacío (4.4 g; la masa está por arriba del rendimiento teórico). El producto se usó sin purificación adicional. ^{1}H RMN (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).

Extremo-14



Extremo-14

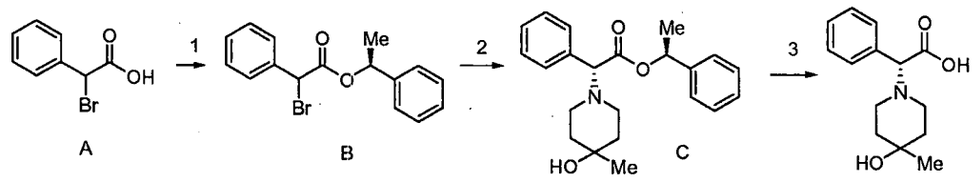
Etapa 1: Una mezcla de éster *ter*-butílico de (R)-(-)-D-fenilglicina (3.00g, 12.3 mmoles), $NaBH_3CN$ (0.773 g, 12.3 mmoles), KOH (0.690 g, 12.3 mmoles) y ácido acético (0.352 mL, 6.15 mmoles) se agitó en metanol a 0°C. A esta mezcla se le añadió dialdehído glutárico (2.23 mL, 12.3 mmoles) por

goteo durante 5 minutos. La mezcla de reacción se agitó mientras se le dejaba calentar a la temperatura ambiente y se continuó agitando a la misma temperatura durante 16 horas. El solvente se removió subsecuentemente y el residuo se dividió con 10% de NaOH acuoso y acetato de etilo. La fase orgánica se separó, se secó ($MgSO_4$), se filtró y se concentró hasta la sequedad para proporcionar un aceite transparente. Este material se purificó mediante HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100 mm; CH_3CN-H_2O-0.1% de TFA) para dar el éster intermediario (2.70 g, 56%) como un aceite transparente. ^1H RMN (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: Análisis calculado para $C_{17}H_{25}NO_2$: 275; encontrado: 276 $(M+H)^+$.

Etapa 2: A una solución agitada del éster intermediario (1.12 g, 2.88 mmoles) en diclorometano (10 mL) se le añadió TFA (3 mL). La mezcla de reacción se agitó a temperatura ambiente durante 4 horas y después se concentró hasta la sequedad para dar un aceite amarillo claro. El aceite se purificó usando HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100 mm; CH_3CN-H_2O-0.1% de TFA). Las fracciones adecuadas fueron combinadas y concentradas hasta la sequedad al vacío. El residuo se disolvió después en una

cantidad mínima de metanol y se aplicó a cartuchos de extracción MCX LP (2 x 6 g). Los cartuchos fueron enjugadas con metanol (40 mL) y después el compuesto deseado se eluyó usando amoniaco 2M en metanol (50 mL). Las fracciones que contenían producto se combinaron y concentraron y el residuo se recogió en agua. La liofilización de esta solución proporcionó el compuesto del título (0.492 g, 78%) como un sólido amarillo claro. ^{1}H RMN (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: Análisis calculado para $C_{13}H_{17}NO_2$: 219; encontrado: 220 $(M+H)^+$.

Extremo-15



Etapa 1 - 2-Bromo-2-fenilàcetato de (S)-1-feniletilo: A una mezcla de ácido α-bromofenilacético (10.75 g, 0.050 moles), (S)-(-)-1-feniletanol (7.94 g, 0.065 moles) y DMAP (0.61 g, 5.0 mmoles) en diclorometano seco (100 mL) se le añadió EDCI sólido (12.46 g, 0.065 moles) todo en una sola vez. La solución resultante se agitó a temperatura ambiente bajo Ar durante 18 horas y después se diluyó con acetato de etilo, se lavó (H_2O x 2, salmuera), se secó (Na_2SO_4), se filtró, y se concentró para dar un aceite amarillo pálido.

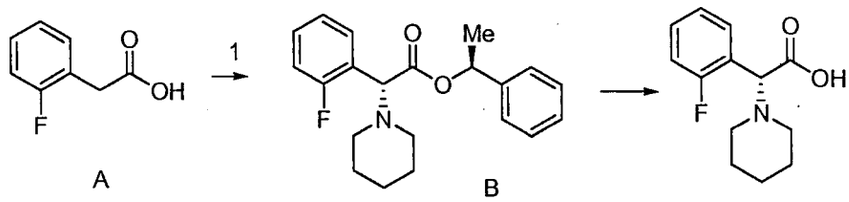
La cromatografía por vaporización (SiO_2/hexano-acetato de etilo, 4:1) de este aceite proporcionó el compuesto del título (11.64 g, 73%) como un sólido blanco. ^1H RMN (400 MHz, $CDCl_3$) δ 7.53-7.17 (m, 10H), 5.95 (q, J = 6.6 Hz, 0.5 H), 5.94 (q, J = 6.6 Hz, 0.5H), 5.41 (s, 0.5H), 5.39 (s, 0.5H), 1.58 (d, J = 6.6 Hz, 1.5 H), 1.51 (d, J = 6.6 Hz, 1.5 H).

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 mmoles) en THF (8 ml) se le añadió trietilamina (0.61 mL, 4.35 mmoles), seguida por yoduro de tetrabutilaminio (0.215 g, 0.58 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 5 minutos y después se añadió una solución de 4-metil-4-hidroxipiperidina (0.251 g, 2.18 mmoles) en THF (2 mL). La mezcla se agitó durante 1 hora a temperatura ambiente y después se calentó a 55-60°C (temperatura de baño de aceite) durante 4 horas. La mezcla de reacción enfriada se diluyó después 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 mediante cromatografía en gel de sílice (0-60% de acetato de etilo-hexano) para proporcionar primero el isómero (S,R) del compuesto del título (0.306 g, 60%) como un sólido blanco y después el isómero (S,S) correspondiente (0.120 g, 23%),

también como un sólido blanco. Isómero (S,R): ^{1}H RMN (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: Análisis calculado para $C_{22}H_{27}NO_3$: 353; encontrado: 354 $(M+H)^+$. Isómero (S,S): ^{1}H RMN (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, 1), 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 (d, 3H). LCMS: Análisis 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 mmoles) en diclorometano (3 mL) se le añadió ácido trifluoroacético (1 mL) y la mezcla se agitó a temperatura ambiente durante 2 horas. Los volátiles fueron posteriormente removidos al vacío y el residuo se purificó mediante HPLC preparativa de fase inversa (Primesphere C-18, 20 x 100 mm; CH_3CN-H_2O-0.1% de TFA) para dar el compuesto del título (como sal TFA) como un sólido azulado pálido (0.128 g, 98%). LCMS: Análisis calculado para $C_{14}H_{19}NO_3$: 249; encontrado: 250 $(M+H)^+$.

Extremo-16



A B

(R)-Extremo-16

Etapa 1 - 2-(2-Fluorofenil)acetato de (S)-1-feniletilo: Una mezcla de ácido 2-fluorofenilacético (5.45 g, 35.4 mmoles), (S)-1-feniletanol (5.62 g, 46.0 mmoles), EDCI (8.82 g, 46.0 mmoles) y DMAP (0.561 g, 4.60 mmoles) en CH_2Cl_2 (100 mL) se agitó a temperatura ambiente durante 12 horas. El solvente se concentró después y el residuo se dividió con H_3O-acetato de etilo. Las fases se separaron y la capa acuosa se volvió a extraer con acetato de etilo (2x). Las fases orgánicas combinadas se lavaron (H_2O, salmuera), se secaron (Na_2SO_4), se filtraron y se concentraron al vacío. el residuo se purificó mediante cromatografía en gel de sílice (Biotage/0-20% de acetato de etilo-hexano) para proporcionar el compuesto del título como un aceite incoloro (8.38 g, 92%). ^{1}H RMN (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).

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-fenletilo (5.00 g, 19.4 mmoles) en THF (1,200 mL) a 0°C se le añadió DBU (6.19 g, 40.7

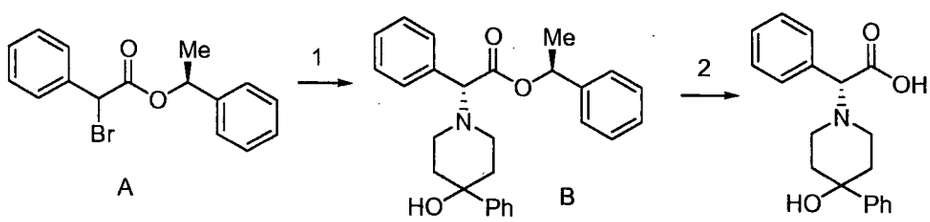
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mmoles) y la solución se dejó calentar a la temperatura ambiente mientras se agitaba durante 30 min. La solución se enfrió después a -78°C y se añadió una solución de CBr_4 (13.5 g, 40.7 mmoles) en THF (100 mL) y la mezcla se dejó calentar a -10°C y se agitó a esta temperatura durante 2 horas. La mezcla de reacción se enfrió rápidamente con NH_4Cl acuoso saturado y las capas se separaron. La capa acuosa se volvió a extraer con acetato de etilo (2x) y las fases orgánicas combinadas se lavaron (H_2O, salmuera), se secaron (Na_2SO_4), se filtraron y se concentraron al vacío. Al residuo se le añadió piperidina (5.73 mL, 58.1 mmoles) y la solución se agitó a temperatura ambiente durante 24 horas. Los volátiles se concentraron después al vacío y el residuo se purificó mediante cromatografía en gel de sílice (Biotage/0-30% de éter dietílico-hexano) para proporcionar una mezcla pura de diastereómeros (relación 2:1 mediante ^1H RMN) como un aceite amarillo (2.07 g, 31%) junto con material de partida no reaccionado (2.53 g, 51%). La cromatografía adicional de la mezcla diastereomérica (Biotage/0-10% de éter dietílico-tolueno) proporcionó el compuesto del título como un aceite incoloro (0.737 g, 11%). ^1H RMN (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: Análisis calculado para

$C_{21}H_{24}FNO_2$: 341; encontrado: 342 $(M+H)^+$.

Etapa 3 - Ácido (R)-2-(2-fluorofenl)-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 mmoles) y 20% de $Pd(OH)_2/C$ (0.070 g) en etanol (30 mL) se hidrogenó a temperatura ambiente y presión atmosférica (balón de H_2) durante 2 h. La solución se purgó después con Ar, se filtró a través de tierra diatomácea (Celite®) y se concentró al vacío. Esto proporcionó el compuesto del título como un sólido incoloro (0.503 g, 98%). ^1H RMN (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: Análisis calculado para $C_{13}H_{16}FNO_2$: 237; encontrado: 238 $(M+H)^+$.

Extremo-17



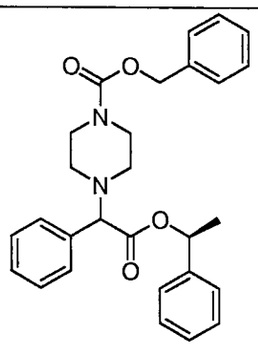
(R)-Extremo-17

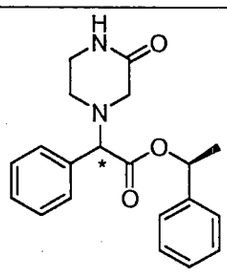
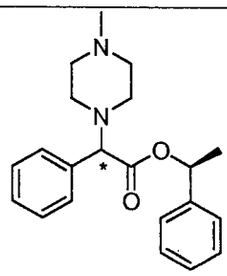
Etapa 1 - (R)-2-(4-Hidroxi-4-fenilpiperidin-1-il)-2-fenilacetato de (S)-1-feniletilo: A una solución de 2-bromo-2-fenilacetato de (S)-1-feniletilo (1.50 g, 4.70 mmoles) en THF (25 mL) se le añadió trietilamina (1.31 mL, 9.42 mmoles), seguida por yoduro de tetrabutilamonio (0.347 g, 0.94

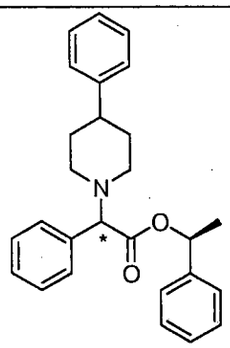
mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 5 minutos y después se añadió una solución de 4-fenil-4-hidroxipiperidina (1.00 g, 5.64 mmoles) en THF (5 mL). La mezcla se agitó durante 16 horas y después se diluyó con acetato de etilo (100 mL), se lavó (H_2O x2, salmuera), se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó en una columna de gel de sílice (0-60% de acetato de etilo-hexano) para proporcionar una mezcla aproximadamente 2:1 de diastereómeros, según se juzga por ^{1}H-RMN. La separación de estos isómeros se llevó a cabo usando cromatografía de fluidos supercríticos (Chiralcel OJ-H, 30 x 250 mm; 20% de etanol en CO_2 a 35°C), para dar primero el isómero (R) del compuesto del título (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): ^{1}H RMN (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: Análisis calculado para $C_{27}H_{29}NO_3$: 415; encontrado: 416 $(M+H)^+$; Isómero

(S,S): ^{1}H RMN (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: Análisis calculado para $C_{27}H_{29}NO_3$: 415; encontrado: 416 $(M+H)^+$.

Los siguientes ésteres fueron preparados de una forma similar empleada en la etapa 1 en la síntesis de *Extremo-17*.

Intermediario 17a		Diastereómero 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. para: $C_{28}H_{30}N_2O_4$ 458.55; Encontrado: 459.44 $(M+H)^+$.

		Diastereómero 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. para: $C_{28}H_{30}N_2O_4$ 458.55; Encontrado: 459.44 $(M+H)^+$.
Intermediario -17b		Diastereómero 1: RT = 11.76 min (Cond'n II); LCMS: Anal. Calcd. para: $C_{20}H_{22}N_2O_3$ 338.4 Found: 339.39 $(M+H)^+$; Diastereómero 2: RT = 10.05 min (Cond'n II); LCMS: Anal. Calcd. para: $C_{20}H_{22}N_2O_3$ 338.4; Encontrado: 339.39 $(M+H)^+$.
Intermediario -17c		Diastereómero 1: T_R = 4.55 min (Cond'n I); LCMS: Anal. Calcd. para: $C_{21}H_{26}N_2O_2$ 338.44 Found: 339.45 $(M+H)^+$; Diastereómero 2: T_R = 6.00 min (Cond'n I); LCMS: Anal. Calcd. para: $C_{21}H_{26}N_2O_2$ 338.44 Encontrado: 339.45 $(M+H)^+$.

Intermediario -17d		Diastereómero 1: RT = 7.19 min (Cond'n I); LCMS: Anal. Calcd. para: $C_{27}H_{29}NO_2$ 399.52 Encontrado: 400.48 $(M+H)^+$; Diastereómero 2: RT = 9.76 min (Cond'n I); LCMS: Anal. Calcd. para: $C_{27}H_{29}NO_2$ 399.52 Encontrado: 400.48 $(M+H)^+$.

Condiciones de SFC quiral para determinar el tiempo de retención para los intermediarios 17b-17d

Condición 1

Columna: Chiralpak AD-H, 4.6X250 mm, 5µm

Solventes: 90% de CO2-10% de metanol con 0.1% de DEA

Temperatura: 35°C

Presión: 150 bares

Velocidad de flujo: 2.0 mL/min.

UV monitoreado @ 220 nm

Inyección: 1.0 mg/3 mL de metanol

Condición 2

Columna: Chiralcel OD-H, 4.6X250 mm, 5µm

Solventes: 90% de CO2-10% de metanol con 0.1% de DEA

Temperatura: 35°C

Presión: 150 bares

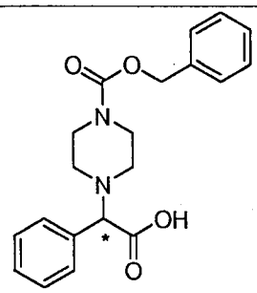
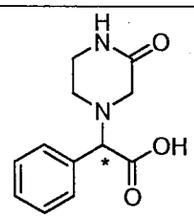
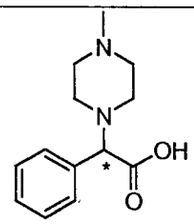
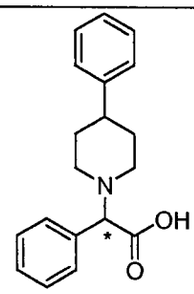
Velocidad de flujo: 2.0 mL/min.

UV monitoreado @ 220 nm

Inyección: 1.0 mg/3 mL de metanol

Extremo-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 mmoles) en diclorometano (5 mL) se le añadió ácido trifluoroacético (1 mL) y la mezcla se agitó a temperatura ambiente durante 2 horas. Los volátiles se removieron subsecuentemente al vacío y el residuo se purificó mediante HPLC preparativa de fase inversa (Primesphere C-18, 20x100 mm; CH_3CN-H_2O-0.1% de TFA) para dar el compuesto del título (como sal TFA) como un sólido blanco (0.230 g, 88%). LCMS: Análisis calculado para $C_{19}H_{21}NO_3$: 311; encontrado 312 $(M+H)^+$.

Los siguientes ácidos carboxílicos fueron preparados de una forma similar:

Extremo-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. para: $C_{20}H_{22}N_2O_4$ 354.40; Encontrado: 355.38 $(M+H)^+$.
Extremo-17b		RT = 0.27 (Cond'n III); LCMS: Anal. Calcd. para: $C_{12}H_{14}N_2O_3$ 234.25; Encontrado: 235.22 $(M+H)^+$.
Extremo-17c		RT = 0.48 (Cond'n II); LCMS: Anal. Calcd. para: $C_{13}H_{18}N_2O_2$ 234.29; Encontrado: 235.31 $(M+H)^+$.
Extremo-17d		RT = 2.21 (Cond'n I); LCMS: Anal. Calcd. para: $C_{19}H_{21}NO_2$ 295.38; Encontrado: 296.33 $(M+H)^+$.

Condiciones de LCMS para determinar tiempo de retención para Extremos 17a-17d

Condición 1

Columna: Phenomenex-Luna 4.6 X 50 mm S10

% B de inicio = 0

% B final = 100

Tiempo gradiente = 4 minutos

Velocidad de flujo = 4 mL/min

Longitud de onda = 220

Solvente A = 10% de metanol - 90% de H_2O-0.1% de TFA

Solvente B = 90% de metanol - 10% de H_2O-0.1% de TFA

Condición 2

Columna: Waters-Sunfire 4.6 X 50 mm S5

% B de inicio = 0

% B final = 100

Tiempo gradiente = 2 minutos

Velocidad de flujo = 4 mL/min

Longitud de onda = 220

Solvente A = 10% de metanol - 90% de H_2O-0.1% de TFA

Solvente B = 90% de metanol - 10% de H_2O-0.1% de TFA

Condición 3

Columna: Phenomenex 10 µ 3.0 X 50 mm

% B de inicio = 0

% B final = 100

Tiempo gradiente = 2 minutos

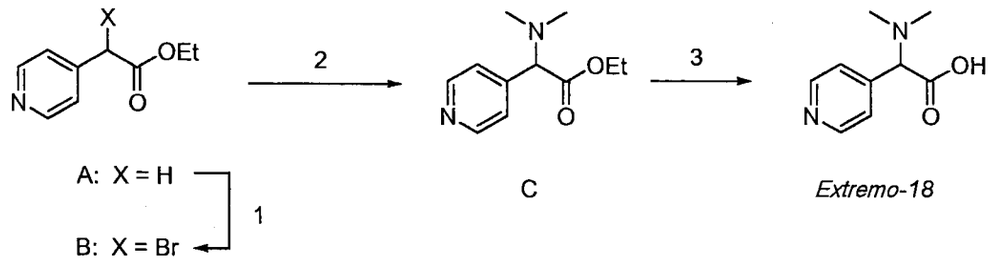
Velocidad de flujo = 4 mL/min

Longitud de onda = 220

Solvente A = 10% de metanol - 90% de H_2O-0.1% de TFA

Solvente B = 90% de metanol - 10% de H_2O-0.1% de TFA

Extremo-18



Etapa 1 - 2-(4-Piridil)-2-bromoacetato de (R,S)-etilo: A una solución de 4-piridilacetato de etilo (1.00 g, 6.05 mmoles) en THF seco (150 mL) a 0°C bajo argón se le añadió DBU (0.99 mL, 6.66 mmoles). La mezcla de reacción se dejó calentar a la temperatura ambiente durante 30 minutos y después se enfrió a -78°C. A esta mezcla se le añadió CBr_4 (2.21 g, 6.66 mmoles) y se continuó agitando a -78°C durante 2 horas. La mezcla de reacción se enfrió después rápidamente con NH_4Cl acuoso saturado y las fases se separaron. La fase orgánica se lavó (salmuera), se secó (Na_2SO_4), se filtró y se concentró al vacío. El aceite amarillo resultante se purificó inmediatamente mediante cromatografía por vaporización (SiO_2/hexano-acetato de etilo, 1:1) para proporcionar el compuesto del título (1.40 g, 95%) como un aceite amarillo un poco inestable. ^1H RMN (400 MHz, $CDCl_3$) δ

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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: Análisis calculado para $C_9H_{10}BrNO_2$: 242, 244; encontrado: 243,245 $(M+H)^+$.

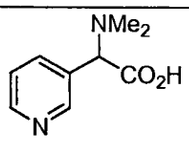
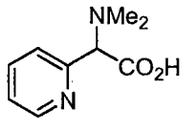
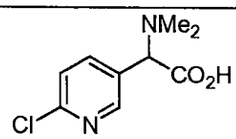
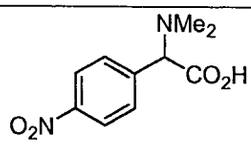
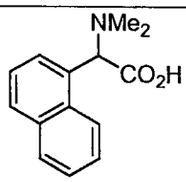
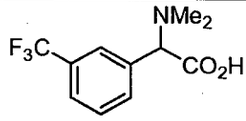
Etapa 2 - 2-(4-Piridil)-2-(N,N-dimetilamino)acetato de (R,S)-etilo: A una solución de 2-(4-piridil)-2-bromoacetato de (R,S)-etilo (1.40 g, 8.48 mmoles) en DMF (10 mL) a temperatura ambiente se le añadió dimetilamina (2M en THF, 8.5 mL, 17.0 mmoles). Después de que concluyera la reacción (según se juzga mediante tlc) los materiales volátiles fueron removidos al vacío y el residuo se purificó mediante cromatografía por vaporización (Biotage, columna 40+M SiO_2; 50%-100% de acetato de etilo-hexano) para proporcionar el compuesto del título (0.539 g, 31%) como un aceite amarillo claro. ^1H RMN (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 Análisis calculado para $C_{11}H_{16}N_2O_2$: 208; encontrado: 209 $(M+H)^+$.

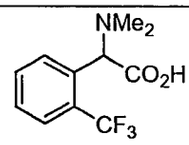
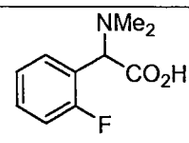
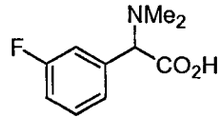
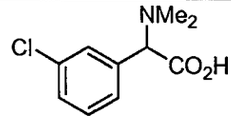
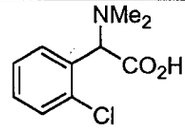
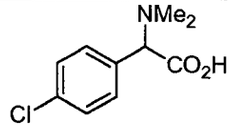
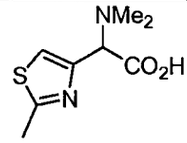
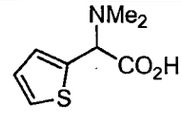
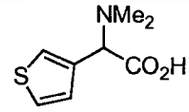
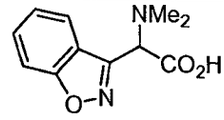
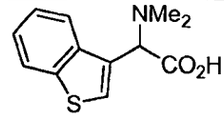
Etapa 3 - Ácido (R,S)-2-(4-piridil)-2-(N,N-dimetilamino)acético: A una solución de 2-(4-piridil)-2-(N,N-dimetilamino)acetato de (R,S)-etilo (0.200 g, 0.960 mmoles) en una mezcla de THF-metanol-H_2O (1:1:1, 6 mL) se le añadió LiOH en polvo (0.120 g, 4.99 mmoles) a temperatura ambiente. La solución se agitó durante 3 horas y después se acidificó a pH 6 usando HCl 1N. La fase acuosa se lavó con acetato de

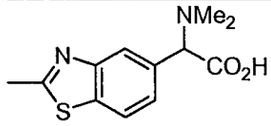
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etilo y después se liofilizó para dar el diclorhidrato del compuesto del título como un sólido amarillo (que contenía LiCl). El producto se usó como tal en etapas subsecuentes. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 5.7 Hz, 2H), 7.34 (d, *J* = 5.7 Hz, 2H), 3.56 (s, 1H), 2.21 (s, 6H).

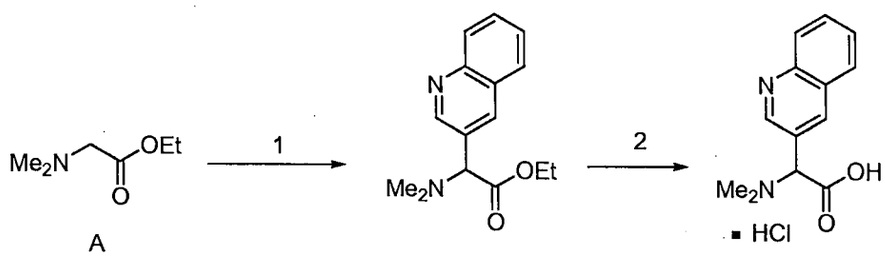
Los siguientes ejemplos se prepararon de una manera similar usando el método descrito arriba.

Extremo-19		LCMS: Anal. Calcd. para: $C_9H_{12}N_2O_2$: 180; Encontrado: 181 $(M+H)^+$.
Extremo-20		LCMS: sin ionización. ^{1}HNMR (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).
Extremo-21		LCMS: Anal. Calcd. for $C_9H_{11}ClN_2O_2$: 214, 216; Encontrado: 215, 217 $(M+H)^+$.
Extremo-22		LCMS: Anal. Calcd. para: $C_{10}H_{12}N_2O_4$: 224; Encontrado: 225 $(M+H)^+$.
Extremo-23		LCMS: Anal. Calcd. para: $C_{14}H_{15}NO_2$: 247; Encontrado: 248 $(M+H)^+$.
Extremo-24		LCMS: Anal. Calcd. para: $C_{11}H_{12}F_3NO_2$: 247; Encontrado: 248 $(M+H)^+$.

Extremo-25		LCMS: Anal. Calcd. para: $C_{11}H_{12}F_3NO_2$: 247; Encontrado: 248 $(M+H)^+$.
Extremo-26		LCMS: Anal. Calcd. para: $C_{10}H_{12}FNO_2$: 247; Encontrado: 248 $(M+H)^+$.
Extremo-27		LCMS: Anal. Calcd. para: $C_{10}H_{12}FNO_2$: 247; Encontrado: 248 $(M+H)^+$.
Extremo-28		LCMS: Anal. Calcd. para: $C_{10}H_{12}ClNO_2$: 213, 215; Encontrado: 214, 217 $(M+H)^+$.
Extremo-29		LCMS: Anal. Calcd. para: $C_{10}H_{12}ClNO_2$: 213, 215; Encontrado: 214, 217 $(M+H)^+$.
Extremo-30		LCMS: Anal. Calcd. para: $C_{10}H_{12}ClNO_2$: 213, 215; Encontrado: 214, 217 $(M+H)^+$.
Extremo-31		LCMS: Anal. Calcd. para: $C_8H_{11}N_2O_2S$: 200; Encontrado: 201 $(M+H)^+$.
Extremo-32		LCMS: Anal. Calcd. para: $C_8H_{11}NO_2S$: 185; Encontrado: 186 $(M+H)^+$.
Extremo-33		LCMS: Anal. Calcd. para: $C_8H_{11}NO_2S$: 185; Encontrado: 186 $(M+H)^+$.
Extremo-34		LCMS: Anal. Calcd. para: $C_{11}H_{12}N_2O_3$: 220; Encontrado: 221 $(M+H)^+$.
Extremo-35		LCMS: Anal. Calcd. para: $C_{12}H_{13}NO_2S$: 235; Encontrado: 236 $(M+H)^+$.

Extremo-36		LCMS: Anal. Calcd. para: $C_{12}H_{14}N_2O_2S$: 250; Encontrado: 251 $(M+H)^+$.

Extremo-37



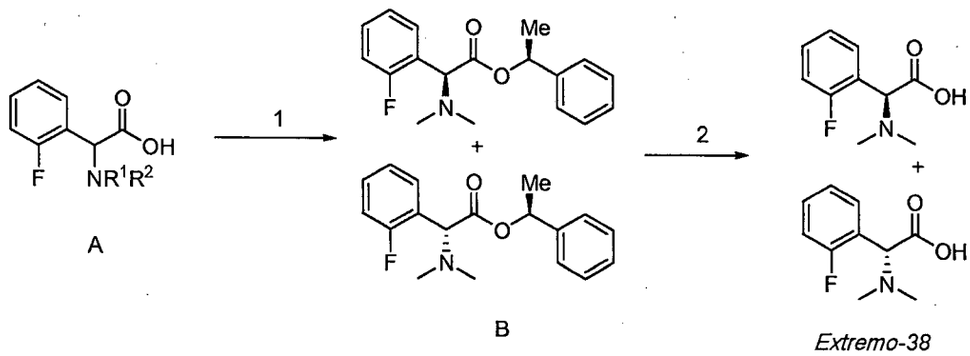
A B *cap-37*

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 mmoles), K_3PO_4 (1.90 g, 8.95 mmoles), $Pd(t\text{-}Bu_3P)_2$ (0.090 g, 0.176 mmoles) y tolueno (10 mL) se desgasificó con una corriente de burbujas de Ar durante 15 minutos. La mezcla de reacción se calentó después a 100°C durante 12 horas, después de lo cual se enfrió a la temperatura ambiente y se vertió en H_2O. La mezcla se extrajo con acetato de etilo (2x) y las fases orgánicas combinadas se lavaron (H_2O, salmuera), se secaron (Na_2SO_4), se filtraron y se concentraron al vacío. El residuo se purificó mediante HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100 mm; CH_3CN-H_2O-5 mM de NH_4OAc) y luego mediante cromatografía por vaporización (SiO_2/hexano-acetato de etilo, 1:1) para proporcionar el compuesto del título (0.128 g, 17%) como un aceite anaranjado. ^1H RMN (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: Análisis 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: Una mezcla de 2-(quinolin-3-il)-2-(N,N-dimetilamino)acetato de (R,S)-etilo (0.122 g, 0.472 mmoles) y HCl 6M (3 mL) se calentó a 100°C durante 12 horas. El solvente se removió al vacío para proporcionar el diclorhidrato del compuesto del título (0.169 g, >100%) como una espuma amarillo claro. El material no purificado se usó en etapas subsecuentes sin purificación adicional. LCMS: Análisis calculado para $C_{13}H_{14}N_2O_2$: 230; encontrado: 231 $(M+H)^+$.

Extremo-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-feniletilo): A una mezcla

de ácido (RS)-2-(dimetilamino)-2-(2-fluorofenl)acético (2.60 g, 13.19 mmoles), DMAP (0.209 g, 1.71 mmoles) y (S)-1-feniletanol (2.09 g, 17.15 mmoles) en CH_2Cl_2 (40 mL) se le añadió EDCl (3.29 g, 17.15 mmoles) y la mezcla se dejó agitar a temperatura ambiente durante 12 horas. El solvente se removió después al vacío y el residuo se dividió con acetato de etilo-H_2O. Las capas se separaron, la capa acuosa se volvió a extraer con acetato de etilo (2x) y las fases orgánicas combinadas se lavaron (H_2O, salmuera), se secaron (Na_2SO_4), se filtraron y se concentraron al vacío. el residuo se purificó mediante cromatografía en gel de sílice (Biotage/-0-50% de éter dietílico-hexano). La mezcla diastereomérica pura resultante se separó después mediante HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100 mm; CH_3CN-H_2O-0.1% de TFA) para dar 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%), ambos como sus sales TFA. Isómero (S,R): ^{1}H RMN (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: Análisis calculado para $C_{18}H_{20}FNO_2$: 301; encontrado: 302 $(M+H)^+$; isómero (S,S). ^{1}H RMN (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: Análisis 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 mmoles) y 20% de $Pd(OH)_2/C$ (0.125 g) en etanol (30 mL) se hidrogenó a temperatura ambiente y presión atmosférica (balón de H_2) durante 4 horas. La solución se purgó después con Ar, se filtró a través de tierra diatomácea (Celite®), y se concentró al vacío. esto dio el compuesto del título como un sólido incoloro (0.503 g, 98%). ^1H RMN (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: Análisis calculado para $C_{10}H_{12}FNO_2$: 197; encontrado: 198 $(M+H)^+$.

El isómero S pudo obtenerse a partir de 2-(dimetilamino)-2-(2-fluorofenil)acetato de (S)-((S)-1-feniletilo), sal TFA de una forma similar.

Extremo-39

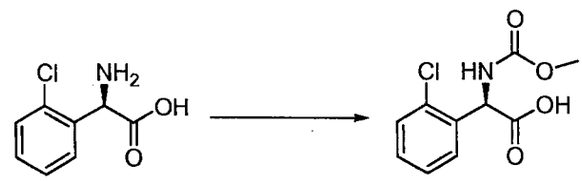


Extremo-39

Una mezcla de (R)-(2-clorofenil)glicina (0.300 g, 1.62 mmoles), formaldehído (solución acuosa al 35%, 0.80 mL,

3.23 mmoles) y 20% de $Pd/OH)_2/C$ (0.050 g) se hidrogenó a temperatura ambiente y presión atmosférica (balón de H_2) durante 4 horas. La solución se purgó después con Ar, se filtró a través de tierra diatomácea (Celite®) y se concentró al vacío. El residuo se purificó mediante HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100 mm; CH_2CN-H_2O-0.1% de TFA) para dar la sal TFA del compuesto del título ácido (R)-2-(dimetilamino)-2-(2-clorofenil)acético como un aceite incoloro (0.290 g, 55%). ^1H RMN (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: Análisis calculado para $C_{10}H_{12}ClNO_2$: 213, 215; encontrado: 214, 216 $(M+H)^+$.

Extremo-40

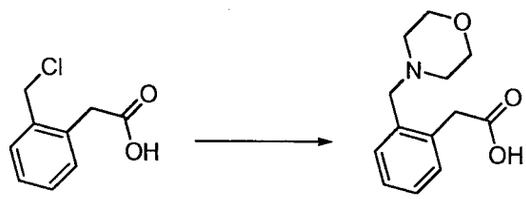


Extremo-40

A una solución enfriada con hielo de (R)-(2-clorofenil)glicina (1.00 g, 5.38 mmoles) y NaOH (0.862 g, 21.6 mmoles) en H_2O (5.5 mL) se le añadió cloroformiato de metilo (1.00 mL, 13.5 mmoles) por goteo. La mezcla se dejó agitar a 0°C durante 1 hora y después se acidificó mediante la adición de HCl concentrado (2.5 mL). La mezcla se extrajo con acetato de etilo (2x) y la fase orgánica combinada se lavó (H_2O, salmuera), se secó (Na_2SO_4), se filtró y se

concentró al vacío para dar el compuesto del título, ácido (R)-2-(metoxicarbonilamino)-2-(2-clorofenil)acético como una espuma amarillo-anaranjado (1.31 g, 96%). ^{1}H RMN (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: Análisis calculado para $C_{10}H_{10}ClNO_4$: 243, 245; encontrado: 244, 246 $(M+H)^+$.

Extremo-41

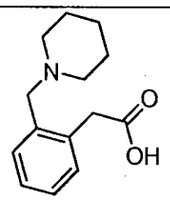
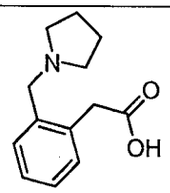
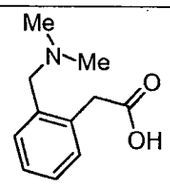
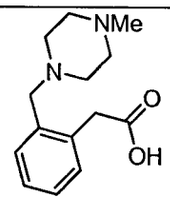


Extremo-41

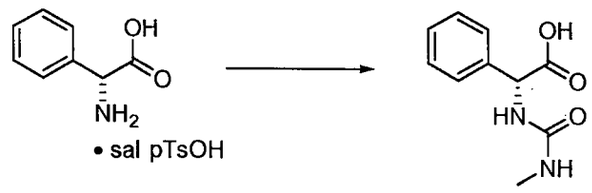
A una suspensión de ácido 2-(2-(clorometil)fenil)acético (2.00 g, 10.8 mmoles) en THF (20 mL) se le añadió morfolina (1.89 g, 21.7 mmoles) y la solución se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se diluyó después con acetato de etilo y se extrajo con H_2O (2x). La fase acuosa se liofilizó y el residuo se purificó mediante cromatografía en gel de sílice (Biotage/0-10% de metanol-CH_2Cl_2) para dar el compuesto del título, ácido 2-(2-(morfolinometil)fenil)acético como un sólido incoloro (2.22 g, 87%). ^{1}H RMN (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: Análisis calculado para $C_{13}H_{17}NO_3$: 235; encontrado: 236 $(M+H)^+$.

Los siguientes extremos fueron preparados

similarmente usando el método descrito para *Extremo-41*:

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

Extremo-45

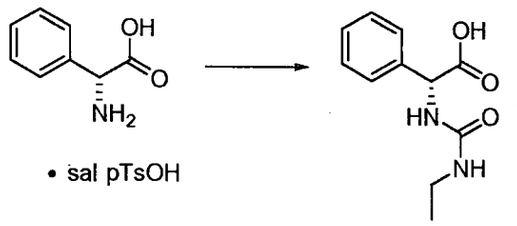


Extremo-45

HMDS (1.85 mL, 8.77 mmoles) se añadió a una suspensión de p-toluensulfonato de ácido (R)-2-amino-2-fenilacético (2.83 g, 8.77 mmoles) 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 mmoles) en una porción y se continuó agitando durante 30 minutos. La

reacción se enfrió rápidamente mediante la adición de H_2O (5 ml) y el precipitado resultante se filtró, se lavó con H_2O y n-hexanos, y se secó al vacío. Ácido (R)-2-(3-metilureido)-2-fenilacético (1.5 g; 82%) fue recuperado como un sólido blanco y se usó sin purificación adicional. ^{1}H RMN (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: Análisis calculado para $C_{10}H_{12}N_2O_3$ 208.08 encontrado 209.121 $(M+H)^+$; HPLC Phenomenex C-18 3.0 x 46 mm, 0 a 100% B durante 2 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, RT = 1.38 min, 90% de índice de homogeneidad.

Extremo-46



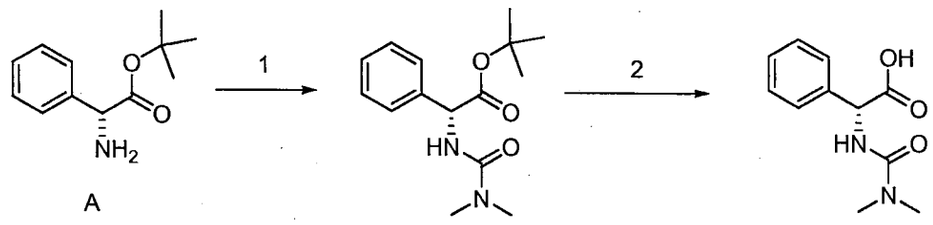
Extremo-46

El producto deseado se preparó de acuerdo con el método descrito para *Extremo-45*. ^{1}H RMN (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: Análisis calculado para $C_{11}H_{14}N_2O_3$ 222.10 encontrado 209.121 $(M+H)^+$.

HPLC XTERRA C-18 3.0 x 506 mm, 0 a 100% B durante 2

minutos, 1 minuto de tiempo de retención, 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, RT = 0.87 min, 90% de índice de homogeneidad.

Extremo-47



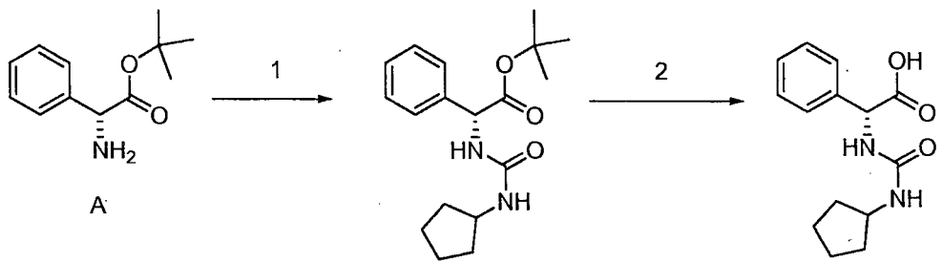
A B *Extremo-47*

Etapa 1 - 2-(3,3-Dimetilureido)-2-fenilacetato de (R)-*ter*-butilo: A una solución agitada de (R)-*ter*-butil-2-amino-2-fenilacetato (1.0 g, 4.10 mmoles) y base de Hunig (1.79 mL, 10.25 mmoles) en DMF (40 mL) se le añadió cloruro de dimetilcarbamoilo (0.38 mL, 4.18 mmoles) por goteo durante 10 minutos. Después de agitar a temperatura ambiente durante 3 horas, la reacción se concentró bajo presión reducida y el residuo resultante se disolvió en acetato de etilo. La capa orgánica se lavó con H_2O, HCl acuoso 1N y salmuera, se secó ($MgSO_4$), se filtró y se concentró bajo presión reducida. 2-(3,3-dimetilureido)-2-fenilacetato de (R)-*ter*-butilo se obtuvo como un sólido blanco (0.86 g, 75%) y se usó sin purificación adicional. ^{1}H RMN (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: Análisis calculado

para $C_{15}H_{22}N_2O_3$ 278.16 encontrado 279.23 $(M+H)^+$; HPLC Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% B durante 4 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, RT = 2.26 min, 97% de índice de homogeneidad.

Etapa 2 - Ácido (R)-2-(3,3-dimetilureido)-2-fenilacético: A una solución agitada de 2-(3,3-dimetilureido)-2-fenilacetato de ((R)-*ter*-butilo (0.86 g, 3.10 mmoles) en CH_2Cl_2 (250 mL) se le añadió TFA (15 mL) por goteo y la solución resultante se agitó a temperatura ambiente durante 3 horas. El compuesto deseado se precipitó después fuera de la solución con una mezcla de EtOAC:hexanos (5:20), se filtró y se secó bajo presión reducida. Ácido (R)-2-(3,3-dimetilureido)-2-fenilacético se aisló como un sólido blanco (0.59 g, 86%) y se usó sin purificación adicional. ^1H RMN (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: Análisis calculado para $C_{11}H_{14}N_2O_3$: 222.24; encontrado: 223.21 $(M+H)^+$. HPLC XTERRA C-18 3.0 x 50 mm, 0 a 100% B durante 2 minutos, 1 minuto de tiempo de retención, 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, RT = 0.75 min, 935 de índice de homogeneidad.

Extremo-48



A B *Extremo-48*

Etapa 1 - 2-(3-Ciclopentilureido)-2-fenilacetato de (R)-*ter*-butilo: A una solución agitada de clorhidrato de ácido (R)-2-amino-2-fenilacético (1.0 g, 4.10 mmoles) y base de Hunig (1.0 mL, 6.15 mmoles) en DMF (15 mL) se le añadió isocianato de ciclopentilo (0.46 mL, 4.10 mmoles) por goteo y durante 10 minutos. Después de agitar a temperatura ambiente durante 3 horas, la reacción se concentró bajo presión reducida y el residuo resultante se recogió en acetato de etilo. La capa orgánica se lavó con H_2O y salmuera, se secó ($MgSO_4$), se filtró y se concentró bajo presión reducida. Se obtuvo 2-(3-ciclopentilureido)-2-fenilacetato de (R)-*ter*-butilo como un aceite opaco (1.32 g; 100%) y se usó sin purificación adicional. ^1H RMN (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: Análogo calculado para $C_{18}H_{26}N_2O_3$ 318.19 encontrado 319.21 $(M+H)^+$; HPLC XTERRA C-18 3.0 x 50 mm, 0 a 100% B durante 4 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1%

de TFA, RT = 2.82 min, 96% de índice de homogeneidad.

Etapa 2 - Ácido (R)-2-(3-ciclopentilureido)-2-fenilacético: A una solución agitada de 2-(3-ciclopentilureido)-2-fenilacetato de (R)-*ter*-butilo (1.31 g, 4.10 mmoles) en CH_2Cl_2 (25 mL) se le añadió TFA (4 mL) y trietilsilano (1.64 mL; 10.3 mmoles) por goteo, y la solución resultante se agitó a temperatura ambiente durante 6 horas. Los componentes volátiles se removieron bajo presión reducida y el producto crudo se recristalizó en acetato de etilo/pentanos para dar ácido (R)-2-(3-ciclopentilureido)-2-fenilacético como un sólido blanco (0.69 g, 64%). ^{1}H RMN (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: Análisis calculado para $C_{14}H_{18}N_2O_3$ = : 262.31; encontrado: 263.15 $(M+H)^+$. HPLC XTERRA C-18 3.0 x 50 mm, 0 a 100% B durante 2 minutos, 1 minuto de tiempo de retención, 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, RT = 1.24 min, 100% de índice de homogeneidad.

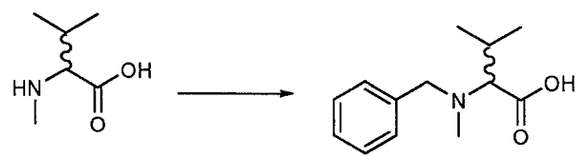
Extremo-49



Extremo-49

A una solución agitada de ácido 2-(bencilamino)acético (2.0 g, 12.1 mmoles) en ácido fórmico (91 mL) se le añadió formaldehído (6.94 mL, 93.2 mmoles). Después de cinco horas a 70°C, la mezcla de reacción se concentró bajo presión reducida hasta 20 mL y se precipitó un sólido blanco. Después de la filtración, los licores madre fueron recogidos y concentrados más bajo presión reducida proporcionando el producto crudo. La purificación mediante HPLC preparativa de fase inversa (Xterra 30 X 100 mm, detección a 220 nm, velocidad de flujo 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 título, ácido 2-(bencil)metil)-amino)acético como su sal TFA (723 mg, 33%) como una cera incolora. ^{1}H RMN (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: Análisis calculado para $C_{10}H_{13}NO_2$ 179.22; encontrado: 180.20 $(M+H)^+$.

Extremo-50

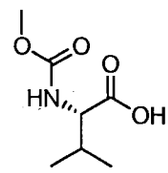


Extremo-50

A una solución agitada de ácido 3-metil-2-(metilamino)butanoico (0.50 g, 3.81 mmoles) en agua (30 mL) se le añadió K_2CO_3 (2.63 g, 19.1 mmoles) y cloruro de bencilo

(1.32 g, 11.4 mmoles). 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 capa acuosa se concentró bajo presión reducida proporcionando el producto crudo que se purificó mediante HPLC preparativa de fase inversa (Xterra 30 x 100 mm, detección a 220 nm, velocidad de flujo 40 mL/min, 20 a 80% de B durante 6 minutos; A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA) para proporcionar ácido 2-(bencil(metil)amino)-3-metilbutanoico. Sal TFA (126 mg, 19%) como una cerca incolora. ^{1}H RMN (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: Análisis calculado para: $C_{13}H_{19}NO_2$ 221.30; encontrado: 222.28 $(M+H)^+$.

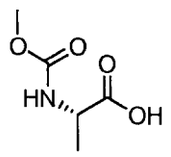
Extremo-51



Na_2CO_3 (1.83 g, 17.2 mmoles) se añadió a una solución en NaOH (33 mL de 1M/H_2O, 33 mmoles) de L-valina (3.9 g, 33.29 mmoles) y la solución resultante se enfrió en un baño de hielo-agua. Se añadió por goteo cloroformiato de metilo (2.8 mL, 36.1 mmoles) durante 15 minutos, el baño de enfriamiento se retiró 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 una región de pH de 1-2, y se extrajo con CH_2Cl_2 (50 mL, 3x). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró al vacío para dar *Extremo-51* como un sólido blanco (6 g). ^1H RMN para el rotámero dominante (DMSO-d_6, δ = 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: Análisis calculado para $[M+H]^+$ $C_7H_{14}NO_4$: 176.0923; encontrado 176.0922.

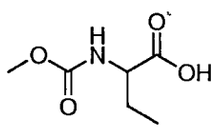
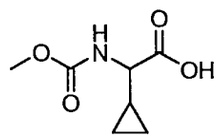
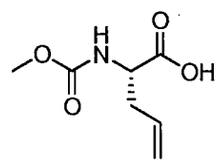
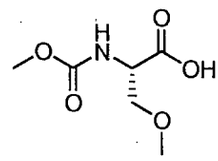
Extremo-52

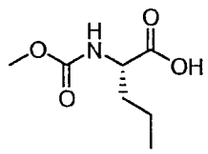
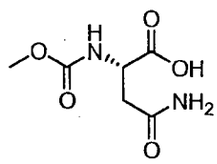
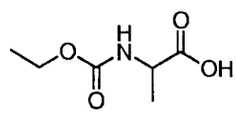
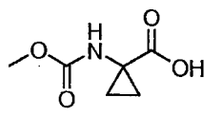
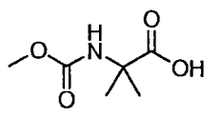


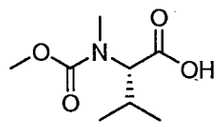
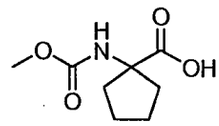
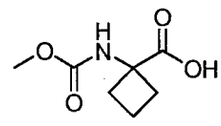
Extremo-52 se sintetizó a partir de L-alanina de acuerdo con el procedimiento descrito para la síntesis de *Extremo-51*. Para propósitos de caracterización, una porción del material crudo se purificó mediante HPLC de fase inversa (H_2O/MeOH/TFA) para dar *Extremo-52* como un aceite viscoso incoloro. ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 500 MHz): 12.49 (br s, 1H), 7.43 (d, J = 7.3, 0.88H), 7.09 (app br s, 0.12 H), 3.97 (m, 1H), 3.53 (s, 3H), 1.25 (d, J = 7.3, 3H).

Extremo-53 a -64 se prepararon a partir de materiales de partida adecuados de acuerdo con el procedimiento descrito para la síntesis de *Extremo*-51, con

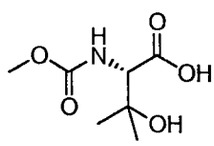
modificaciones indicadas si las hubiera.

Extremo	Estructura	Datos
Extremo-53a: (R) *Extremo-53b*: (S)		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 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 minutos (Cond. 2); LC/MS: Anal. Calcd. para: $[M+Na]^+$ $C_6H_{11}NNaO_4$: 184.06;Encontrado:184.07. HRMS Calcd. para: $[M+Na]^+$ $C_6H_{11}NNaO_4$: 184.0586; Encontrado: 184.0592.
Extremo-54a: (R) *Extremo-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. para: $[M+H]^+$ $C_7H_{12}NO_4$: 174.0766;Encontrado:174.0771
Extremo-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).
Extremo-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).

Extremo-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. para: $[M+H]^+$ $C_7H_{14}NO_4$: 176.09;Encontrado:176.06.
Extremo-58		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.63 (bs, 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. para: $[M+H]^+$ $C_6H_{11}N_2O_5$: 191.07;Encontrado:191.14.
Extremo-59a: (R) *Extremo-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. para: $[M+H]^+$ $C_6H_{12}NO_4$: 162.0766; Encontrado: 162.0771.
Extremo-60		El material crudo se purificó con una HPLC de fase inversa (H_2O/MeOH/TFA) para dar un aceite viscoso incoloro que se cristalizó hasta un sólido blanco luego de exposición a alto vacío. ^{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. para: $[M+H]^+$ $C_6H_{10}NO_4$: 160.0610;Encontrado:160.0604.
Extremo-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. para: $[M+H]^+$ $C_6H_{12}NO_4$: 162.0766;Encontrado:162.0765.

Extremo-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 (dos singuletes , 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. para: $[M-H]^-$ $C_8H_{14}NO_4$: 188.09;Encontrado:188.05.
Extremo-63		[Nota: la reacción se dejó proceder por más tiempo que aquel que se indicó para el procedimiento general] ^{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. para: $[M+H]^+$ $C_8H_{14}NO_4$: 188.09;Encontrado:188.19.
Extremo-64		[Nota: la reacción se dejó proceder por más tiempo que aquel que se indicó para el procedimiento general] ^{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 (br s traslapante, 0.18H), 3.50 (s, 3H), 2.47-2.40 (m, 2H), 2.14-2.07 (m, 2H), 1.93-1.82 (m, 2H).

Extremo-65

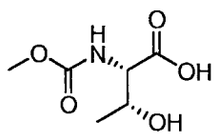


Cloroformiato de metilo (0.65 mL, 8.39 mmoles) se añadió por goteo durante 5 minutos a una mezcla enfriada (hielo-agua) de Na_2CO_3 (0.449 g, 4.23 mmoles), NaOH (8.2 mL de 1M/H_2O, 8.2 mmoles) y ácido (*S*)-3-hidroxi-2-(metoxicarbonilamino)-3-

metilbutanoico (1.04 g, 7.81 mmoles). La mezcla de reacción se agitó durante 45 minutos, y después el baño de enfriamiento se retiró y se continuó agitando durante 3.75 horas más. La mezcla de reacción se lavó con CH_2Cl_2, y la fase acuosa se enfrió con un baño de hielo-agua y se acidificó con HCl concentrado hasta una región de pH de 1-2. Los componentes volátiles se removieron al vacío y el residuo se recogió en una mezcla 2:1 de $MeOH/CH_2Cl_2$ (15 mL) y se filtraron, y el filtrado se evaporó giratoriamente para dar *Extremo*-65 como una espuma semi-viscosa blanca (1.236 g). ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 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).

Extremo-66 y -67 se prepararon a partir de materiales de partida disponibles comercialmente y adecuados al emplear el procedimiento descrito para la síntesis de *Extremo*-65.

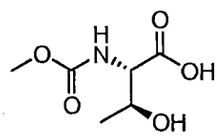
Extremo-66



^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.58 (br s, 1H), 7.07 (d, J = 8.3, 0.13H), 6.81 (d, J = 8.8, 0.67 H), 4.10-4.02 (m, 1.15H), 3.91 (dd, J =

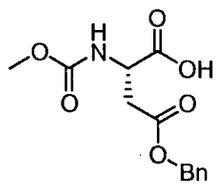
9.1, 3.5, 0.85H), 3.56 (s, 3H), 1.09 (d, J = 6.2, 3H). [Nota: sólo las señales dominantes de NH fueron indicadas].

Extremo-67



^{1}H RMN (DMSO-d_6, δ = 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). [Nota: sólo las señales dominantes de NH fueron indicadas].

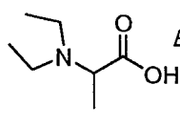
Extremo-68



Cloroformiato de metilo (0.38 ml, 4.9 mmoles) se añadió por goteo a una mezcla de NaOH 1N (acuoso) (9.0 ml, 9.0 mmoles), $NaHCO_3$ 1M (acuoso) (9.0 ml, 9.0 moles), éster β-bencílico de ácido L-aspártico (1.0 g, 4.5 mmoles) y dioxano (9 ml). La mezcla de reacción se agitó a condiciones ambiente durante 3 horas, y después se lavó con acetato de etilo (50 ml, 3 x). La capa acuosa se acidificó con HCl 12N hasta un pH de ~1-2, y se extrajo con acetato de etilo (3 x

50 ml). Las capas orgánicas combinadas se lavaron con salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron al vacío para dar *Extremo*-68 como un aceite amarillo claro (1.37 g; la masa está por arriba del rendimiento teórico, y el producto se usó sin purificación adicional). ^{1}H RMN (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: Análisis calculado para $[M+H]^+$ $C_{13}H_{16}NO_6$: 282.10; encontrado 282.12.

Extremos 69a y 69b



Extremo-69a: enantiómero (R)
Extremo-69b: enantiómero (S)

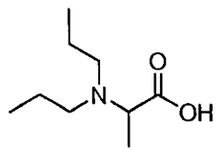
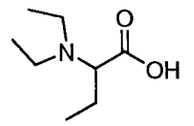
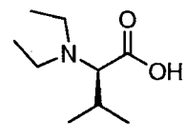
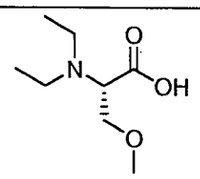
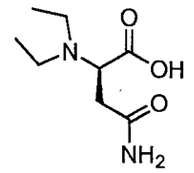
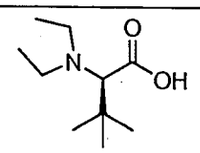
$NaCNBH_3$ (2.416 g, 36.5 mmoles) se añadió en lotes a una solución enfriada (~15°C) de agua (17 mL)/MeOH (10 mL) de alanina (1.338 g, 15.0 mmoles). Pocos minutos más tarde se añadió por goteo acetaldehído (4.0 mL, 71.3 mmoles) durante 4 minutos, se retiró el baño de enfriamiento y la mezcla de reacción se agitó a condición ambiente durante 6 horas. Se añadió acetaldehído adicional (4.0 mL) y la reacción se agitó durante 2 horas. Se añadió

000441

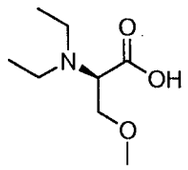
lentamente HCl concentrado a la mezcla de reacción hasta que el pH alcanzara ~1.5, y la mezcla resultante se calentó durante 1 hora a 40°C. La mayoría de los componentes volátiles fueron removidos al vacío y el residuo se purificó con una resina de intercambio iónico Dowex® 50WX8-100 (la columna se lavó con agua, y el compuesto fue eluido con NH_4OH diluido, preparado al mezclar 18 ml de NH_4OH y 282 ml de agua) para dar *Extremo-69* (2.0 g) como un sólido higroscópico suave blanquecino. ^1H RMN (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).

Extremos-70 a -74x fueron preparados de acuerdo con el procedimiento descrito para la síntesis de *Extremo-69* al emplear materiales de partida adecuados.

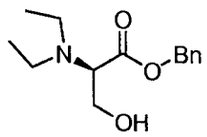
000443

Extremo-70a: (R) *Extremo-70b*: (S)		^{1}H 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. para: $[M+H]^+$ $C_9H_{20}NO_2$: 174.15; encontrado 174.13.
Extremo-71a: (R) *Extremo-71b*: (S)		^{1}H 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. para: $[M+H]^+$ $C_8H_{18}NO_2$: 160.13; encontrado 160.06.
Extremo-72		^{1}H 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. para: $[M+H]^+$ $C_9H_{20}NO_2$: 174.15; encontrado 174.15.
Extremo-73		^{1}H 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).
Extremo-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 minutos (Cond. 2); LC/MS: Anal. Calcd. para: $[M+H]^+$ $C_8H_{17}N_2O_3$: 189.12; encontrado 189.13.
Extremo-74x		LC/MS: Anal. Calcd. para: $[M+H]^+$ $C_{10}H_{22}NO_2$: 188.17; encontrado 188.21

Extremo-75



Extremo-75, etapa a

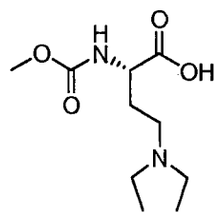


$NaBH_3CN$ (1.6 g, 25.5 mmoles) se añadió a una solución enfriada (baño de hielo/agua) de agua (25 ml)/metanol (15 ml) de H-D-Ser-OBzl HCl (2.0 g, 8.6 mmoles). Se añadió por goteo acetaldehído (1.5 ml, 12.5 mmoles) durante 5 minutos, se retiró el baño de enfriamiento y la mezcla de reacción se agitó a condición ambiente durante 2 horas. La reacción se enfrió rápidamente de manera cuidadosa con HCl 2N y se concentró al vacío. El residuo se disolvió en agua y se purificó con una HPLC de fase inversa ($MeOH/H_2O$/TFA) para dar la sal TFA de 2-(dietilamino)-3-hidroxipropanoato de (R)-bencilo como un aceite viscoso incoloro (1.9 g). ^1H RMN (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: Análisis calculado para $[M+H]^+$. $C_{14}H_{22}NO_3$: 252.16; encontrado 252.19.

Extremo-75

NaH (0.0727 g, 1.82 mmoles, 60%) se añadió a una solución enfriada (hielo-agua) en THF (3.0 mL) de la sal TFA 2-(dietilamino)-3-hidroxipropanoato de (R)-bencilo (0.3019 g, 0.8264 mmoles) preparada arriba, y la mezcla se agitó durante 15 minutos. Se añadió yoduro de metilo (56 µL, 0.90 mmoles) y se continuó agitando durante 18 horas mientras se permitía que el baño se descongelara a condición ambiente. La reacción se enfrió rápidamente con agua y se cargó en un cartucho MCX preacondicionado con MeOH (6 g), y se lavó con metanol seguido por la elución del compuesto con NH_3 2N/metanol. La remoción del componente volátil al vacío dio *Extremo-75*, contaminado con ácido (R)-2-(dietilamino)-3-hidroxipropanoico, como un semi-sólido amarillo (100 mg). El producto se usó como tal sin purificación adicional.

Extremo-76



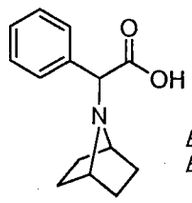
$NaCNBH_3$ (1.60 g, 24.2 mmoles) se añadió por lotes a una solución enfriada (~15°C) en agua/MeOH (212 mL cada uno) de ácido (*S*)-4-amino-2-(*ter*-butoxicarbonilamino)butanoico (2.17 g, 9.94 mmoles). Pocos minutos más tarde se añadió por goteo acetaldehído (2.7 mL, 48.1 mmoles) durante 2 minutos,

se retiró el baño de enfriamiento y la mezcla de reacción se agitó a condición ambiente durante 3.5 horas. Se añadió acetaldehído adicional (2.7 mL, 48.1 mmoles) y la reacción se agitó durante 20.5 horas. La mayoría del componente MeOH se removió al vacío, y la mezcla restante se trató con HCl concentrado hasta que su pH alcanzara ~ 1.0 y después se calentó durante 2 horas a 40°C. El componente volátil se removió al vacío, y el residuo se trató con HCl 4M/dioxano (20 mL) y se agitó a condición ambiente durante 7.5 horas. El componente volátil fue removido al vacío y el residuo se purificó con resina de intercambio iónico Dowex® 50WX8-100 (la columna se lavó con agua y el compuesto fue eluido con NH_4OH diluido, preparado a partir de 18 ml de NH_4OH y 282 ml de agua) para dar el intermediario ácido (S)-2-amino-4-(dietilamino)butanoico como un sólido blanquecino (1.73 g).

Cloroformiato de metilo (0.36 mL, 4.65 mmoles) se añadió por goteo durante 11 minutos a una mezcla enfriada (hielo-agua) de Na_2CO_3 (0.243 g, 2.29 mmoles), NaOH (4.6 mL de 1M/H_2O, 4.6 mmoles) y el producto anterior (802.4 mg). La mezcla de reacción se agitó durante 55 minutos, y después el baño de enfriamiento se retiró y se continuó agitando durante 5.25 horas más. 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 un baño de hielo-agua y se acidificó con HCl concentrado hasta una región de pH de 2.

El componente volátil se removió después al vacío y el material crudo se hizo en base libre con resina MCX (6.0 g; la columna se lavó con agua, y la muestra fue eluida con NH_3 2.0M/MeOH) para dar *Extremo-76* impuro como un sólido blanquecino (704 mg). ^1H RMN (MeOH-d_4, δ = 3.29 ppm, 400 MHz): δ 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: Análisis calculado para $[M+H]^+$ $C_{10}H_{21}N_2O_4$: 233.15; encontrado 233.24.

Extremos 77a y 77b

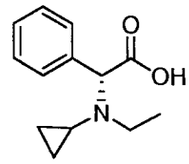


Extremo-77a: enantiómero 1
Extremo-77b: enantiómero 2

La síntesis de *Extremo-77* se condujo de acuerdo con el procedimiento descrito para *Extremo-7* usando 7-azabiciclo[2.2.1]heptano para la etapa de desplazamiento de SN_2, y al llevar a cabo la separación enantiomérica del intermediario 2-(7-azabiciclo[2.2.1]heptan-7-il)-2-fenilacetato de bencilo usando la siguiente condición: el intermediario (303.7 mg) se disolvió en etanol, y la solución resultante se inyectó en una columna de 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 a una temperatura de 35°C para proporcionar 124.5 mg del enantiómero 1 y 133.8 mg del

enantiómero 2. Estos ésteres bencílicos fueron hidrogenolizados de acuerdo con la preparación de *Extremo*-7 para proporcionar *Extremo*-77: ^{1}H RMN (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: Análisis calculado para $[M+H]^+$ $C_{14}H_{18}BrNO_2$: 232.1338; encontrado 232.1340.

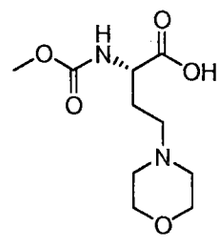
Extremo-78



$NaCNBH_3$ (0.5828 g, 9.27 mmoles) se añadió a una mezcla de la sal HCl de ácido (*R*)-2-(etilamino)-2-fenilacético (un intermediario en la síntesis de *Extremo-3*; 0.9923 mg, 4.60 mmoles) y (1-etoxiciclopropoxi)trimetilsilano (1.640 g, 9.40 mmoles) en MeOH (10 mL), y la mezcla semi-heterogénea fue calentada a 50°C con un baño de aceite durante 20 horas. Se añadieron más (1-etoxiciclopropoxi)trimetilsilano (150 mg, 0.86 mmoles) y $NaCNBH_3$ (52 mg, 0.827 mmoles) y la mezcla de reacción se calentó durante 3.5 horas más. Se dejó enfriar después a la temperatura ambiente y se acidificó a una región de ~ pH de 2 con HCl concentrado, y la mezcla se filtró y el filtrado se evaporó giratoriamente. El material crudo resultante se recogió en *i*-PrOH (6 mL) y se calentó para llevar a cabo la

disolución, y la parte no disuelta fue filtrada y el filtrado se concentró al vacío. Aproximadamente 1/3 del material crudo resultante se purificó con una HPLC de fase inversa (H_2O/MeOH/TFA) para dar la sal TFA de *Extremo-78* como un aceite viscoso incoloro (353 mg). ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz; después del cambio por D_2O): 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: Análisis calculado para $[M+H]^+$ $C_{13}H_{18}NO_2$: 220.13; encontrado 220.21. HRMS: Análisis calculado para $[M+H]^+$ $C_{13}H_{18}NO_2$: 220.1338; encontrado 220.1343.

Extremo-79



Se burbujeó ozono a través de una solución enfriada (-78°C) en CH_2Cl_2 (5.0 mL) de *Extremo*-55 (369 mg, 2.13 mmoles) durante alrededor de 50 minutos hasta que la mezcla de reacción lograra un tinte de color zul. Me_2S (10 gotas de pipeta) fue añadido, y la mezcla de reacción se agitó durante 35 min. El baño a -78°C fue reemplazado con un baño a -10°C y se continuó agitando durante 30 minutos más, y luego el

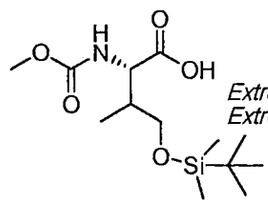
componente volátil se removió al vacío para dar un aceite viscoso incoloro.

Se añadió $NaBH_3CN$ (149 mg, 2.25 mmoles) a una solución en MeOH (5.0 mL) del material crudo anterior y morfolina (500 µL, 5.72 mmoles) y la mezcla se agitó a condición ambiente durante 4 horas. Se enfrió a la temperatura de agua enfriada y se trató con HCl concentrado para llevar su pH a ~2.0, y después se agitó durante 2.5 horas. El componente volátil fue removido al 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) para dar *Extremo-79* que contenía una cantidad desconocida de morfolina.

Para consumir la morfolina contaminante, el material anterior se disolvió en CH_2Cl_2 (1.5 mL) y se trató con Et_3N (0.27 mL, 1.94 mmoles) seguido por anhídrido acético (0.10 mL, 1.06 mmoles) y se agitó a condición ambiente 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 removió al vacío, y el residuo resultante se pasó a través de una resina MCX (lavado con MeOH; elución con NH_3 2.0/MeOH) para dar *Extremo-79* impuro como un aceite viscoso café, el cual se usó para la siguiente etapa

sin purificación adicional.

Extremos 80a y 80b



Extremo-80a: diastereómero S/S
Extremo-80b: diastereómero S/R

$SOCl_2$ (6.60 mL, 90.5 mmoles) se añadió por goteo durante 15 minutos a una mezcla enfriada (hielo-agua) de ácido (S)-3-amino-4-(benciloxi)-4-oxobutanoico (10.04 g, 44.98 mmoles) y MeOH (300 mL), el baño de enfriamiento se retiró y la mezcla de reacción se agitó a condición ambiente durante 29 horas. La mayoría del componente volátil se removió al vacío y el residuo se dividió 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 combinadas se secó ($MgSO_4$), se filtró y se concentró al vacío para dar 4-metil-2-aminosuccinato de (S)-1-bencilo como un aceite incoloro (9.706 g). ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 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: Análisis calculado para $[M+H]^+$ $C_{12}H_{16}NO_4$: 238.11; encontrado 238.22.

$Pb(NO_3)_2$ (6.06 g, 18.3 mmoles) se añadió 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 mmoles), 9-

bromo-9-fenil-9*H*-fluoreno (6.44 g, 20.0 mmoles) y Et_3N (3.0 mL, 21.5 mmoles), y la mezcla heterogénea se agitó a condición ambiente 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 crudo resultante se sometió a una purificación Biotage (350 g de gel de sílice, elución con CH_2Cl_2) para dar 4-metil-2-(9-fenil-9H-fluoren-9-ilamino)succinato de (S)-1-bencilo como un aceite incoloro altamente viscoso (7.93 g). ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 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 traslapado con solvente). LC (Cond. 1): RT = 2.16 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{31}H_{28}NO_4$: 478.20; encontrado 478.19.

LiHMDS (9.2 mL de 1.0 M/THF, 9.2 mmoles) se añadió por goteo durante 10 minutos a una solución enfriada (-78°C) (50 mL) en THF de 4-metil-2-(9-fenil-9H-fluoren-9-ilamino)succinato de (S)-1-bencilo (3.907 g, 8.18 mmoles) y se agitó durante ~1 hora. Se añadió MeI (0.57 mL, 9.2 mmoles) por goteo durante 8 minutos a la mezcla, y se continuó agitando durante 16.5 horas mientras se permitía que el baño de enfriamiento se descongelara a la temperatura ambiente. Luego de enfriar rápidamente con solución de NH_4Cl saturado (5 mL), la mayoría del componente orgánico se removió al vacío y el residuo se dividió entre CH_2Cl_2 (100 mL)

y agua (40 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se concentró al vacío, y el material crudo resultante se purificó con una Biotage (350 g de gel de sílice; 25% de EtOAc/hexanos) para dar 3.65 g de mezcla diastereomérica de 2S/3S y 2S/3R de 3-metil-2-(9-fenil-9H-fluoren-9-ilamino)succinato de 1-bencilo 4-metilo en una relación de ~1.0:0.65 (^1H RMN). La estereoquímica del isómero dominante no fue determinada en su unión, y la mezcla fue sometida a la siguiente etapa sin separación. Datos de ^1H RMN parciales (DMSO-d_6, δ = 2.5 ppm, 400 MHz): diastereómero principal, δ 4.39 (d, J = 12.3, 1H de CH_2), 3.33 (s, 3H, traslapado con señal de H_2O), 3.50 (d, J = 10.9, NH), 1.13 (d, J = 7.1, 3H); diastereómero menor, δ 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). LC (Cond. 1): RT = 2.19 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{32}H_{30}NO_4$: 492.22; encontrado 492.15.

Hidruro de diisobutilaluminio (20.57 ml de 1.0 M en hexanos, 20.57 mmoles) se añadió por goteo durante 10 minutos 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 mmoles) preparada arriba, y se agitó a -78°C durante 20 horas. La mezcla de reacción se retiró del baño de enfriamiento y se vertió rápidamente en ~1M H_3PO_4/H_2O (250 mL) con agitación, y la mezcla se extrajo con éter (100 mL, 2x). La fase orgánica combinada se lavó con salmuera, se

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secó ($MgSO_4$), se filtró y se concentró al vacío. Una malla de gel de sílice del material crudo se preparó y se sometió a cromatografía (25% de EtOAc/hexanos; elución por gravedad) para dar 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 viscoso incoloro 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 posterior se volvió a someter a las mismas condiciones de purificación para cromatografía en columna para dar 750 mg de material purificado como una espuma blanca. [Nota: el isómero (2S,3S) eluye antes que el isómero (2S,3R) bajo la condición anterior]. Isómero (2S,3S): ^{1}H RMN (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, traslapado con la señal de solvente), 1.58 (m, 1H), 0.88 (d, J = 6.8, 3H). LC (Cond. 1): RT = 2.00 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{31}H_{30}NO_3$: 464.45; encontrado 464.22. Isómero (2S, 3R): ^{1}H RMN (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: Análisis

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 con base en estudios NOE llevados a cabo en derivados de lactona preparados a partir de cada isómero al emplear el siguiente protocolo: LiHMDS (50 µL de1.0 M/THF, 0.05 mmoles) se añadió 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 mmoles), y la mezcla de reacción se agitó a temperatura similar durante ~ 2 horas. El componente volátil se removió al vacío y el residuo se dividió entre CH_2Cl_2 (30 mL), agua (20 mL) y solución acuosa saturada de NH_4Cl (1 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se concentró al vacío, y el material crudo resultante se sometió a una purificación Biotage (40 g de gel de sílice; 10-15% de EtOAc/hexanos) para dar (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). 4-hidroxi-3-metil-2-(9-fenil-9*H*-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo se elaboró de manera similar a (3S,4R)-4-metil-3-(9-fenil-9*H*-fluoren-9-ilamino)dihidrofuran-2(3*H*)-ona. Isómero de lactona (3S,4S): ^1H RMN (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, parcialmente traslapado con señal de solvente),

2.16 8M, 1H), 0.27 (d, J = 6.6, 3H). LC (Cond. 1): RT = 1.98 min; LC/MS: Análisis calculado para $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378.15; encontrado 378.42. Isómero de lactona (3S,4R). ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 7.89 (d, J = 7.6, 1H), 7.83 (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: Análisis calculado para $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378.15; encontrado 378.49.

TBDMS-Cl (48 mg, 0.312 mmoles) seguido por imidazol (28.8 mg, 0.423 mmoles) se añadieron 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 (199.5 mg, 0.258 mmoles), y la mezcla se agitó a condición ambiente durante 14.25 horas. La mezcla de reacción se diluyó después con CH_2Cl_2 (30 mL) y se lavó con agua (15 mL), y la capa orgánica se secó ($MgSO_4$), se filtró y se concentró al vacío. El material crudo resultante se purificó con una Biotage (40 g de gel de sílice; 5% de EtOAc/hexanos) para dar 4-(*ter*-butildimetilsililoxi)-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3S)-bencilo, contaminado con impurezas a base de TBDMS, como un aceite viscoso incoloro (124.4 mg). 4-Hidroxi-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo se elaboró similarmente a 4-(*ter*-butildimetilsililoxi)-3-metil-2-(9-fenil-9H-fluoren-

9-ilamino)butanoato de (2S,3R)-bencilo. Isómero en éter silílico (2S,3S): ^{1}H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 7.82 (d, J = 4.1, 1H), 7.80 (d, J = 4.0, 1H), 7.38-7.07 (m, 16H), 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, en donde el tiempo de ejecución se extendió a 4 minutos): RT = 3.26 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{37}H_{44}NO_3Si$: 578.31; encontrado 578.40. Isómero en éter silíico (2S,3R). ^{1}H RMN (DMSO-d_6, δ = 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).

Un balón de hidrógeno se fijó a una mezcla de 4-(*ter*-butildimetilsililoxi)-3-metil-2-(9-fenil-9*H*-fluoren-9-ilamino)butanoato de (2S,3S)-bencilo (836 mg, 1.447 mmoles) y 10% de Pd/C (213 mg) en EtOAc (16 mL) y la mezcla se agitó a temperatura ambiente durante ~21 horas, cuando el balón se recargó con H_2 según fuera necesario. La mezcla de reacción se diluyó con CH_2Cl_2 y se filtró a través de una almohadilla de tierra diatomácea (Celite-545®), y la almohadilla se lavó con EtOAc (200 mL), EtOAc/MeOH (mezcla 1:1, 200 mL) y MeOH /750 mL). La fase orgánica combinada se concentró, y una

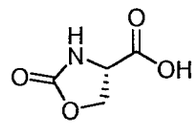
malla de gel de sílice se preparó a partir del material crudo resultante y se sometió a una cromatografía por vaporización (mezcla 8:2:1 de EtOAc/i-PrOH/H_2O) para dar ácido (2S,3S)-2-amino-4-(*ter*-butildimetilsililoxi)-3-metilbutanoico como un sólido esponjoso blanco (325 mg). 4-(*ter*-butildimetilsililoxi)-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo se elaboró similarmente a ácido (2S,3R)-2-amino-4-(*ter*-butildimetilsililoxi)-3-metilbutanoico. Isómero del (2S,3S)-aminoácido: ^1H RMN (Metanol-d_4, δ = 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: Análisis calculado para $[M+H]^+$ $C_{11}H_{26}NO_3Si$: 248.17; encontrado 248.44. Isómero del (2S,3R)-aminoácido: ^1H RMN (Metanol-d_4, δ = 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). Análisis calculado para $[M+H]^+$ $C_{11}H_{26}NO_3Si$: 248.17; encontrado 248.44.

Agua (1 mL) y NaOH (0.18 mL de 1.0 M/H_2O, 0.18 mmoles) se añadieron a una mezcla de ácido (2S,3S)-2-amino-4-(*ter*-butildimetilsililoxi)-3-metilbutanoico (41.9 mg, 0.169 mmoles) y Na_2CO_3 (11.9 mg, 0.112 mmoles), y se sonificó durante alrededor de 1 minuto para llevar a cabo la disolución de los reactivos. La mezcla se enfrió después con un baño de hielo-agua, se añadió cloroformiato de metilo

(0.02 mL, 0.259 mmoles) durante 30 segundos, y se continuó la agitación vigorosa a temperatura similar durante 40 minutos y después a temperatura ambiente durante 2.7 horas. La mezcla de reacción se diluyó con agua (5 mL), se enfrió con un baño de hielo-agua y se trató por goteo con solución acuosa de HCl 1.0 N (~0.23 mL). La mezcla se diluyó más con agua (10 mL) y se extrajo con CH_2Cl_2 (15 mL, 2x). La fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró al vacío para dar *Extremo-80*a como un sólido blanquecino. Ácido (2S,3R)-2-amino-4-(*ter*-butildimetilsililoxi)-3-metilbutanoico se elaboró similarmente a *Extremo-80b*. *Extremo-80a*: ^{1}H RMN (DMSO-d_6, δ = 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 (dos singuletes, 3H), 3.48-3.40 (m, 32H), 2.22-2.10 (m, 1H), 0.85 (s, 9H), ~0.84 (d, 0.9H, traslapado con señal de t-Bu), 0.79 (d, *J* = 7, 2.1 H), 0.02/0.01/0.00 (tres singuletes traslapados, 6H). LC/MS: Análisis calculado para $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328.16; encontrado 238.46. *Extremo-80b*: ^{1}H RMN ($CDCl_3$, δ = 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: Análisis calculado para $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328.16; encontrado 328.53. Los productos crudos se utilizaron sin

purificación adicional.

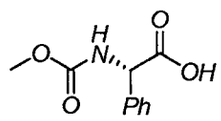
Extremo-81



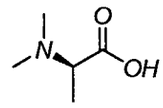
Preparado de acuerdo con el protocolo descrito por Falb et al., *Synthetic Communications* 1993, *23*, 2839.

Extremo-82 a Extremo-85

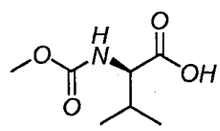
Extremo-82 a *Extremo*-85 fueron sintetizados a partir de materiales de partida adecuados de acuerdo con el procedimiento descrito para *Extremo*-51. Las muestras exhibieron perfiles espectrales similares a aquellos de sus enantiómeros (es decir, *Extremo-4*, *Extremo-13*, *Extremo-51* y *Extremo-52*, respectivamente)



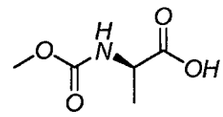
Extremo-82



Extremo-83

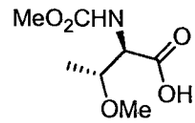


Extremo-84



Extremo-85

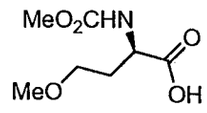
Extremo-86



A una mezcla de O-metil-L-treonina (3.0 g, 22.55 mmoles), NaOH (0.902 g, 22.55 mmoles) en H_2O (15 mL) se le añadió $ClCO_2Me$ (1.74 mL, 22.55 mmoles) por goteo a 0°C. La mezcla se dejó agitar durante 12 horas y se acidificó a pH 1 usando HCl 1N. La fase acuosa se extrajo con EtOAc y (2x250

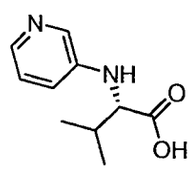
mL) y 10% de MeOH en CH_2Cl_2 (250 mL) y las fases orgánicas combinadas se concentraron al vacío para dar un aceite incoloro (4.18 g, 97%) que tenía suficiente pureza como para usarse en etapas subsecuentes. ^{1}H RMN (400 MHz, $CDCl_3$) δ 4.19 (s, 1H), 3.92-3.97 (m, 1H), 3.66 (s, 3H), 1.17 (d, *J* = 7.7 Hz, 3H). LCMS: Análisis calculado para $C_7H_{13}NO_5$: 191; encontrado: 190 $(M-H)^-$.

Extremo-87



A una mezcla de L-homoserina (2.0 g, 9.79 mmoles), Na_2CO_3 (2.08 g, 19.59 mmoles) en H_2O (15 mL) se le añadió $ClCO_2Me$ (0.76 mL, 9.79 mmoles) por goteo a 0°C. La mezcla se dejó agitar durante 48 horas y se acidificó a pH 1 usando HCl 1N. La fase acuosa se extrajo con EtOAc y (2X250 mL) y las fases orgánicas combinadas se concentraron al vacío para dar un sólido incoloro (0.719 g, 28%) el cual tenía suficiente pureza para usarse en etapas subsecuentes. ^{1}H RMN (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: Análisis calculado para $C_7H_{13}NO_5$: 191; encontrado: 192 $(M+H)^+$.

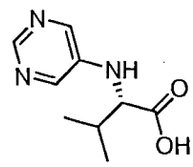
Extremo-88



000462

Una mezcla de L-valina (1.0 g, 8.54 mmoles), 3-bromopiridina (1.8 mL, 18.7 mmoles), K_2CO_3 (2.45 g, 17.7 mmoles) y CuI (169 mg, 0.887 mmoles) en DMSO (10 mL) se calentó a 100°C durante 12 horas. La mezcla de reacción se enfrió a la temperatura ambiente, se vertió en H_2O (alrededor de 150 mL) y se lavó con EtOAc (x2). Las capas orgánicas se extrajeron con una pequeña cantidad de H_2O y las fases acuosas combinadas se acidificaron a alrededor de pH 2 con HCl 6N. El volumen se redujo a aproximadamente un tercio y se añadieron 20 g de resina de intercambio catiónico (Strata). La suspensión se dejó reposar durante 20 minutos y se cargó en una almohadilla de resina de intercambio catiónico (Strata) (alrededor de 25 g). La almohadilla se lavó con H_2O (200 mL), MeOH (200 mL), y luego NH_3 (3M en MeOH, 2X200 mL). Las fracciones adecuadas se concentraron al vacío y el residuo (alrededor de 1.1 g) se disolvió en H_2O, se congeló y se liofilizó. El compuesto del título se obtuvo como una espuma (1.02, g, 62%). ^{1}H RMN (400 MHz, DMSO-d_3) 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: Análisis calculado para $C_{10}H_{14}N_2O_2$: 194; encontrado: 195 $(M+H)^+$.

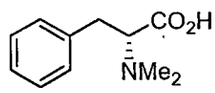
Extremo-89



Una mezcla de L-valina (1.0 g, 8.54 mmoles), 5-bromopirimidina (4.03 g, 17.0 mmoles) K_2CO_3 (2.40 g, 17.4 mmoles) y CuI (179 mg, 0.94 mmoles) en DMSO (10 mL) se calentó a 100°C durante 12 horas. La mezcla de reacción se enfrió a la temperatura ambiente, se diluyó en H_2O (alrededor de 150 mL) y se lavó con EtOAc (x2). Las capas orgánicas se extrajeron con una pequeña cantidad de H_2O y las fases acuosas combinadas se acidificaron a alrededor de pH 2 con HCl 6N. El volumen se redujo a aproximadamente un tercio y 20 g de resina de intercambio catiónico (Strata) fueron añadidos. La suspensión se dejó reposar durante 20 minutos y se cargó en una almohadilla de resina de intercambio catiónico (Strata) (alrededor de 25 g). La almohadilla se lavó con H_2O (200 mL), MeOH (200 mL), y luego NH_3 (3M en MeOH; 2x200 mL). Las fracciones adecuadas se concentraron al vacío y el residuo (alrededor de 1.1 g) se disolvió en H_2O, se congeló y se liofilizó. El compuesto del título se obtuvo como una espuma (1.02 g, 625). ^1H RMN (400 MHz, CD_3OD) mostró que la mezcla contenía valina y la pureza no pudo ser estimada. El material se usó como tal en reacciones subsecuentes. LCMS: Análisis calculado para $C_9H_{13}N_3O_2$: 195;

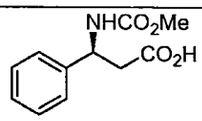
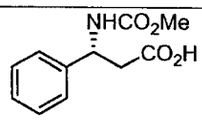
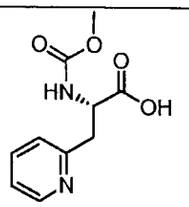
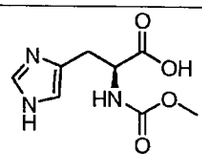
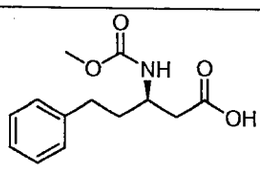
encontrado: 196 $(M+H)^+$.

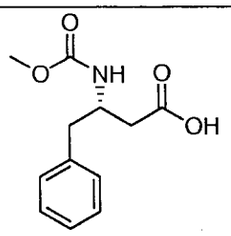
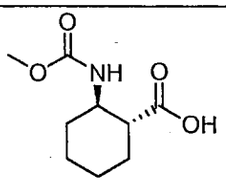
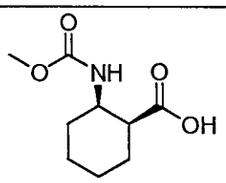
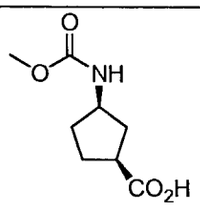
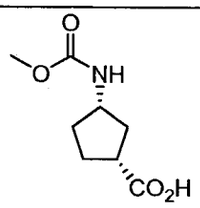
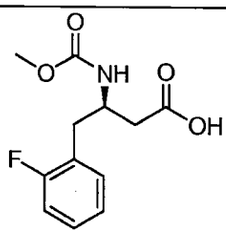
Extremo-90

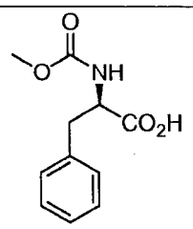
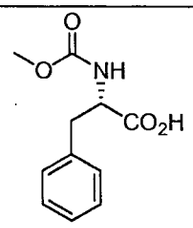
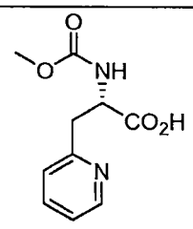
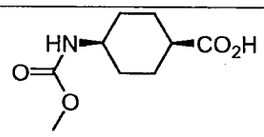
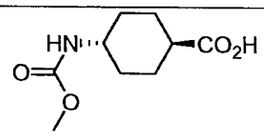
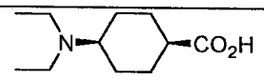


Extremo-90 se preparó de acuerdo con el método descrito para la preparación de *Extremo-1*. El material crudo se usó como tal en etapas subsecuentes. LCMS: Análisis calculado para $C_{11}H_{15}NO_2$: 193; encontrado: 192 $(M-H)^-$.

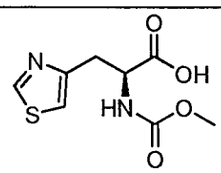
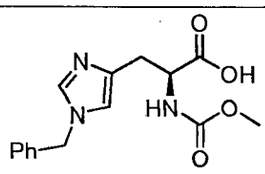
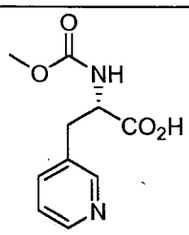
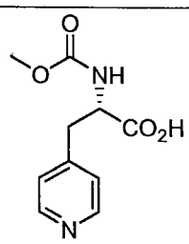
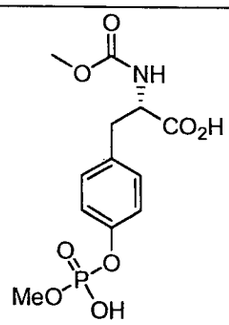
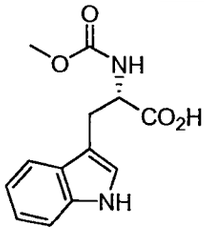
Los siguientes extremos fueron preparados de acuerdo con el método del *Extremo*-51:

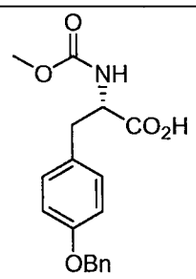
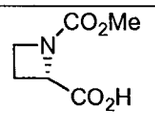
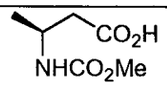
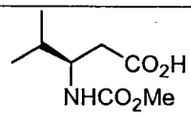
Extremo	Estructura	LCMS
Extremo-91		LCMS: Anal. Calcd. para: $C_{11}H_{13}NO_4$: 223;encontrado: 222 $(M-H)^-$.
Extremo-92		LCMS: Anal. Calcd. para: $C_{11}H_{13}NO_4$: 223;encontrado: 222 $(M-H)^-$.
Extremo-93		LCMS: Anal. Calcd. para: $C_{10}H_{12}N_2O_4$: 224;encontrado: 225 $(M+H)^+$.
Extremo-94		LCMS: Anal. Calcd. para: $C_8H_{11}N_3O_4$: 213;encontrado: 214 $(M+H)^+$.
Extremo-95		LCMS: Anal. Calcd. para: $C_{13}H_{17}NO_4$: 251;encontrado: 250 $(M-H)^-$.

Extremo-96		LCMS: Anal. Calcd. para: $C_{12}H_{15}NO_4$: 237;encontrado: 236 $(M-H)^-$.
Extremo-97		LCMS: Anal. Calcd. para: $C_9H_{15}NO_4$: 201;encontrado: 200 $(M-H)^-$.
Extremo-98		LCMS: Anal. Calcd. para: $C_9H_{15}NO_4$: 201;encontrado: 202 $(M+H)^+$.
Extremo-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).
Extremo-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).
Extremo-100		LCMS: Anal. Calcd. para: $C_{12}H_{14}NO_4F$: 255;encontrado: 256 $(M+H)^+$.

Extremo-101		LCMS: Anal. Calcd. para: $C_{11}H_{13}NO_4$: 223;encontrado: 222 $(M-H)^-$.
Extremo-102		LCMS: Anal. Calcd. para: $C_{11}H_{13}NO_4$: 223;encontrado: 222 $(M-H)^-$
Extremo-103		LCMS: Anal. Calcd. para: $C_{10}H_{12}N_2O_4$: 224;encontrado: 225 $(M+H)^+$.
Extremo-104		^{1}HNMR (400 MHz, CD_3OD) δ 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).
Extremo-105		^{1}HNMR (400 MHz, CD_3OD) δ 3.60 (s, 3H), 3.33 – 3.35 (m, 1H, parcialmente oscurecido por solvente) 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).
Extremo-106 *(preparado siguiendo el procedimiento descrito*		^{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

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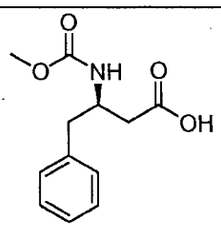
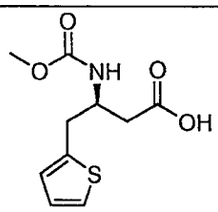
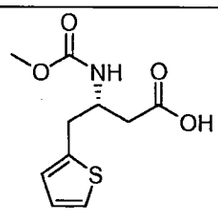
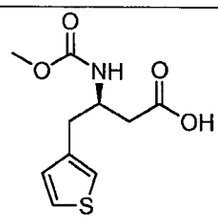
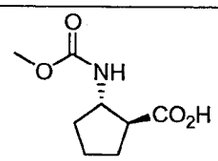
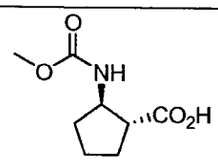
para Extremo 2))		dt J = 4.0, 12.9 Hz, 2H), 1.26 (t, J = 7.3 Hz, 6H).
Extremo-107		LCMS: Anal. Calcd. para: $C_8H_{10}N_2O_4S$: 230;encontrado: 231 $(M+H)^+$.
Extremo-108		LCMS: Anal. Calcd. para: $C_{15}H_{17}N_3O_4$: 303;encontrado: 304 $(M+H)^+$.
Extremo-109		LCMS: Anal. Calcd. para: $C_{10}H_{12}N_2O_4$: 224;encontrado: 225 $(M+H)^+$.
Extremo-110		LCMS: Anal. Calcd. para: $C_{10}H_{12}N_2O_4$: 224;encontrado: 225 $(M+H)^+$.
Extremo-111		LCMS: Anal. Calcd. para: $C_{12}H_{16}NO_8P$: 333;encontrado: 334 $(M+H)^+$.
Extremo-112		LCMS: Anal. Calcd. para: $C_{13}H_{14}N_2O_4$: 262;encontrado: 263 $(M+H)^+$.

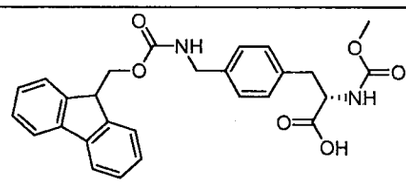
Extremo-113		LCMS: Anal. Calcd. para: $C_{18}H_{19}NO_5$: 329;encontrado: 330 $(M+H)^+$.
Extremo-114		^{1}HNMR (400 MHz, $CDCl_3$) δ 4.82 – 4.84 (m, 1H), 4.00 – 4.05 (m, 2H), 3.77 (s, 3H), 2.56 (s, br, 2H)
Extremo-115		^{1}HNMR (400 MHz, $CDCl_3$) δ 5.13 (s, br, 1H), 4.13 (s, br, 1H), 3.69 (s, 3H), 2.61 (d, *J* = 5.0 Hz, 2H), 1.28 (d, *J* = 9.1 Hz, 3H).
Extremo-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).

Extremo-117 a Extremo-123

Para la preparación de extremos *Extremo*-117 a *Extremo*-123 los Boc aminoácidos fueron disponibles comercialmente y fueron desprotegidos mediante tratamiento con 25% de TFA en CH_2Cl_2. Después de que la reacción se completó según se juzga por LCMS los solventes fueron removidos al vacío y la sal TFA correspondiente del aminoácido se carbamoiló con cloroformiato de metilo de acuerdo con el procedimiento para *Extremo*-51.

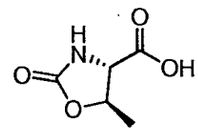
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Extremo	Estructura	LCMS
Extremo-117		LCMS: Anal. Calcd. para: $C_{12}H_{15}NO_4S$: 237; encontrado: 238 $(M+H)^+$.
Extremo-118		LCMS: Anal. Calcd. para: $C_{10}H_{13}NO_4S$: 243; encontrado: 244 $(M+H)^+$.
Extremo-119		LCMS: Anal. Calcd. para: $C_{10}H_{13}NO_4S$: 243; encontrado: 244 $(M+H)^+$.
Extremo-120		LCMS: Anal. Calcd. para: $C_{10}H_{13}NO_4S$: 243; encontrado: 244 $(M+H)^+$.
Extremo-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).
Extremo-122		^{1}HNMR (400 MHz, $CDCl_3$) δ 5.28 and 5.12 (s, br, 1H), 3.66 (s, 3H), 2.64 – 2.74 (m, 1H), 1.86 - 2.12 (m, 3H), 1.67 – 1.74 (m, 2H), 1.39 – 1.54 (m, 1H).

Extremo-123		LCMS: Anal. Calcd. para: $C_{27}H_{26}N_2O_6$: 474; encontrado: 475 $(M+H)^+$.

Preparación de *Extremo*-124

Ácido (4S,5R)-5-metil-2-oxooxazolidin-4-carboxílico



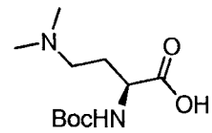
Extremo-124

La sal clorhidrato del éster *ter*-butílico de L-treonina fue carbamoilada de acuerdo con el procedimiento para *Extremo*-51. La mezcla de reacción cruda se acidificó con HCl 1N a pH ~1 y la mezcla se extrajo con EtOAc (2X50 mL). Las fases orgánicas combinadas se concentraron al vacío para dar un aceite incoloro que se solidificó después del reposo. La capa acuosa se concentró al vacío y la mezcla resultante de producto y sales inorgánicas se trituró con EtOAc-CH_2Cl_2-MeOH (1:1:0.1) y luego la fase orgánica se concentró al vacío para dar un aceite incoloro que mostró mediante LCMS ser el producto deseado. Ambos cosechas fueron combinados para dar 0.52 g de un sólido. ^{1}H RMN (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: Análisis calculado para $C_5H_7NO_4$: 145;

encontrado: 146 $(M+H)^+$.

Preparación de *Extremo*-125

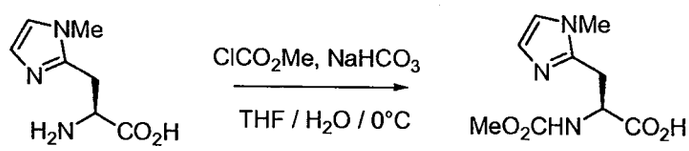
Ácido (S)-2-(*ter*-butoxicarbonilamino)-4-(dimetilamino)butanoico



Extremo-125

Extremo-125 se preparó de acuerdo con el procedimiento para la preparación de *Extremo*-1. El producto crudo se usó como tal en reacciones subsecuentes. LCMS: Análisis calculado para $C_{11}H_{22}N_2O_4$: 246; encontrado: 247 $(M+H)^+$.

Preparación de ácido (S)-2-(metoxicarbonilamino)-3-(1-metil-1H-imidazol-2-il)propanoico (*Extremo*-126)



cj-25 *Extremo-126*

Este procedimiento es una modificación de aquél usado para preparar *Extremo*-51. A una suspensión de ácido (S)-2-amino-3-(1-metil-1H-imidazol-2-il)propanoico (0.80 g, 4.70 mmoles) en THF (10 mL) y H_2O (10 mL) a 0°C se le añadió $NaHCO_3$ (0.88 g, 10.5 mmoles). La mezcla resultante se trató con $ClCO_2Me$ (0.40 mL, 5.20 mmoles) y la mezcla se dejó

agitar a 0°C. Después de agitar durante alrededor de 2 horas la LCMS no mostró material de partida restante. La reacción se acidificó a pH 2 con HCl 6N.

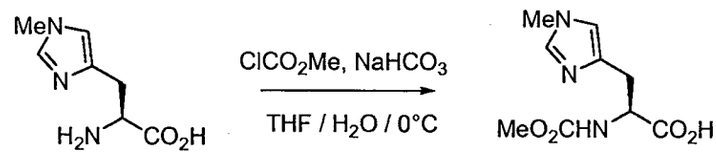
Los solventes fueron removidos al vacío y el residuo se suspendió en 20 mL de MeOH al 20% en CH_2Cl_2. La mezcla se filtró y se concentró para dar una espuma amarillo claro (1.21 g). LCMS y ^1H RMN mostraron que el material era una mezcla 9:1 del éster metílico y el producto deseado. Este material se recogió en THF (10 mL) y H_2O (10 mL), se enfrió a 0°C y se añadió LiOH (249.1 mg, 10.4 mmoles). Después de agitar a alrededor de 1 hora la LCMS mostró que ningún éster permanecía. Por lo tanto la mezcla se acidificó con HCl 6N y los solventes se removieron al vacío. LCMS y ^1H RMN confirman la ausencia del éster. El compuesto del título se obtuvo como su sal HCl contaminada con sales inorgánicas (1.91 g, >100%). El compuesto se usó como tal en etapas subsecuentes sin purificación adicional.

^1H RMN (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 mediante solvente), 3.12 (dd,

J = 9.0, 15.6 Hz, 1H).

LCMS: Análisis calculado para $C_{17}H_{15}NO_2$: 392; encontrado: 393 $(M+H)^+$.

Preparación de ácido (S)-2-(metoxicarbonilamino)-3-(1-metil-1H-imidazol-4-il)propanoico (*Extremo*-127)



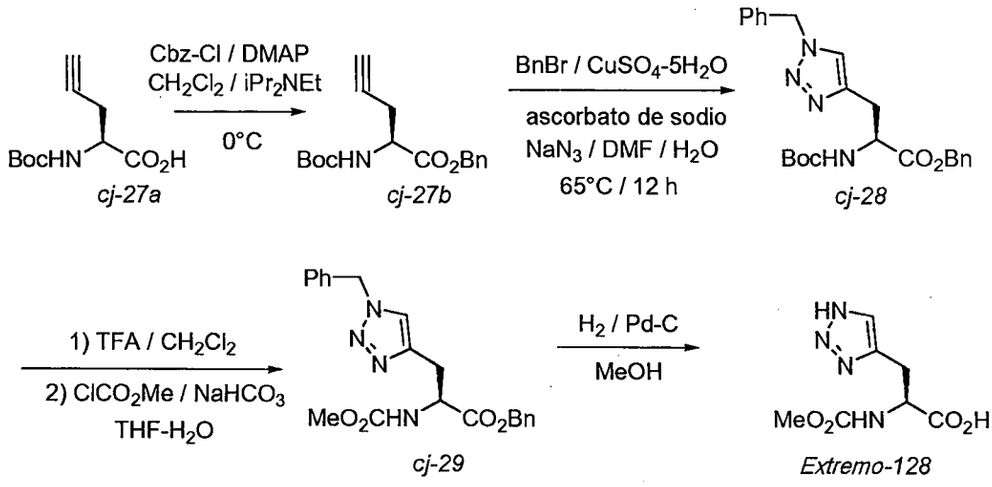
cj-26 *Extremo-127*

Extremo-127 se preparó de acuerdo con el método para *Extremo*-126 arriba iniciando a partir de ácido (S)-2-amino-3-(1-metil-1H-imidazol-4-il)propanoico (1.11 g, 6.56 mmoles), $NaHCO_3$ (1.21 g, 14.4 mmoles) y $ClCO_2Me$ (0.56 mL, 7.28 mmoles). El compuesto del título se obtuvo como su sal HCl (1.79 g, >100%) contaminada con sales inorgánicas. LCMS y ^1H RMN mostraron la presencia de alrededor de 5% del éster metílico. La mezcla cruda se usó como tal sin purificación adicional.

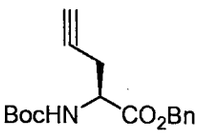
^1H RMN (400 MHz, CD_3OD) δ 8.90 (s, 1H), 7.35 (s, 1H), 4.48 (dd, *J* = 5.0, 8.6 Hz, 1H), 3.89 (s, 3H), 3.62 (s, 3H), 3.35 (m, 1H), 3.08 (m, 1H).

LCMS: Análisis calculado para $C_{17}H_{15}NO_2$: 392; encontrado: 393 $(M+H)^+$.

Preparación de ácido (S)-2-(metoxicarbonilamino)-3-(1H-1,2,3-triazol-4-il)propanoico (*Extremo*-128)



Etapa 1. Preparación de 2-(*ter*-butoxicarbonilamino)pent-4-inoato de (S)-bencilo (cj-27b)

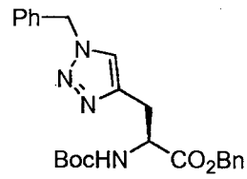


cj-27b

A una solución de cj-27a (1.01 g, 4.74 mmoles), DMAP (58 mg, 0.475 mmoles) e iPr_2Net (1.7 mL, 9.8 mmoles) en CH_2Cl_2 (100 mL) a 0°C se le añadió Cbz-Cl (0.68 mL, 4.83 mmoles). La solución se dejó agitar durante 4 horas a 0°C, se lavó (1N $KHSO_4$, salmuera), se secó (Na_2SO_4), se filtró y se concentró al vacío. El residuo se purificó mediante cromatografía en columna por vaporización (TLC 6:1 hex:EtOAc) para dar el compuesto del título (1.30 g, 91%) como un aceite incoloro. ^1H RMN (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: Análisis 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-(*ter*-butoxicarbonilamino)propanoato de (S)-bencilo (cj-28)

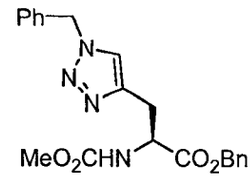


cj-28

A una mezcla de 2-(*ter*-butoxicarbonilamino)pent-4-inoato de (S)-bencilo (0.50 g, 1.65 mmoles), ascorbato de sodio (0.036 g, 0.18 mmoles), $CuSO_4$-$5H_2O$ (0.022 g, 0.09 mmoles) y NaN_3 (0.13 g, 2.1 mmoles) en DMF-H_2O (5 mL, 4:1) a temperatura ambiente se le añadió BnBr (0.24 mL, 2.02 mmoles) y la mezcla se calentó a 65°C. Después de 5 horas la LCMS 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 capas se separaron y la capa acuosa se extrajo 3x con EtOAc y las fases orgánicas combinadas se lavaron (H_2Ox3, salmuera), se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo se purificó mediante cromatografía por vaporización (Biotage, 40+M 0-5% de MeOH en CH_2Cl_2; TLC 3% de MeOH en CH_2Cl_2) para dar un aceite amarillo claro que se solidificó después del

reposo (748.3 mg, 104%). La RMN fue consistente con el producto deseado pero sugiere la presencia de DMF. El material se usó como tal sin purificación adicional. ^{1}H RMN (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: Análisis calculado para $C_{24}H_{28}N_4O_4$: 436; encontrado: 437 $(M+H)^+$.

Etapa 2. Preparación de 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(metoxicarbonilamino)propanoato de (S)-bencilo (cj-29)

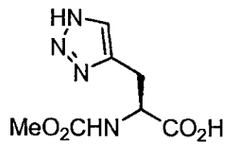


cj-29

Una solución de 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(*ter*-butoxicarbonilamino)propanoato de (S)-bencilo (0.52 g, 1.15 mmoles) en CH_2Cl_2 se le añadió TFA (4 mL). La mezcla se dejó agitar a la temperatura ambiente durante 2 horas. La mezcla se concentró al vacío para dar un aceite incoloro que se solidificó después del reposo. Este material se disolvió en THF-H_2O y se enfrió a 0°C. Se añadió $NaHCO_3$ sólido (0.25 g, 3.00 mmoles) seguido por $ClCO_2Me$ (0.25 mL, 3.25 mmoles). Después de agitar durante 1.5 horas la mezcla se acidificó a pH ~2 con HCl 6N y luego se vertió en H_2O-EtOAc. Las capas

se separaron y la fase acuosa se extrajo 2x con EtOAc. Las capas orgánicas combinadas se lavaron (H_2O, salmuera), se secaron (Na_2SO_4), se filtró y se concentraron al vacío para dar un aceite incoloro (505.8 mg, 111%, RMN sugirió la presencia de una impureza no identificada) que se solidificó mientras reposaba en la bomba. El material se usó como tal sin purificación adicional. ^1H RMN (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: Análisis calculado para $C_{21}H_{22}N_4O_4$: 394; encontrado: 395 $(M+H)^+$.

Etapa 3. Preparación de ácido (S)-2-(metoxicarbonilamino)-3-(1H-1,2,3-triazol-4-il)propanoico (*Extremo*-128)



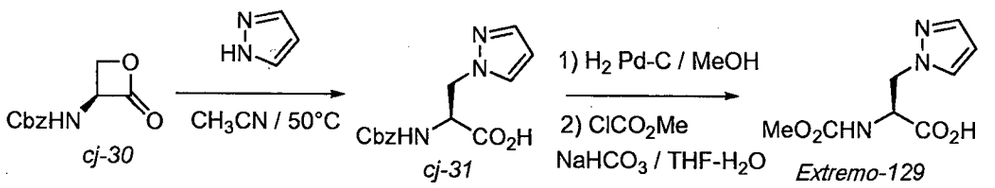
Extremo-128

3-(1-Bencil-1H-1,2,3-triazol-4-il)-2-(metoxicarbonilamino)propanoato de (S)-bencilo (502 mg, 1.11 mmoles) se hidrogenó en presencia de Pd-C (82 mg) en MeOH (5 mL) a presión atmosférica durante 12 horas. La mezcla se filtró a través de tierra diatomácea (Celite®) y se concentró al vacío. Se obtuvo ácido (S)-2-(metoxicarbonilamino)-3-(1H-1,2,3-triazol-4-il)propanoico como una goma incolora (266 mg,

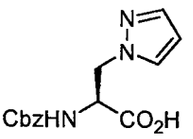
111%) la cual estaba contaminada con alrededor de 10% del éster metílico. El material se usó como tal sin purificación adicional.

^{1}H RMN (400 MHz, DMSO-d_6) δ 12.78 (s, br, 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). LCMS: Análisis calculado para $C_7H_{10}N_4O_4$: 214; encontrado: 215 $(M+H)^+$.

Preparación de ácido (S)-2-(metoxicarbonilamino)-3-(1H-pirazol-1-il)propanoico (*Extremo*-129)



Etapa 1. Preparación de ácido (S)-2-(benciloxicarbonilamino)-3-(1H-pirazol-1-il)propanoico (cj-31)



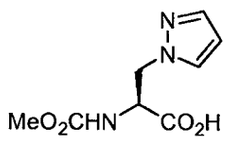
cj-31

Una suspensión de 2-oxooxetan-3-ilcarbamato de (S)-bencilo (0.67 g, 3.03 mmoles) y pirazol (0.22 g, 3.29 mmoles) en CH_3CN (12 mL) se calentó a 50°C durante 24 horas. La mezcla se enfrió a la temperatura ambiente durante la noche y el sólido se filtró para dar ácido (S)-2-(benciloxicarbonilamino)-3-(1H-pirazol-1-il)propanoico (330.1

mg). El filtrado se concentró al vacío y luego se trituró con una pequeña cantidad de CH_3CN (alrededor de 4 mL) para dar un segundo cosecha (43.5 mg). Rendimiento total 370.4 mg (44%).

P.f. 165.5-168°C. Lit p.f. 168.5-169.5 Vederas et al. *J. Am. Chem. Soc.* 1985, *107*, 7105. ^{1}H RMN (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: Análisis 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 (*Extremo-129*)



Extremo-129

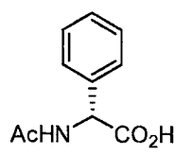
Ácido (S)-2-(benciloxicarbonilamino)-3-(1H-pirazol-1-il)propanoico (0.20 g, 0.70 mmoles) se hidrogenó en presencia de Pd-C (45 mg) en MeOH (5 mL) a presión atmosférica durante 2 horas. El producto pareció ser insoluble en MeOH, por lo tanto la mezcla rxn se diluyó con 5 mL de H_2O y pocas gotas de HCl 6N. La solución homogénea se filtró a través de tierra diatomácea (Celite®), y el MeOH se removió al vacío. la solución restante se congeló y se

liofilizó para dar una espuma amarilla (188.9 mg). Este material se suspendió en THF-H_2O (1:1, 10 mL) y luego se enfrió a 0°C. La mezcla fría se añadió $NaHCO_3$ (146.0 mg, 1.74 mmoles) cuidadosamente (evolución de CO_2). Después de que cesó la evolución de gas (alrededor de 15 minutos), se añadió por goteo $ClCO_2Me$ (0.06 mL, 0.78 mmoles). La mezcla se dejó agitar durante 2 horas y se acidificó a pH ~2 con HCl 6N y se vertió en EtOAc. Las capas se separaron y la fase acuosa se extrajo con EtOAc (x5). Las capas orgánicas combinadas se lavaron (salmuera), se secaron (Na_2SO_4), se filtraron y se concentraron para dar el compuesto del título como un sólido incoloro (117.8 mg, 79%).

^1H RMN (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: Análisis calculado para $C_8H_{11}N_3O_4$: 213; encontrado: 214 $(M+H)^+$.

Extremo-130

N-acetil-(R)-fenilglicina



Extremo-130

Extremo-130 se preparó mediante acilación de (R)-fenilglicina disponible comercialmente en forma análoga al procedimiento dado en: Calmes, M.; Daunis J.; Jacquier, R.;

Verducci, J. *Tetrahedron*, 1987, *43*(10), 2285.

Ejemplos

La presente invención se describirá ahora en relación con ciertas modalidades que no se intenta que limiten su alcance. Por el contrario, la presente invención cubre todas las alternativas, modificaciones y equivalentes que puedan incluirse dentro del alcance de las reivindicaciones. Así, los siguientes ejemplos, los cuales incluyen modalidades específicas, ilustrarán una práctica de la presente invención, siendo entendido que los ejemplos tienen propósitos de ilustración de ciertas modalidades y se presentan para proporcionar lo que se cree es la descripción más útil y más fácilmente entendida de sus procedimientos y aspectos conceptuales.

Los porcentajes de solución expresan una relación de peso a volumen, y las relaciones de solución expresan una relación de volumen a volumen, a menos que se indique lo contrario. Los aspectos de resonancia magnética nuclear (RMN) se registraron ya sea en un espectrómetro Bruker 300, 400 ó 500 MHz; los desplazamientos químicos (δ) se reportan en partes por millón. La cromatografía por vaporización se llevó a cabo en gel de sílice (SiO_2) de acuerdo con la técnica de cromatografía por vaporización de Still (*J. Org. Chem.* **1978**, *43*, 2923).

La evaluación de la pureza y el análisis de masas

de baja resolución se llevaron a cabo en un sistema Shumadzu LC acoplado con un sistema Waters Micromass ZQ MS. Debe notarse que los tiempos de retención pueden variar ligeramente entre máquinas. Las condiciones de LC empleadas para determinar el tiempo de retención (RT) fueron:

Condición 1

Columna = Phenomenex-Luna 3.0X 50 mm S10

% B de inicio = 0

% B final = 100

Tiempo gradiente = 2 minutos

Tiempo de detención = 3 minutos

Velocidad de flujo = 4 mL/min

Longitud de onda = 220 nm

Solvente A = 0.1% de TFA en 10% de metanol/90% de H_2O

Solvente B = 0.1% de TFA en 90% de metanol/10% de H_2O

Condición 2

Columna = Phenomenex-Luna 4.6X50 mm S10

% B de inicio = 0

% B final = 100

Tiempo gradiente = 2 minutos

Tiempo de detención = 3 minutos

Velocidad de flujo = 5 mL/min

Longitud de onda = 220 nm

Solvente A = 0.1% de TFA en 10% de metanol/90% de H_2O

Solvente B = 0.1% de TFA en 90% de metanol/10% de H_2O

Condición 3

Columna = HPLC XTERRA C18 3.0 x 50 mm S7

% B de inicio = 0

% B final = 100

Tiempo gradiente = 3 minutos

Tiempo de detención = 4 minutos

Velocidad de flujo = 4 mL/min

Longitud de onda = 220 nm

Solvente A = 0.1% de TFA en 10% de metanol/90% de H_2O

Solvente B = 0.1% de TFA en 90% de metanol/10% de H_2O

Método A: LCMS - Xterra MS C-18 3.0 x 50 mm, 0 a 100% de B durante gradiente de 30.0 minutos, 1 minuto de tiempo de retención, A = 5% de acetonitrilo, 95% de agua, 10 mm de acetato de amonio, B = 95% de acetonitrilo, 5% de agua, 10 mm de acetato de amonio.

Método B: HPLC - X-Terra C-18 4.6 x 50 mm, 0 a 100% de B durante gradiente de 10.0 minutos, 1 minuto de tiempo de retención, A = 10% de metanol, 90% de agua, 0.1% de TFA, B = 90% de metanol, 10% de agua, 0.1% de TFA.

Método C: HPLC- YMC C-18 4.6 x 50 mm, 0 a 100% de B durante gradiente de 10.0 minutos, 1 minuto de tiempo de retención, A = 10% de metanol, 90% de agua, 0.2% de H_3PO_4, B = 90% de metanol, 10% de agua, 0.2% de H_3PO_4.

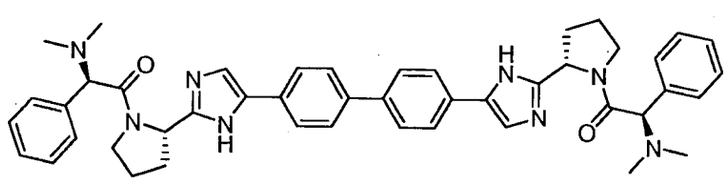
Método D: HPLC - Phenomenex C-18 4.6 x 150 mm, 0 a 100% de B durante gradiente de 10.0 minutos, 1 minuto de tiempo de retención, A = 10% de metanol, 90% de agua, 0.2% de H_3PO_4, B = 90% de metanol, 10% de agua, 0.2% de H_3PO_4.

Método E: LCMS - Gemini C-18 4.6 x 50 mm, 0 a 100% de B durante gradiente de 10.0 minutos, 1 minuto de tiempo de retención, A = 5% de acetonitrilo, 95% de agua, 10 mm de acetato de amonio, B = 95% de acetonitrilo, 5% de agua, 10 mm de acetato de amonio.

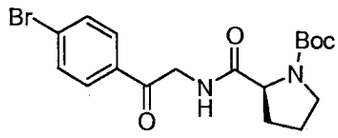
Método F: LCMS-Luna C-18 3.0 x 50 mm, 0 a 100% de B durante gradiente de 7.0 minutos, 1 minuto de tiempo de retención, A = 5% de acetonitrilo, 95% de agua, 10 mm de acetato de amonio, B = 95% de acetonitrilo, 5% de agua, 10 mm de acetato de amonio.

Ejemplo 1

(1R,1'R)-2,2'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(N,N-dimetil-2-oxo-1-feniletanamina)



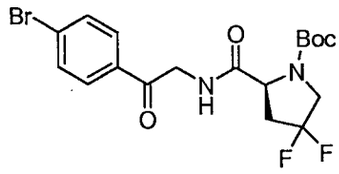
Ejemplo 1, etapa a



1a

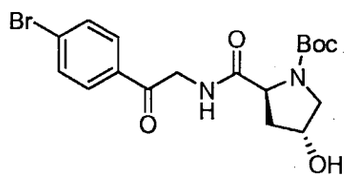
N,N-Diisopropiletilamina (18 mL, 103.3 mmoles) se añadió por goteo, durante 15 minutos, a una mezcla heterogénea de *N*-Boc-L-prolina (7.139 g, 33.17 mmoles), HATU (13.324 g, 35.04 mmoles), la sal HCl de 2-amino-1-(4-bromofenil)etanona (8.127 g, 32.44 mmoles) y DMF (105 mL), y se agitó a condición ambiente durante 55 minutos. La mayoría del componente volátil se removió al vacío, y el residuo resultante se dividió entre acetato de etilo (300 mL) y agua (200 mL). La capa orgánica se lavó con agua (200 mL) y salmuera, se secó ($MgSO_4$), se filtró y se concentró al vacío. Una malla de gel de sílice se preparó a partir del residuo y se sometió a cromatografía por vaporización (gel de sílice; 50-60% de acetato de etilo/hexanos) para proporcionar cetoamida 1a (12.8 g). ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 8.25-8.14 (m, 1H), 7.92 (br d, J = 8.0, 2H), 7.75 (br d, J = 8.6, 2H), 4.61 (dd, J = 18.3, 5.7, 1H), 4.53 (dd, J = 18.1, 5.6, 1H), 4.22-4.12 (m, 1H), 3.43-3.35 (m, 1H), 3.30-3.23 (m, 1H), 2.18-2.20 (m, 1H), 1.90-1.70 (m, 3H), 1.40/1.34 (dos app br s, 9H). LC (Cond. 1): RT = 1.70 min; LC/MS: Análisis calculado para $[M+Na]^+$ $C_{18}H_{23}BrN_2NaO_4$: 433.07; encontrado 433.09.

Compuestos análogos tales como el intermediario 1-1a a 1-5a pueden prepararse al incorporar aminoácido sustituido adecuadamente e isómero de bromuro de arilo.



1-1a

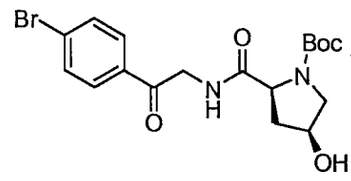
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.35/1.40 (dos br s, 9H), 2.27-2.42 (m, 1H), 2.73-2.95 (m, 1H), 3.62-3.89 (m, 2H), 4.36-4.50 (m, 1H), 4.51-4.60 (m, 1H), 4.62-4.73 (m, 1H), 7.75 (d, *J* = 8.24 Hz, 2H), 7.92 (d, *J* = 7.63 Hz, 2H), 8.31-8.49 (m, 1H). HPLC XTERRA C-18 4.6 x 30mm, 0 a 100% de B durante 4 minutos, 1 minuto de tiempo de retención, 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, RT = 1.59 minutos, 99% de índice de homogeneidad. LCMS: Análisis calculado para $C_{18}H_{21}BrF_2N_2O_4$: 446.06; encontrado: 445.43 $(M-H)^-$.



1-2a

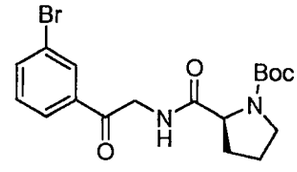
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm (8.25 1H, s), 7.91 (2H, d, *J* = 8.24 Hz), 7.75 (2H, d, *J* = 8.24 Hz), 4.98 (1H, s), 4.59-4.63 (1H, m), 4.46-4.52 (1H, m), 4.23 (1H, m), 3.37 (1H, s), 3.23-3.28 (1H, m), 2.06 (1H, m), 1.88 (1H, s), 1.38

(3H, s), 1.33 (6H, s). LCMS-Phenomenex C-18 3.0 x 50 mm, 0 a 100% de B sobre gradiente de 4.0 minutos, 1 minuto de tiempo de retención, A = 10% de metanol, 90% de agua, 0.1% de TFA, B = 90% de metanol, 10% de agua, 0.1% de TFA fase móvil, RT = 3.34 minutos, Análisis calculado para $C_{18}H_{23}BrN_2O_5$ 427.30; encontrado 428.08 $(M+H)^+$.



1-3a

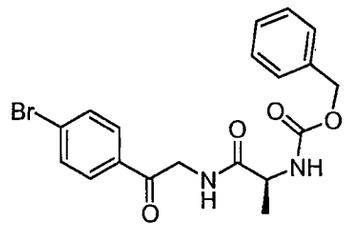
^1H RMN (500 MHz, DMSO-d_6) δ ppm 8.30 (1H, s), 7.93-7.96 (2H, m) 7.76 (2H) d, *J* = 8.24 Hz) 5.13 (1H, s) 4.66-4.71 (1H, m) 4.52-4.55 (1H, m) 4.17 (1H, m) 3.51 (1H, s), 3.16-3.19 (1H, m) 2.36 (1H, m) 1.78 (1H, s) 1.40 (s, 3H), 1.34 (s, 6H). LCMS-Phenomenex C-18 3.0 x 50 mm, 0 a 100% de B sobre gradiente de 4.0 minutos, 1 minuto de tiempo de retención, A = 10% de metanol, 90% de agua, 0.1% de TFA, B = 90% de metanol, 10% de agua, 0.1% de TFA, RT = 3.69 minutos, Análisis calculado para $C_{18}H_{23}BrN_2O_5$ 427.30; encontrado 428.16 $(M+H)^+$.



1-4a

^1H RMN (500 MHz, DMSO-d_6) δ ppm 1.29-1.47 (m, 9H),

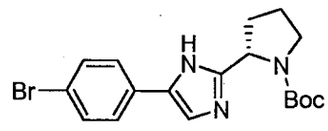
1.67-1.90 (m, 3H), 2.00-2.20 (m, 1H), 3.23-3.30 (m, 1H), 3.34-3.44 (m, 1H), 4.16 (dd, 1H), 4.57 (q, 2H), 7.51 (t, *J* = 7.78 Hz, 1H), 7.86 (dd, *J* = 7.93, 1.22 Hz, 1H), 7.98 (d, *J* = 7.63 Hz, 1H), 8.11 (s, 1H), 8.15-8.29 (m, 1H). LC/MS $(M+Na)^+$ = 433.12/435.12.



1-5a

Condiciones LCMS: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 2 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección. RT = 1.93 min; LRMS: Análogo calculado para $C_{19}H_{18}BrN_2O_4$ 418.05; encontrado: 419.07 $(M+H)^+$.

Ejemplo 1, etapa b



1b

Una mezcla de la cetoamida 1a (12.8 g, 31.12 mmoles) y NH_4OAc (12.0 g, 155.7 mmoles) en xilenos (155 mL) se calentó en un tubo sellado a 140°C durante 2 horas. El componente volátil se removió al vacío, y el residuo se dividió cuidadosamente entre acetato de etilo y agua, con lo

cual se añadió suficiente solución saturada de $NaHCO_3$ como para hacer el pH de la fase acuosa ligeramente básico después de la agitación del sistema bifásico. Las capas se separaron, y la capa acuosa se extrajo con acetato de etilo adicional. La fase orgánica combinada se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró al vacío. El material resultante se recristalizó a partir de acetato de etilo/hexanos para proporcionar dos cosechas de imidazol 1b como un sólido denso amarillo claro, que pesaba 5.85 g. El licor madre se concentró al vacío y se sometió a una cromatografía por vaporización (gel de sílice; 30% de acetato de etilo/hexanos) para proporcionar 2.23 g adicionales de imidazol 1b. ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.17/11.92/11.86 (m, 1H), 7.72-7.46/7.28 (m, 5H), 4.86-4.70 (m, 1H), 3.52 (app br s, 1H), 3.36 (m, 1H), 2.30-1.75 (m, 4H), 1.40/1.15 (app br s, 9H). LC (Cond. 1): RT = 1.71 min; >98% de índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{18}H_{23}BrN_3O_2$: 392.10; encontrado 391.96; HRMS: Análisis calculado para $[M+H]^+$ $C_{18}H_{23}BrN_3O_2$: 392.0974; encontrado 392.0959.

La pureza óptica de las dos muestras 1b se evaluó usando las condiciones HPLC quiral indicadas

abajo (ee >99% para las cosechas combinadas; ee = 96.7% para la muestra de cromatografía por vaporización):

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

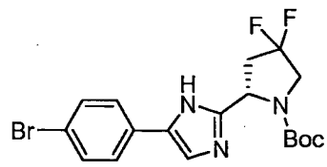
Solvente: 2% de etanol/heptano (isocrático)

Velocidad de flujo: 1 mL/min

Longitud de onda: ya sea 220 ó 254 nm

Tiempo de retención relativo: 2.83 minutos (*R*), 5.34 minutos (*S*)

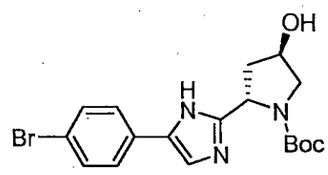
Compuestos análogos tales como los intermediarios 1-1b a 1-4b pueden prepararse al incorporar la cetoamida adecuada.



1-1b

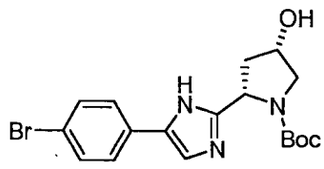
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.17/1.40 (dos br s, 9H), 2.50-2.74 (m, *J* = 25.64 Hz, 1H), 2.84-3.07 (m, 1H), 3.88 (d, *J* = 10.07 Hz, 2H), 5.03 (s, 1H), 7.50 (d, *J* = 8.55 Hz, 2H), 7.60 (s, 1H), 7.70 (d, *J* = 8.55 Hz, 2H), 12.10 (s, 1H). HPLC XTERRA C-18 4.6 x 30 mm, 0 a 100% de B durante 4 minutos, 1 minuto de tiempo de retención, 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, RT = 1.59 minutos, 99%

de índice de homogeneidad; LCMS: análisis calculado para $C_{18}H_{20}BrF_2N_3O_2$: 428.27; encontrado: 428.02 $(M)^+$.



1-2b

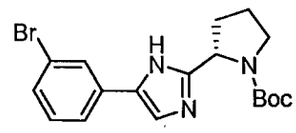
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 11.89-11.99 (1H, m), 7.68 (2H, d, *J* = 8.54 Hz), 7.52-7.59 (1H, m), 7.48 (2H, d, *J* = 8.54 Hz), 4.80 (1H, m), 4.33 (1H, s), 3.51-3.60 (1H, m), 3.34 (1H, d, *J* = 10.99 Hz), 2.14 (1H, s), 1.97-2.05 (1H, m), 1.37 (3H, s), 1.10 (6H, s); LCMS - Phenomenex C-18 3.0 x 50 mm, 0 a 100% de B durante gradiente de 4.0 minutos, 1 minuto de tiempo de retención, A = 10% de metanol, 90% de agua, 0.1% de TFA, B = 90% de metanol, 10% de agua, 0.1% de TFA, (RT = 3.23 min) análogo calculado para $C_{18}H_{22}BrN_3O_3$ 408.30; encontrado 409.12 $(M+H)^+$.



1-3b

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 12.06-12.24 (1H, m), 7.58-7.69 (5H, m), 4.84-4.95 (1H, m), 4.34 (1H, s), 3.61 (1H, s), 3.34-3.40 (1H, m), 2.52 (1H, s), 1.92-2.20 (1H, m), 1.43 (3H, s), 1.22 (6H, s); LCMS - Phenomenex C-18 3.0 x 50 mm, 0 a 100% de B durante gradiente de 4.0 minutos, 1 minuto de

tiempo de retención, A = 10% de metanol, 90% de agua, 0.1% de TFA, B = 90% de metanol, 10% de agua, 0.1% de TFA, (RT = 3.41 min) análogo calculado para $C_{18}H_{22}BrN_3O_3$ 408.30; encontrado 409.15 $(M+H)^+$.



1-4b

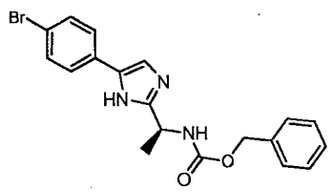
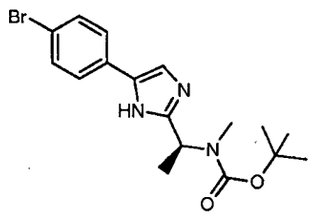
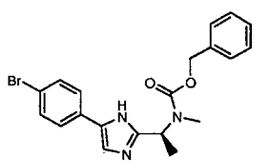
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 0.98-1.151 (m, 9H), 1.82-2.12 (m, 3H), 2.31-2.48 (m, 1H), 3.30-3.51 (m, 1H), 3.52-3.66 (m, 1H), 4.88-5.16 (m, 1H), 7.47 (t, *J* = 7.93 Hz, 1H), 7.61 (d, *J* = 7.93 Hz, 1H), 7.81 (d, *J* = 7.93 Hz, 1H), 8.04 (s, 1H), 8.12 (d, *J* = 28.38 Hz, 1H), 14.65 (s, 1H). LC/MS $(M+H)^+$ = 391.96/393.96.

Análogos de imidazol adicionales se hicieron siguiendo procedimientos similares a aquellos descritos arriba.

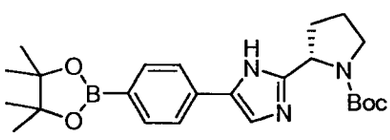
Condiciones de LC: *Condición 1*: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

Condición 2: Phenomenex LUNA C-18 4.6 x 50

mm, 0 a 100% de B durante 2 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

Ejemplo	*Estructura*	*Datos*
1-5b		RT = 1.70 minutos (condición 2, 98%); LRMS: Anal. Calcd. para: $C_{19}H_{18}BrN_3O_2$ 399.05; encontrado: 400.08 $(M+H)^+$.
1-6b		RT = 1.64 minutos (condición 2, 98%); LRMS: Anal. Calcd. para: $C_{17}H_{22}N_3O_2$ 379.09; encontrado: 380.06 $(M+H)^+$.
1-7b		RT = 2.28 minutos (95%); LRMS: Anal. Calcd. para: $C_{20}H_{21}BrN_3O_2$ 414.08; encontrado: 414.08 $(M+H)^+$; HRMS: Anal. Calcd. para: $C_{20}H_{21}BrN_3O_2$ 414.0817; encontrado: 414.0798 $(M+H)^+$.

Ejemplo 1, etapa c



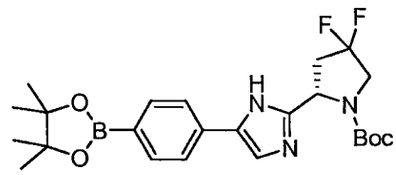
1c

$Pd(Ph_3P)_4$ (469 mg, 0.406 mmoles) se añadió a un tubo

de presión que contenía una mezcla de bromuro 1b (4.008 g, 10.22 mmoles), bis(pinacolato)diboro (5.422 g, 21.35 mmoles), acetato de potasio (2.573 g, 26.21 mmoles) y 1,4-dioxano (80 mL). El matraz de reacción se purgó con nitrógeno, se tapó y se calentó con un baño de aceite a 80°C durante 16.5 horas. La mezcla de reacción se filtró y el filtrado se concentró al vacío. El material crudo se dividió cuidadosamente entre CH_2Cl_2 (150 mL) y un medio acuoso (solución de 50 mL de agua + 10 mL de $NaHCO_3$ saturado). La capa acuosa se extrajo con CH_2Cl_2, y la fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró al vacío. El material resultante se purificó con cromatografía por vaporización (la muestra se cargó con solvente de elución; 20-35% de acetato de etilo/CH_2Cl_2) para proporcionar el boronato 1c, contaminado con pinacol, como un sólido denso blanquecino; la relación molar relativa de 1c a pinacol fue aproximadamente 10:1 (^1H RMN). La muestra pesaba 3.925 g después de ~ 2.5 días de exposición a alto vacío. ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.22/11.94/11.87 (m, 1H), 7.79-7.50/7.34-7.27 (m, 5H), 4.86-4.70 (m, 1H), 3.52 (app br s, 1H), 3.36 (m, 1H), 2.27-1.77 (m, 4H), 1.45-1.10 (m, 21H). LC (Cond. 1): RT = 1.64 min; LC/MS: análisis calculado para $[M+H]^+$ $C_{24}H_{35}BN_3O_4$: 440.27;

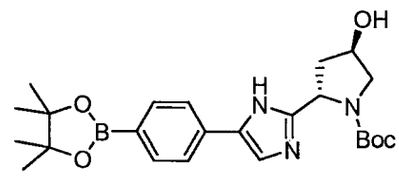
encontrado 440.23.

Compuestos análogos tales como los intermediarios 1-1c a 1-4c pueden prepararse al incorporar el bromuro de alilo adecuado.



1-1c

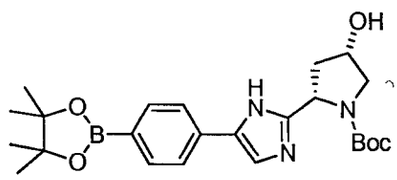
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.16 (s, 8H), 1.29 (s, 13H), 2.51-2.72 (m, 1H), 2.84-3.03 (m, 1H), 3.79-4.00 (m, 2H), 4.88-5.21 (m, 1H), 7.62 (d, *J* = 7.93 Hz, 2H), 7.67 (s, 1H), 7.76 (d, *J* = 7.93 Hz, 2H), 12.11/12.40 (dos br s, 1H). HPLC GEMINI C-18 4.6 x 50 mm, 0 a 100% de B durante 4 minutos, 1 minuto de tiempo de retención, A = 95% de agua, 5% de acetonitrilo, 0.1% de NH_4OAc, B = 5% de agua, 95% de acetonitrilo, 0.1% de NH_4OAc, RT = 1.62 minutos, 99% de índice de homogeneidad. LCMS: análisis calculado para $C_{34}H_{32}BF_2N_3O_4$: 475.34; encontrado: 474.78 $(M-H)^-$.



1-2c

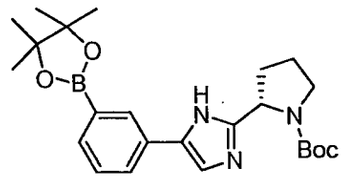
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 11.97 (1H, m), 7.62-7.75 (5H, m), 5.05 (1H, d, *J* = 3.36 Hz),

4.82 (m, 1H), 4.35 (m, 1H), 3.58 (1H, m), 2.389 (1H, s), 2.17 (1 H, m), 1.38 (3H, s), 1.30 (12H, s), 1.1 (6H, s); LCMS - Phenomenex C-18 3.0 x 50 mm, 0 a 100% de B durante gradiente de 4.0 minutos, 1 minuto de tiempo de retención, A = 5% de acetonitrilo, 95% de agua, 10 mm de acetato de amonio, B = 95% de acetonitrilo, 5% de agua, 10 mm de acetato de amonio, RT = 3.63 minutos, análogo calculado para $C_{24}H_{34}BN_3O_5$ 455.30; encontrado 456.31 $(M+H)^+$.



1-3c

^1H RMN (500 MHz, DMSO-d_6) δ ppm 12.05-12.24 (1H, m), 7.61-7.73 (5H, m), 4.83-5.01 (1H, m), 4.33 (1H, s), 3.54-3.63 (1H, m), 3.39-3.80 (1H, m), 2.38-2.49 (1H, m), 1.98-2.01 (1H, m), 1.42 (3H, s), 1.34 (12H, s), 1.21 (6H, s); LCMS-Phenomenex C-18 3.0 x 50 mm, 0 a 100% de B durante gradiente de 4.0 minutos, 1 minuto de tiempo de retención, A = 10% de metanol, 90% de agua, 0.1% de TFA, B = 90% de metanol, 10% de agua, 0.1% de TFA, RT = 3.64 minutos, análisis calculado para $C_{24}H_{34}BN_3O_5$ 455.30; encontrado 456.30 $(M+H)^+$.



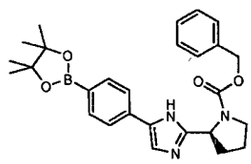
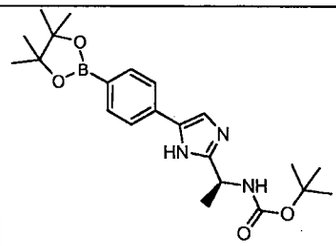
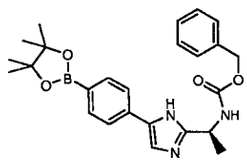
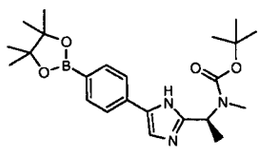
1-4c

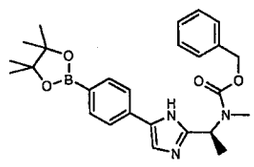
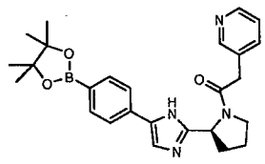
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.02-1.54 (m, 21H), 1.75-2.07 (m, 3H), 2.09-2.33 (m, 1H), 3.32-3.44 (m, 1H), 3.55 (s, 1H), 4.69-4.94 (m, 1H), 7.33 (t, *J* = 7.32 Hz, 1H), 7.41-7.57 (m, 2H), 7.84 (d, *J* = 7.32 Hz, 1H), 8.08 (s, 1H), 11.62-12.07 (m, 1H). LC/MS $(M+H)^+$ = 440.32.

Esteres borónicos adicionales: Condiciones para 1-5c a 1-10c.

Condiciones LCMS: *Condición 1*: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

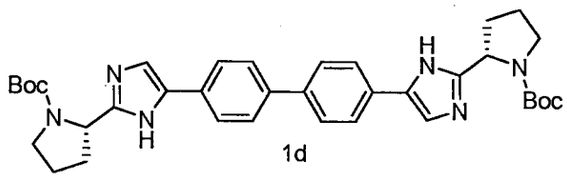
Condición 2: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 2 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

1-5c		RT = 1.84 minutos (condición 2); LCMS: Anal. Calcd. para: $C_{27}H_{32}BN_3O_4$ 473; encontrado: 474 $(M+H)^+$.
1-6c		RT = 1.84 minutos (condición 2); LCMS: Anal. Calcd. para: $C_{22}H_{32}BN_3O_4$ 413; encontrado: 414 $(M+H)^+$.
1-7c		RT = 1.85 minutos (condición 2); LRMS: Anal. Calcd. para: $C_{25}H_{31}BN_3O_4$ 448; encontrado: 448 $(M+H)^+$.
1-8c		RT = 2.49 (76%, éster borónico) y 1.81 (21.4%, ácido borónico); LCMS: Anal. Calcd. para: $C_{23}H_{35}N_3O_4B$ 428.27; encontrado: 428.27 $(M+H)^+$; HRMS: Anal. Calcd. para: $C_{23}H_{35}N_3O_4B$ 428.2721; encontrado:

		428.2716 $(M+H)^+$.
1-9c		RT = 2.54 (74.2%, éster borónico) y 1.93 (25.8%, ácido borónico); LRMS: Anal. Calcd. para: $C_{26}H_{33}N_3O_4B$ 462.26; encontrado: 462.25 $(M+H)^+$; HRMS: Anal. Calcd. para: $C_{26}H_{33}N_3O_4B$ 462.2564; encontrado: 462.2570 $(M+H)^+$.
1-10c		RT = 1.91 (64.5 %, éster borónico) y 1.02 (33.8 %, ácido borónico); LRMS: Anal. Calcd. para: $C_{26}H_{32}N_4O_3{}^{10}B$ 458.26; encontrado: 458.28 $(M+H)^+$; HRMS: Anal. Calcd. para: $C_{26}H_{32}N_4O_3{}^{10}B$ 458.2604; encontrado: 458.2617 $(M+H)^+$.

Ejemplo 1, etapa d

(2S,2'S)-2,2'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil)di(1-pirrolidincarboxilato) de di-ter-butilo



1d

$Pd(Ph_3P)_4$ (59.9 mg, 0.0518 mmoles) se añadió a una mezcla de bromuro 1b (576.1 mg, 1.469 mmoles), boronato 1c (621.8 mg, 1.415 mmoles), $NaHCO_3$ (400.4 mg, 4.766 mmoles) en

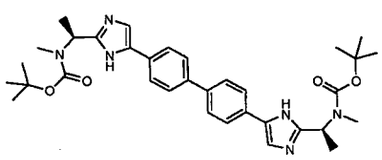
1,2-dimetoxietano (12 mL) y agua (4 mL). La mezcla de reacción se enjuagó con nitrógeno, se calentó con un baño de aceite a 80°C durante 5.75 horas, y después el componente volátil se removió al vacío. El residuo se dividió entre 20% de metanol/$CHCl_3$ (60 mL) y agua (30 mL), y la fase acuosa se extrajo con 20% de metanol/$CHCl_3$ (30 mL). La fase orgánica combinada se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró al vacío. una malla de gel de sílice se preparó a partir del material crudo resultante y se sometió a cromatografía por vaporización (acetato de etilo) para proporcionar el dímero 1d, contaminado con Ph_3PO, como un sólido blanquecino (563 mg). ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.21-12-16/11.95-11.78 (m, 2H), 7.85-7.48/7.32-7.25 (m, 10H), 4.90-4.71 (m, 2H), 3.60-3.32 (m, 4H), 2.30-1.79 (m, 8H), 1.46-1.10 (m, 18H). LC (Cond. 1b): RT = 1.77 min; LC/MS: análisis calculado para $[M+H]^+$ $C_{36}H_{45}BN_6O_4$: 625.35; encontrado 625.48.

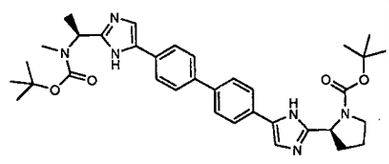
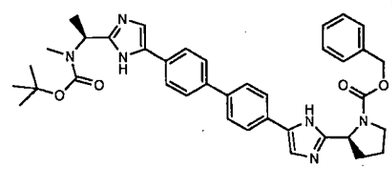
Análogos de bifenilo adicionales se prepararon similarmente.

Condiciones LC para los ejemplos 1-5d a 1-7d: *Condición 1*: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

Condición 2: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a

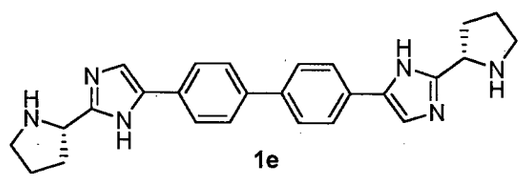
100% de B durante 2 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL volumen de inyección.

Ejemplo	*Nombre del Compuesto*	*Estructura*	*Datos de Caracterización*
1-5d	(4,4'-bifenildiilbis (1H-imidazol-5,2-diil(1S)-1,1-etandiil))bis (metilcarbamato) de di-ter-butilo	 Preparado de 1-8c y 1-6b	RT = 1.64 minutos (>95%); Condición 2; LCMS: Anal. Calcd $C_{34}H_{45}N_6O_4$ 601.35; encontrado: 601.48 $(M+H)^+$; LRMS: Anal. Calcd. para: $C_{34}H_{44}N_6O_4$ 600.34; encontrado: 601.32 $(M+H)^+$.

1-6d	(2S)-2-(5-(4'-(2-((1S)-1-((ter-butoxicarbonil)(metil)amino)etil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidincarboxilato de ter-butilo	 Preparado de 1-8c y 1b	RT = 1.63 minutos (>95%); Condición 2; LCMS: Anal. Calcd $C_{35}H_{45}N_6O_4$ 613.34; encontrado: 613.56 $(M+H)^+$; LRMS: Anal. Calcd. para: $C_{35}H_{44}N_6O_4$ 612.34; encontrado: 613.33 $(M+H)^+$.
1-7d	(2S)-2-(5-(4'-(2-((1S)-1-((ter-butoxicarbonil)(metil)amino)etil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidincarboxilato de bencilo	 Preparado de 1-6b y 1-5c	RT = 1.65 minutos (>95%); Condición 2; LCMS: Anal. Calcd $C_{38}H_{43}N_6O_4$ 647.33; encontrado: 647.44 $(M+H)^+$; LRMS: Anal. Calcd. para: $C_{38}H_{42}N_6O_4$ 646.33; encontrado: 647.34 $(M+H)^+$.

Ejemplo 1, etapa e

5,5'-(4,4'-bifenildiil)bis(2-((2S)-2-pirrolidinil)-1H-imidazol)

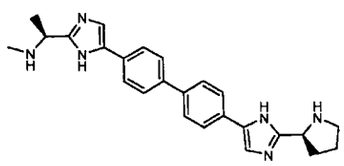
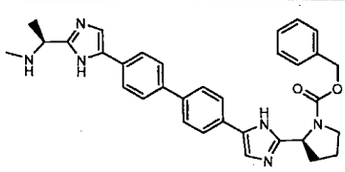
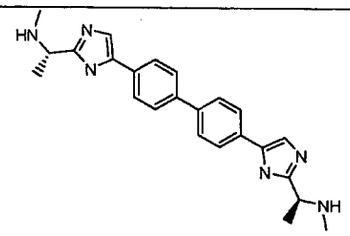


1e

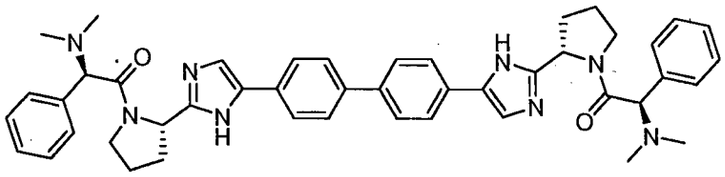
Una mezcla del carbamato 1d (560 mg) y 25% de TFA/CH_2Cl_2 (9.0 mL) se agitó a condición ambiente durante 3.2 horas. El componente volátil se removió al vacío, y el

material resultante se hizo base libre usando una columna MCX (lavado con metanol; elución con NH_3 2.0 M/metanol) para proporcionar la pirrolidina 1e como un sólido amarillo bruto (340 mg). ^{1}H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 11.83 (br s, 2H), 7.80 (d, J = 8.1, 4H), 7.66 (d, J = 8.3, 4H), 7.46 (br s, 2H), 4.16 (app t, J = 7.2, 2H), 2.99-2.69 (m, 6H), 2.09-2.00 (m, 2H), 1.94-1.66 (m, 6H). LC (Cond. 1): RT = 1.27 min; >98% índice de homogeneidad; LC/MS: Análisis Calculado para $[M+H]^+$ $C_{26}H_{29}N_6$: 425.25; encontrado 425.25; HRMS: Análisis calculado para $[M+H]^+$ $C_{26}H_{29}N_6$: 425.2454; encontrado 425.2448.

Análogos adicionales se prepararon similarmente:

Ejemplo	*Nombre del Compuesto*	*Estructura*	*Datos*
1-5e		 Preparado de 1-6d	RT = 1.37 min; LCMS: Anal. Calcd. para: $C_{25}H_{28}N_6$ 412; encontrado: 413 $(M+H)^+$.
1-6e		 Preparado de 1-7d	RT = 1.43 min; LCMS: Anal. Calcd. para: $C_{33}H_{35}N_6O_2$ 547; encontrado: 547 $(M+H)^+$.
1-7e		 Preparado de 1-5d	RT = 1.12 min; LRMS: Anal. Calcd. para: $C_{24}H_{28}N_6$ 400.24; encontrado: 401.22 $(M+H)^+$.

Condiciones LC para 1-5e a 1-7e: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 2 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

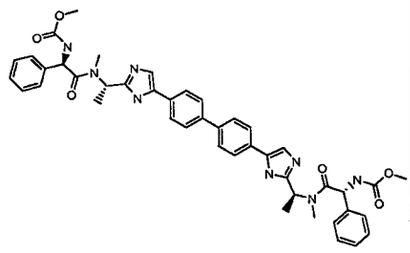


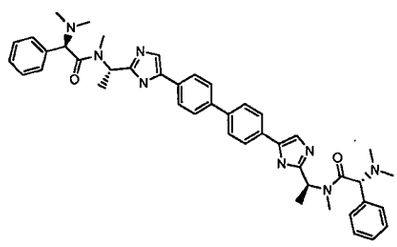
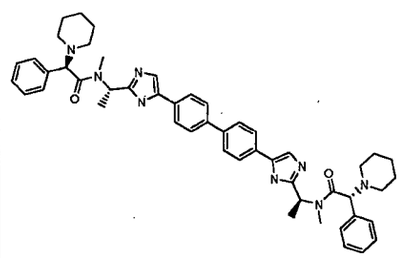
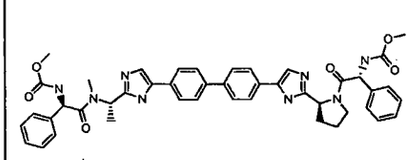
Ejemplo 1

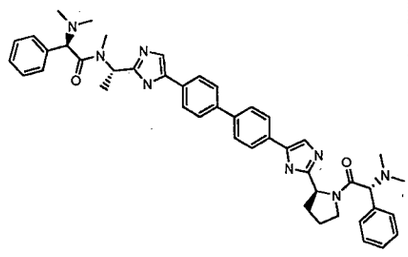
(1R,1'R)-2,2'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(N,N-dimetil-2-oxo-1-feniletanamina)

HATU (44.6 mg, 0.117 mmoles) se añadió a una mezcla de pirrolidina 1e (22.9 mg, 0.054 mmoles), diisopropiletilamina (45 µL, 0.259 mmoles) y *Extremo*-1 (28.1 mg, 0.13 mmoles) en DMF (1.5 mL) y la mezcla resultante se agitó a temperatura ambiente durante 90 minutos. El componente volátil se removió al vacío, y el residuo se purificó primero mediante MCX (lavado con metanol; elución con NH_3 2.0 M/metanol) y luego mediante un sistema de HPLC de fase inversa (H_2O/metanol/TFA) para proporcionar la sal TFA del ejemplo 1 como una espuma blanquecina (44.1 mg). ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 10.25 (br s, 2H), 8.20-7.10 (m, 20H), 5.79-5.12 (m, 4H), 4.05-2.98 (m, 4H), 2.98-2.62 (m, 6H), 2.50-1.70 (m, 14H), [Nota: la señal del imidazol NH fue demasiado amplia como para asignar un desplazamiento

químico]; LC (Cond. 1): RT = 1.40 min; >98% de índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{46}H_{51}N_8O_2$: 747.41; encontrado 747.58.

Ejemplo	*Nombre del Compuesto*	*Estructura*	*Datos de Caracterización*
24-18-1	(4,4'-bifenildiilbis (1H-imidazol-5,2-diil(1S)-1,1-etandiil (metilimino)((1R)-2-oxo-1-fenil-2,1-etandiil))) biscarbamato de dimetilo	 de 1-7e y *Extremo*-4	RT = 1.55 min[1]; LRMS: Anal. Calcd. para: $C_{44}H_{46}N_8O_6$ 782.35; encontrado: 783.37 $(M+H)^+$; HRMS: Anal. Calcd. para: $C_{44}H_{47}N_8O_6$ 783.3619encontrado: 783.3630 $(M+H)^+$.

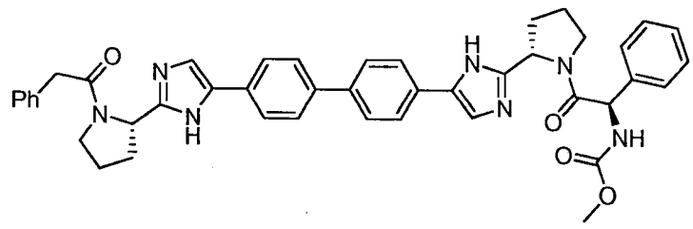
24-18-2	(2R,2'R)-N,N'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(1S)-1,1-etandiil))bis(2-(dimetilamino)-N-metil-2-fenilacetamida)	 de 1-7e y *Extremo*-1	RT = 1.16 min[1]; LRMS: Anal. Calcd. para: $C_{44}H_{50}N_8O_2$ 722.41; encontrado: 723.41 $(M+H)^+$; HRMS: Anal. Calcd. para: $C_{44}H_{51}N_8O_2$ 723.4135 encontrado: 723.4152 $(M+H)^+$.
24-18-3	(2R,2'R)-N,N'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(1S)-1,1-etandiil))bis(N-metil-2-fenil-2-(1-piperidinil)acetamida)	 de 1-7e y *Extremo*-14	RT = 1.28 min[1]; LRMS: Anal. Calcd. para: $C_{50}H_{58}N_8O_2$ 802.47; encontrado: 803.50 $(M+H)^+$; HRMS: Anal. Calcd. para: $C_{50}H_{59}N_8O_2$ 803.4761 encontrado: 803.4778 $(M+H)^+$.
24-18-4	((1R)-2-((2S)-2-(5-(4'-(2-((1S)-1-(((2R)-2-((metoxicarbonil) amino)-2-fenilacetil) (metil)amino)etil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Preparado de 1-5e y *Extremo*-4	RT = 1.53 min[1]; LRMS: Anal. Calcd. para: $C_{45}H_{46}N_8O_6$ 794.35; encontrado: 795.39 $(M+H)^+$; HRMS: Anal. Calcd. para: $C_{45}H_{47}N_8O_6$ 795.3619 encontrado: 795.3616 $(M+H)^+$.

24-18-5	(2R)-2-(dimetilamino)-N-((1S)-1-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)etil)-N-metil-2-fenilacetamida	 Preparado de 1-5e y *Extremo*-1	RT = 1.21[1]; LRMS: Anal. Calcd. para: $C_{45}H_{50}N_8O_2$ 734.41; encontrado: 735.46 $(M+H)^+$; HRMS: Anal. Calcd. para: $C_{45}H_{51}N_8O_2$ 735.4135encontrado: 735.4136 $(M+H)^+$.

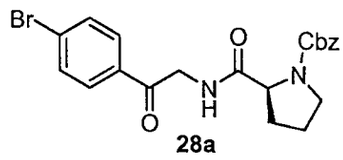
[1]Condiciones de LC para 24-18-1 a 24-18-5: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 2 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

Ejemplo 28

((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)carbamato de metilo



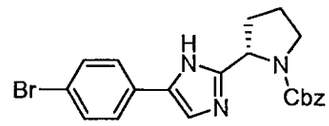
Ejemplo 28, etapa a



28a

HATU (19.868 g, 52.25 mmoles) se añadió a una mezcla homogénea de *N*-Cbz-L-prolina (12.436 g, 49.89 mmoles) y la sal HCl de 2-amino-1-(4-bromofenil)etanona (12.157 g, 48.53 mmoles) en DMF (156 mL). La mezcla se bajó en un baño de hielo-agua, e inmediatamente después se añadió *N,N*-diisopropiletilamina (27 mL; 155 mmoles) por goteo durante 13 minutos. Después de que se completó la adición de la base, se retiró el baño de enfriamiento y la mezcla de reacción se agitó durante 50 minutos más. El componente volátil se removió al vacío; se añadió agua (125 mL) al sólido crudo resultante y se agitó durante aproximadamente 1 hora. El sólido blanquecino se filtró y se lavó con agua copiosa, y se secó al vacío para proporcionar la cetoamida 28a como un sólido blanco (20.68 g). ^{1}H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 8.30 (m, 1H), 7.91 (m, 2H), 7.75 (d, J = 8.5, 2H), 7.38-7.25 (m, 5H), 5.11-5.03 (m, 2H), 4.57-4.48 (m, 2H), 4.33-4.26 (m, 1H), 3.53-3.36 (m, 2H), 2.23-2.05 (m, 1H), 1.94-1.78 (m, 3H); LC (Cond. 1): RT = 1.65 min; 98% de índice de homogeneidad; LC/MS: análisis calculado para $[M+H]^+$ $C_{21}H_{22}BrN_2O_4$: 445.08; encontrado 445.31.

Ejemplo 28, etapa b



28b

La cetoamida 28a (10.723 g, 24.08 mmoles) se convirtió en 28b de acuerdo con el procedimiento descrito para la síntesis del carbamato 1b, con la excepción de que el material crudo se purificó mediante cromatografía por vaporización (la muestra se cargó con solvente de elución; 50% de acetato de etilo/hexanos). Se recuperó un bromuro 28 como una espuma blanquecina (7.622 g). ^{1}H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.23/12.04/11.97 (m, 1H), 7.73-6.96 (m, 10H), 5.11-4.85 (m, 3H), 3.61 (m, 1H), 3.45 (m, 1H), 2.33-184 (m, 4H). LC (Cond. 1): RT = 1.42 min; >95% de índice de homogeneidad; LC/MS: análisis calculado para $[M+H]^+$ $C_{21}H_{21}BrN_3O_2$: 426.08; encontrado 426.31; HRMS: análisis calculado para $[M+H]^+$ $C_{21}H_{21}BrN_3O_2$: 426.0817; encontrado 426.0829. La pureza óptica de 28b se evaluó usando los siguientes métodos de HPLC quiral, y un ee de 99% fue observado.

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

Solvente: 20% de etanol/heptano (isocrático)

Velocidad de flujo: 1 mL/min

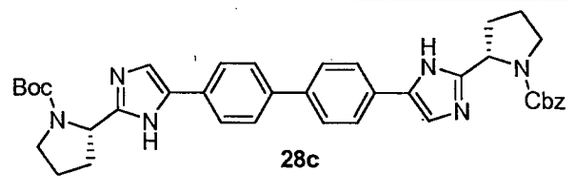
Longitud de onda: 254 nm

Tiempo de retención relativo: 1.82 minutos (*R*),

5.23 minutos (*S*).

Ejemplo 28, etapa c

(2S,2'S)-2,2'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil))di(1-pirrolidincarboxilato de bencil ter-butilo



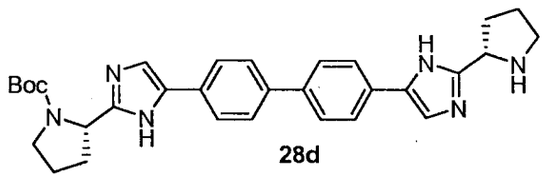
28c

$Pd(Ph_3P)_4$ (711.4 mg, 0.616 mmoles) se añadió a una mezcla de éster boronato 1c (7.582 g, ~17 mmoles), bromuro 28b (7.62 g, 17.87 mmoles), $NaHCO_3$ (4.779 g, 56.89 mmoles) en 1,2-dimetoxietano (144 mL) y agua (48 mL). La mezcla de reacción se purgó con N_2 y se calentó con un baño de aceite a 80°C durante 15.5 horas, y después el componente volátil se removió al vacío. El residuo se dividió entre CH_2Cl_2 y agua, y la capa acuosa se extrajo con CH_2Cl_2. La fase orgánica combinadas se secó ($MgSO_4$), se filtró y se concentró al vacío. el material resultante se sometió a cromatografía por vaporización (la muestra se cargó como una malla de gel de sílice; se usó acetato de etilo como eluyente) para proporcionar el bifenilo 28c como una espuma blanquecina que contenía impurezas de Ph_3PO (7.5 g). ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.24-12.19 (m, 0.36H), 12.00-11.82 (m, 1.64H), 7.85-6.98 (15H), 5.12-4.74 (4H), 3.68-3.34 (4H), 2.34-1.79 (8H), 1.41/1.17 (dos br S, 9H); LC (Cond. 1): RT = 1.41 minutos; LC/MS: análisis calculado para $[M+H]^+$ $C_{39}H_{43}N_6O_4$:

659.34; encontrado 659.52; HRMS: análisis calculado para $[M+H]^+$ $C_{39}H_{43}N_6O_4$: 659.3346; encontrado 659.3374.

Ejemplo 28, etapa d

(2S)-2-(5-(4'-(2-((2S)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidincarboxilato de ter-butilo



28d

K_2CO_3 (187.8 mg, 1.36 mmoles) se añadió a una mezcla del catalizador (10% de Pd/C; 205.3 mg), carbamato 28c (1.018 g, ~1.5 mmoles), metanol (20 mL) y 3 gotas de pipeta de agua. Un balón de H_2 se fijó y la mezcla se agitó durante 6 horas. Después se añadieron catalizador adicional (10% de Pd/C, 100.8 mg) y K_2CO_3 (101.8 mg, 0.738 mmoles) y se continuó agitando durante 3.5 horas. Durante el proceso de hidrogenación, el balón de H_2 se cambió a intervalos tres veces. La mezcla de reacción se filtró a través de una almohadilla de tierra diatomácea (Celite® 521), y el filtrado se removió al vacío. El material crudo resultante se sometió a cromatografía por vaporización usando una columna corta (la muestra se cargó como una malla de gel de sílice; 0-20% de metanol/CH_2Cl_2 usado como eluyente) para proporcionar 28d de una espuma amarillo claro (605.6 mg). ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.18/11.89/11.82 (tres br s, 2H), 7.83-

000512

7.29 (m, 10H), 4.89-4.73 (m, 1H), 4.19 (app, t, *J* = 7.2, 1H), 3.55 (app br s, 1H), 3.40-3.35 (m, 1H), 3.02-2.96 (m, 1H), 2.91-2.84 (m, 1H), 2.30-1.69 (m, 8H), 1.41/1.16 (dos br s, 9H). Nota: La señal de la pirrolidina NH parece haberse traslapado con las señales en la región de 3.6-3.2 ppm; LC (Cond.1): RT = 1.21 min; >95% de índice de homogeneidad; LC/MS: análisis calculado para $[M+H]^+$ $C_{31}H_{37}N_6O_2$: 525.30; encontrado 525.40.

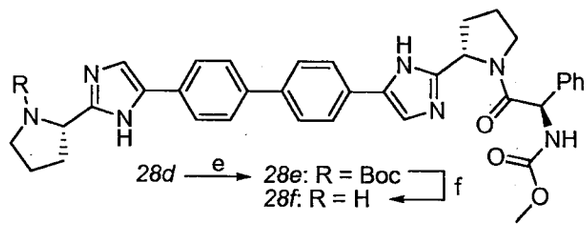
Ejemplo 28, etapas e-f

Ejemplo 28 etapa e

(2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidincarboxilato de ter-butilo

Ejemplo 28 etapa f

((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)carbamato de metilo

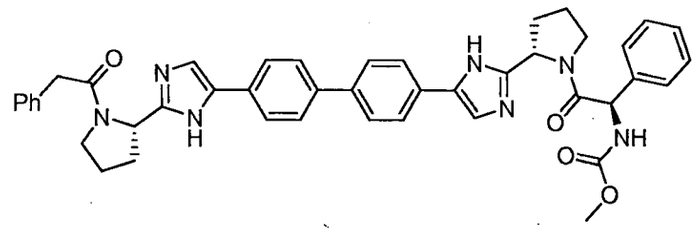


Etapa e: HATU (316.6 mg, 0.833 mmoles) se añadió a una solución en DMF (7.0 mL) de pirrolidina 28d (427 mg, 0.813 mmoles), *Extremo*-4 (177.6 mg, 0.849 mmoles) y diisopropiletilamina (0.32 mL, 1.84 mmoles), y la mezcla de reacción se agitó durante 45 minutos. El componente volátil se removió al vacío, y el residuo se dividió entre CH_2Cl_2 (50 mL) y un medio acuoso (20 mL de H_2O + 1 mL de solución de $NaHCO_3$ saturado). La fase acuosa se volvió a extraer con CH_2Cl_2, y la fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró al vacío. El aceite amarillo resultante se purificó mediante cromatografía por vaporización (gel de sílice; acetato de etilo) para proporcionar 28e como una espuma amarilla (336 mg). LC (Cond. 1): RT = 1.68 min; 91% de índice de homogeneidad; LC/MS: análisis calculado para $[M+H]^+$ $C_{41}H_{46}N_7O_5$: 716.35; encontrado 716.53.

Etapa f: El carbamato 28e se elaboró a la amina 28f al emplear el procedimiento descrito en la conversión de 1d en 1e. LC (Cond. 1): RT = 1.49 min; >98% de índice de homogeneidad. LC/MS: análisis calculado para $[M+H]^+$ $C_{36}H_{38}N_7O_3$: 616.30; encontrado 616.37; HRMS: análisis calculado para $[M+H]^+$ $C_{36}H_{38}N_7O_3$: 616.3036; encontrado 616.3046.

Ejemplo 28

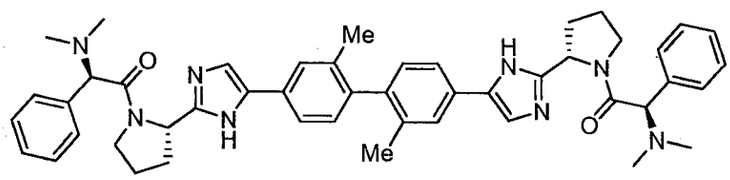
((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)carbamato de metilo



La amina 28f se convirtió en la sal TFA del ejemplo 28 al emplear la última etapa de la síntesis del ejemplo 1. ^{1}H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 8.21-7.03 (m, 21H), 5.78-5.14 (3H), 3.98-3.13 (m, 9H; incluyendo la señal para OCH_3 en 3.54 & 3.53), 2.45-1.72 (m, 8H). LC (Cond. 1): RT = 1.66 minutos, >98% de índice de homogeneidad; LC/MS: análisis calculado para $[M+H]^+$ $C_{44}H_{44}N_7O_4$: 734.35; encontrado 734.48; HRMS: análisis calculado para $[M+H]^+$ $C_{44}H_{44}N_7O_4$: 734.3455; 734.3455.

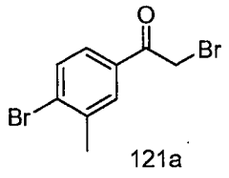
Ejemplo 121

(1R,1'R)-2,2'-((2,2'-dimetil-4,4'-bifenildiil)bis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(N,N-dimetil-2-oxo-1-feniletanamina)

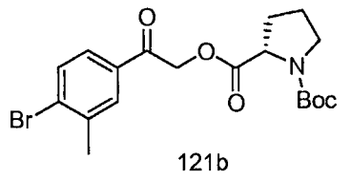


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Ejemplo 121, etapa a-b



121a



121b

$PdCl_2(Ph_3P)_2$ (257 mg, 0.367 mmoles) se añadió a una solución en dioxano (45 mL) de 1-bromo-4-yodo-2-metilbenceno (3.01 g, 10.13 mmoles) y tri-*n*-butil(1-etoxivinil)estanano (3.826 g, 10.59 mmoles) y se calentó a 80°C durante ~17 horas. La mezcla de reacción se trató con agua (15 mL), se enfrió a ~0°C (hielo/agua), y después se añadió NBS (1.839 g, 10.3 mmoles) por lotes durante 7 minutos. Luego de aproximadamente 25 minutos de agitación, se removió el componente volátil al vacío, y el residuo se dividió entre CH_2Cl_2 y agua. La capa acuosa se extrajo con CH_2Cl_2, y la fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró al vacío. El material crudo resultante se purificó mediante una cromatografía de gravedad (gel de sílice; 4% de acetato de etilo/hexanos) para proporcionar el bromuro 121a como un sólido parduzco-amarillo (2.699 g); la muestra es impura y contiene impurezas derivadas de estanano, entre otras. ^1H RMN ($CDCl_3$, δ = 7.24 ppm, 400 MHz): 7.83 (s, 1H), 7.63 (s, 2H), 4.30 (s, 2H), 2.46 (s, 3H).

Una solución en CH_3CN (15 mL) de 121a (2.69 g, <9.21 mmoles) se añadió por goteo durante 3 minutos a una solución en CH_3CN (30 mL) de (*S*)-Boc-prolina (2.215 g, 10.3

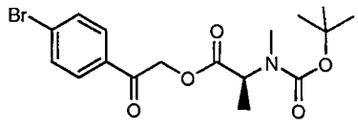
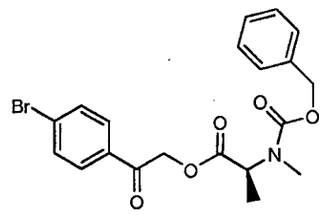
mmoles) y trietilamina (1.40 mL, 10.04 mmoles), y se agitó durante 90 minutos. El componente volátil se removió al vacío, y el residuo se dividió entre agua y CH_2Cl_2, y la fase orgánica se secó ($MgSO_4$), se filtró y se concentró al vacío. El material crudo resultante se purificó mediante una cromatografía por vaporización (gel de sílice; 15-20% de acetato de etilo/hexanos) para proporcionar 121b como un aceite viscoso incoloro (2.74 g). ^1H RMN (DMSO-d_6, δ = 2.50, 400 MHz): δ 7.98 (m, 1H), 7.78 (d, J = 8.3, 1H), 7.72-7.69 (m, 1H), 5.61-5.41 (m, 2H), 4.35-4.30 (m, 1H), 3.41-3.30 (m, 2H), 2.43 (s, 3H), 2.33-2.08 (m, 2H), 1.93-1.83 (m, 2H), 1.40/1.36 (s, 9H); LC (Cond. 1): RT = 1.91 min; >95% de índice de homogeneidad; LC/MS: análisis calculado para $[M+Na]^+$ $C_{19}H_{24}BrNNaO_5$ 448.07; encontrado 448.10.

Ceto-ésteres adicionales pueden prepararse de una manera análoga.

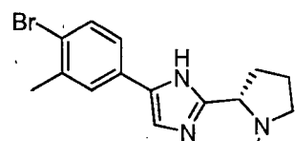
Condiciones de LC: *Condición 1*: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

Condición 2: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 2 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de

inyección.

Ejemplo	*Estructura*	*Datos*
121b-1		RT = 2.15 minutos (condición 2, 98%); LRMS: Anal. Calcd. para: $C_{17}H_{22}NO_5$ 399.07; encontrado: 400.10 $(M+H)^+$.
121b-2		RT = 2.78 minutos (condición 1, >90%); LRMS: Anal. Calcd. para: $C_{20}H_{20}{}^{37}BrNO_5$ 435.05 encontrado: 458.02 $(M+Na)^+$.

Ejemplo 121, etapa c

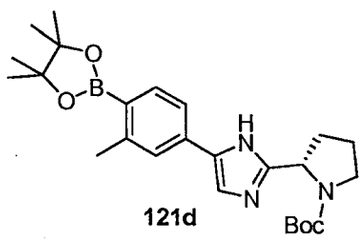


121c

Una mezcla del cetoéster 121b (1.445 g, 3.39 mmoles) y NH_4OAc (2.93 g, 38.0 mmoles) en xilenos (18 mL) se calentó con un microondas a 140°C durante 80 minutos. El componente volátil se removió al vacío, y el residuo se dividió cuidadosamente entre CH_2Cl_2 y agua, cuando se añadió solución de $NaHCO_3$ saturada suficiente para neutralizar el medio acuoso. La fase acuosa se extrajo con CH_2Cl_2, y la fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró al vacío. El producto crudo se purificó mediante una cromatografía por vaporización (gel de sílice, 40% de acetato de etilo/hexanos) para proporcionar el imidazol 212c como un

sólido blanquecino (1.087 g). ^{1}H RMN (DMSO-d_6, δ = 2.50, 400 MHz): 12.15/11.91/11.84 (br s, 1H), 7.72-7.24 (m, 4H), 4.78 (m, 1H), 3.52 (m, 1H), 3.38-3.32 (m, 1H), 2.35 (s, 3H), 2.28-1.77 (m, 4H), 1.40/1.14 (s, 9H); LC (Cond. 1): RT = 1.91 min; >98% de índice de homogeneidad; LC/MS: análisis calculado para $[M+H]^+$ $C_{19}H_{25}BrN_3O_2$ 405.96; encontrado 406.11.

Ejemplo 121, etapa d



121d

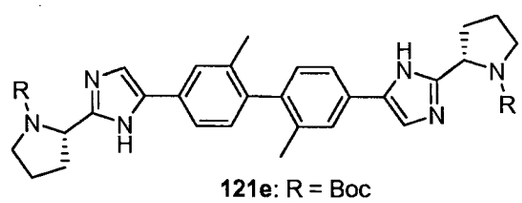
$PdCl_2dppf{\cdot}CH_2Cl_2$ (50.1 mg, 0.061 mmoles) se añadió a un tubo de presión que contenía una mezcla del bromuro 121c (538.3 mg, 1.325 mmoles), bis(pinacolato)diboro (666.6 mg, 2.625 mmoes), acetato de potasio (365.8 mg, 3.727 mmoles) y DMF (10 mL). La mezcla de reacción se burbujeó con N_2 y se calentó a 80°C durante 24.5 horas. El componente volátil se removió al vacío y el residuo se dividió entre CH_2Cl_2 y agua, cuando se añadió suficiente solución de $NaHCO_3$ saturada para hacer el pH del medio acuoso neutro. La fase acuosa se extrajo con CH_2Cl_2; y la fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró al vacío. el material resultante se purificó mediante un sistema Biotage (gel de sílice, 40-50% de acetato de etilo/hexanos) para proporcionar el boronato 121d como una espuma blanca (580 mg). De acuerdo

con ^{1}H RMN la muestra contiene pinacol residual en una relación producto/pinacol de ~3. ^{1}H RMN (DMSO-d_6, δ = 2.50, 400 MHz): δ 12.16/11.91/11.83 (br s, 1H), 7.63-7.25 (m, 4H), 4.78 (m, 1H), 3.53 (m, 1H), 3.39-3.32 (m, 1H), 2.48/2.47 (s, 3H), 2.28-1.78 (m, 4H), 1.40/1.14/1.12 (br s, 9H), 1.30 (s, 12H); LC (Cond. 1): RT = 1.62 min; LC/MS: análisis calculado para $[M+H]^+$ $C_{25}H_{37}BN_3O_4$ 454.29; encontrado 454.15.

Ejemplo 121, etapa e

Y

ejemplo 121, etapa f

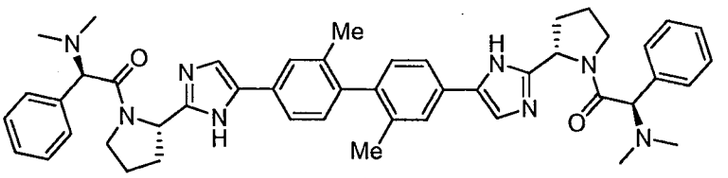


121e: R = Boc
121f: R = H

El carbamato 121e se preparó a partir del bromuro 121c y el boronato 121d de acuerdo con la preparación del dímero 1d; LC (Cond. 1): RT = 1.43 min; LC/MS: análisis calculado para $[M+H]^+$ $C_{38}H_{49}N_6O_4$ 653.38; encontrado 653.65.

La desprotección del carbamato 121e, de acuerdo con la preparación de la pirrolidina 1e, proporcionó 121f como una espuma blanquecina. ^{1}H RMN (DMSO-d_6, δ = 2.50, 400 MHz): 11.79 (br s, 2H), 7.66 (s, 2H), 7.57 (d, J = 7.8, 2H), 7.41 (br s, 2H), 7.02 (d, J = 7.8, 2H), 4.15 (app t, J = 7.2, 2H), 3.00-2.94 (m, 2H), 2.88-2.82 (m, 2H), 2.09-2.01 (m, 2H), 2.04 (s, 6H), 1.93-1.85 (m, 2H), 1.82-1.66 (m, 4H). Nota: Aunque

señales amplias que corresponden a la pirrolidina NH aparecen en la región de 2.8-3.2 ppm, el intervalo real para su desplazamiento químico no pudo ser determinado. LC (Cond. 1): RT = 1.03 min; LC/MS: análisis calculado para $[M+H]^+$ $C_{28}H_{33}N_6$ 453.28; encontrado 453.53.

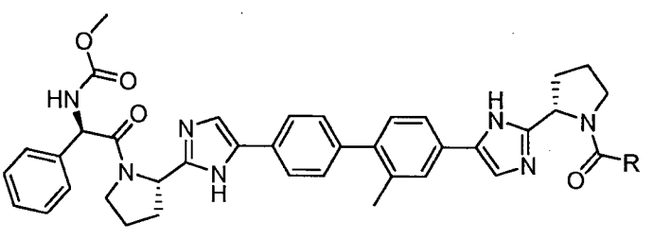


Ejemplo 121

(1R,1'R)-2,2'-((2,2'-dimetil-4,4'-bifenildiil)bis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(N,N-dimetil-2-oxo-1-feniletanamina)

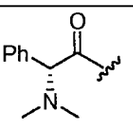
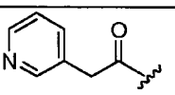
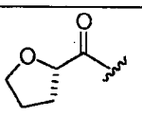
El ejemplo 121 (sal TFA) se sintetizó a partir de 121f de acuerdo con la preparación del ejemplo 1 a partir de 1e; LC (Cond. 1): RT = 1.14 min; >98% de índice de homogeneidad; LC/MS: análisis calculado para $[M+H]^+$ $C_{48}H_{55}N_8O_2$ 775.45; 775.75; HRMS: análisis calculado para $[M+H]^+$ $C_{48}H_{55}N_8O_2$ 775.4448; encontrado 775.4473.

Ejemplos 126-128



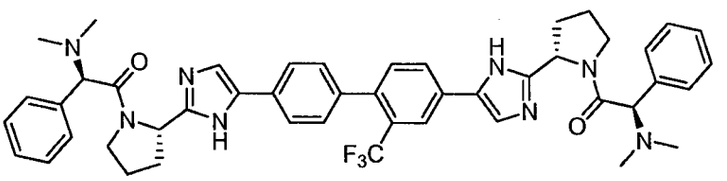
Los ejemplos 126-128 se prepararon iniciando a partir del bromuro 28b y el boronato 121d usando los métodos

descritos en el ejemplo 28 iniciando con la etapa c.

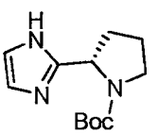
Ejemplo	*Nombre del Compuesto*		*RT (LC-Cond.); índice de % de homogeneidad; datos de MS*
126	((R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-2'-metil-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 *Extremo-1*	1.22min (Cond. 1); >98%; LC/MS: Anal. Calcd. para: $[M+H]^+$ $C_{47}H_{51}N_8O_4$: 791.40; encontrado 791.70; HRMS: Anal. Calcd. para: $[M+H]^+$ $C_{47}H_{51}N_8O_4$: 791.4033; encontrado 791.4061
127	((1R)-2-((2S)-2-(5-(2'-metil-4'-(2-((2S)-1-(3-piridilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.19 minutos (Cond. 1); >98%; LC/MS: Anal. Calcd. para: $[M+H]^+$ $C_{44}H_{45}N_8O_4$: 749.36; encontrado 749.62; HRMS: Anal. Calcd. para: $[M+H]^+$ $C_{44}H_{45}N_8O_4$: 749.3564; encontrado 749.3592
128	((1R)-2-((2S)-2-(5-(2'-metil-4'-(2-((2S)-1-((2S)-tetrahidro-2-furancarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.27 minutos (Cond. 1); >98%; LC/MS: Anal. Calcd. para: $[M+H]^+$ $C_{42}H_{46}N_7O_5$: 728.36; encontrado 728.59; HRMS: Anal. Calcd. para: $[M+H]^+$ $C_{42}H_{46}N_7O_5$: 728.3560; encontrado 728.3593

Ejemplo 130

(1R,1'R)-2,2'-((2-(trifluorometil)-4,4'-bifenildiil)bis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(N,N-dimetil-2-oxo-1-feniletanamina)



Ejemplo 130, etapa a



130a

Glioxal (2.0 mL de 40% en agua) se añadió por goteo durante 11 minutos a una solución en metanol de NH_4OH (32 mL) y (S)-Boc-prolinal (8.564 g, 42.98 mmoles) y se agitó a temperatura ambiente durante 19 horas. El componente volátil se removió al vacío y el residuo se purificó mediante una cromatografía por vaporización (gel de sílice, acetato de etilo) seguida por una recristalización (acetato de etilo, temperatura ambiente) para proporcionar el imidazol 130a como un sólido esponjoso blanco (4.43 g). ^1H RMN (DMSO-d_6, δ = 2.50, 400 MHz): 11.68/11.59 (br s, 1H), 6.94 (s, 1H), 6.76 (s, 1H), 4.76 (m, 1H), 3.48 (m, 1H), 3.35-3.29 (m, 1H), 2.23-1.73 (m, 4H), 1.39/1.15 (s, 9H). LC (Cond. 1): RT = 0.87 min; >95% de índice de homogeneidad; LC/MS: análisis calculado para $[M+H]^+$ $C_{12}H_{20}N_3O_2$ 238.16; encontrado 238.22. El

imidazol 130a tuvo una ee de 98.9% cuando se analizó bajo condiciones de HPLC quiral indicadas abajo.

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

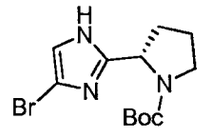
Solvente: 1.7% de etanol/heptano (isocrático)

Velocidad de flujo: 1 mL/min

Longitud de onda: ya sea 220 ó 256 nm

Tiempo de retención relativo: 3.25 min (*R*), 5.78 minutos (*S*).

Ejemplo 130, etapa b

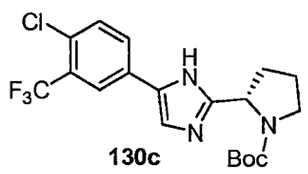


130b

N-bromosuccinimida (838.4 mg, 4.71 mmoles) se añadió por lotes, durante 15 minutos, a una solución enfriada (hielo/agua) en CH_2Cl_2 (20 mL) del imidazol 130a (1.0689 g, 4.504 mmoles), y se agitó a temperatura similar durante 75 minutos. El componente volátil se removió al vacío. El material crudo se purificó mediante un sistema de HPLC de fase inversa (H_2O/metanol/TFA) para separar el bromuro 130b de su análogo dibromo y el material de partida no consumido. El eluto de HPLC se neutralizó con un exceso de NH_3/metanol y el componente volátil se removió al vacío. El residuo se dividió entre CH_2Cl_2 y agua, y la capa acuosa se extrajo con agua. La fase orgánica

combinada se secó ($MgSO_4$), se filtró y se concentró al vacío para proporcionar 130b como un sólido blanco (374 mg). ^1H RMN (DMSO-d_6, δ = 2.50, 400 MHz): 12.12 (br s, 1H), 7.10 (m, 1H), 4.70 (m, 1H), 3.31 (m, 1H; traslapado con señal de agua), 2.25-1.73 (m, 4H), 1.39/1.17 (s, 3.8H + 5.2H). LC (Cond. 1): RT = 1.10 min; >95% de índice de homogeneidad; LC/MS: análisis calculado para $[M+H]^+$ $C_{12}H_{19}BrN_3O_2$ 316.07; encontrado 316.10.

Ejemplo 130, etapa c

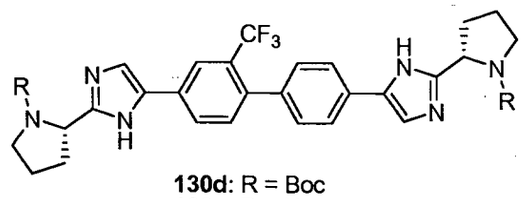


130c

$Pd(Ph_3P)_4$ (78.5 mg, 0.0679 mmoles) se añadió a una mezcla del bromuro 130b (545 mg, 1.724 mmoles), 2-(4-cloro-3-(trifluorometil)fenil-4,4,5,5-tetrametil-1,3,2-dioxaborolano (542.8 mg, 1.771 mmoles) (disponible comercialmente), $NaHCO_3$ (477 mg, 5.678 mmoles) en 1,2-dimetoxietano (12.5 mL) y agua (4.2 mL). La mezcla de reacción se purgó con nitrógeno, se calentó con un baño de aceite a 80°C durante 27 horas, y luego el componente volátil se removió al vacío. El residuo se dividió entre CH_2Cl_2 y agua, y la capa orgánica se secó ($MgSO_4$), se filtró y se concentró al vacío. El material crudo resultante se purificó mediante un sistema Biotage (gel de sílice, 40-50% de acetato de etilo/hexanos) seguido

por una HPLC de fase inversa (agua/metanol/TFA). El eluto de HPLC se trató con un exceso de NH_3/metanol y se concentró. El residuo se dividió entre agua y CH_2Cl_2; y la capa orgánica se secó ($MgSO_4$), se filtró y se concentró al vacío para proporcionar 130c como una espuma blanca (317.4 mg). ^1H RMN (DMSO-d_6, δ = 2.50, 400 MHz): 12.36/12.09/12.03 (br s, 1H), 8.15 (d, J = 1.8, 0.93H), 8.09 (br s, 0.07H), 8.01 (dd, J = 8.3/1.3, 0.93H), 7.93 (m, 0.07H), 7.74 (m, 1H), 7.66 (d, J = 8.3, 0.93H), 7.46 (m, 0.07H), 4.80 (m, 1H), 3.53 (m, 1H), 3.36 (m, 1H), 2.30-1.77 (m, 4h), 1.40/1.15 (s, 3.8H+5.2H). LC (Cond. 1): RT = 1.52 min; >95% de índice de homogeneidad; LC/MS: análisis calculado para $[M+H]^+$ $C_{19}H_{22}ClF_3N_3O_2$ 416.14; encontrado 416.17.

Ejemplo 130, etapa d-e



130d: R = Boc
130e: R = H

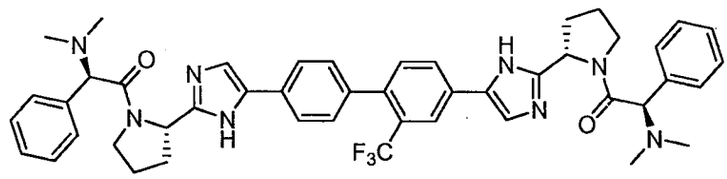
$Pd[P(t\text{-}Bu)_3]_2$ (48 mg, 0.094 mmoles) se añadió a una mezcla del cloruro 130c (245 mg, 0.589 mmoles), boronato 1c (277.1 mg, 0.631 mmoles), KF (106.7 mg, 1.836 mmoles) en DMF (6 mL), y se calentó a 110°C durante ~30 horas. El componente volátil se removió al vacío y el residuo se dividió entre CH_2Cl_2 (50 mL), agua (20 mL) y

$NaHCO_3$ saturado (1 mL). La capa acuosa se extrajo con CH_2Cl_2 (2x) y la fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró al vacío. El material resultante se purificó mediante un sistema Biotage (gel de sílice, acetato de etilo) para proporcionar el carbamato 130d como una espuma blanquecina (297 mg). LC (Cond. 1): RT = 1.44 min; >95% de índice de homogeneidad; LC/MS: análisis calculado para $[M+H]^+$ $C_{37}H_{44}F_3N_6O_4$ 693.34; encontrado 693.34.

La desprotección de 130d, la cual se llevó a cabo de acuerdo con la preparación de la pirrolidina 1e, proporcionó 130e como una espuma amarillo claro. ^1H RMN (DMSO-d_6, δ = 2.50, 400 MHz): 11.88 (br s, 2H), 8.16 (d, J = 1.5, 1H), 8.02 (d, J = 7.8, 1H), 7.78 (d, J = 8.1, 2H), 7.66 (br s, 1H), 7.48 (br s, 1H), 7.37 (d, J = 8.1, 1H), 7.28 (d, J = 8.3, 2H), 4.18 (m, 2H), 2.99-2.93 (m, 2H), 2.89-2.83 (m, 2H), 2.11-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.82-1.67 (m, 4H). Nota: Aunque señales antes que correspondían a la pirrolidina NH aparecen en la región de 2.8-3.2 ppm, el intervalo real para su desplazamiento químico no pudo ser determinado. LC (Cond. 1): RT = 1.12 min; >95% de índice de homogeneidad; LC/MS: análisis calculado para $[M+H]^+$ $C_{27}H_{28}F_3N_6$ 493.23; encontrado 493.14.

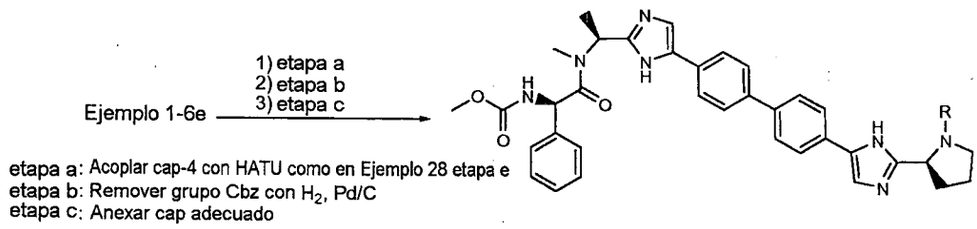
Ejemplo 130

(1R,1'R)-2,2'-((2-(trifluorometil)-4,4'-bifenildiil)bis(1H-imidazol-5,2-diil)2S)-2,1-pirrolidindiil))bis(N,N-dimetil-2-oxo-1-feniletanamina)



El ejemplo 130 (sal TFA) se preparó a partir de 130e y *Extremo*-1 de acuerdo con la preparación del ejemplo 1 a partir de la pirrolidina 1e. LC (Cond. 1): RT = 1.17 min; >98% de índice de homogeneidad; LC/MS: análisis calculado para $[M+H]^+$ $C_{47}H_{50}F_3N_8O_2$ 815.40; encontrado 815.44; HRMS: análisis calculado para $[M+H]^+$ $C_{47}H_{50}F_3N_8O_2$ 815.4009; encontrado 815.4013.

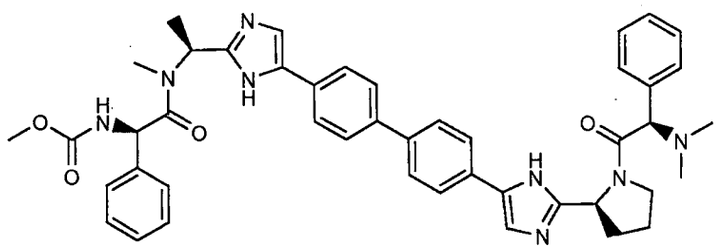
Ejemplo 131, 1-1 a 131, 1-2



Los ejemplos 131.1-1 a 131.1-2 se prepararon de una forma similar a la del ejemplo 28 por medio de la intermediación del intermediario 1-6e luego de anexar un *Extremo*-4.

Ejemplo 131.1-1

((1R)-2-(((1S)-1-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)etil)(metil)amino)-2-oxo-1-feniletil)carbamato de metilo



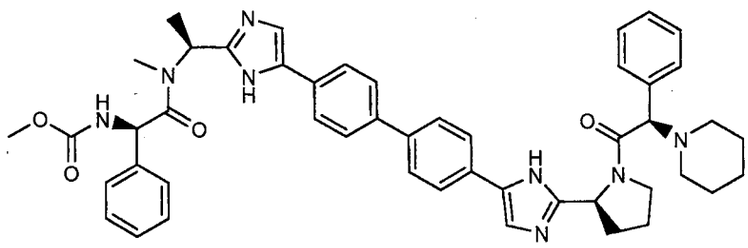
Extremo-1 se anexó después de que el carbamato CBz se removiera de 1-6e con $Pd/C/H_2$.

Condiciones de LCMS: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección, t_g = 1.42 min. LRMS: Análisis calculado para $C_{45}H_{49}N_8O_4$ 765.39; encontrado: 765.38 $(M+H)^+$.

HRMS: análisis calculado para $C_{45}H_{49}N_8O_4$ calculado 765.3877 encontrado: 765.3905 $(M+H)^+$.

Ejemplo 131.1-2

((1R)-2-(metil((1S)-1-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)etil)amino)-2-oxo-1-feniletil)carbamato de metilo



Extremo-14 se anexó después de que el carbamato se removiera de 1-6e con $Pd/C/H_2$.

Condiciones de LCMS: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección, t_R = 1.45 min (>95%).

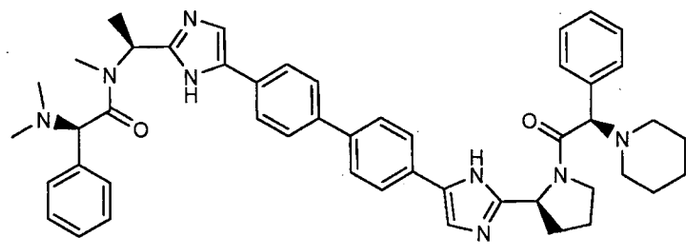
LRMS: análisis calculado para $C_{48}H_{52}N_8O_4$ 805.42; encontrado: 805.41 $(M+H)^+$.

HRMS: análisis calculado para $C_{48}H_{52}N_8O_4$ calculado 805.4190 encontrado: 805.4214 $(M+H)^+$.

000530

Ejemplo 131.2

(2R)-2-(dimetilamino)-N-metil-2-fenil-N-((1S)-1-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)etil)acetamida



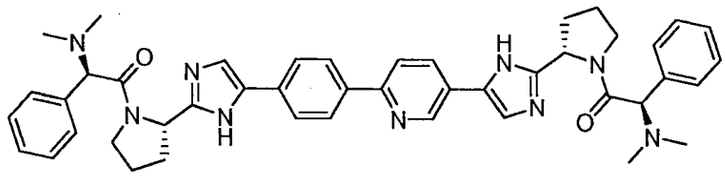
El ejemplo 131.2 se preparó de una manera similar a la del ejemplo 131.1-1 y el ejemplo 131.1-2 por medio de la intermediación del intermediario 1-6e después de anexar *Extremo*-1. *Extremo*-14 se anexó después de que el carbamato CBz fuera removido con $Pd/C/H_2$. Condiciones de LCMS: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección, t_R = 1.28 min.

LRMS: análisis calculado para $C_{48}H_{54}N_8O_2$ 775.44; encontrado: 775.45 $(M+H)^+$.

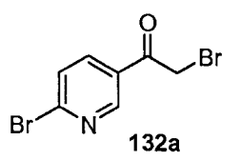
HRMS: análisis calculado para $C_{48}H_{54}N_8O_2$ calculado 775.4448, encontrado: 775.4460 $(M+H)^+$.

Ejemplo 132

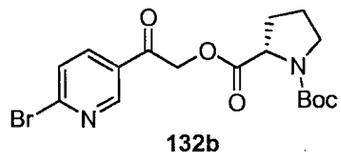
(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-3-piridinil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina



Ejemplo 132, etapa a-b



132a



132b

Una solución en CH_2Cl_2 (10 mL) de Br_2 (7.63 g, 47.74 mmoles) se añadió por goteo durante 5 minutos a una solución en CH_2Cl_2 enfriada (hielo/agua) (105 mL) de 1-(6-bromopiridin-3-il)etanona (9.496 g, 47.47 mmoles) y 48% de HBr (0.4 mL). El baño de enfriamiento se retiró 40 minutos más tarde, y se continuó agitando a temperatura ambiente durante alrededor de 66 horas. La torta de sólido que se formó se filtró, se lavó con CH_2Cl_2 y se secó al vacío para dar 132a impuro como un sólido blanquecino (15.94 g).

Boc-L-prolina (9.70 g, 45.06 mmoles) se añadió en un lote a una mezcla heterogénea de 132a crudo (15.4 g) y CH_3CN (150 mL), e inmediatamente después se añadió Et_3N (13.0 mL, 93.2 mmoles) por goteo durante 6 minutos. La mezcla de

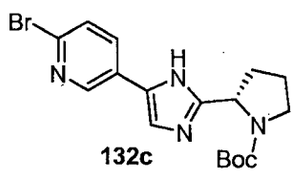
reacción se agitó durante 50 minutos, el componente volátil se removió al vacío y el residuo se dividió entre CH_2Cl_2 y agua. La capa de CH_2Cl_2 se secó ($MgSO_4$), se filtró y se concentró al vacío, y el material resultante se purificó mediante cromatografía por vaporización (gel de sílice; la muestra se cargó con solvente de elución; 25% de EtOAc/hexanos) para dar 132b como un aceite amarillo altamente viscoso (11.44 g). ^1H RMN (DMSO-d_6, δ = 2.5 ppm; 400 MHz): 8.95 (m, 1H), 8.25-8.21 (m, 1H), 7.88 (d, J = 8.3, 1H), 5.65-5.46 (m, 2H), 4.36-4.31 (m, 1H), 3.41-3.29 (m, 2H), 2.36-2.22 (m, 1H), 2.14-2.07 (m, 1H), 1.93-1.83 (m, 2H), 1.40 & 1.36 (dos s, 9H).

LC (Cond. 1): RT = 2.01 min; >90% de índice de homogeneidad.

LC/MS: Análisis calculado para $[M+Na]^+$ $C_{17}H_{21}NaBrN_2O_5$: 435.05; encontrado 435.15.

HRMS: análisis calculado para $[M+H]^+$ $C_{17}H_{22}BrN_2O_5$: 413.0712; encontrado 413.0717.

Ejemplo 132, etapa c



132c

Una mezcla el cetoéster 132b (1.318 g, 3.19 mmoles) y NH_4OAc (2.729 g, 35.4 mmoles) en xilenos (18 mL) se calentó con un microondas a 140°C durante 90 min. El componente

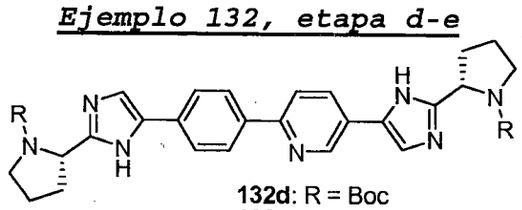
volátil se removió al vacío y el residuo se dividió entre CH_2Cl_2 y agua, cuando se añadió suficiente solución de $NaHCO_3$ saturada para neutralizarla en medio acuoso. La fase acuosa se extrajo con CH_2Cl_2, y la fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró al vacío. el material crudo resultante se purificó mediante un sistema Biotage (gel de sílice; 50% de EtOAc/hexanos) para dar el imidazol 132c como una espuma blanquecina (1.025 g). ^1H RMN (DMSO-d_6, δ = 2.5 ppm; 400 MHz): 12.33/12.09/12.02 (br m, 1H), 8.74 (d, J = 2.3, 0.93H), 8.70 (app br s, 0.07H), 8.03/7.98 (dd para el primer pico, J = 8.3, 1H), 7.69/7.67 (br m, 1H), 7.58/7.43 (d para el primer pico, J = 8.3, 1H), 4.80 (m, 1H), 3.53 (m, 1H), 3.36 (m, 1H), 2.33-2.11 (m, 1H), 2.04-1.79 (m, 3H), 1.39/1.15 (app br s, 3.9H+5.1H).

LC (Cond. 1): RT = 1.52 min; >98% de índice de homogeneidad.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{17}H_{22}BrN_4O_2$: 393.09; encontrado 393.19.

HRMS: Análisis calculado para $[M+H]^+$ $C_{17}H_{22}BrN_4O_2$: 393.0926; encontrado 393.0909.

Ejemplo 132, etapa d-e



132d: R = Boc
132e: R = H

$Pd(Ph_3P)_4$ (115.1 mg, 0.10 mmoles) se añadió a una

mezcla del bromuro 132c (992 mg, 2.52 mmoles), boronato 1c (1.207 g, 2.747 mmoles), $NaHCO_3$ (698.8 mg, 8.318 mmoles) en 1,2-dimetoxietano (18 mL) y agua (4 mL). La mezcla de reacción se enjuagó con nitrógeno, se calentó con un baño de aceite a 90°C durante 37 horas y se dejó enfriar a la temperatura ambiente. La suspensión que se formó se filtró y se lavó con agua seguida por 1,2-dimetoxietano, y se secó al vacío. Una malla de gel de sílice se preparó a partir del sólido crudo y se sometió a cromatografía por vaporización (gel de sílice; EtOAc) para dar el carbamato 132d como un sólido blanco, el cual se hizo ligeramente amarillo después de reposar a condiciones ambiente (1.124 g). La ^1H RMN indicó que la muestra contiene MeOH residual en una relación molar de producto/MeOH 1.3.

LC (Cond. 1): RT = 1.71 min; >98% de índice de homogeneidad.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{35}H_{44}N_7O_4$: 626.35; encontrado 626.64.

HRMS: Análisis calculado para $[M+H]^+$ $C_{35}H_{44}N_7O_4$: 626.3455; 626.3479.

El carbamato 132d (217 mg) se trató con 25% de TFA/CH_2Cl_2 (3.6 mL) y se agitó a condición ambiente durante 6 horas. El componente volátil se removió al vacío, y el material resultante se hizo en base libre con una columna MCX (lavada con MeOH; elución con NH_3 2.0 M/MeOH) para dar 132e

como una espuma amarillo mate que se solidificó gradualmente después del reposo (150.5 mg; la masa está por arriba del rendimiento teórico). ^{1}H RMN (DMSO-d_6, δ = 2.5 ppm; 400 MHz): 11.89 (muy amplia, 2H), 9.01 (d, J = 1.8, 1H), 8.13 (dd, J = 8.3, 2.2, 1H), 8.07 (d, J = 8.6, 2H), 7.92 (d, J = 8.3, 1H), 7.83 (d, J = 8.5, 2H), 7.61 (br s, 1H), 7.50 (br s, 1H), 4.18 (m, 2H), 3.00-2.93 (m, 2H), 2.90-2.82 (m, 2H), 2.11-2.02 (m, 2H), 1.94-1.85 (m, 2H), 1.83-1.67 (m, 4H). [Nota: Los hidrógenos de pirrolidina intercambiables no fueron observados].

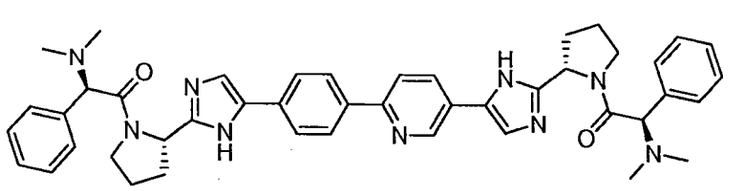
LC (Cond. 1): RT = 1.21 min; >98% de índice de homogeneidad.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{25}H_{28}N_7$: 426.24; encontrado 426.40.

HRMS: Análisis calculado para $[M+H]^+$ $C_{25}H_{28}N_7$: 426.2406; encontrado 426.2425.

Ejemplo 132

(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-3-piridinil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina



HATU (41.4 mg, 0.109 mmoles) se añadió a una mezcla de pirrolidina 132e (23.1 mg, 0.054 mmoles), (*i*-Pr)$_2$EtN (40 µL, 0.23 mmoles) y *Extremo*-1 (25.3 mg, 0.117 mmoles) en DMF (1.5 mL), y la mezcla se agitó a temperatura ambiente durante 1 hora. El componente volátil se removió al vacío, y el residuo se purificó primero mediante MCX (lavado con MeOH; elución con NH_3 2.0 M/MeOH) y luego mediante una HPLC de fase inversa (H_2O/MeOH/TFA) para dar la sal TFA del ejemplo 132 como una espuma amarilla (39.2 mg).

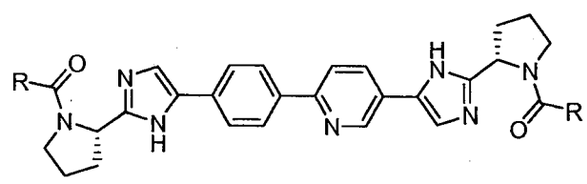
LC (Cond. 1): RT = 1.37 min; >98% de índice de homogeneidad.

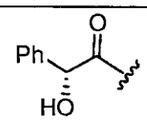
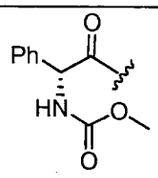
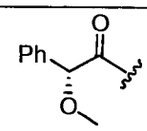
LC/MS: Análisis calculado para $[M+H]^+$ $C_{45}H_{50}N_9:O_2$: 748.41; encontrado 748.53.

HRMS: Análisis calculado para $[M+H]^+$ $C_{45}H_{50}N_9O_2$: 748.4087; encontrado 748.4090.

Los ejemplos 133-135 se prepararon como sales TFA a partir de 132e usando el mismo método de preparación que el ejemplo 132 y reactivos adecuados.

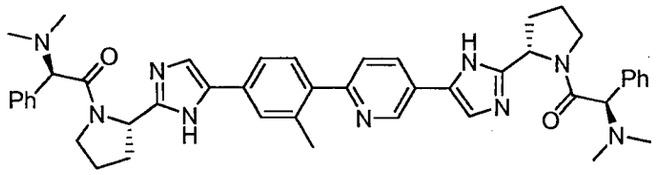
Ejemplos 133-135



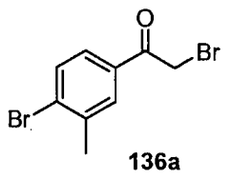
Ejemplo	*Nombre del Compuesto*		*RT (LC-Cond.); índice de % de homogeneidad; datos de MS*
133	(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-hidroxi-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-3-piridinil)-1H-imidazol-2-il)-1-pirrolidnil)-2-oxo-1-feniletanol		1.49 min (Cond. 1); >98% LC/MS: Anal. Calcd. para: $[M+H]^+$ $C_{41}H_{40}N_7O_4$: 694.31; encontrado 694.42 HRMS: Anal. Calcd. para: $[M+H]^+$ $C_{41}H_{40}N_7O_4$: 694.3142, encontrado: 694.3164
134	((1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-3-piridinil)1H-imidazol-2-il)-1-pirrolidnil)-2-oxo-1-feniletil) carbamato de metilo	 *Cap-4*	1.60 min (Cond. 1); >98% LC/MS: Anal. Calcd. para: $[M+H]^+$ $C_{45}H_{46}N_9O_6$: 808.36; encontrado 808.51 HRMS: Anal. Calcd. para: $[M+H]^+$ $C_{45}H_{46}N_9O_6$: 808.3571; encontrado 808.3576
135	5-(2-((2S)-1-((2R)-2-metoxi-2-fenilacetil)-2-pirroldinil)-1H-imidazol-5-il)-2-(4-(2-((2S)-1-((2R)-2-metoxi-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)piridina		1.60 min (Cond. 1); >98% LC/MS: Anal. Calcd. para: $[M+H]^+$ $C_{43}H_{44}N_7O_4$: 722.35; encontrado 722.40 HRMS: Anal. Calcd. para:

Ejemplo 136

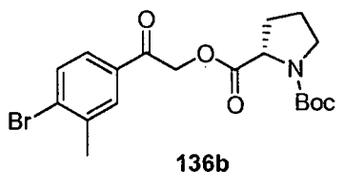
(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-metilfenil)-3-piridinil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina



Ejemplo 136, etapas a y b



136a



136b

$PdCl_2(Ph_3P)_2$ (257 mg, 0.367 mmoles) se añadió a una solución en dioxano (45 mL) de 1-bromo-4-yodo-2-metilbenceno (3.01 g, 10.13 mmoles) y tri-*n*-butil(1-etoxivinil)estanano (3.826 g, 10.59 mmoles) y se calentó a 80°C durante ~17 horas. La mezcla de reacción se trató con agua (15 mL), se enfrió a ~0°C (hielo/agua), y después se añadió NBS (1.839 g, 10.3 mmoles) por lotes durante 7 min. Aproximadamente 25 minutos de agitación, el componente volátil se removió al vacío, y el residuo se dividió entre CH_2Cl_2 y agua. La capa acuosa se extrajo con CH_2Cl_2, y la fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró al vacío. El material crudo resultante se purificó

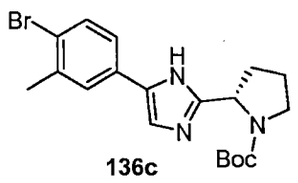
mediante una cromatografía de gravedad (gel de sílice; 4% de EtOAc/hexanos) para dar el bromuro 136a como un sólido parduzco-amarillo (2.699 g); la muestra es impura y contiene impurezas derivadas de estanano, entre otras. ^{1}H RMN ($CDCl_3$, δ = 7.24, 400 MHz): 7.83 (s, 1H), 7.63 (s, 2H), 4.30 (s, 2H), 2.46 (s, 3H).

Una solución en CH_3CN (15 mL) de 136a (2.69 g, <9.21 mmoles) se añadió por goteo durante 3 minutos a una solución en CH_3CN (30 mL) de (*S*)-Boc-prolina (2.215 g, 10.3 mmoles) y Et_3N (1.40 mL, 10.04 mmoles), y se agitó durante 90 min. El componente volátil se removió al vacío, y el residuo se dividió entre agua y CH_2Cl_2, y la fase orgánica se secó ($MgSO_4$), se filtró y se concentró al vacío. El material crudo resultante se purificó mediante una cromatografía por vaporización (gel de sílice; 15-20% de EtOAc/hexanos) para dar 136b como un aceite viscoso incoloro (2.74 g). ^{1}H RMN (DMSO-d_6, δ = 2.50, 400 MHz): 7.98 (m, 1H), 7.78 (d, *J* = 8.3, 1H), 7.72-7.69 (m, 1H), 5.61-5.41 (m, 2H), 4.35-4.30 (m, 1H), 3.41-3.30 (m, 2H), 2.43 (s, 3H), 2.33-2.08 (m, 2H), 1.93-1.83 (m, 2H), 1.40/1.36 (s, 9H).

LC (Cond. 1): RT = 1.91 min; >95% de índice de homogeneidad.

LC/MS: Análisis calculado para $[M+Na]^+$ $C_{19}H_{24}BrNNaO_5$: 448.07; encontrado 448.10.

Ejemplo 136, etapa c



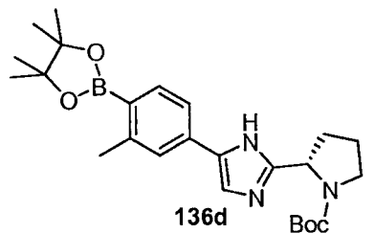
136c

Una mezcla del cetoéster 136b (1.445 g, 3.39 mmoles) y NH_4OAc (2.93 g, 38.0 mmoles) en xilenos (18 mL) se calentó con un microondas a 140°C durante 80 min. El componente volátil se removió al vacío, y el residuo se dividió cuidadosamente entre CH_2Cl_2 y agua, cuando se añadió suficiente solución de $NaHCO_3$ saturada para neutralizar el medio acuoso. La fase acuosa se extrajo con CH_2Cl_2, y la fase orgánica combinadas se secó ($MgSO_4$), se filtró, y se concentró al vacío. El crudo se purificó mediante una cromatografía por vaporización (gel de sílice, 40% de EtOAc/hexanos) para dar el imidazol 136c como un sólido blanquecino (1.087 g). ^1H RMN (DMSO-d_6, δ = 2.50, 400 MHz): 12.15/11.91/11.84 (br s, 1H), 7.72-7.24 (m, 4H), 4.78 (m, 1H), 3.52 (m, 1H), 3.38-3.32 (m, 1H), 2.35 (s, 3H), 2.28-1.77 (m, 4H), 1.40/1.14 (s, 9H).

LC (Cond. 1): RT = 1.91 min; >98% de índice de homogeneidad.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{19}H_{25}BrN_3O_2$: 405.96; encontrado 406.11.

Ejemplo 136, etapa d



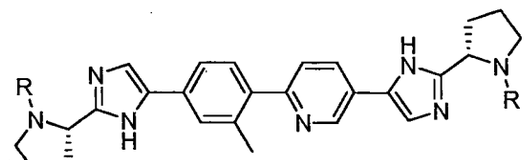
136d

$PdCl_2dppf.CH_2Cl_2$ (50.1 mg, 0.061 mmoles) se añadió a un tubo de presión que contenía una mezcla del bromuro 136c (538.3 mg, 1.325 mmoles), bis(pinacolato)diboro (666.6 mg, 2.625 mmoles), KOAc (365.8 mg, 3.727 mmoles) y DMF (10 mL). La mezcla de reacción se enjuagó con N_2 y se calentó a 80°C durante 24.5 horas. El componente volátil se removió al vacío y el residuo se dividió entre CH_2Cl_2 y agua, cuando se añadió suficiente solución de $NaHCO_3$ saturado como para hacer el pH del medio acuoso neutro. La fase acuosa se extrajo con CH_2Cl_2, y la fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró al vacío. El material resultante se purificó mediante un sistema Biotage (gel de sílice, 40-50% de EtOAc/hexanos) para dar el boronato 136d como una espuma blanca (580 mg). De acuerdo con ^1H RMN, la muestra contiene pinacol residual en una elación producto/pinacol de ~3. ^1H RMN (DMSO-d_6, δ = 2.50, 400 MHz): 12.16/11.91/11.83 (br s, 1H), 7.63-7.25 (m, 4H), 4.78 (m, 1H), 3.53 (m, 1H), 3.39-3.32 (m, 1H), 2.48/2.47 (s, 3H), 2.28-1.78 (m, 4H), 1.40/1.14/1.12 (br s, 9H), 1.30 (s, 12H).

LC (Cond. 1): RT = 1.62 min.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{25}H_{37}BN_3O_4$ 454.29; encontrado 454.15.

Ejemplo 136, etapas e-f



136e: R = Boc
136f: R = H

El biarilo 136e se preparó a partir del bromuro 132c y el boronato 136d de acuerdo con la condición de acoplamiento descrita para la preparación del biarilo 132d.

LC (Cond. 1a): RT = 1.32 min; >90% de índice de homogeneidad.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{36}H_{45}N_7O_4$ 640.36; encontrado 640.66.

La desprotección del biarilo 136e se hizo de acuerdo con la preparación de la pirrolidina 132e para dar 136f como una espuma amarillo claro. ^1H RMN (DMSO-d_6, δ = 2.50, 400 MHz): 11.88 (br s, 2H), 9.02 (d, J = 2, 1H), 8.12 (dd, J = 8.4, 2.3, 1H), 7.67 (s, 1H), 7.64-7.62 (m, 2H), 7.50 (d, J = 8.3, 1H), 7.46 (br s, 1H), 7.40 (d, J = 7.8, 1H), 4.21-4.14 (m, 2H), 3.00-2.93 (m, 2H), 2.90-2.82 (m, 2H), 2.40 (s, 3H), 2.11-2.01 (m, 2H), 1.94-1.85 (m, 2), 1.82-1.66

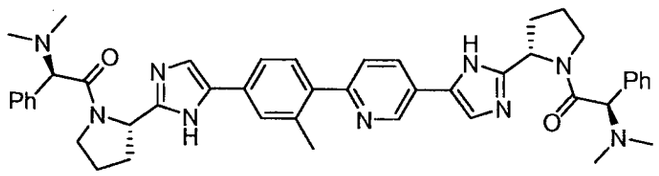
(m, 4H). [Nota: La señal para la pirrolidina NH aparece en la región de 3.22-2.80 y es demasiado amplia como para hacer una designación de desplazamiento químico].

LC (Cond. 1): RT = 0.84 min.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{26}H_{30}N_7$ 440.26; encontrado 440.50.

Ejemplo 136

(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-metilfenil)-3-piridinil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina



El ejemplo 136 (sal TFA) se sintetizó a partir de 136f de acuerdo con la preparación del ejemplo 132 a partir de 132e.

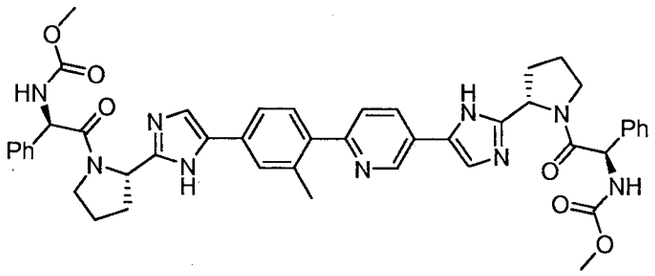
1.05 min. (Cond. 1); >98%.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{46}H_{52}N_9O_2$: 762.42, encontrado: 762.77.

HRMS: Análisis calculado para $[M+H]^+$ $C_{46}H_{52}N_9O_2$: 762.4244; encontrado 762.4243.

Ejemplo 138

((1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo



El ejemplo 138 se preparó de manera similar a partir de la pirrolidina 136f y *Extremo*-4.

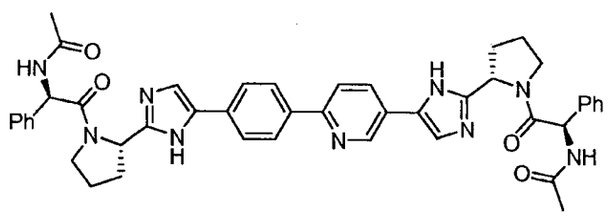
1.60 min (Cond. 1); >98%.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{46}H_{48}N_9O_6$: 822.37; encontrado 822.74.

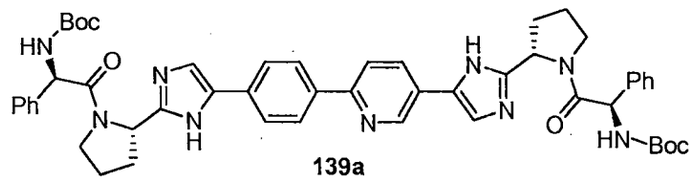
HRMS: Análisis calculado para $[M+H]^+$ $C_{46}H_{48}N_9O_6$: 822.3728; encontrado 822.3760.

Ejemplo 139

N-((1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-acetamido-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-3-piridinil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)acetamida



Ejemplo 139, etapa a



139a

HATU (99.8 mg, 0.262 mmoles) se añadió a una mezcla de 132e (54.1 mg, 0.127 mmoles), ácido (*R*)-2-(*t*-butoxicarbonilamino)-2-fenilacético (98.5 mg, 0.392 mmoles) y *i*-Pr_2EtN (100 µL, 0.574 moles), y la mezcla de reacción se agitó durante 70 min. El componente volátil se removió al vacío, y el residuo se purificó mediante una HPLC de fase inversa (H_2O/MeOH/TFA), cuando el eluto de HPLC se trató con un exceso de NH_3 2.0 N/MeOH antes de la remoción del componente volátil al vacío. el material resultante se dividió entre CH_2Cl_2 y agua, y la fase acuosa se extrajo con CH_2Cl_2 (2x). La fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró al vacío. El carbamato 139a se obtuvo como una película blanca de espuma (832.3 mg).

LC (Cond. 1): RT = 1.97 min; >95% de índice de homogeneidad.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{51}H_{58}N_9O_6$: 892.45; encontrado 892.72.

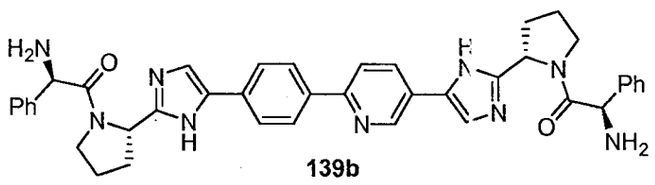
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Ejemplo 139b, etapa b



139b

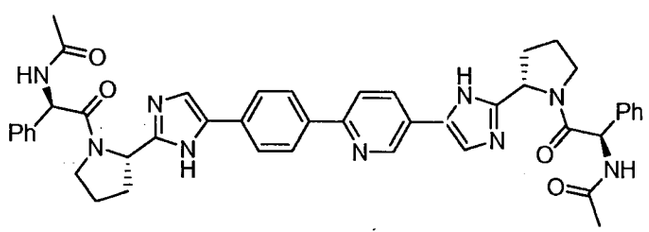
El carbamato 139a se desprotegió a la amina 139b usando el procedimiento descrito para la preparación de la pirrolidina 132e a partir de 132d.

LC (Cond. 1): RT = 1.37 min; >95% de índice de homogeneidad.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{42}N_9O_2$: 692.35; encontrado 692.32.

Ejemplo 139

N-((1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-acetamido-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-3-piridinil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)acetamida



Anhídrido acético (20 µL, 0.212 mmoles) se añadió a una solución en DMF (1.5 mL) de 139b (31.2 mg, 0.045 mmoles), y la mezcla de reacción se agitó durante 1 hora. Se añadió NH_3/MeOH (1.0 ML de 2N) a la mezcla de reacción y se continuó agitando durante 100 min. El componente volátil se removió

al vacío y el material crudo resultante se purificó mediante una HPLC de fase inversa (H_2O/MeOH/TFA) para dar la sal TFA del ejemplo 139 como un sólido amarillo claro (24.1 mg).

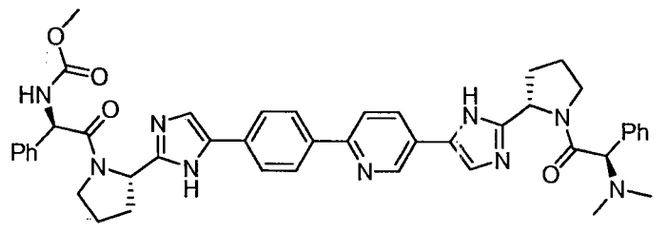
LC (Cond. 1): RT = 1.53 min; >98% de índice de homogeneidad.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{45}H_{46}N_9O_4$: 776.37; encontrado 776.38.

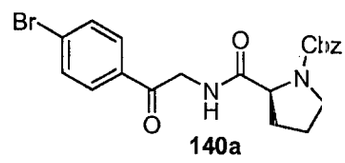
HRMS: Análisis calculado para $[M+H]^+$ $C_{45}H_{46}N_9O_4$: 776.3673; encontrado 776.3680.

Ejemplo 140

((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirrinidil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo



Ejemplo 140, etapa a



140a

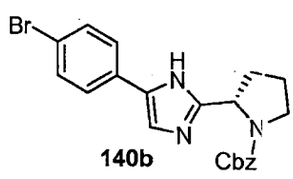
HATU (19.868 g, 52.25 mmoles) se añadió a una

mezcla heterogénea de *N*-Cbz-L-prolina (12.436 g, 49.89 mmoles) y la sal HCl de 2-amino-1-(4-bromofenil)-etanona (12.157 g, 48.53 mmoles) en DMF (156 mL). La mezcla se bajó en un baño de hielo-agua, e inmediatamente después se añadió *N,N*-diisorpopiletilamina (27 mL, 155 mmoles) por goteo a ésta durante 13 min. Después de que la adición de la base se completó, el baño de enfriamiento de retiró y la mezcla de reacción se agitó durante 50 minutos más. El componente volátil se removió al vacío; se añadió agua (125 mL) al sólido crudo resultante y se agitó durante aproximadamente 1 hora. El sólido blanquecino se filtró y se lavó con agua copiosa, y se secó al vacío para dar la cetoamida 140a como un sólido blanco (20.68 g). ^{1}H RMN (DMSO-d_6, δ = 2.5 ppm; 400 MHz): 8.30 (m, 1H), 7.91 (m, 2H), 7.75 (d, J = 8.5, 2H), 7.38-7.25 (m, 5H), 5.11-5.03 (m, 2H), 4.57-4.48 (m, 2H), 4.33-4.26 (m, 1H), 3.53-3.36 (m, 2H), .2.23-2.05 (m, 1H), 1.94-1.78 (m, 3H).

LC (Cond. 1): RT = 1.65 min; 98% de índice de homogeneidad.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{21}H_{22}BrN_2O_4$: 445.08; encontrado 445.31.

Ejemplo 140, etapa b



140b

La cetoamida 140a (10.723 g, 24.08 mmoles) se convirtió en 140b de acuerdo con el procedimiento descrito para la síntesis del carbamato 132c, con la excepción de que el material crudo se purificó mediante cromatografía por vaporización (gel de sílice; 50% de EtOAc/hexanos). El bromuro 140b se recuperó como una espuma blanquecina (7.622 g). ^{1}H RMN (DMSO-d_6, δ = 2.5 ppm; 400 MHz): 12.23/12.04/11.97 (m, 1H), 7.73-6.96 (m, 10H), 5.11-4.85 (m, 3H), 3.61 (m, 1H), 3.45 (m, 1H), 2.33-184 (m, 4H).

LC (Cond. 1): RT = 1.42 min; >95% de índice de homogeneidad.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{21}H_{21}BrN_3O_2$: 426.08; encontrado 426.31.

HRMS: Análisis calculado para $[M+H]^+$ $C_{21}H_{21}BrN_3O_2$: 426.0817; encontrado: 426.0829.

La pureza óptica de 140b se evaluó usando los siguientes métodos de HPLC quiral, y un ee de 99% fue observado.

Columna: Chiralpak AD, 10 um, 4.6 x 50 mm.

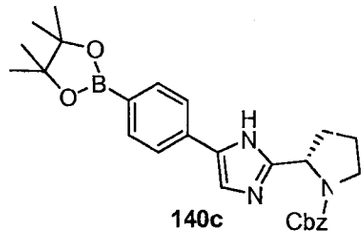
Solvente: 20% de etanol/heptano (isocrático).

Velocidad de flujo: 1 ml/min.

Longitud de onda: 254 nm.

Tiempo de retención relativo: 1.82 min (*R*), 5.23 min (*S*).

Ejemplo 140, etapa c



140c

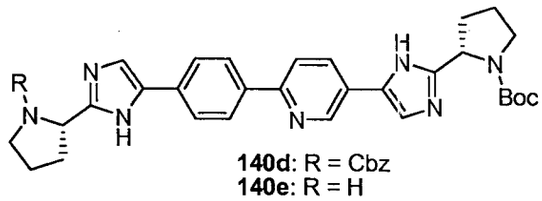
$Pd(Ph_3P)_4$ (208 mg, 0.180 mmoles) se añadió a un tubo de presión que contenía una mezcla de bromuro 140b (1.80 g, 4.22 mmoles), bis(pinacolato)diboro (2.146 g, 8.45 mmoles), KOAc (1.8 g, 11.0 mmoles) y 1,4-dioxano (34 mL). El matraz de reacción se purgó con nitrógeno, se tapó y se calentó con un baño de aceite a 80°C durante 23 horas. El componente volátil se removió al vacío, y el residuo se dividió cuidadosamente entre CH_2Cl_2 (70 mL) y un medio acuoso (22 mL de agua + 5 mL de solución saturada de $NaHCO_3$). La capa acuosa se extrajo con CH_2Cl_2, y la fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró al vacío. el residuo aceitoso se cristalizó a partir de EtOAc/hexanos para dar dos cultivos del boronato 140c como un sólido amarillo (1.52 g). El licor madre se evaporó al vacío y el material resultante se purificó mediante cromatografía por vaporización (gel de sílice: 20-35% de EtOAc/CH_2Cl_2) para dar 140c adicional como un

sólido blanquecino, que contenía pinacol residual (772 mg).

LC (Cond. 1): RT = 1.95 min.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{27}H_{33}BN_3O_4$: 474.26; encontrado 474.31.

Ejemplo 140, etapas d-e



140d: R = Cbz
140e: R = H

El bromuro de arilo 132c fue acoplado con el boronato 140c para dar 140d usando el mismo procedimiento que el descrito para la síntesis del diario 132d. La muestra contiene la versión desbromo de 132c como una impureza. Se procedió a la siguiente etapa sin purificación adicional.

LC (Cond. 1): RT = 1.72 min; ~85% de índice de homogeneidad.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{42}N_7O_4$: 660.33; encontrado 660.30.

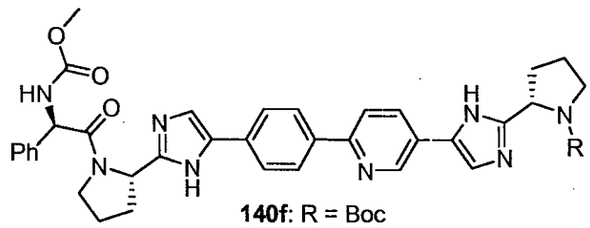
Una mezcla de 10% de Pd/C (226 mg), biarilo 140d (1.25 g) y MeOH (15 mL) se agitó bajo un balón de hidrógeno durante ~160 horas, cuando se reabasteció el suministro de hidrógeno periódicamente según se requiriera. La mezcla de reacción se filtró

a través de una almohadilla de tierra diatomácea (Celite®), y el filtrado se evaporó al vacío para dar el crudo 140e como una espuma amarillenta-café (911 mg). Se procedió a la siguiente etapa sin purificación adicional.

LC (Cond. 1): RT = 1.53 min.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{30}H_{36}N_7O_2$: 526.29; encontrado 526.23.

Ejemplo 140, etapas f-g



140f: R = Boc
140g: R = H

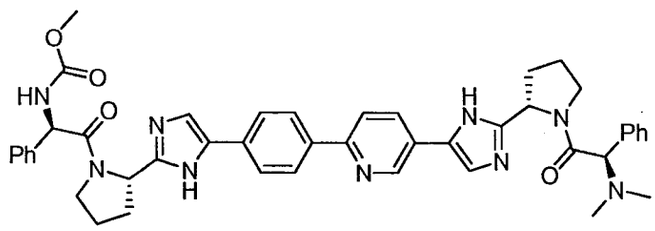
La pirrolidina 140g se preparó a partir de 140e y *Extremo*-4, por medio de la intermediación del carbamato 140f, al emplear secuencialmente los protocolos de formación de amida y desprotección con Boc usados en la síntesis del ejemplo 132.

LC (Cond. 1): RT = 1.09 min; ~94% de índice de homogeneidad.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{35}H_{37}N_8O_3$: 617.30; encontrado 617.38.

Ejemplo 140

((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-piridinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo



La sal TFA del ejemplo 140 se sintetizó a partir de pirrolidina 140g y *Extremo*-1 usando el procedimiento descrito para la preparación del ejemplo 132 a partir del intermediario 132e.

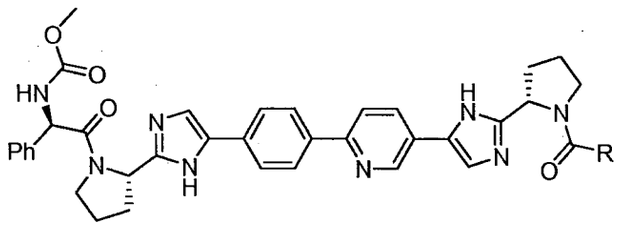
1.15 min (Cond. 1); >98% de índice de homogeneidad.

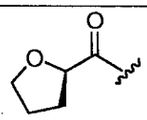
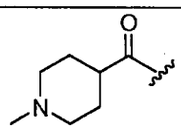
LC/MS: Análisis calculado para $[M+H]^+$ $C_{45}H_{40}N_7O_4$: 778.38; encontrado 778.48.

HRMS: Análisis calculado para $[M+H]^+$ $C_{45}H_{40}N_7O_4$: 778.3829; encontrado 778.3849.

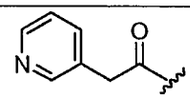
La sal TFA del ejemplo 141-143 se sintetizó a partir del intermediario 140g y reactivos adecuados de una manera similar.

Ejemplos 141-143



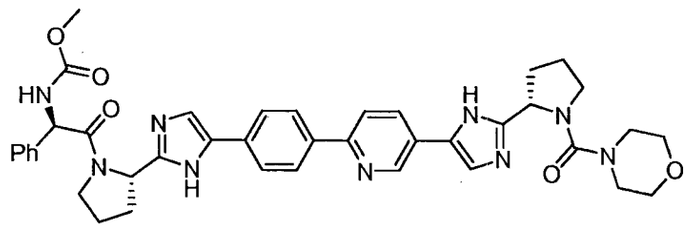
Ejemplo	Nombre del Compuesto		RT (LC-Cond.); índice de % de homogeneidad; datos de MS
141	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-2-piridinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)etil)carbamato de metilo		1.15 min (Cond. 1); >98% LC/MS: Anal. Calcd. para: $[M+H]^+$ $C_{40}H_{43}N_8O_5$: 715.34; encontrado 715.44 HRMS: Anal. Calcd. para: $[M+H]^+$ $C_{40}H_{43}N_8O_5$: 715.3356; encontrado 715.3381
142	((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((1-metil-4-piperidinil)carbonil)-2-pirrolidinil)-1H-imidazol-		1.07 min (Cond. 1); >98% LC/MS: Anal. Calcd. para: $[M+H]^+$ $C_{42}H_{48}N_9O_4$: 742.38; encontrado 742.48

000555

	5-il)-2-piridinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		HRMS: Anal. Calcd. para: $[M+H]^+$ $C_{42}H_{48}N_9O_4$: 742.3829; encontrado 742.3859
143	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4-(5-(2-((2S)-1-(3-piridinilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-piridinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		1.09 min (Cond. 1); >98% LC/MS: Anal. Calcd. para: $[M+H]^+$ $C_{42}H_{42}N_9O_4$: 736.34; encontrado 736.44 HRMS: Anal. Calcd. para: $[M+H]^+$ $C_{42}H_{42}N_9O_4$: 736.3360; 736.3344

Ejemplo 144

((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-(4-morfolinilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-2-piridinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo



Una solución en DMF (1.5 mL) de cloruro de morfolin-4-carbonilo (8.5 mg, 0.057 mmoles) se añadió a una mezcla de *i*-Pr_2EtN (20 µL, 0.115 mmoles) y 140g (27.3 mg, 0.044 mmoles), y se agitó durante 100 min. El componente volátil se removió al vacío y el residuo se purificó mediante

una HPLC de fase inversa (H_2O/MeOH/TFA) para dar la sal TFA del ejemplo 144 como una espuma amarilla (34.6 mg).

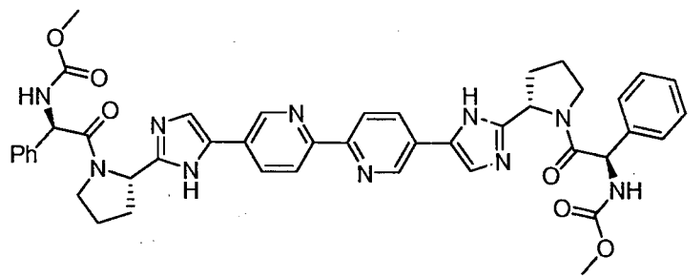
1.17 min (Cond. 1); >98%.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{44}N_9O_5$: 730.35; encontrado 730.42.

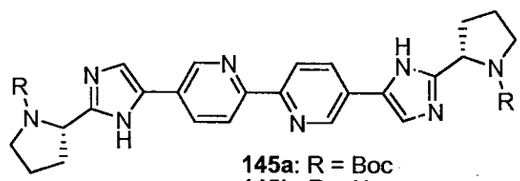
HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{44}N_9O_5$: 730.3465; encontrado 730.3477.

Ejemplo 145

(2,2'-bipiridin-5,5'-diilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))biscarbamato de dimetilo



Ejemplo 145, etapas a-b



145a: R = Boc
145b: R = H

$Pd(Ph_3P)_4$ (9.6 mg, 0.008 mmoles) y LiCl (28 mg, 0.67 mmoles) se añadieron a una mezcla de bromuro de arilo 132c (98.7 mg, 0.251 mmoles) y hexametilestaño (51.6 mg, 0.158 mmoles), y se calentaron a 80°C durante ~3 días. El componente volátil se removió al vacío y el material crudo

resultante se purificó mediante cromatografía por vaporización (gel de sílice; 0-10% de MeOH/EtOAc) seguido por una HPLC de fase inversa (H_2O/MeOH/TFA). El eluto de HPLC se neutralizó con un exceso de NH_3 2.0N/MeOH, y el componente volátil se removió al vacío. El residuo se dividió entre CH_2Cl_2 y agua, y la fase acuosa se lavó con CH_2Cl_2 (2x). La fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró al vacío para dar el carbamato 145a como una película de aceite (8.7 mg).

LC (Cond. 1): RT = 1.68 min; >98% de índice de homogeneidad.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{34}H_{43}N_8O_4$: 627.34; encontrado 627.47.

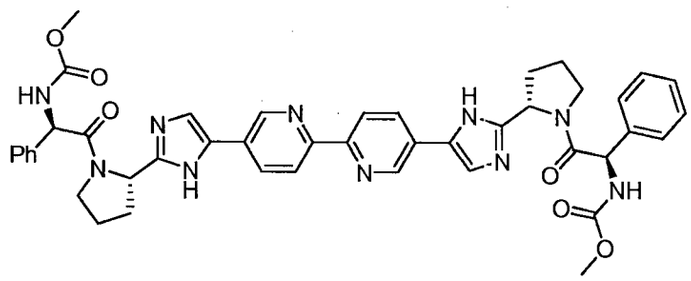
El carbamato 145a se elaboró a la pirrolidina 145b de acuerdo con la preparación de 132e a partir de 132d. ^1H RMN (DMSO-d_6, δ = 2.5 ppm; 400 MHz): 12.02 (br de señal, 2H), 9.04 (d, J = 1.6, 2H), 8.34 (d, J = 8.3, 2H), 8.20 (dd, J = 8.3, 2.3, 2H), 7.67 (br s, 1H), 4.21 (m, 2H), 3.00-2.85 (m, 4H), 2.12-2.04 (m, 2H), 1.95-1.68 (m, 6H). [Nota: La señal de pirrolidina-NH no se observó].

LC (Cond. 1): RT = 1.17 min; >98% de índice de homogeneidad.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{24}H_{27}N_8$: 427.24; encontrado 427.13.

Ejemplo 145

(2,2'-bipiridin-5,5'-diilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))biscarbamato de dimetilo



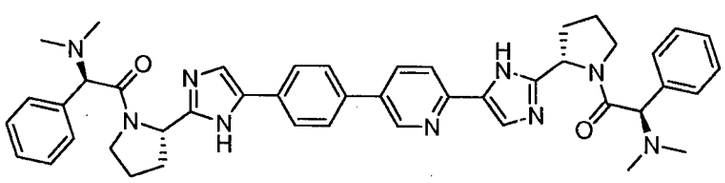
El ejemplo 145 (sal TFA) se sintetizó a partir de 145b de acuerdo con la preparación del ejemplo 132 a partir de 132e.

LC (Cond. 1): RT = 1.63 min; 98% de índice de homogeneidad.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{45}N_{10}O_6$: 809.35; encontrado 809.40.

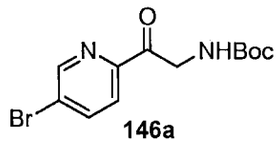
Ejemplo 146

(1R)-2-((2S)-2-(5-(5-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-2-piridinil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina



000559

Ejemplo 146, etapa a



146a

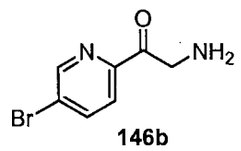
n-BuLi (12.0 mL de 2.5M/hexanos, 30 mmoles) se añadió por goteo durante 15 minutos a una semi-solución en tolueno enfriada (-78°C) (300 mL) de 2,5-dibromopiridina (6.040 g, 25.5 mmoles), y se agitó durante 2.5 horas. Se añadió 2-(metoxi(metil)amino)-2-oxoetilcarbamato de *t*-butilo (2.809 g, 12.87 mmoles) en lotes durante 7 minutos, y se continuó agitando durante 1.5 horas a -78°C. El baño de -78°C fue reemplazado con un baño de -60°C, el cual se dejó calentar hasta -15°C durante 2.5 horas. La reacción se enfrió rápidamente con solución saturada de NH_4Cl (20 mL); y la mezcla se dejó descongelar a la temperatura ambiente y la capa orgánica se separó y se evaporó al vacío. El material crudo resultante se purificó mediante cromatografía por vaporización (gel de sílice; 15% de EtOAc/hexanos) para dar un semisólido rojizo café, el cual se lavó con hexanos para remover el residuo de color. La piridina 146a fue recuperada como un sólido color ceniza (842 mg). ^1H RMN (DMSO-d_6, δ = 2.5 ppm; 400 MHz): 8.89 (d, J = 2.3, 1H), 8.30 (dd, J = 8.4, 2.4, 1H), 7.90 (d, J = 8.3, 1H), 7.03 (br t, J = 5.7; 0.88H), 6.63 (app br s, 0.12H), 4.55 (d, J = 5.8, 2H), 1.40/1.28 (dos app s, 7.83H + 1.17H).

000560

LC (Cond. 1): RT = 2.00 min; >95% de índice de homogeneidad.

LC/MS: Análisis calculado para $[M+Na]^+$ $C_{12}H_{15}BrNaN_2O_3$: 337.02; encontrado 337.13.

Ejemplo 146, etapa b



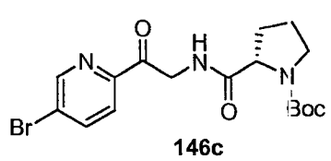
146b

HBr al 48% (1.0 mL) se añadió por goteo a una solución en dioxano (5.0 mL) del carbamato 146a (840 mg, 2.66 mmoles) durante 3 minutos, y la mezcla de reacción se agitó a temperatura ambiente durante 17.5 horas. El precipitado se filtró y se lavó con dioxano, y se secó al vacío para dar la amina y la sal HBr de 146b como un sólido blanquecino (672.4 mg; el equivalente molar exacto de la sal HBr no fue determinado). ^1H RMN (DMSO-d_6, δ = 2.5 ppm; 400 MHz): 8.95 (d, J = 2.3, 1H), 8.37 (dd, J = 8.4, 2.3, 1H), 8.2 (br s, 3H), 8.00 (d, J = 8.3, 1H), 4.61 (s, 2H).

LC (Cond. 1): RT = 0.53 min.

LC/MS: Análisis calculado para $[M+H]^+$ $C_7H_8BrN_2O$: 214.98; encontrado 215.00.

Ejemplo 146, etapa c



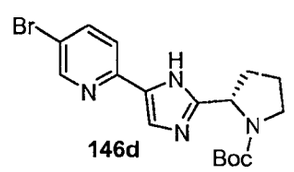
146c

i-Pr_2EtN (2.3 mL, 13.2 mmoles) se añadió por goteo durante 15 minutos a una mezcla heterogénea de la amina 146b (1.365 g), (*S*)-Boc-prolina (0.957 g, 4.44 mmoles) y HATU (1.70 g, 4.47 mmoles) en DMF (13.5 mL), y se agitó a temperatura ambiente durante 1 hora. El componente volátil se removió al vacío y el residuo se dividió entre EtOAc (40 mL) y un medio acuoso (20 mL de agua + 1 ml de solución saturada de $NaHCO_3$). La capa acuosa se lavó con EtOAc (20 mL), y la fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró al vacío. El material crudo resultante se purificó mediante cromatografía por vaporización (gel de sílice; 40-50% de EtOAc/hexanos) para dar la cetoamida 146c como un sólido amarillo pálido (1.465 g). ^1H RMN (DMSO-d_6, δ = 2.5 ppm; 400 MHz): 8.90 (d, J = 2.3, 1H), 8.30 (dd, J = 8.5, 2.4, 1H), 8.01-8.07 (m, 1H), 7.90 (d, J = 8.3, 1H), 4.6 (m, 1H), 4.64 (dd, J = 19.1, 5.5, 1H); 4.19 (m, 1H), 3.39 (m, 1H), 3.32-3.26 (m, 1H), 2.20-2.01 (m, 1H), 1.95-1.70 (m, 3H), 1.40/1.35 (dos app s, 9H).

LC (Cond. 1): RT = 1.91 min.

LC/MS: Análisis calculado para $[M+Na]^+$ $C_{17}H_{22}BrN_3NaO_4$: 434.07; encontrado 433.96.

Ejemplo 146, etapa d



146d

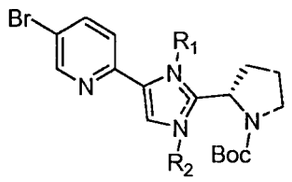
Una mezcla de la cetoamida 146c (782.2 mg, 1.897 mmoles) y NH_4OAc (800 mg, 10.4 mmoles) en xilenos se calentó con un microcndas (140°C) durante 90 min. El componente volátil se removió al vacío y el residuo se dividió cuidadosamente entre CH_2Cl_2 y agua, cuando se añadió suficiente solución de $NaHCO_3$ saturada como para neutralizarla. La fase acuosa se extrajo con CH_2Cl_2 (2x), y la fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró al vacío. El material crudo resultante se purificó mediante cromatografía por vaporización (gel de sílice; 50% de CH_2Cl_2/EtOAc) para dar el imidazol 146d como un sólido blanquecino (552.8 mg). ^1H RMN (DMSO-d_6, δ = 2.5 ppm; 400 MHz): 12.49/12.39/12.15/12.06 (br s, 1H), 8.62 (app br s, 0.2H), 8.56 (d, J = 2, 0.8H), 8.02 (br d, J = 8.5, 0.2H), 7.97 (br d, J = 7.8, 0.8H), 7.77 (d, J = 8.6, 0.8H), 7.72 (d, J = 8.6, 0.2H), 7.61-7.49 (m, 1H), 4.93-4.72 (m, 1H), 3.53 (m, 1H), 3.41-3.32 (m, 1H), 2.33-1.77 (m, 4H), 1.39/1.14 (app br s, 3.7H+5.3H).

LC (Cond. 1): RT = 1.67 min; >95% de índice de homogeneidad.

LC/MS: Análisis calculado para $[M+Na]^+$ $C_{17}H_{21}BrN_4NaO_2$: 415.08; encontrado 415.12.

000563

Ejemplo 146, etapa e

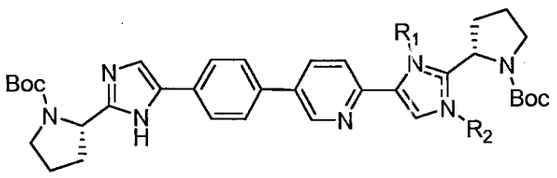


NaH (60%; 11.6 mg, 0.29 mmoles) se añadió en un lote a una mezcla heterogénea del imidazol 146d (80 mg, 0.203 mmoles) y DMF (1.5 mL), y se agitó a la condición ambiente durante 30 min. Se añadió por goteo SEM-Cl (40 µL, 0.226 mmoles) durante 2 minutos a la mezcla de reacción anterior, y se continuó agitando durante 14 horas. El componente volátil se removió al vacío y el residuo se dividió entre agua y CH_2Cl_2. La capa acuosa se extrajo con CH_2Cl_2, y la fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró al vacío. El material crudo se purificó mediante una cromatografía por vaporización (gel de sílice; 20% de EtOAc/hexanos) para dar 146e como un aceite viscoso incoloro (87.5 mg). La regioquímica exacta de 146e no fue determinada. ^1H RMN ($CDCl_3$, δ = 7.4 ppm; 400 MHz): 8.53 (d, J = 2.2, 1H), 7.90-7.72 (m, 2H), 7.52 (s, 1H), 5.87 (m, 0.46H), 5.41 (m, 0.54H), 5.16 (d, J = 10.8, 1H), 5.03-4.85 (m, 1H), 3.76-3.42 (m, 4H), 2.54-1.84 (m, 4H), 1.38/1.19 (br s, 4.3H+4.7 H), 0.97-0.81 (m, 2H), -0.03 (s, 9H).

LC (Cond. 1): RT = 2.1 min.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{23}H_{36}BrN_4O_3Si$: 523.17; encontrado 523.24.

Ejemplo 146, etapa f



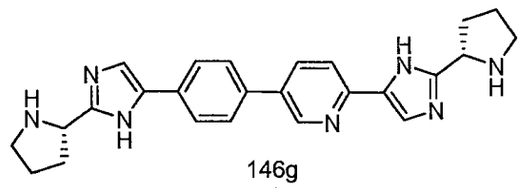
$Pd(Ph_3P)_4$ (24.4 mg, 0.021 mmoles) se añadió a una mezcla del imidazol 146e (280 mg, 0.535 mmoles), 1c (241.5 mg, 0.55 mmoles) y $NaHCO_3$ (148.6 mg, 1.769 mmoles) en 1,2-dimetoxietano (4.8 mL) y agua (1.6 mL). La mezcla de reacción se enjuagó con nitrógeno, se calentó con un baño de aceite A 80°C durante ~24 horas y después el componente volátil se removió al vacío. El residuo se dividió entre CH_2Cl_2 y agua, y la fase orgánica se secó ($MgSO_4$), se filtró y se concentró al vacío. El material crudo se purificó mediante un sistema Biotage (gel de sílice; 75-100% de EtOAc/hexanos) seguida por una HPLC de fase inversa (H_2O/MeOH/TFA). El eluto de HPLC se neutralizó con NH_3 2M/MeOH y se evaporó al vacío, y el residuo se dividió entre agua y CH_2Cl_2. La capa orgánica se secó ($MgSO_4$), se filtró y se concentró al vacío para dar 146f como una espuma blanca (162 mg).

LC (Cond. 1): RT = 2.1 min.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{58}N_7O_5Si$: 756.43; encontrado 756.55.

000565

Ejemplo 146, etapa g



146g

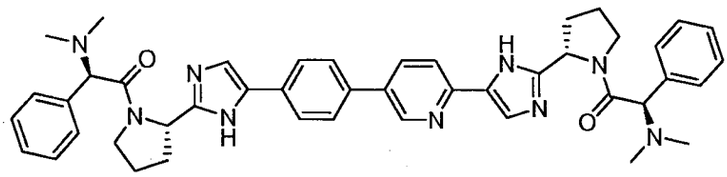
El carbamato 146f (208 mg, 0.275 mmoles) se trató con 25% de TFA/CH_2Cl_2 (4.0 mL) y se agitó a temperatura ambiente durante 10 horas. El componente volátil se removió al vacío y el residuo se hizo primero base libre mediante MCX (lavado con MeOH; elución con NH_3 2.0M/MeOH) y luego se purificó mediante una HPLC de fase inversa (H_2O/MeOH/TFA), y el material resultante se hizo base libre de nuevo (MCX) para dar la pirrolidina 146g como una película de aceite (53.7 mg). ^1H RMN (DMSO-d_6, δ = 2.5 ppm; 400 MHz): 1.88 (app br s, 2H), 8.83 (d, J = 2.1, 1H), 8.07 (dd, J = 8.3/2.3, 1H0, 7,87 (d, J = 8.5, 1H), 7.84 (d, J = 8.3, 2H), 7.71 (d, J = 8.3, 2H), 7.55 (s, 1H), 7.50 (br s, 1H), 4.18 (m, 2H), 3.00-2.94 (m, 2H), 2.89-2.83 (m, 2H), 2.11-2.02 (m, 2H), 1.95-1.86 (m, 2H), 1.83-1.67 (m, 4H).

LC (Cond. 1): RT = 0.95 min; >98% de índice de homogeneidad.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{25}H_{28}N_7$: 426.24; encontrado 426.27.

Ejemplo 146

(1R)-2-((2S)-2-(5-(5-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-2-piridinil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina



El ejemplo 146 (sal TFA) se sintetizó a partir de la pirrolidina 146g de acuerdo con la preparación del ejemplo 132 a partir del intermediario 132e.

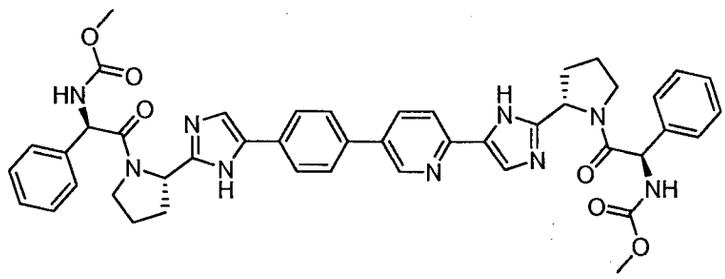
LC (Cond. 1): RT = 1.42 min; 96.5% de índice de homogeneidad.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{45}H_{50}N_9O_2$: 748.41; encontrado 748.57.

HRMS: Análisis calculado para $[M+H]^+$ $C_{45}H_{50}N_9O_2$: 748.4087; encontrado 748.4100.

Ejemplo 147

((1R)-2-((2S)-2-(5-(5-(4-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-2-piridinil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo



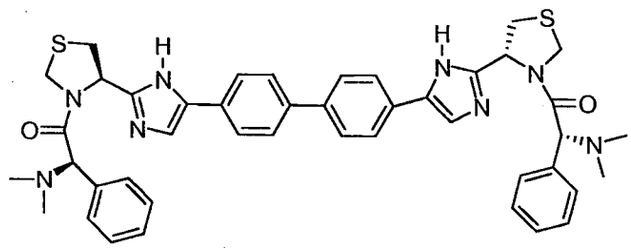
La sal TFA del ejemplo 147 se preparó de manera similar a partir del intermediario 146g usando *Extremo*-4.

LC (Cond. 1): RT = 1.66 min; 95% de índice de homogeneidad.

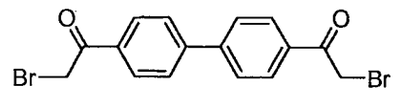
LC/MS: Análisis calculado para $[M+H]^+$ $C_{45}H_{46}N_9O_6$: 808.36; encontrado 808.55.

Ejemplo 148

(1R,1'R)-2,2'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(4R)-1,3-tiazolidin-4,3-diil))bis(N,N-dimetil-2-oxo-1-feniletanamina)



Ejemplo 148, etapa a

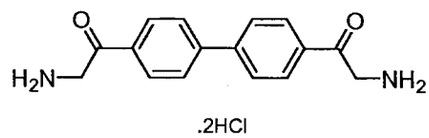


Una solución de bromuro (1.3 mL, 25.0 mmoles) en 15 mL de ácido acético glacial se añadió por goteo a una solución de 4-4'-diacetilbifenilo (3.0 g, 12.5 mmoles) en 40 mL de ácido acético a 50°C. Después de concluir la adición la mezcla se agitó a temperatura ambiente durante la noche. El producto precipitado se filtró y se recristalizó a partir de cloroformo para dar 1,1'-(bifenil-4,4'-diil)bis(2-bromoetanona) (3.84 g, 77.5%) como un sólido blanco.

^{1}H RMN (500 MHz, CLOROFORMO-D) δ ppm 8.09 (4 H, d, *J* = 7.93 Hz), 7.75 (4 H, d, *J* = 8.24 Hz), 4.47 (4 H, s).

Nominal/LRMS - Análisis calculado para 369.07 encontrado; $(M+H)^+$ - 397.33, $(M-H)^-$ - 395.14.

Ejemplo 148, etapa b



.2HCl

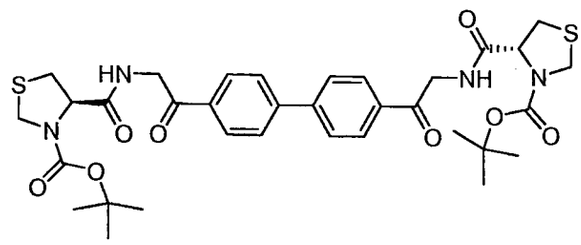
Diformilamida de sodio (3.66 g, 38.5 mmoles) se añadió a una suspensión de 1,1'-(bifenil-4,4'-diil)bis(2-bromoetanona) (6.1 g, 15.4 mmoles) en 85 mL de acetonitrilo. La mezcla se calentó a reflujo durante 4 horas y se concentró bajo presión reducida. El residuo se suspendió en 300 mL de HCl al 5% en etanol y se calentó a reflujo durante 3.5 horas.

La reacción se enfrió a la temperatura ambiente y se puso en el congelador durante 1 hora. El sólido precipitado se recogió, se lavó con 200 mL de 1:1 de etanol/éter seguido por 200 mL de pentano, y se secó al vacío para dar diclorhidrato de 1,1'-(bifenil-4,4'-diil)bis(2-aminoetanona) (4.85 g, 92%). Se pasó a la siguiente etapa sin purificación.

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 8.47-8.55 (4H, m) 8.11-8.17 (4 H, m) 8.00 (4 H, d, *J* = 8.42 Hz) 4.59-4.67 (4 H, m).

LCMS - Phenomenex C-18 3.0 x 50 mm, 0 a 100% de B durante gradiente de 4.0 minutos, 1 minuto de tiempo de retención, A = 10% de metanol, 90% de agua, 0.1% de TFA, B = 90% de metanol, 10% de agua, 0.1% de TFA, t_g = 0.44 minutos. Análisis calculado para $C_{16}H_{16}N_2O_2$ 268.31 encontrado; 269.09 $(M+H)^+$.

Ejemplo 148, etapa c



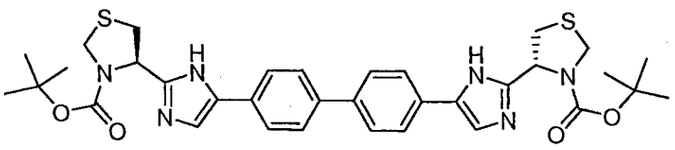
A una solución agitada de diclorhidrato de 1,1'-(bifrenil-4,4'-diil)bis(2-aminoetanona) (0.7 g, 2.1 mmoles), N-(*ter*-butoxicarbonil)-L-tioprolina (0.96 g, 4.2 mmoles) y HATU (1.68 g, 4.4 mmoles) en 14 mL de DMF se le añadió diisopropiletilamina (1.5 mL, 8.4 mmoles) por goteo durante 5

minutos. La solución amarillo claro resultante se agitó a temperatura ambiente durante la noche (14 horas) y se concentró bajo presión reducida. El residuo se dividió entre 20% de metanol/cloroformo y agua. La fase acuosa se lavó una vez con 20% de metanol/cloroformo. Los orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron bajo presión reducida. El producto crudo se cromatografió en gel de sílice mediante elución por gradiente con 10-50% de acetato de etilo/CH_2Cl_2 para dar 4,4'-(2,2'-(bifenil-4,4'-diil)bis(2-oxoetan-2,1-diil))bis(azandiil)bis(oxometilen)ditiazolidin-3-carboxilato de (4S,4'S)-*ter*-butilo (0.39 g, 27%) como una espuma anaranjada.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8.38 (2 H, s) 8.12 (4 H, d, *J* = 8.56 Hz) 7.94 (4 H, d, *J* = 8.56 Hz) 4.60-4.68 (4 H, m) 4.33-4.38 (2 H, m) 3.58-3.68 (2 H, m) 3.38 (2 H, s) 3.08-3.18 (2 H, m) 1.40 (18 H, s).

LCMS - Sunfire C-18 4.6 x 50 mm, 0 a 100% de B durante gradiente de 4.0 minutos, 1 minuto de tiempo de retención, A = 10% de metanol, 90% de agua, 0.1% de TFA, B = 90% de metanol, 10% de agua, 0.1% de TFA, t_g = 3.69 minutos, Análisis calculado para $C_{34}H_{42}N_4O_8S_2$ 698.85 encontrado; 699.12 $(M+H)^+$.

Ejemplo 148, etapa d

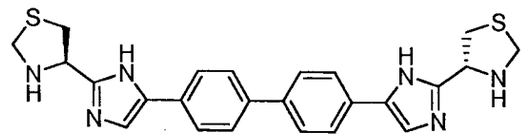


4,4'-(5,5'-(bifenil-4,4'-diil)bis(1H-imidazol-5,2-diil)ditiazolidin-3-carboxilato de (4S,4'S)-*ter*-butilo (0.39 g, 0.56 mmoles) y acetato de amonio (0.43 g, 5.6 mmoles) se suspendieron en 8 mL de o-xileno en un recipiente de reacción de microondas. La mezcla se calentó bajo condiciones de microondas estándares a 140°C durante 70 minutos y se concentró bajo presión reducida. El residuo se disolvió en 30 mL de metanol/cloroformo al 20% y se lavó con 10% de $NaHCO_3$ (acuoso). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró bajo presión reducida. El producto crudo se sometió a cromatografía en gel de sílice mediante elución por gradientes con 1-6% de metanol/CH_2Cl_2 para dar 4,4'-(5,5'-(bifenil-4,4'-diil)bis(1H-imidazol-5,2-diil)ditiazolidin-3-carboxilato de (4S,4'S)-*ter*-butilo (0.15 g, 41%) como un sólido amarillo. ^1H RMN (500 MHz, DMSO-d_6) δ ppm 12.02 (2 H, s), 7.70-7.88 (10 H, m) 5.28-5.37 (2 H, m) 4.68 (2 H, d, J = 9.16 Hz) 4.47-4.55 (2 H, m) 3.46 (2 H, s) 3.23 (2 H, s) 1.26-1.43 (18 H, m).

LCMS-Luna C-18 3.0 x 50 mm, 0 a 100% de B durante gradiente de 3.0 minutos, 1 minuto de tiempo de retención, A = 5% de acetonitrilo, 95% de agua, 10 mm de acetato de

amonio, B = 95% de acetonitrilo, 5% de agua, 10 mm de acetato de amonio, t_R = 1.96 min, análisis calculado para $C_{34}H_{40}N_6O_4S_2$ 660.85 encontrado; 661.30 $(M+H)^+$, 659.34 (M-H).

Ejemplo 148, etapa e



.4HCl

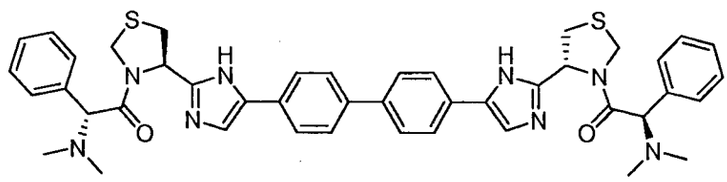
A una solución de 4,4'-(5,5'-(bifenil-4,4'-diil)bis(1H-imidazol-5,2-diil)ditiazolidin-3-carboxilato de (4S,4'S)-*ter*-butilo en 1 mL de dioxano se le añadió 0.3 mL de una solución 4.0M de HCl en dioxano. La reacción se agitó durante 3 horas a temperatura ambiente y se concentró bajo presión reducida. El sólido pardo resultante se secó al vacío para dar tetraclorhidrato de 4,4'-bis(2-((S)-tiazolidin-4-il)-1H-imidazol-5-il)bifrenilo (0.12 g, 100%) como un sólido amarillo.

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.09 (2 H, s) 8.01 (4 H, d, *J* = 8.55 Hz) 7.90 (4 *J* = 9.46 Hz) 3.48-3.54 (2 H, m), 3.35-3.41 (2 H, m).

LCMS-Luna C-18 3.0 x 50 mm, 0 a 100% de B durante gradiente de 40 minutos, 1 minuto de tiempo de retención, A = 5% de acetonitrilo, 95% de agua, 10 mm de acetato de amonio, B = 95% de acetonitrilo, 5% de agua, 10 mm de acetato de amonio, t_R = 1.70 min., análisis calculado para $C_{24}H_{24}N_6S_2$ 460.62 encontrado; 461.16 $(M+H)^+$, 459.31 $(M-H)^-$.

Ejemplo 148

(1R,1'R)-2,2'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(4R)-1,3-tiazolidin-4,3-diil))bis(N,N-dimetil-2-oxo-1-feniletanamina)



A una solución agitada de tetracloruro de (4,4'-bis(2-((S)-tiazolidin-4-il)-1H-imidazol-5-il)bifenilo (0.028 g, 0.046 mmoles), ácido (R)-2-(dimetilamino)-2-fenilacético (*Extremo*-1, 0.017 g, 0.0.10 mmoles), y HATU (0.039 g, 0.10 mmoles) en 2 mL de DMF se añadió diisopropiletilamina (0.05 mL, 0.28 mmoles). La reacción se agitó a temperatura ambiente durante la noche (16 horas) y se concentró bajo presión reducida. El producto crudo se purificó mediante HPLC preparativa de fase inversa para proporcionar (2R,2'R)-1,1'-((4S,4'S)-4,4'-(5,5'-(bifenil-4,4'-diil)bis(1H-imidazol-5,2-diil))bis(tiazolidin-4,3-diil))bis(2-(dimetilamino)-2-feniletanona), sal TFA (0.012 g, 21%).

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 7.59-7.91 (20 H, m) 5.62 (2 H, dd, J = 6.56, 2.59 Hz) 4.99 (2 H, d, J = 8.85 Hz) 4.82/4.35 (2 H, s) 4.22 (2 H, s) 3.42 (2 H, s) 3.25 (2 H, s) 2.35-2.61 (12H, m).

LCMS - Luna C-18 3.0 x 50 mm, 0 a 100% de B durante gradiente de 7.0 minutos, 1 minuto de tiempo de retención, A

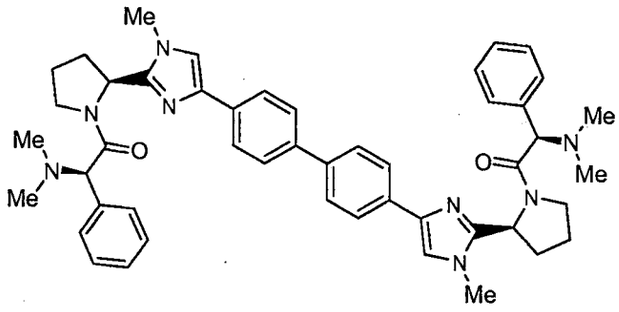
= 5% de acetonitrilo, 95% de agua, 10 mm de acetato de amonio, B = 95% de acetonitrilo, 5% de agua, 10 mm de fase móvil de acetato de amonio t_R = 3.128 min.

Nominal/LRMS - calculado para $C_{44}H_{46}N_8O_2S_2$ 783.03; encontrado 783.28 $(M+H)^+$.

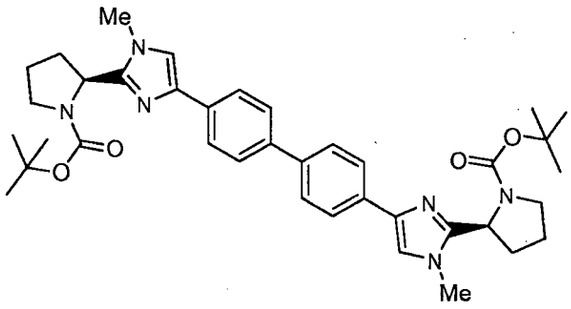
Preciso/HRMS - calculado para $C_{44}H_{47}N_8O_2S_2$ 783.3263; 783.3246 $(M+H)^+$.

Ejemplo 151

(1R,1'R)-2,2'-(4,4'-bifenildiilbis((1-metil-1H-imidazol-4,2-diil)(2S)-2,1-pirrolidindiil))bis(N,N-dimetil-2-oxo-1-feniletanamina)



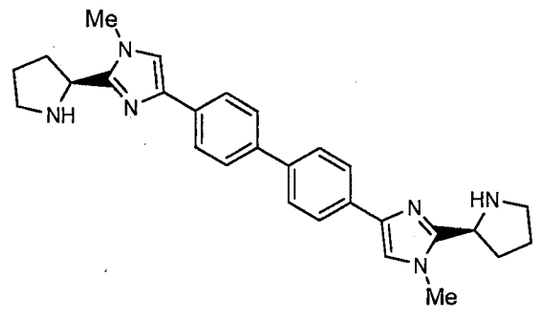
Ejemplo 151, etapa a



A una solución agitada de 1d, 2,2'-(4,4'-(bifenil-4,4'-diil)bis(1H-imidazol-4,2-diil))diporrolidin-1-carboxilato de (2S,2'S)-*ter*-butilo (100 mg, 0.16 mmoles) y

yodometano (40 µL, 0.16 mmoles) en CH_2Cl_2 (2 mL) se le añadió hidruro de sodio (40%) (21.2 mg, 0.352 mmoles). Después de 5 horas a temperatura ambiente, se concentró bajo presión reducida. El producto de reacción crudo 151a, 2,2'-(4,4'-(bifenil-4,4'-diil)bis(1-metil-1H-imidazol-4,2-diil))dipirrolidin-1-carboxilato de (2S,2'S)-*ter*-butilo (~90 mg) se pasó a la siguiente etapa sin purificación adicional (pureza ~85%) LCMS: Análisis calculado para: $C_{38}H_{48}N_6O_4$ 652.83; encontrado 653.51 $(M+H)^+$. Se debe reconocer que varios isómeros de metilación son posibles en esta reacción y no se hizo un intento por asignarlos.

Ejemplo 151, etapa b



151a, 2,2'-(4,4'-(bifenil-4,4'-diil)bis(1-metil-1H-imidazol-4,2-diil))dipirrolidin-1-carboxilato de (2S,2'S)-*ter*-butilo (100 mg, 0.153 mmoles) fue tratado con HCl 4M/dioxano (20 mL). Después de tres horas a temperatura ambiente, se concentró bajo presión reducida. El producto de reacción crudo, 2,4'-bis(1-metil-2-((S)-pirrolidin-2-il)-1H-imidazol-4-il)bifenilo (~110 mg, sal HCl) se pasó a la siguiente etapa sin purificación adicional (pureza ~85%)

LCMS: Análisis calculado para $C_{28}H_{32}N_6$ 452.59; encontrado 453.38 $(M+H)^+$. Varios isómeros de imidazol estuvieron presentes y se llevaron a la siguiente etapa.

Ejemplo 151

HATU (58.9 mg, 0.150 mmoles) se añadió a una mezcla de 151b, 4,4'-bis(1-metil-2-((S)-pirrolidin-2-il)-1H-imidazol-4-il)bifenilo (45.0 mg, 0.075 mmoles), $(i\text{-Pr})_2$EtN (78 µL, 0.451 mmoles) y *Extremo*-1, ácido (*R*)-2-(dimetilamino)-2-fenilacético (0.026 mg, 0.150 mmoles) en DMF (1.0 mL). La mezcla resultante se agitó a temperatura ambiente hasta que el acoplamiento se completara según se determina mediante el análisis LC/MS. La purificación se logró mediante HPLC preparativa de fase inversa (Waters-Sunfire 30 x 100 mm S5, detección a 220 nm, velocidad de flujo 30 mL/min, 0 a 90% de B durante 14 minutos; A = 90% de agua, 10% de ACN, 0.1% de TFA, B = 10% de agua, 90% de ACN, 0.1% de TFA) para proporcionar dos isómeros de 151, (2R,2'R)-1,1'-((2S,2'S)-2,2'-(4,4'-(bifenil-4,4'-diil)bis(1-metil-1H-imidazol-4,2-diil))bis(pirrolidin-2,1-diil))bis(2-(dimetilamino)-2-feniletanona), sales TFA.

Isómero 1: *(1R,1'R)-2,2'-(4,4'-bifenildiilbis(1-metil-1H-imidazol-4,2-diil)(2S)-2,1-pirrolidindiil))bis(N,N-dimetil-2-oxo-1-feniletanamina)* (8 mg, 8.6%) como una cera incolora.

^{1}RMN (500 MHz, MDSO-d_6) δ ppm 1.84-2.25 (m, 8 H)

2.32-2.90 (m, 12 H) 3.67-3.92 (m, 8 H) 4.07 (s, 2 H) 5.23 (s, 2 H) 5.51 (s, 2 H) 7.51-7.91 (m, 20 H) HPLC Xterra 4.6 X 50 mm, 0 a 100% de B durante 10 minutos, un minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.2% de ácido fosfórico, B = 10% de agua, 90% de metanol, 0.2% de ácido fosfórico, RT = 2.74 min, 98%.

LCMS: Análisis calculado para $C_{48}H_{54}N_8O_2$ 775.02; encontrado 775.50 $(M+H)^+$.

Isómero 2: *(1R,1'R)-2,2'-(4,4'-bifenildiilbis(1-metil-1H-imidazol-4,2-diil)(2S)-2,1-pirrolidindiil))bis(N,N-dimetil-2-oxo-1-feniletanamina)*

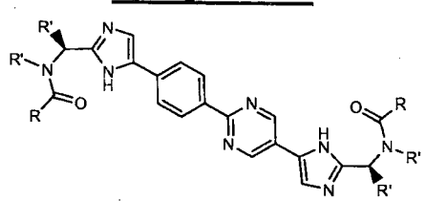
(10.2 mg, 1%) como una cera incolora.

^{1}RMN (500 MHz, MDSO-d_6) δ ppm 1.83-2.26 (m, 8 H) 2.30-2.92 (m, 12 H) 3.68-3.94 (m, 8 H) 4.06 (s, 2 H) 5.25 (d, *J* = 2.14 Hz, 2 H) 5.50 (s, 2 H) 7.52-7.91 (m, 20 H).

HPLC Xterra 4.6 X 50 mm, 0 a 100% de B durante 10 minutos, un minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.2% de ácido fosfórico, B = 10% de agua, 90% de metanol, 0.2% de ácido fosfórico, RT = 2.75 min, 90%.

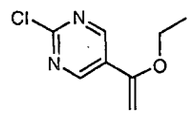
LCMS: Análisis calculado para $C_{48}H_{54}N_8O_2$ 775.02; encontrado: 775.52 $(M+H)^+$.

Ejemplo 152



Ejemplo 152a-1 etapa a

2-cloro-5-(1-etoxivinil)pirimidina



A una solución de 5-bromo-2-cloropirimidina (12.5 g, 64.62 mmoles) en DMF seco (175 mL) bajo N_2 se le añadieron tributil(1-etoxivinil)estaño (21.8 mL, 64.62 mmoles) y diclorobis(trifenilfosfina)paladio (II) (2.27 g, 3.23 mmoles). La mezcla se calentó a 100°C durante 3 horas antes de que se le permitiera agitar a temperatura ambiente durante 16 horas. La mezcla se diluyó después con éter (200 mL) y se trató con solución acuosa de KF (55 g de fluoruro de potasio en 33 mL de agua). La mezcla de dos fases se agitó vigorosamente durante 1 hora a temperatura ambiente antes de ser filtrada a través de tierra diatomácea (Celite®). El filtrado se lavó con solución saturada de $NaHCO_3$ y salmuera antes de secar (Na_2SO_4). La fase acuosa original se extrajo con éter (2x) y la fase orgánica se trató como arriba. La repetición en 13.5 g de 5-bromo-2-cloropirimidina y purificación combinada mediante cromatografía por vaporización Biotage™ en gel de sílice (elución por gradiente en una columna 65M usando 3% de acetato de etilo en hexanos a 5% de acetato de etilo en hexanos con 3.0 L) dio el compuesto del título como un sólido blanco y cristalino (18.2 g, 73%).

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^{1}RMN (500 MHz, MDSO-d_6) δ ppm 8.97 (s, 2H), 5.08 (d, J = 3.7 Hz, 1H), 4.56 (s, J = 3.4 Hz, 1H), 3.94 (q, J = 7.0 Hz, 2H), 1.35 (t, J = 7.0 Hz, 3H).

LCMS Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, RT = 2.53 min, 98.8% de índice de homogeneidad.

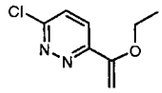
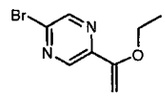
LCMS: Análisis calculado para $C_8H_{10}CIN_2O$ 185.05; encontrado: 185.04 $(M+H)^+$.

HRMS: Análisis calculado para $C_8H_{10}CIN_2O$ 185.0482; encontrado: 185.0490 $(M+H)^+$.

Se usó el mismo método para la preparación de los ejemplos 152a-2 y 152a-3:

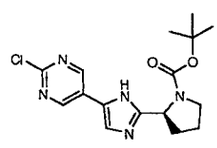
Condiciones LC: *Condición 1*: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA,220 nm, 5 µL de volumen de inyección.

Condición 2: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 2 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

Ejemplo 152a-2	 a partir de dicloropiridazina	t_R = 2.24 min 96.4%, condición 1 LRMS: Anal. Calcd. para: $C_8H_{10}ClN_2O$ 185.05; encontrado: 185.06 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_8H_{10}ClN_2O$ 185.0482; encontrado: 185.0476 $(M+H)^+$.
Ejemplo 152a-3	 a partir de dibromopirazina	t_R = 2.82 min (52.7%, inseparable con 2,5-dibromopirazina (t_R =1.99 min, 43.2%)); condición 1 LRMS: Anal. Calcd. para: $C_8H_{10}BrN_2O$ 229.00; encontrado: 228.93 $(M+H)^+$.

Ejemplo 152b-1, etapa b

2-(5-(2-Cloropirimidin-5-il)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-ter-butilo o éster ter-butílico de ácido (S)-2-[5-(2-cloro-pirimidin-5-il)-1H-imidazol-2-il]-pirrolidin-1-carboxílico



NBS (16.1 g, 90.7 mmoles) se añadió en una

porción a una solución agitada de 2-cloro-5-(1-etoxivinil)pirimidina (152a-1, 18.2 g, 98.6 mmoles) en THF (267 mL) y H_2O (88 mL) a 0°C bajo N_2. La mezcla se agitó durante 1 hora a 0°C antes de que se eluyera con más H_2O y se extrajera con acetato de etilo (2x). Los extractos combinados se lavaron con solución saturada de $NaHCO_3$ y salmuera antes del secado (Na_2SO_4), filtración y evaporación del solvente. LCMS Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, RT = 1.52 min (pico asimétrico).

LCMS: Análisis calculado para $C_6H_{14}BrClN_2O$ 235.92; encontrado: 236.85 $(M+H)^+$.

Ejemplo 152c-1, etapa c

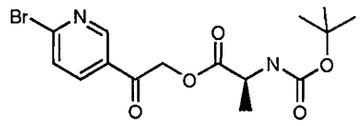
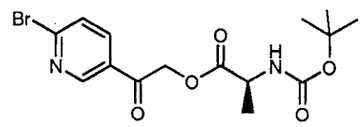
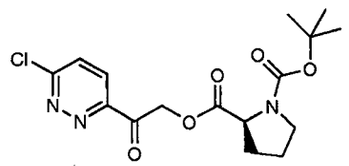
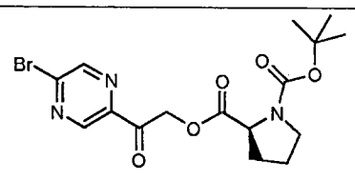
La mitad del residuo crudo (2-bromo-1-(2-cloropirimidin-5-il)etanona, ~14.5 g) se disolvió en acetonitrilo anhidro (150 mL) y se trató directamente con N-Boc-L-prolina (9.76 g, 45.35 mmoles) y diisopropiletilamina (7.9 mL, 45.35 mmoles). Después de haber sido agitada durante 3 horas, el solvente se removió al vacío y el residuo se dividió entre acetato de etilo y agua. La fase orgánica se lavó con ácido clorhídrico 0.1 N, solución saturada de

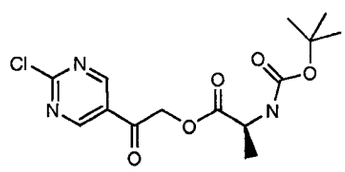
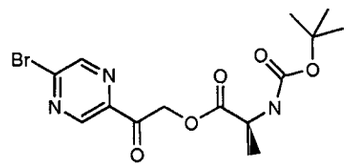
$NaHCO_3$ y salmuera antes del secado (Na_2SO_4), filtración y concentración. LCMS Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, RT = 2.66 min.

Se usó el mismo método para preparar los ejemplos 152c-2 a 152c-6.

Condiciones de LC: *Condición 1*: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µ de volumen de inyección.

Condición 2: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 2 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

Ejemplo 152c-2		t_R = 1.81 min (condición 2, ~95 %) LRMS: Anal. Calcd. para: $C_{15}H_{19}BrN_4O_2$ 386.05 encontrado: 387.07 $(M+H)^+$.
Ejemplo 152c-3		t_R = 1.84 min (condición 2, 94%) LRMS: Anal. Calcd. para: $C_{15}H_{19}BrN_2O_5$ 386.05; encontrado: 387.07 $(M+H)^+$.
Ejemplo 152c-3a		t_R = 2.65 min; condición 1 LCMS: Anal. Calcd. para: $C_{16}H_{20}ClN_3O_5$ 369.11 encontrado: 391.89 $(M+Na)^+$.
Ejemplo 152c-4		t_R = 1.94 min, (condición 2) LCMS: Anal. Calcd. para:

		$C_{16}H_{21}BrN_3O_5$ 414.07 encontrado: 414.11 $(M+H)^+$.
Ejemplo 152c-5		t_R = 2.22 min; condición 1 LCMS: Anal. Calcd. para: $C_{14}H_{18}ClN_3O_5$ 343.09 encontrado: indeterminado
Ejemplo 152c-6		t_R = 2.41 min, condición 1 LCMS: Anal. Calcd. para: $C_{14}H_{18}{}^{37}BrN_3O_5$ 389.04 encontrado: 412.03 $(M+Na)^+$.

Ejemplo 152d-1, etapa d

El residuo 2-(2-(2-cloropirimidin-5-il)-2-oxoetil)pirrolidin-1,2-dicarboxilato) de ((S)-1-*ter*-butilo se recogió en xilenos (200 mL) y se trató a NH_4OAc (17.5 g, 0.23 moles). La mezcla se calentó a 140°C durante 2 horas en un matraz de parte superior con rosca y de paredes gruesas antes de que se enfriara a temperatura ambiente y se filtrara por succión. El filtrado fue después concentrado, dividido en acetato de etilo y solución saturada de $NaHCO_3$ y lavado con salmuera antes del secado (Na_2SO_4), filtración y concentración. El precipitado original se dividió en solución acuosa de $NaHCO_3$ y acetato de etilo y se sonificó

durante 2 minutos antes de haber sido filtrado por succión. El filtrado se lavó con salmuera, se secó sobre (Na_2SO_4), se filtró y se concentró hasta la sequedad. La purificación de los residuos combinados mediante cromatografía por vaporización Biotage™ en gel de sílice (columna 65M, pre-equilibrio con 2% de B para 900 mL seguida por elución de gradiente con 2% de B a 2% de B para 450 nl seguida por 2% de B a 40% de B para 3,000 mL en donde B = metanol y A = diclorometano) dio el compuesto del título (7.0 g, 44% de rendimiento, 2 etapas, fracción pura) como una espuma anaranjada amarillenta. Las fracciones mezcladas se sometieron a una segunda cromatografía Biotage™ en gel de sílice (columna 40 M, pre-equilibrio con 1% de B para 600 mL seguido por una elución por gradientes con 1% de B a 1% de B para 150 ml seguido por 1% de B a 10% de B para 1,500 mL en donde B = MeOH y A = CH_2Cl_2) dio el compuesto del título adicional (2.8 g, 18%) como una espuma parduzca-anaranjada. ^1H RMN (500 MHz, DMSO-d_6) δ 12.24-12.16 (m, 1H), 9.05 (s, 2H), 7.84-7.73 (m, 1H), 4.90-4.73 (m, 1H), 3.59-3.46 (m, 1H), 3.41-3.31 (m, 1H), 2.32-2.12 (m, 1H), 2.03-1.77 (m, 3H), 1.39 y 1.15 (2s, 9H).

LCMS Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, RT = 1.92 min, 94.7% de índice de

homogeneidad.

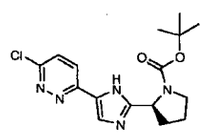
LRMS: Análisis calculado para $C_{16}H_{21}ClN_5O_2$ 350.14; encontrado: 3502.3 $(M+H)^+$.

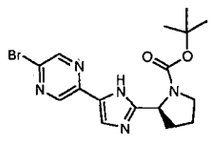
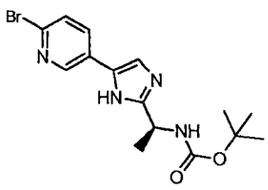
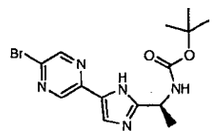
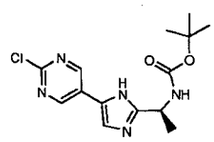
HRMS: Análisis calculado para $C_{16}H_{21}ClN_5O_2$ 350.1384; encontrado: 350.1398 $(M+H)^+$.

Se usó el mismo método para preparar los ejemplos 152d-2 a 152d-6.

Condiciones de LC: *Condición 1*: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µ de volumen de inyección.

Condición 2: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 2 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

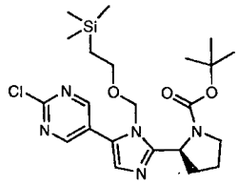
Ejemplo 152d-2	 a partir de 152c-3a	t_R = 1.92 min (86.5%); condición 1 LRMS: Anal. Calcd. para: $C_{16}H_{21}ClN_5O_2$ 350.14; encontrado: 350.23 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{16}H_{21}ClN_5O_2$ 350.1384; encontrado: 350.1393 $(M+H)^+$.

Ejemplo 152d-3	 a partir de 152c-4	t_R = 1.90min (>95%); condición 1 LRMS: Anal. Calcd. para: $C_{16}H_{21}BrN_5O_2$ 394.09;encontrado: 393.82 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{16}H_{21}BrN_5O_2$ 394.0879; encontrado: 394.0884 $(M+H)^+$.
Ejemplo 152d-4	 a partir de 152c-3	t_R = 1.45 min (condición 2, 100%) LRMS: Anal. Calcd. para: $C_{15}H_{19}BrN_4O_2$ 366.07encontrado: 367.07 $(M+H)^+$.
Ejemplo 152d-5	 a partir de 152c-6	t_R = 1.88 min (>95%); condición 1 LRMS: Anal. Calcd. para: $C_{14}H_{18}BrN_5O_2$ 367.06;encontrado: 368.10 $(M+H)^+$.
Ejemplo 152d-6	 a partir de 152c-5	t_R = 1.66 min (85%); condición 1 LRMS: Anal. Calcd. para: $C_{14}H_{18}ClN_5O_2$ 323.11;encontrado: 324.15 $(M+H)^+$.

Ejemplo 152e-1, etapa e

Ejemplo 152e-1

2-(5-(2-cloropirimidin-5-il)-1-((2-(trimetil-silil)etoxi)metil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-ter-butilo



Hidruro de sodio (dispersión al 60% en aceite mineral, 0.23 g, 5.72 mmoles) se añadió en una porción a una solución agitada de 2-(5-(2-cloropirimidin-5-il)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*ter*-butilo (152d-1, 2.0 g, 5.72 mmoles) en DMF seco (45 mL) a temperatura ambiente bajo N_2. La mezcla se agitó durante 5 minutos antes de que se añadiera cloruro de SEM (1.01 mL, 5.72 mmoles) en incrementos de aproximadamente 0.1 mL. La mezcla se agitó durante 3 horas antes de ser enfriada rápidamente con solución saturada de NH_4Cl y se diluyó con acetato de etilo. La fase orgánica se lavó con solución saturada de $NaHCO_3$ y salmuera, se secó sobre (Na_2SO_4), se filtró y se concentró. La fase acuosa original se extrajo dos veces más y el residuo combinado se purificó mediante cromatografía por vaporización Biotage™ (columna 40M, 50 mL/min, pre-equilibrio con 5% de B para 750 mL, seguido por elución en gradiente de etapas con 5% de B a 5% de B para 150 mL, 5% de B a 75% de B para 1,500

mL, después 75% de B a 100% de B para 750 mL en donde el solvente B es acetato de etilo y el solvente A es hexanos). La concentración del eluyente dio el compuesto del título como una espuma amarillo pálido (2.35 g, 85%).

^{1}H RMN (500 MHz, DMSO-d_6) δ 9.04 (s, 2H), 7.98-7.95 (m, 1H), 5.70-5.31 (3m, 2H), 5.02-4.91 (m, 1H), 3.59-3.49 (m, 3H), 3.45-3.35 (m, 1H), 2.30-2.08 (m, 2H), 1.99-1.83 (m, 2H), 1.36 y 1.12 (2s, 9H), 0.93-0.82 (m, 2H), -0.02 (s, 9H).

LCMS Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 2 minutos, 2 minutos de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, RT = 2.38 min, 95% de índice de homogeneidad.

LRMS: Análisis calculado para $C_{22}H_{35}ClN_5O_3Si$ 480.22; encontrado: 480.23 $(M+H)^+$.

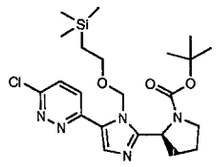
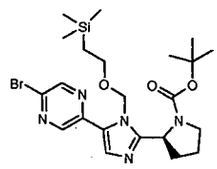
HRMS: Análisis calculado para $C_{22}H_{35}ClN_5O_3Si$ 480.2198; encontrado: 480.2194 $(M+H)^+$.

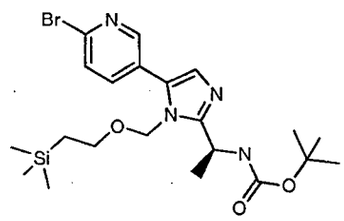
Se usó el mismo método para preparar 152e-2 a 152e-4.

Condiciones de LC: *Condición 1*: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

Condición 2: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a

100% de B durante 2 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

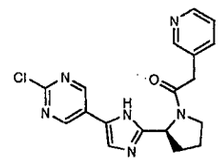
Ejemplo 152e-2	 de 152d-2	t_R = 2.34 min (85.7%); condición 1 LCMS: Anal. Calcd. para: $C_{22}H_{35}ClN_5O_3Si$ 480.22; encontrado: 480.22 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{22}H_{35}ClN_5O_3Si$ 480.2198 encontrado: 480.2198 $(M+H)^+$.
Ejemplo 152e-3	 de 152d-3	t_R = 3.18 min (>95%); condición 1 LCMS: Anal. Calcd. para: $C_{22}H_{35}{}^{37}BrN_5O_3Si$ 526.17; encontrado: 525.99 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{22}H_{35}{}^{37}BrN_5O_3Si$ 526.1692; encontrado: 526.1674 $(M+H)^+$.

Ejemplo 152e-4	 de 152d-4	t_R = 2.14 min (condición 2, 96%) LRMS: Anal. Calcd. para: $C_{21}H_{33}BrN_4O_3Si$ 496.15 encontrado: 497.13 $(M+H)^+$.

Ejemplos 152f-1 a 152f-2

Ejemplo 152f-1

(S)-1-(2-(5-(2-cloropirimidin-5-il)-1H-imidazol-2-il)pirrolidin-1-il)-2-(piridin-3-il)etanona



HCl 4*N* frío (0°C) en dioxanos (5 mL) se añadió por medio de una jeringa a 2-(5-(2-cloropirimidin-5-il)-1*H*-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*ter*-butilo (152d-1, 0.50 g, 1.43 mmoles) en un matraz en forma de pera de 100 mL seguido por MeOH (1.0 mL). La suspensión se agitó a temperatura ambiente durante 4 horas antes de que se concentrara hasta la sequedad y se pusiera al alto vacío durante 1 hora. Hubo un intermediario aislado triclorhidrato de (S)-2-cloro-5-(2-(pirrolidin-2-il)-1*H*-imidazol-5-il)pirimidina como un sólido amarillo (con un tinte anaranjado) que se usó sin purificación adicional.

Se añadió HATU (0.60 g, 1.57 mmoles) en una porción

a una solución agitada del intermediario triclorhidrato de (S)-2-cloro-5-(2-(pirrolidin-2-il)-1H-imidazol-5-il)pirimidina (0.46 g, 1.43 mmoles, cantidad teórica), ácido 2-(piridin-3-il)acético (0.25 g, 1.43 mmoles) y DIEA (1.0 mL, 5.72 mmoles) en DMF anhidro (10 mL) a temperatura ambiente. La mezcla se agitó a temperatura ambiente durante 2 horas antes de que la DMF se removiera al vacío. el residuo se recogió en CH_2Cl_2 y se sometió a cromatografía por vaporización Biotage™ en gel de sílice (columna 40 M, pre-equilibrio con 0% de B para 600 mL seguido por una elución con gradiente de etapas con 0% de B a 0% de B para 150 mL seguido por 0% de B a 15% de B para 1,500 mL, seguido por 15% de B a 25% de B para 999 mL en donde B = MeOH y A = CH_2Cl_2). Se aisló el compuesto del título (0.131 g, 25%, 2 etapas) como un sólido amarillo.

^{1}H RMN (500 MHz, DMSO-d_6) δ 9.10-9.08 (2s, 2H), 8.72-8.55 (series de m, 2H), 8.21-8.20 y 8.11-8.10 (2m, 1H), 8.00 y 7.93 (2s, 1H), 7.84-7.77 (series de m, 1H), 5.43-5.41 y 5.17-5.15 (2m, 1H), 4.02-3.94 (3m, 2H), 3.90-3.58 (3m, 2H), 2.37-2.26 (m, 1H), 2.16-1.85 (2m, 3H).

LCRMS Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, RT = 0.92 minutos, 95.1% de índice de homogeneidad.

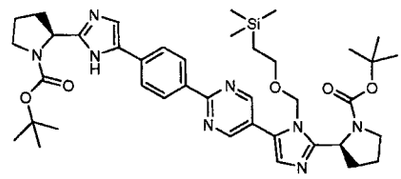
LRMS: Análisis calculado para $C_{18}H_{18}CIN_6O$ 369.12; encontrado: 369.11 $(M+H)^+$.

HRMS: Análisis calculado para $C_{18}H_{18}CIN_6O$ 369.1231; encontrado: 369.1246 $(M+H)^+$.

Ejemplos 152g-1 a 152g-17

Ejemplo 152g-1 a partir de 1c y 152e-1

Éster ter-butílico de ácido (S)-2-[5-(2-{4-[2-((S)-1-ter-butoxicarbonil-pirrolidin-2-il)-3H-imidazol-4-il]-fenil}-pirimidin-5-il)-1-(2-trimetilsilanil-etoximetil)-1H-imidazol-2-il]-pirrolidin-1-carboxílico



$Pd(Ph_3)_4$ (0.12 g, 0.103 mmoles) se añadió en una porción a una suspensión agitada de 2-(5-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*ter*-butilo (1c, 1.00 g, 2.27 mmoles), 2-(5-(2-cloropirimidin-5-il)-1-((2-trimetilsilil)etoxi)metil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*ter*-butilo (152c-1, 0.99 g, 2.06 mmoles) y $NaHCO_3$ (0.87 g, 10.3 mmoles) en una solución de DME (20 mL) y H_2O (6 mL) a temperatura ambiente bajo N_2. El recipiente se selló y la mezcla se puso en un baño de aceite precalentado (80°C) y se agitó a 80°C durante 16 horas antes de que se

añadiera un catalizador adicional (0.12 g). Después de calentar la mezcla durante 12 horas más a 80°C, la mezcla se enfrió a la temperatura ambiente, se diluyó con acetato de etilo y se lavó con solución saturada de $NaHCO_3$ y salmuera antes de secar con sulfato de sodio anhidro y de la concentración del solvente. La purificación del residuo mediante cromatografía por vaporización Biotage™ en gel de sílice usando una columna 40M (pre-equilibrada con 40% de B seguido por la elución en gradiente de etapas con 40% de B a 40% de B para 150 mL, 40% de B a 100% de B para 1,500 mL, 100% de B a 100% de B para 1,000 mL en donde B = acetato de etilo y A = hexanos) dio el compuesto del título como una espuma amarilla (1.533 g, 98%). Una pequeña cantidad de la espuma amarilla se purificó más para propósitos de caracterización mediante pHPLC (Phenomenex GEMINI, 30 x 100 mm, S10, 10 a 100% de B durante 13 minutos, 3 minutos de tiempo de retención, 40 mL/min, A = 95% de agua, 5% de acetonitrilo, 10 mM de NH_4OAc, B = 10% de agua, 90% de acetonitrilo, 10 mM de NH_4OAc) para producir 95% del compuesto del título puro como un sólido blanco.

^1H RMN (500 MHz, DMSO-d_6) δ 12.30-11.88 (3 m, 1H), 9.17-9.16 (m, 2H), 8.43-8.31 (m, 2H), 7.99-7.35 (series de m, 4H), 5.72-5.30 (3m, 2H), 5.03-4.76 (2m, 2H), 3.64-3.50 (m, 4H), 3.48-3.31 (m, 2H), 2.36-2.07 (m, 2H), 2.05-1.80 (m, 4H), 1.46-1.08 (2m, 18H), 0.95-0.84 (m, 2H), -0.01 (s, 9H).

HPLC Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, RT = 2.91 min, 95% de índice de homogeneidad.

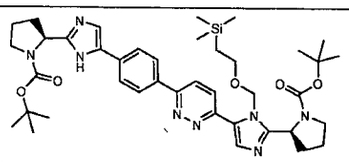
LRMS: Análisis calculado para $C_{40}H_{57}N_8O_5Si$ 757.42; encontrado: 757.42 $(M+H)^+$.

HRMS: Análisis calculado para $C_{40}H_{57}N_8O_5Si$ 757.4221; encontrado: 757.4191 $(M+H)^+$.

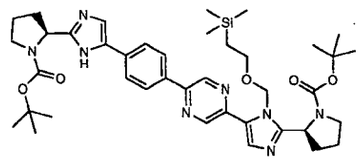
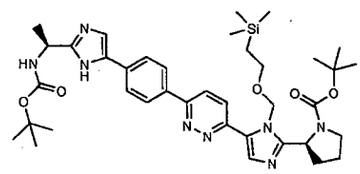
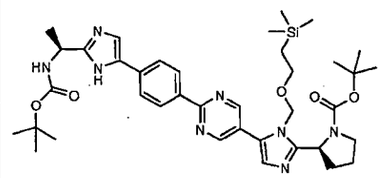
Se usó el mismo procedimiento para preparar los ejemplos 152g-2 a 152g-17:

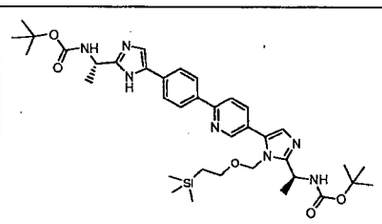
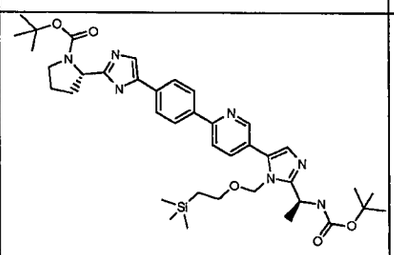
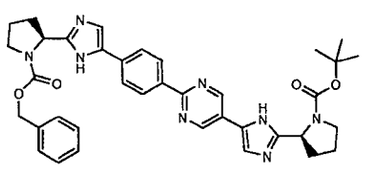
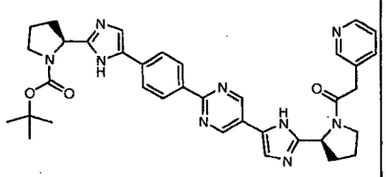
Condiciones de LC: *Condición 1*: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

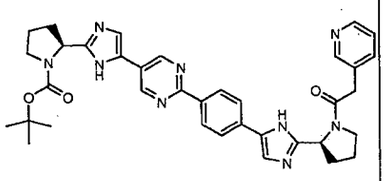
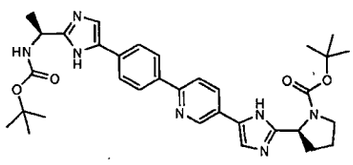
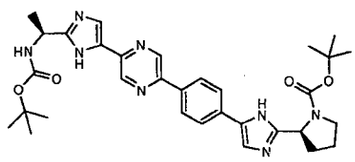
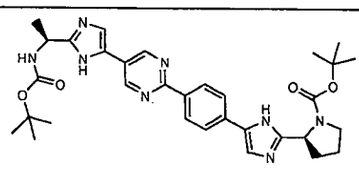
Condición 2: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 2 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

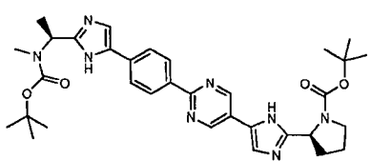
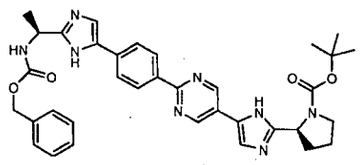
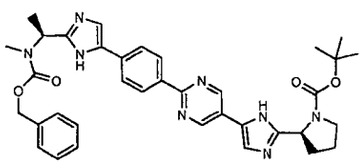
Ejemplo 152g-2	 Preparado de 1c y 152e-2	t_R = 2.81 min (79%); Condición 1 LRMS: Anal. Calcd. para: $C_{40}H_{57}N_8O_5Si$ 757.42; encontrado: 758.05 $(M+H)^+$.

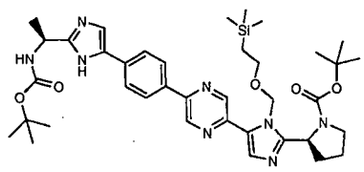
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		HRMS: Anal. Calcd. para: $C_{40}H_{57}N_8O_5Si$ 757.4221; encontrado: 757.4196 $(M+H)^+$.
Ejemplo 152g-3	 Preparado de 1c y 152e-3	t_R = 2.89 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{40}H_{57}N_8O_5Si$ 757.42;encontrado: 757.35 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{40}H_{57}N_8O_5Si$ 757.4221;encontrado: 757.4191 $(M+H)^+$.
Ejemplo 152g-4	 Preparado de 1-6c y 152e-2	t_R = 2.87 min (97%); Condición 1 LRMS: Anal. Calcd. para: $C_{38}H_{55}N_8O_5S_i$ 731.41;encontrado: 731.26 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{38}H_{55}N_8O_5S_i$ 731.4065; encontrado: 731.4070 $(M+H)^+$.
Ejemplo 152g-5	 Preparado de 1-6c y 152e-1	t_R = 2.94 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{38}H_{55}N_8O_5Si$ 731.41;encontrado: 731.26 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{38}H_{55}N_8O_5Si$ 731.4065;encontrado: 731.4046 $(M+H)^+$.

Ejemplo 152g-6	 Preparado de 1-6c y 152e-4	t_R = 1.99 min (condición 2, 96%) LRMS: Anal. Calcd. para: $C_{37}H_{53}N_7O_2Si$ 703.39; encontrado: 704.34 $(M+H)^+$.
Ejemplo 152g-7	 Preparado de 1c y 152e-4	t_R = 1.99 min (condición 2, 96%) LRMS: Anal. Calcd. para: $C_{39}H_{55}N_7O_5Si$ 729.40 encontrado: 730.42 $(M+H)^+$.
Ejemplo 152g-8	 Preparado de 1-5c y 152d-1	t_R = 2.15 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{37}H_{41}N_8O_4$ 661.33; encontrado: 661.39 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{37}H_{41}N_8O_4$ 661.3251; encontrado: 661.3268 $(M+H)^+$.
Ejemplo 152g-9	 Preparado de 1c y 152f-1	t_R = 1.71 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{36}H_{40}N_9O_3$ 646.76; encontrado: 646.47 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{36}H_{40}N_9O_3$ no hecha encontrado: no hecha $(M+H)^+$.

Ejemplo 152g-10	 Preparado de 152d-1 y 1-10c	t_R = 1.71 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{36}H_{40}N_9O_3$ 646.33;encontrado: 646.37 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{36}H_{40}N_9O_3$ 646.3254; encontrado: 646.3240 $(M+H)^+$.
Ejemplo 152g-11	 Preparado de 1-6c y 152e-4	t_R = 2.12 min (>93.9%); Condición 1 LRMS: Anal. Calcd. para: $C_{33}H_{42}N_7O_4$ 600.33;encontrado: 600.11 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{33}H_{42}N_7O_4$ 600.3298; encontrado: 600.3312 $(M+H)^+$.
Ejemplo 152g-12	 Preparado de 1c y 152d-5	t_R = 2.13 min (97.3%); Condición 1 LRMS: Anal. Calcd. para: $C_{32}H_{41}N_8O_4$ 601.33;encontrado: 601.36 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{32}H_{41}N_8O_4$ 601.3251; encontrado: 601.3253 $(M+H)^+$.
Ejemplo 152g-13		t_R = 2.11 min (98.5%); Condición 1 LRMS: Anal. Calcd. para: $C_{32}H_{41}N_8O_4$ 601.33;encontrado: 601.36

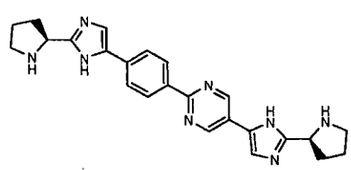
	Preparado de 1c y 152d-6	$(M+H)^+$. HRMS: Anal. Calcd. para: $C_{32}H_{41}N_8O_4$ 601.3251; encontrado: 601.3253 $(M+H)^+$.
Ejemplo 152g-14	 Preparado de 1-8c y 152d-1	t_R = 2.18 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{33}H_{43}N_8O_4$ 615.34; encontrado: 615.38 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{33}H_{43}N_8O_4$ 615.3407; encontrado: 615.3433 $(M+H)^+$.
Ejemplo 152g-15	 Preparado de 1c y 152d-1	t_R = 2.20 min (97.7%); Condición 1 LRMS: Anal. Calcd. para: $C_{35}H_{39}N_8O_4$ 635.31; encontrado: 635.36 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{35}H_{39}N_8O_4$ 635.3094; encontrado: 635.3119 $(M+H)^+$.
Ejemplo 152g-16	 Preparado de 1-9c y 152d-1	t_R = 2.26 min (>95%); Condición 1 LRMS: Anal. Calcd $C_{36}H_{41}N_8O_4$ 649.33; encontrado: 649.39 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{36}H_{41}N_8O_4$ 649.3251; encontrado: 649.3276 $(M+H)^+$.

Ejemplo 152g-17	 Preparado de 1-6c y 152e-3	t_R = 2.98 min (98.5%); Condición 1 LRMS: Anal. Calcd. para: $C_{38}H_{54}N_8O_5Si$ 730.39; encontrado: 731.40 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{38}H_{54}N_8O_5Si$ 731.4065; encontrado: 731.4045 $(M+H)^+$.

Ejemplo 152h-1-152h-7

Ejemplo 152h-1 a partir de 152g-1

5-((S)-2-pirrolidin-2-il-3H-imidazol-4-il)-2-[4-((S)-2-pirrolidin-2-il-3H-imidazol-4-il)-fenil]-pirimidina



TFA (8 mL) se añadió en una porción a una solución agitada de éster *ter*-butílico de ácido (S)-2-[5-(2-{4-[2-((S)-1-*ter*-butoxicarbonil-pirrolidin-2-i)-3*H*-imidazol-4-il]-fenil}-pirimidin-5-il)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-2-il]-pirrolidin-1-carboxílico (1.50 g, 1.98 mmoles) en CH_2Cl_2 seco (30 mL) a temperatura ambiente. El matraz se selló y la mezcla se agitó a temperatura ambiente durante 16 horas antes de que los solventes se removieran al vacío. El residuo se recogió en metanol, se filtró a través de un filtro de jeringa PVDF (13 mm x 0.45 µm), se distribuyó a 8

frascos para pHPLC y se sometió a cromatografía mediante HPLC (elución de gradiente de 10% de B a 100% de B durante 13 minutos en una columna Phenomenex 18, 30 x 100 mm, 10 µm, en donde A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA). Después de la concentración de los tubos de ensayo seleccionados mediante evaporación al vacío rápida, el producto se disolvió en metanol y se neutralizó al pasar la solución a través de un cartucho de intercambio aniónico UCT CHQAX 110M75. Se aisló el compuesto del título como un sólido color mostaza amarillo (306.7 mg, 36% de rendimiento) después de la concentración del eluyente.

^{1}H RMN (500 MHz, DMSO-d_6) µ 12.50-11.80 (br m, 2H), 9.18 (s, 2H), 8.36 (d, *J* = 8.5 Hz, 2H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.77 (s, 1H), 7.61(s, 1H), 4.34-4.24 (m, 2H), 3.09-2.89 (m, 4H), 2.18-2.07 (m, 2H), 2.02-1.89 (m, 2H), 1.88-1.72 (m, 4H).

LCMS Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, RT = 1.33 min, >95% de índice de homogeneidad.

LRMS: Análisis calculado para $C_{24}H_{27}N_8$ 427.24; encontrado: 427.01 $(M+H)^+$.

HRMS: Análisis calculado para $C_{24}H_{27}N_8$ 427.2359;

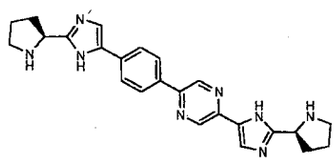
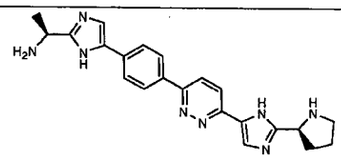
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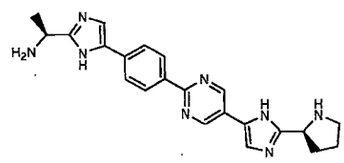
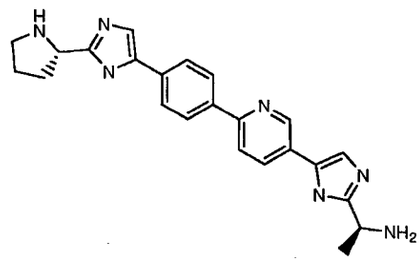
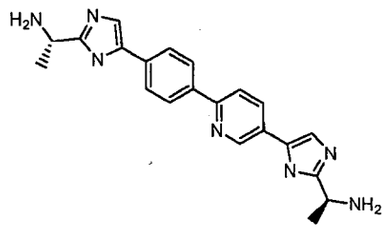
encontrado: 427.2363 $(M+H)^+$.

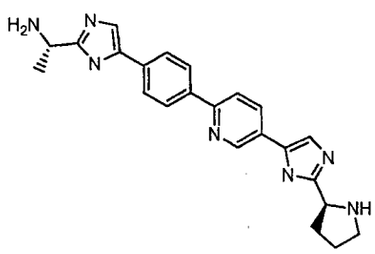
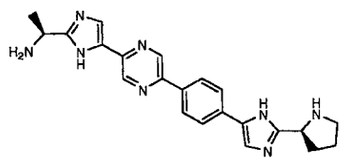
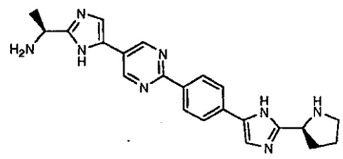
Se usaron las mismas condiciones para preparar los ejemplos 152h-2 a 152h-14.

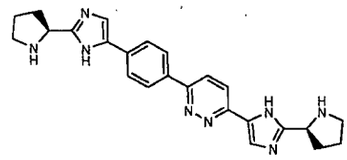
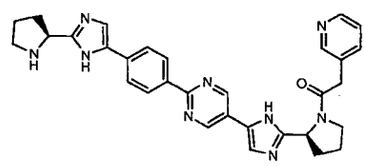
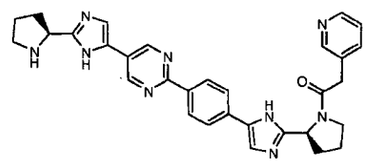
Condiciones de LC: *Condición 1*: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

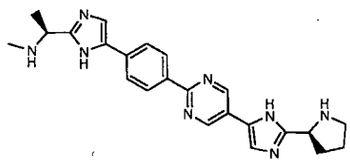
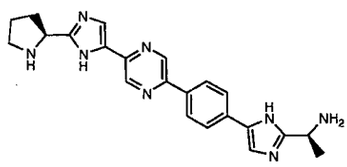
Condición 2: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 2 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

Ejemplo 152h-2	 Preparado de 152g-3	t_R = 1.36 min (98%); Condición 1 LRMS: Anal. Calcd. para: $C_{24}H_{27}N_8$ 427.24; encontrado: 427.48 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{24}H_{27}N_8$ 427.2359; encontrado: 427.2339 $(M+H)^+$.
Ejemplo 152h-3	 Preparado de 152g-4	t_R = 1.17 min (>95%); Condición 1 LRMS: Anal. Calcd.

		for $C_{22}H_{25}N_8$ 401.22; encontrado: 401.16 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{22}H_{25}N_8$ 401.2202; encontrado: 401.2193 $(M+H)^+$.
Ejemplo 152h-4	 Preparado de 152g-5	t_R = 1.28 min (89.3%); Condición 1 LRMS: Anal. Calcd. para: $C_{22}H_{25}N_8$ 401.22; encontrado: 401.16 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{22}H_{25}N_8$ 401.2202; encontrado: 401.2201 $(M+H)^+$.
Ejemplo 152h-5	 Preparado de 152g-7	t_R = 0.93 min; Condición 2 LRMS: Anal. Calcd. para: $C_{23}H_{25}N_7$ 399; encontrado: 400 $(M+H)^+$.
Ejemplo 152h-6	 Preparado de 152g-6	t_R = 0.81 min; Condición 2 LRMS: Anal. Calcd. para: $C_{21}H_{23}N_7$ 373; encontrado: 374 $(M+H)^+$.

Ejemplo 152h-7	 Preparado de 152g-11	t_R = 1.14 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{23}H_{26}N_7$ 400.23; encontrado: 400.14 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{23}H_{26}N_7$ 400.2250; encontrado: 400.2234 $(M+H)^+$.
Ejemplo 152h-8	 Preparado de 152g-12	t_R = 1.29 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{22}H_{25}N_8$ 401.22; encontrado: 401.21 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{22}H_{25}N_8$ 401.2202; encontrado: 401.2204 $(M+H)^+$.
Ejemplo 152h-9	 Preparado de 152g-13	t_R = 1.29 min (97.6%); Condición 1 LRMS: Anal. Calcd. para: $C_{22}H_{25}N_8$ 401.22; encontrado: 401.21 $(M+H)^+$. HRMS: Anal. Calcd.

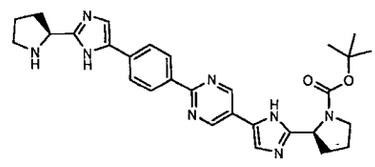
		para: $C_{22}H_{25}N_8$ 401.2202; encontrado: 401.2220 $(M+H)^+$.
Ejemplo 152h-10	 Preparado de 152g-2	t_R = 1.26 min (86.4%); Condición 1 LRMS: Anal. Calcd. para: $C_{24}H_{27}N_8$ 427.24; encontrado: 427.48 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{24}H_{27}N_8$ 427.2359; encontrado: 427.2339 $(M+H)^+$.
Ejemplo 152h-11	 Preparado de 152g-9	t_R = 1.26 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{31}H_{32}N_9O$ 546.27; encontrado: 546.28 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{31}H_{32}N_9O$ 546.2730 encontrado: 546.2739 $(M+H)^+$.
Ejemplo 152h-12	 Preparado de 152g-10	t_R = 1.39 min (95%); Condición 1 LRMS: Anal. Calcd. para: $C_{31}H_{32}N_9O$ 546.27; encontrado: 546.32 $(M+H)^+$.

		HRMS: Anal. Calcd. para: $C_{31}H_{32}N_9O$ 546.2730; encontrado: 546.2719 $(M+H)^+$.
Ejemplo 152h-13	 Preparado de 152g-14	t_R = 1.42 min; Condición 1 LRMS: Anal. Calcd. para: $C_{23}H_{26}N_8$ 414.24; encontrado: 415.27 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{23}H_{26}N_8$ 415.2359; encontrado: 415.2371 $(M+H)^+$.
Ejemplo 152h-14	 Preparado de 152g-17	t_R = 1.30 min; Condición 1 LRMS: Anal. Calcd. para: $C_{22}H_{24}N_8$ 400.21; encontrado: 401.24 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{22}H_{24}N_8$ 401.2202; encontrado: 401.2198 $(M+H)^+$.

Ejemplo 152i-1 a 152i-3

Ejemplo 152i-1 a partir de 152g-8

Éster ter-butílico de ácido (S)-2-(5-{2-[4-((S)-2-pirrolidin-2-il-3H-imidazol-4-il)-fenil]-pirimidin-5-il}-1H-imidazol-2-il)-pirrolidin-1-carboxílico



Una solución de éster *ter*-butílico de ácido (S)-2-[5-(2-{4-[2-((S)-1-benciloxicarbonil-pirrolidin-2-il)-3*H*-imidazol-4-il]-fenil}-pirimidin-5-il)-1*H*-imidazol-2-il]-pirrolidin-1-carboxílico (317.1 mg, 0.48 mmoles) en MeOH (1 mL) se añadió a una suspensión agitada de 10% de paladio en carbón (60 mg) y K_2CO_3 (70 mg) en una solución de MeOH (5 mL) y H_2O (0.1 mL) a temperatura ambiente bajo N_2. El matraz se cargó y se evacuó tres veces con H_2 y se agitó durante 3 horas a presión atmosférica. Después se añadió catalizador adicional (20 mg) y la mezcla de reacción se agitó más durante 3 horas antes de que fuera filtrada por succión a través de tierra diatomácea (Celite®) y concentrada. El residuo se diluyó con MeOH, se filtró a través de un filtro de jeringa de PVDF (13 mm x 0.45 µm), se distribuyó a 4 frascos de pHPLC y se cromatografió (elución de gradiente de 20% de B a 100% de B durante 10 minutos en una columna Phenomenex-Gemini C18 (30 x 100 mm, 10 µm) en donde A = 95%

de agua, 5% de acetonitrilo, NH_4OAc 10 mM, B = 10% de agua, 90% de acetonitrilo, 10 mM de NH_4OAc). Después de la concentración de los tubos de ensayo seleccionados mediante evaporación al vacío por velocidad, se aisló el compuesto del título como un sólido amarillo (142.5 mg, 56% de rendimiento).

^1H RMN (400 MHz, DMSO-d_6) δ 12.35-12.09 (br m, 1H), 9.17 (s, 2H), 8.35 (d, *J* = 8.3 Hz, 2H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.80-7.72 (m, 1H), 7.56 (s, 1H), 4.92-4.77 (m, 1H), 4.21-4.13 (m, 1H), 3.61-3.05 (2m, 4H), 3.02-2.80 (2m, 2H), 2.37-1.67 (series de m, 6H), 1.41 y 1.17 (2s, 9H).

LCMS Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, RT = 1.77 min, >95% de índice de homogeneidad.

LRMS: Análisis calculado para $C_{29}H_{35}N_8O_2$ 527.29; encontrado: 527.34 $(M+H)^+$.

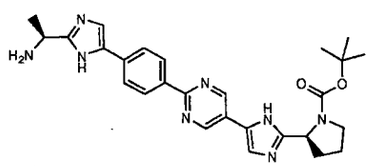
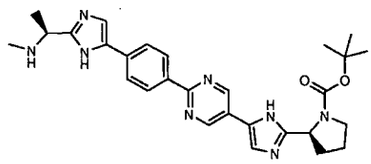
HRMS: Análisis calculado para $C_{29}H_{35}N_8O_2$ 527.2883; encontrado: 527.2874 $(M+H)^+$.

Se usó el mismo procedimiento para preparar los ejemplos 152i-2 a 152i-3.

Condiciones de LC: *Condición 1*: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de

TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

Condición 2: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 2 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

Ejemplo 152i-2	 Preparado de 152g-15	t_R = 1.70 min (95.7%); Condición 1 LRMS: Anal. Calcd. para: $C_{27}H_{33}N_8O_2$ 501.27; encontrado: 501.35 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{27}H_{33}N_8O_2$ 501.2726 encontrado: 501.2709 $(M+H)^+$.
Ejemplo 152i-3	 Preparado de 152g-16	t_R = 1.77 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{28}H_{35}N_8O_2$ 515.29; encontrado: 515.37 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{28}H_{35}N_8O_2$ 515.2883 encontrado: 515.2869 $(M+H)^+$.

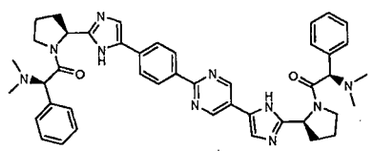
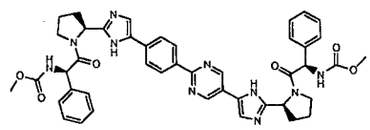
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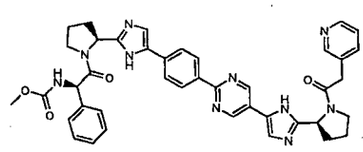
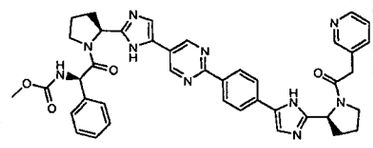
Ejemplos 152j-1 a 152j-28

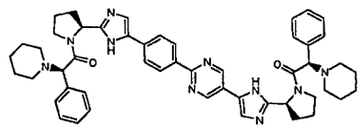
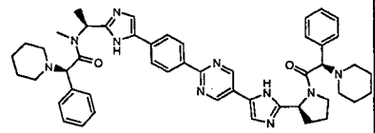
Los ejemplos 152j fueron aislados como sales TFA o AcOH preparadas usando el procedimiento para convertir el ejemplo 148e en 148.

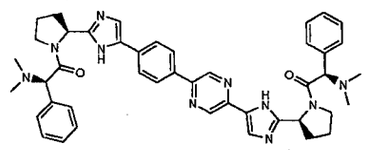
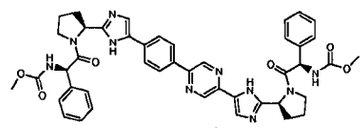
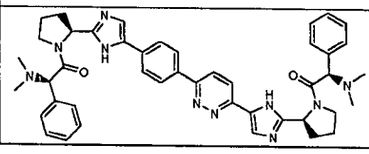
Condiciones de LC: *Condición 1*: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

Condición 2: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 2 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

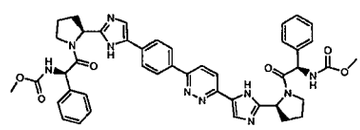
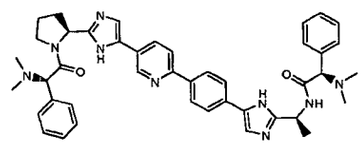
Ejemplo	*Nombre del Compuesto*	*Estructura*	*Datos*
Ejemplo 152j-1	(1R)-2-((2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-5-pirimidinil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina	 Preparado de 152h-1 y *Extremo*-1.	t_R = 1.61 min; (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{44}H_{49}N_{10}O_2$ 749.40 encontrado: 749.32 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{44}H_{49}N_{10}O_2$ 749.4040 encontrado: 749.4042 $(M+H)^+$
Ejemplo 152j-2	((1R)-2-((2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-((metoxicarbonil) amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-5-pirimidinil)-1H-	 Preparado de 152h-1 y *Extremo*-4	t_R = 1.99 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{44}H_{45}N_{10}O_6$ 809.35 encontrado: 809.17 $(M+H)^+$

	imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		HRMS: Anal. Calcd. para: $C_{44}H_{45}N_{10}O_6$ 809.3524 encontrado: 809.3505 $(M+H)^+$
Ejemplo 152j-3	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4-(5-(2-((2S)-1-(3-piridinilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirimidinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo	 Preparado de 152h-11 y *Extremo-4*	t_R = 1.65 min (92.3%); Condición 1 LRMS: Anal. Calcd. para: $C_{41}H_{41}N_{10}O_2$ 737.33 encontrado: 737.49 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{41}H_{41}N_{10}O_4$ 737.3312 encontrado: 737.3342 $(M+H)^+$
Ejemplo 152j-4	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(2-(4-(2-((2S)-1-(3-piridinilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-5-pirimidinil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo	 Preparado de 152h-12 y *Extremo-4*	t_R = 1.64 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{41}H_{41}N_{10}O_4$ 737.33 encontrado: 737.75 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{41}H_{41}N_{10}O_4$

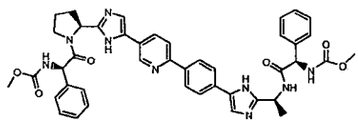
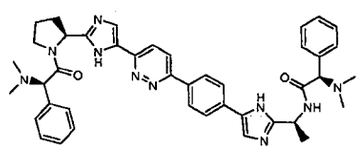
			737.3312 encontrado: 737.3284 $(M+H)^+$
Ejemplo 152j-5	5(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil) acetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-(4-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil) acetil)-2-pirrolidinil)-1H-imidazol-4-il) fenil)pirimidina	 Preparado de 152h-1 y *Extremo-14*	t_R = 1.70 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{50}H_{57}N_{10}O_2$ 829.47 encontrado: 829.39 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{50}H_{57}N_{10}O_2$ 829.4666 encontrado: 829.4658 $(M+H)^+$
Ejemplo 152j-6	(2R)-N-metil-2-fenil-N-((1S)-1-(4-(4-(5-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidnil) acetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirimidinil)fenil)-1H-imidazol-2-il)etil)-2-(1-piperidinil) acetamida piperidinyl)acetamide	 Preparado de 152h-13 y *Extremo-14*	t_R = 1.66 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{49}H_{57}N_{10}O_2$ 817.47 encontrado: 817.44 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{49}H_{57}N_{10}O_2$ 817.4666 encontrado: 817.4673 $(M+H)^+$

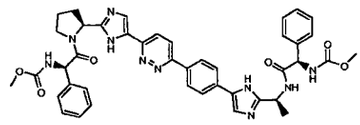
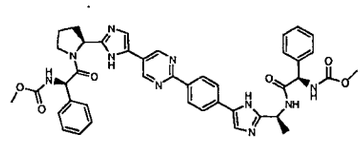
Ejemplo 152j-7	(1R)-2-((2S)-2-(5-(5-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-2-pirazinil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina	 Preparado de 152h-2 y *Extremo*-1	t_R = 1.60 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{41}H_{49}N_{10}O_2$ 749.40 encontrado: 749.31 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{44}H_{49}N_{10}O_2$ 749.4040 encontrado: 749.4031 $(M+H)^+$
Ejemplo 152j-8	((1R)-2-((2S)-2-(5-(5-(4-(2-((2S)-1-((2R)-2-((metoxicarbonil) amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-2-pirazinil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) carbamato de metilo	 Preparado de 152h-2 y *Extremo*-4	t_R = 2.01 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{44}H_{45}N_{10}O_6$ 809.35 encontrado: 809.24 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{44}H_{45}N_{10}O_6$ 809.3523 encontrado: 809.3493 $(M+H)^+$
Ejemplo 152j-9	(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-		t_R = 1.76 min (>95%); Condición 1

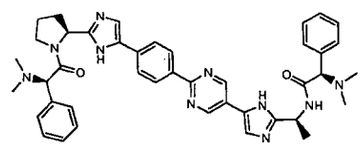
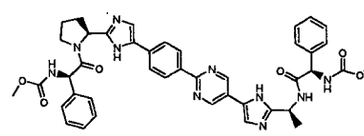
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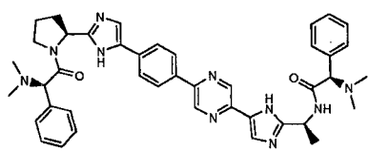
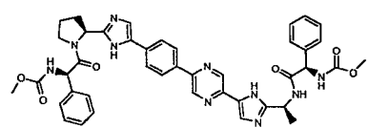
	fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-3-piridazinil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina	Preparado de 152h-10 y *Extremo*-1	LRMS: Anal. Calcd. para: $C_{44}H_{49}N_{10}O_2$ 749.40 encontrado: no obs $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{44}H_{49}N_{10}O_2$ 749.4040 encontrado: 749.4056 $(M+H)^+$
Ejemplo 152j-10	((1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-((metoxicarbonil) amino)-2-(fenilacetil) -2-pirrolidinil)-1H-imidazol-5-il)fenil)-3-piridazinil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Preparado de 152h-10 y *Extremo*-4	t_R = 2.17 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{44}H_{45}N_{10}O_6$ 809.35 encontrado: 809.59 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{44}H_{45}N_{10}O_6$ 809.3524 encontrado: 809.3499 $(M+H)^+$
Ejemplo 152j-11	(2R)-2-(dimetilamino) -N-((1S)-1-(5-(4-(5-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-	 Preparado de 152h-7 y *Extremo*-1	t_R = 1.56 min (>95%); Condición 1 LRMS: Anal. Calcd. para:

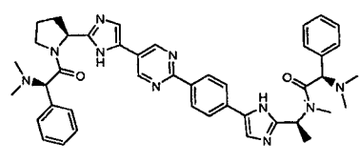
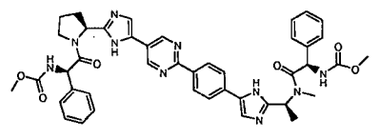
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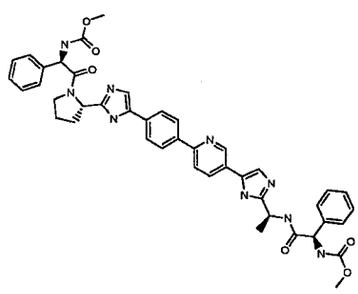
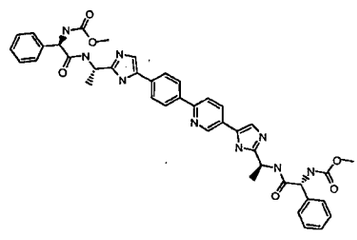
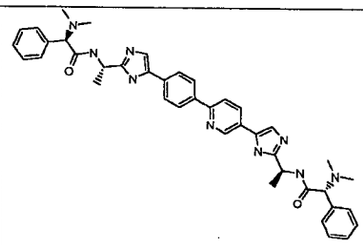
	pirrolidinil)-1H-imidazol-5-il)-2-piridinil)fenil)-1H-imidazol-2-il)etil)-2-fenilacetamida		$C_{43}H_{48}N_9O_2$ 722.39 encontrado: 722.89 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{43}H_{48}N_9O_2$ 722.3931 encontrado: 722.3930 $(M+H)^+$
Ejemplo 152j-12	((1R)-2-((2S)-2-(5-(6-(4-(2-((1S)-1-(((2R)-2-((metoxicarbonil) amino)-2-fenilacetil) amino)etil)-1H-imidazol-5-il)fenil)-3-piridinil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) carbamato de metilo	 Preparado de 152h-7 y *Extremo*-4	t_R = 1.95 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{43}H_{44}N_9O_6$ 782.34 encontrado: 782.93 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{43}H_{44}N_9O_6$ 782.3415 encontrado: 782.3398 $(M+H)^+$
Ejemplo 152j-13	(2R)-2-(dimetilamino)-N-((1S)-1-(5-(4-(6-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-3-piridazinil)fenil)-	 Preparado de 152h-3 y *Extremo*-1	t_R = 1.55 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{42}H_{47}N_{10}O_2$ 723.39encontrado: 723.88 $(M+H)^+$

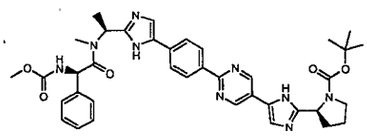
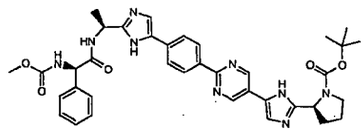
	1H-imidazol-2-il)etil)-2-fenilacetamida		HRMS: Anal. Calcd. para: $C_{42}H_{47}N_{10}O_2$ 723.3883 encontrado: 723.3903 $(M+H)^+$
Ejemplo 152j-14	((1R)-2-((2S)-2-(5-(6-(4-(2-((1S)-1-(((2R)-2-((metoxicarbonil) amino)-2-fenilacetil) aminoetil)-1H-imidazol-5-il)fenil)-3-piridazinil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Preparado de 152h-3 y *Extremo*-4	t_R = 1.95 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{42}H_{43}N_{10}O_6$ 783.34 encontrado: 783.95 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{42}H_{43}N_{10}O_6$ 783.3367 encontrado: 783.3337 $(M+H)^+$
Ejemplo 152j-15	((1R)-2-((2S)-2-(5-(2-(4-(2-((1S)-1-(((2R)-2-((metoxicarbonil) amino)-2-fenilacetil) amino)etil)-1H-imidazol-5-il)fenil)-5-pirimidinil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-	 Preparado de 152h-4 y *Extremo*-4	t_R = 1.97 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{42}H_{43}N_{10}O_6$ 783.34 encontrado: 783.97 $(M+H)^+$ HRMS: Anal. Calcd. para:

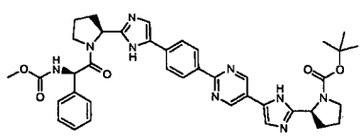
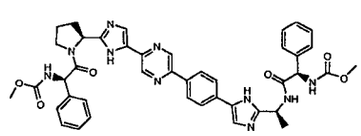
	feniletil)carbamato de metilo		$C_{42}H_{43}N_{10}O_6$ 783.3367 encontrado: 783.3357 $(M+H)^+$
Ejemplo 152j-16	(2R)-2-(dimetilamino) -N-((1S)-1-(5-(2-(4-(2 -((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-5-pirimidinil)-1H-imidazol-2-il)etil)-2-fenilacetamida	 Preparado de 152h-9 y *Extremo*-1	t_R = 1.61 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{42}H_{47}N_{10}O_2$ 723.39 encontrado: 723.52 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{42}H_{47}N_{10}O_2$ 723.3883 encontrado: 723.3893 $(M+H)^+$
Ejemplo 152j-17	((1R)-2-((2S)-2-(5-(4-(5-(2-((1S)-1-(((2R)-2 -((metoxicarbonil) amino)-2-fenilacetil) aminoetil)-1H-imidazol-5-il)-2-pirimidinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Preparado de 152h-9 y *Extremo*-4	t_R = 1.99 min (95.6%); Condición 1 LRMS: Anal. Calcd. para: $C_{42}H_{43}N_{10}O_6$ 783.34 encontrado: 783.44 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{42}H_{43}N_{10}O_6$ 783.3367 encontrado: 783.3328 $(M+H)^+$

Ejemplo 152j-18	(2R)-2-(dimetilamino)-N-((1S)-1-(5-(5-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-2-pirazinil)-1H-imidazol-2-il)etil)-2-fenilacetamida	 Preparado de 152h-8 y *Extremo*-1	t_R = 1.60 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{42}H_{47}N_{10}O_2$ 723.39 encontrado: 723.47 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{42}H_{47}N_{10}O_2$ 723.3883 encontrado: 723.3861 $(M+H)^+$
Ejemplo 152j-19	((1R)-2-((2S)-2-(5-(4-(5-(2-((1S)-1-(((2R)-2-((metoxicarbonil) amino)-2-fenilacetil) amino)etil)-1H-imidazol-5-il)-2-pirazinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Preparado de 152h-8 y *Extremo*-4	t_R = 1.97 min (94.7%); Condición 1 LRMS: Anal. Calcd. para: $C_{42}H_{43}N_{10}O_6$ 783.34 encontrado: 783.69 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{42}H_{43}N_{10}O_6$ 783.3367 encontrado: 783.3345 $(M+H)^+$

Ejemplo 152j-20	(2R)-2-(dimetilamino)-N-((1S)-1-(5-(4-(5-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirimidinil)fenil)-1H-imidazol-2-il)etil)-N-metil-2-fenilacetamida	 Preparado de 152h-13 y *Extremo-1*	t_R = 1.54 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{43}H_{49}N_{10}O_2$ 737.40 encontrado: 737.54 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{43}H_{49}N_{10}O_2$ 737.4040 encontrado: 7374066 $(M+H)^+$
Ejemplo 152j-21	((1R)-2-((2S)-2-(5-(2-(4-(2-((1S)-1-(((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)(metil)amino)etil)-1H-imidazol-5-il)fenil)-5-pirimidinil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Preparado de 152h-13 y *Extremo-4*	t_R = 2.00 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{43}H_{45}N_{10}O_6$ 797.35 encontrado: 797.38 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{43}H_{45}N_{10}O_6$ 797.3524 encontrado: 797.3528 $(M+H)^+$

Ejemplo 152j-22	((1R)-2-((2S)-2-(5-(4-(5-(2-((1S)-1-(((2R)-2-((metoxicarbonil) amino)-2-fenilacetil) amino)etil)-1H-imidazol-5-il)-2-piridinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Preparado de 152h-5 y *Extremo*-4	t_R = 1.46 min (condición 2, 98%) LRMS: Anal. Calcd. para: $C_{43}H_{43}N_9O_6$ 781.33; encontrado: 782.34 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{43}H_{44}N_9O_6$ 782.3415 encontrado: 782.3417 $(M+H)^+$
Ejemplo 152j-23	((1R)-2-(((1S)-1-(5-(6-(4-(2-((1S)-1-(((2R)-2-((metoxicarbonil) amino)-2-fenilacetil) amino)etil)-1H-imidazol-5-il)fenil)-3-piridinil)-1H-imidazol-2-il)etil)amino)-2-oxo-1-feniletil) carbamato de metilo	 Preparado de 152h-6 y *Extremo*-4	t_R = 1.44 min condición 2, 90%) LRMS: Anal. Calcd. para: $C_{41}H_{41}N_9O_6$ 755.32; encontrado: 756.35 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{41}H_{42}N_9O_6$ 756.3258 encontrado: 756.3239 $(M+H)^+$.
Ejemplo 152j-24	(2R)-2-(dimetilamino)-N-((1S)-1-(5-(6-(4-(2-((1S)-1-(((2R)-2-(dimetilamino)-2-		t_R = 1.18 min (condición2, 91%) LRMS: Anal. Calcd. para:

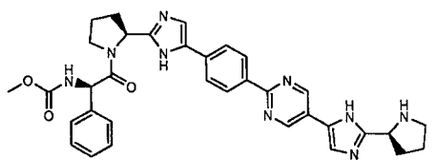
	fenilacetil)amino)etil) -1H-imidazol-5-il) fenil)-3-piridinil)-1H-imidazol-2-il)etil)-2-fenilacetamida	Preparado de 152h-6 y *Extremo* 1	$C_{41}H_{45}N_9O_2$ 695.37;encontrado: 696.37 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{41}H_{46}N_9O_2$ 696.3774 encontrado: 696.3806 $(M+H)^+$.
Ejemplo 152j-25		 Preparado de 152i-3 y *Extremo*-4	t_R = 2.08 min (95.8 %); Condición 1 LRMS: Anal. Calcd. para: $C_{38}H_{44}N_9O_5$ 706.35;encontrado: 706.53 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{38}H_{44}N_9O_5$ 706.3465; encontrado: 706.3492 $(M+H)^+$.
Ejemplo 152j-26		 Preparado de 152i-2 y *Extremo*-4	t_R = 2.04 min (96.4 %); Condición 1 LRMS: Anal. Calcd. para: $C_{37}H_{42}N_9O_5$ 692.33;encontrado: 692.49 $(M+H)^+$. HRMS: Anal.

			Calcd. para: $C_{37}H_{42}N_9O_5$ 692.3309; encontrado: 692.3322 $(M+H)^+$.
Ejemplo 152j-27		 Preparado de 152i-1 y *Extremo*-4	t_R = 2.04 min (>95 %); Condición 1 LRMS: Anal. Calcd. para: $C_{39}H_{44}N_9O_5$ 718.35;encontrado: 718.49 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{39}H_{44}N_9O_5$ 718.3465; encontrado: 718.3483 $(M+H)^+$.
Ejemplo 152j-28	((1R)-2-((2S)-2-(5-(5-(4-(2-((1S)-1-(((2R)-2-((metoxicarbonil) amino)-2-fenilacetil) amino)etil)-1H-imidazol-5-il)fenil)-2-pirazinil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) carbamato de metilo	 Preparado de 152h-14 y *Extremo*-4	t_R = 2.00 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{42}H_{43}N_{10}O_6$ 783.34encontrado: 783.96 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{42}H_{43}N_{10}O_6$ 783.3367 encontrado: 783.3375 $(M+H)^+$

Ejemplos 152k-1 a 152k-

Ejemplo 152k-1 a partir de 152j-27

Éster metílico de ácido {(R)-2-oxo-1-fenil-2-[(S)-2-(5-{4-[5-((S)-2-pirrolidin-2-il-3H-imidazol-4-il)-pirimidin-2-il]-fenil}-1H-imidazol-2-il)-pirrolidin-1-il]-etil}-carbámico



HCl 4 *N* frío (0°C) en dioxanos (4 mL) se añadió con una jeringa a éster *ter*-butílico de ácido (S)-2-{5-[2-(4-{2-[(S)-1-((R)-2-metoxicarbonilamino-2-fenil-acetil)-pirrolidin-2-il]-3*H*-imidazol-4-il}-fenil)-pirimidin-5-il]-1*H*-imidazol-2-il}-pirrolidin-1-carboxílico (104.6 mg, 0.146 mmoles) en un matraz en forma de pera de 100 mL seguido por MeOH (0.5 mL). La mezcla homogénea se agitó a temperatura ambiente durante 15 minutos antes de que se observara un precipitado. Después de agitar más durante 1.75 horas, la suspensión se diluyó con éter y hexanos. La filtración por succión de una porción pequeña de la suspensión produjo el compuesto del título como un sólido amarillo que se usó para propósitos de caracterización. El resto de la suspensión se concentró hasta la sequedad y se puso al alto vacío durante 16 horas. Se aisló el resto del compuesto del título como un sólido amarillo (137.7 mg, 123%) que se usó sin purificación adicional.

^{1}H RMN (500 MHz, DMSO-d_6) δ 15.20 y 14.66 (2m, 1H), 10.29 (br s, 0.7H), 9.38-9.36 (m, 2H), 8.55-8.00 (series de m, 4H), 7.42-7.28 (2m, 3H), 5.53-4.00 (series de m, 7H), 3.99-3.13 (series de m, 4H), 3.57 y 3.52 (2s, 3H), 2.50-1.84 (series de m, 8H).

LCMS Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, RT = 1.79 min, >95% de índice de homogeneidad.

LRMS: Análisis calculado para $C_{34}H_{36}N_9O_3$ 618.29; encontrado: 618.42 $(M+H)^+$.

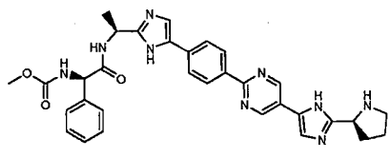
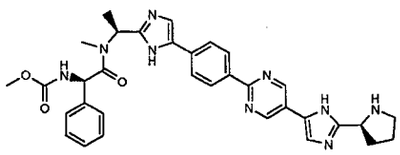
HRMS: Análisis calculado para $C_{34}H_{36}N_9O_3$ 618.2921; encontrado: 618.2958 $(M+H)^+$.

Se usó el mismo procedimiento para preparar los ejemplos 152k-2 a 152k-3.

Condiciones de LC: *Condición 1*: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

Condición 2: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 2 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de

inyección.

Ejemplo	*Nombre del Compuesto*	*Estructura*	*Datos*
Ejemplo 152k-2		 Preparado de 152j-26	t_R = 1.74 min (>95 %); Condición 1 LRMS: Anal. Calcd. para: $C_{32}H_{34}N_9O_3$ 592.28; encontrado: 592.41 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{32}H_{34}N_9O_3$ 592.2785; encontrado: 592.2775 $(M+H)^+$.
Ejemplo 152k-3		 Preparado de 152j-25	t_R = 1.79 min (>95 %); Condición 1 LRMS: Anal. Calcd. para: $C_{33}H_{36}N_9O_3$ 606.29; encontrado:

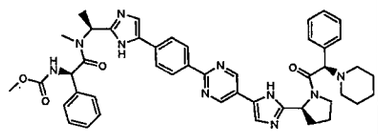
			606.43 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{33}H_{36}N_9O_3$ 606.2941; encontrado: 606.2925 $(M+H)^+$.

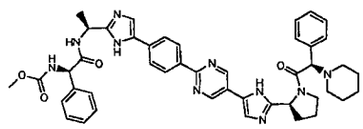
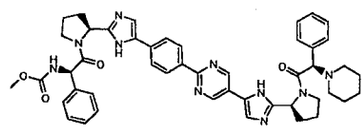
Ejemplos 1521-1 a 1521-3

Los ejemplos 152l-1 a 152l-3 fueron aislados como sales TFA o AcOH preparados usando el mismo procedimiento que para convertir el ejemplo 148e en 148.

Condiciones de LC: *Condición 1*: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

Condición 2: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 2 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

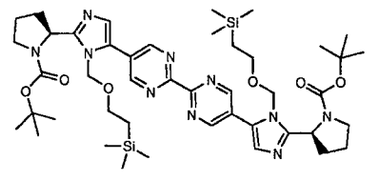
Ejemplo	*Nombre del Compuesto*	*Estructura*	*Datos*
Ejemplo 152l-1	((1R)-2-(metil((1S)-1-(4-(4-(5-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil) acetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirimidinil)fenil)-1H-imidazol-2-il)etil)amino)-2-oxo-1-feniletil) carbamamato de metilo	 Preparado de 152k-3 y *Extremo-14*	t_R = 1.87 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{46}H_{51}N_{10}O_4$ 807.41 encontrado: 807.57 $(M+H)^+$ HRMS: Anal. Calcd. para:

			$C_{46}H_{51}N_{10}O_4$ 807.4095 encontrado: 807.4128 $(M+H)^+$
Ejemplo 152l-2	((1R)-2-oxo-1-fenil-2-(((1S)-1-(4-(4-(5-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirimidinil)fenil)-1H-imidazol-2-il)etil)amino)etil)carbamato de metilo	 Preparado de 152k-2 y *Extremo-14*	t_R = 1.83 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{45}H_{49}N_{10}O_4$ 793.39 encontrado: 793.52 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{45}H_{49}N_{10}O_4$ 793.3938 encontrado: 793.3934 $(M+H)^+$
Ejemplo 152l-3	((1R)-2-oxo-1-fenil-2-((2S)-2-(4-(4-(5-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirimidinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)etil)carbamato de metilo	 Preparado de 152k-1 y *Extremo-14*	t_R = 1.87 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{47}H_{51}N_{10}O_4$ 819.41 encontrado: 819.50 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{47}H_{51}N_{10}O_4$ 819.4095 encontrado: 819.4127 $(M+H)^+$

Ejemplos 153a-1 a 153a-4

Ejemplo 153a-1 preparado a partir de 152e-1

Éster ter-butílico de ácido (S)-2-[5-{5'-[2-((S)-1-ter-butoxicarbonil-pirrolidin-2-il)-3-(2-trimetilsilanil-etoximetil)-3H-imidazol-4-il]-[2,2']bipirimidinil-5-il}-1-(2-trimetilsilanil-etoximetil)-1H-imidazol-2-il]-pirrolidin-1-carboxílico



A una solución agitada de 2-(5-(2-cloropirimidin-5-il)-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*ter*-butilo (1.0 g, 2.08 mmoles) y diclorobis(benzonitrilo)paladio (40 mg, 0.104 mmoles) en DMF seco (10 mL) a temperatura ambiente bajo argón se le añadió tetrakis(dimetilamino)etileno concentrado (1.0 mL, 4.16 mmoles). La mezcla se calentó a 60°C durante 15 horas antes de que fuera diluida con acetato de etilo y se filtró por succión a través de tierra diatomácea (Celite®). El filtrado se lavó con solución saturada de $NaHCO_3$ y salmuera antes de secar con Na_2SO_4 y de la evaporación del solvente. La purificación del residuo mediante cromatografía por vaporización Biotage™ en gel de sílice (elución con gradiente de etapas con 15% de B a 15% de B para 150 mL, 15% de B a 75% de B para 1,500 mL, 75% de B a 100% de B para

1,000 mL, 100% de B a 100% de B para 1,000 mL en donde B = acetato de etilo y A = hexano seguida por una segunda elución de gradientes con 10% de B a 100% de B para 700 mL en donde B = metanol y A = acetato de etilo) dio el compuesto del título como un aceite viscoso color caramelo (487.8 mg, 26% de rendimiento).

^{1}H RMN (500 MHz, DMSO-d_6) δ 9.27 (s, 4H), 8.09-8.06 (m, 2H), 5.73-5.66 y 5.50-5.44 (2m, 2H), 5.06-4.93 (m, 2H), 3.60-3.39 (2m, 8H),2.32-2.08 (3m, 4H), 2.00-1.85 (m, 4H), 1.37 y 1.14 (2s, 18H), 0.95-0.84 (m, 4H), -0.01 (s, 18H).

LCMS Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, RT = 3.37 min, >95% de índice de homogeneidad.

LRMS: Análisis calculado para $C_{44}H_{69}N_{10}O_6S_{i2}$ 889.49; encontrado: 889.57 $(M+H)^+$.

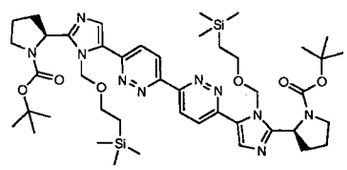
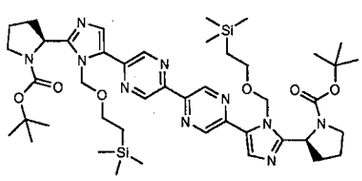
HRMS: Análisis calculado para $C_{44}H_{69}N_{10}O_6S_{i2}$ 889.4940; encontrado: 889.4920 $(M+H)^+$.

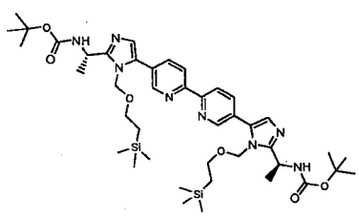
Se usó el mismo procedimiento para preparar los ejemplos 153a-2 a 153a-4.

Condiciones de LC: *Condición 1*: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5

µL de volumen de inyección.

Condición 2: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 2 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

Ejemplo	*Nombre del Compuesto*	*Estructura*	*Datos*
Ejemplo 153a-2		 Preparado de 152e-2	t_R = 3.37 min (89.6%); Condición 1 LRMS: Anal. Calcd. para: $C_{44}H_{69}N_{10}O_6Si_2$ 889.49; encontrado: 889.56 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{44}H_{69}N_{10}O_6Si_2$ 889.494; encontrado: 889.4951 $(M+H)^+$.
Ejemplo 153a-3		 Preparado de 152e-3	t_R = 3.37 min (95%); Condición 1 LRMS: Anal. Calcd. para: $C_{44}H_{69}N_{10}O_6Si_{12}$ 889.49; encontrado: 889.51 $(M+H)^+$.

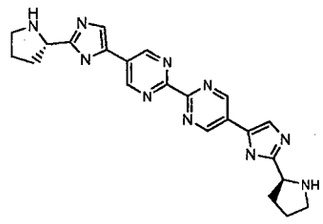
			HRMS: Anal. Calcd. para: $C_{44}H_{69}N_{10}O_6Si_2$ 889.4940; encontrado: 889.4915 $(M+H)^+$.
Ejemplo 153a-4		 Preparado de 152e-4	t_R = 2.3 min (condición 2) LRMS: Anal. Calcd. para: $C_{42}H_{66}N_8Si_2$ 834; encontrado: 835 $(M+H)^+$.

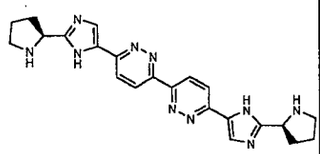
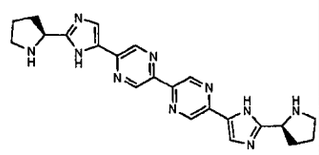
Ejemplo 153b-1-153-b3

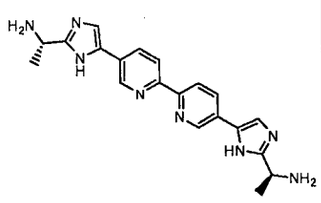
Las reacciones de hidrólisis fueron llevadas a cabo como arriba para el ejemplo 152h.

Condiciones de LC: *Condición 1*: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

Condición 2: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 2 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

Ejemplo	*Nombre del Compuesto*	*Estructura*	*Datos*
Ejemplo 153b-1		 Preparado de 153a-1	t_R = 1.18 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{22}H_{25}N_{10}$ 429.23; encontrado: 429.01 $(M+H)^+$.

			HRMS: Anal. Calcd. para: $C_{22}H_{25}N_{10}$ 429.2264; encontrado: 429.2259 $(M+H)^+$.
Ejemplo 153b-2		 Preparado de 153a-2	t_R = 1.26 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{41}H_{41}N_{10}O_2$ 737.33 encontrado: 737.49 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{41}H_{41}N_{10}O_4$ 737.3312 encontrado: 737.3342 $(M+H)^+$
Ejemplo 153b-3		 Preparado de 153a-3	t_R = 1.40 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{22}H_{25}N_{10}$ 429.23; encontrado: 429.20 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{22}H_{25}N_{10}$: 429.2264; encontrado:

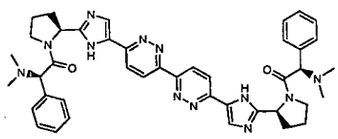
			429.2254 $(M+H)^+$
Ejemplo 153b-4		 Preparado de 153a-4	t_R = 0.85 min (condición 1) LCMS: Anal. Calcd. para: $C_{20}H_{22}N_8$ 374;encontrado: 375 $(M+H)^+$.

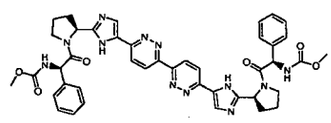
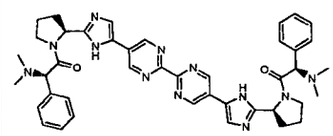
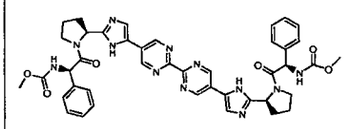
Ejemplos 153c-1 a 153c-7

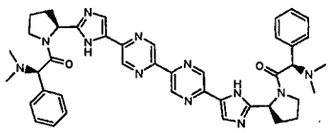
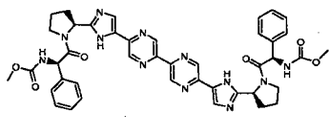
Los ejemplos 153c-1 a 153c-7 fueron aislados como sales TFA o AcOH usando el procedimiento usado para convertir el ejemplo 148e a 148.

Condiciones de LC: *Condición 1*: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

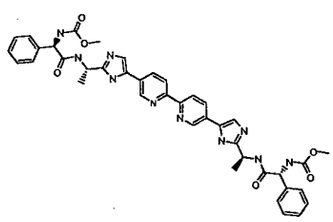
Condición 2: Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 2 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, 220 nm, 5 µL de volumen de inyección.

Ejemplo	*Nombre del Compuesto*	*Estructura*	*Datos*
Ejemplo 153c-1	(1R,1'R)-2,2'-(3,3'-bipiridazin-6,6'-diilbis (1H-imidazol-5,2-diil (2S)-2,1-pirrolidindiil))bis(N,N-dimetil-2-oxo-1-feniletanamina)	 Preparado de 153b-2 y *Extremo*-1	t_R = 1.55 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{42}H_{47}N_{12}O_2$ 751.39encontrado: 751.64 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{42}H_{47}N_{12}O_2$ 751.3945 encontrado:

			751.3936 $(M+H)^+$
Ejemplo 153c-2	(3,3'-bipiridazin-6,6'-diilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))biscarbamato de dimetilo	 Preparado de 153b-2 y *Extremo*-4	t_R = 1.95 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{42}H_{43}N_{12}O_6$ 811.34 encontrado: 811.22 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{42}H_{43}N_{12}O_6$ 811.3429 encontrado: 811.3406 $(M+H)^+$
Ejemplo 153c-3	(1R,1'R)-2,2'-(2,2'-bipirimidin-5,5'-diilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(N,N-dimetil-2-oxo-1-feniletanamina)	 Preparado de 153b-1 y *Extremo*-1	t_R = 1.51 min (>90%*); Condición 1 LRMS: Anal. Calcd. para: $C_{42}H_{47}N_{12}O_2$ 751.39 encontrado: 751.21 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{42}H_{47}N_{12}O_2$ 751.3945 encontrado: 751.3921 $(M+H)^+$
Ejemplo 153c-4	(2,2'-bipirimidin-5,5'-diilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))biscarbamato de dimetilo	 Preparado de 153b-1 y *Cap*-4	t_R = 1.88 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{42}H_{43}N_{12}O_6$ 811.34 encontrado: 811.10 $(M+H)^+$

			HRMS: Anal. Calcd. para: $C_{42}H_{43}N_{12}O_6$ 811.3429 encontrado: 811.3401 $(M+H)^+$
Ejemplo 153c-5	(1R,1'R)-2,2'-(2,2'-bipirazin-5,5'-diilbis (1H-imidazol-5,2-diil (2S)-2,1-pirrolidindiil))bis(N,N-dimetil-2-oxo-1-feniletanamina)	 Preparado de 153b-3 y *Extremo*-1	t_R = 1.61 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{42}H_{47}N_{12}O_2$ 751.39 encontrado: 751.30 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{42}H_{47}N_{12}O_2$ 751.3945 encontrado: 751.3943 $(M+H)^+$
Ejemplo 153c-6	(2,2'-bipirazin-5,5'-diilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))biscarbamato de dimetilo	 Preparado de 153b-3 y *Extremo*-4	t_R = 2.00 min (>95%); Condición 1 LRMS: Anal. Calcd. para: $C_{42}H_{43}N_{12}O_6$ 811.34 encontrado: 811.23 $(M+H)^+$ HRMS: Anal. Calcd. para: $C_{42}H_{43}N_{12}O_6$ 811.3429 encontrado: 811.3407 $(M+H)^+$

000640

Ejemplo 153c-7.	(2,2'-bipiridin-5,5'-diilbis(1H-imidazol-5,2-diil(1S)-1,1-etandiilimino((1R)-2-oxo-1-fenil-2,1-etandiil)))biscarbamato de dimetilo	 Preparado de 153b-4 y *Extremo*-4	t_R = 1.42 min (condición 2, 94%) LRMS: Anal. Calcd. para: $C_{40}H_{40}N_{10}O_6$ 756.31; encontrado: 757.34 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{40}H_{41}N_{10}O_6$ 757.3211 encontrado: 757.3180 $(M+H)^+$.

Sección F

Condiciones de LC para determinar tiempo de retención

Condición 7

Columna: Phenomenex C18 10u 4.6 X 30 mm

% B de inicio = 0

% B final = 100

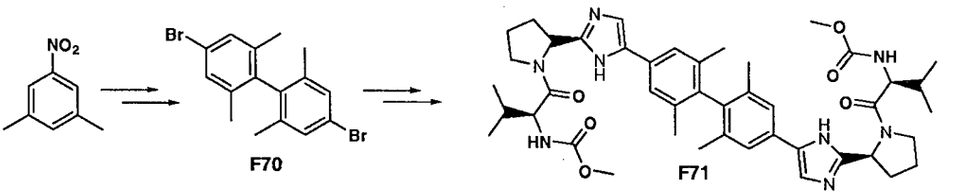
Tiempo gradiente = 3 min

Velocidad de flujo = 4 mL/Min

Longitud de onda = 220

Solvente A = 10% de metanol-90% de H_2O-0.1% de TFA

Solvente B = 90% de metanol-10% de H_2O-0.1% de TFA



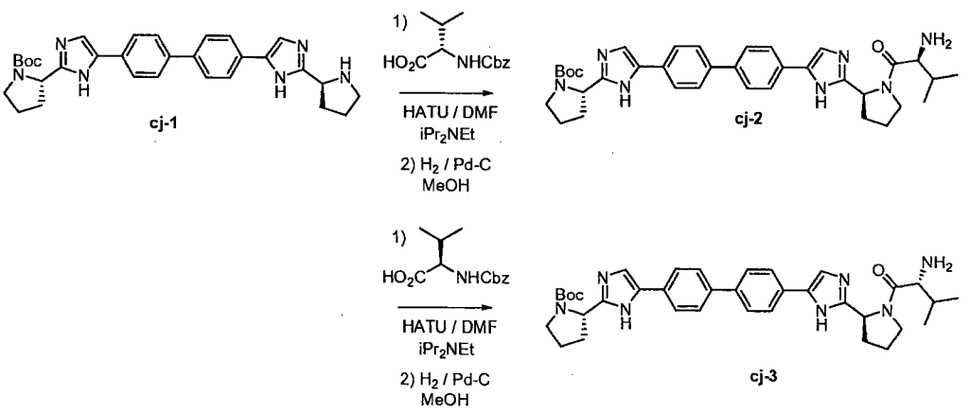
El compuesto F70 se preparó siguiendo el procedimiento descrito en Anna Helms et al., *J. Am. Chem. Soc.* 1992 114(15) pág. 6227-6238.

El compuesto F71 se preparó de manera análoga al procedimiento usado para sintetizar el ejemplo 1.

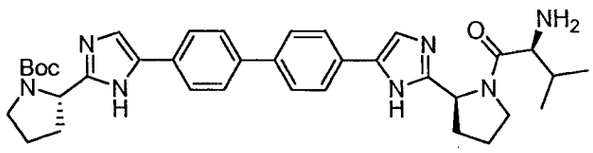
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 0.69-0.95 (m, 12H) 1.92 (s, 12H) 1.97-2.27 (m, 8H) 2.40 (s, 2H) 3.55 (s, 6H) 3.73-3.97 (m, 4H) 4.12 (t, *J* = 7.78 Hz, 2H) 5.14 (t, *J* = 7.02 Hz, 2H) 7.34 (d, *J* = 8.24 Hz, 2H) 7.49-7.70 (m, 4H) 8.04 (s, 2H) 14.59 (s, 2H) RT = 2.523 minutos (condición 7, 96%); LRMS: Análisis calculado para C44H58N8O6 794.45; encontrado: 795.48 $(M+H)^+$.

Sección cj: Síntesis de reemplazados de carbamato

Ejemplos cj-2 y cj-3



Preparación de 2-(5-(4'-(2-((*S*)-1-((*S*)-2-amino-3-metilbutanoil)pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-carboxilato de (*S*)-*ter*-butilo (cj-2)



A una solución de 2-(5-(4'-(2-((*S*)-pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-carboxilato de (*S*)-*ter*-butilo (cj-1) (1.00 g, 1.91 mmoles), iPr_2Net (1.60 mL, 9.19 mmoles) y *N*-Z-valina (0.62 g, 2.47 mmoles) en DMF (10 mL) se le añadió HATU (0.92 g, 2.42 mmoles). La solución se dejó agitar a temperatura ambiente durante 1 hora y luego se vertió en agua helada (alrededor de 250 mL) y se dejó reposar durante 20 minutos. La mezcla se filtró y el sólido se lavó con agua y luego se secó al vacío durante la noche para dar un sólido incoloro (1.78 g) que se usó como tal en la siguiente etapa. LCMS: Análisis calculado para $C_{44}H_{51}N_7O_5$: 757; encontrado 758 $(M+H)^+$.

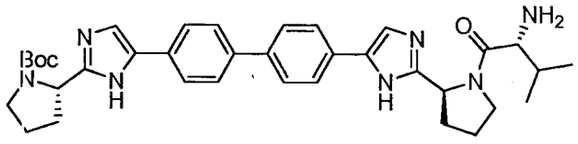
Una mezcla de este material (1.70 g) y 10% de Pd-C (0.37 g) en MeOH (100 mL) se hidrogenó (presión de balón) durante 12 horas. La mezcla se filtró después y el solvente se removió al vacío. El residuo se purificó mediante cromatografía en gel de sílice (sistema Biotage/0-10% de MeOH-CH_2Cl_2) para dar el compuesto del título como una espuma

amarillo claro (0.90 g, 76%).

^{1}H RMN (400 MHz, DMSO-d_6) δ 12.18 (s, 0.35H), 11.73 (s, 0.65H), 11.89 (s, 0.65H), 11.82 (s, 0.35H), 7.77-7.81 (m, 3H), 7.57-7.71 (m, 5H), 7.50-7.52 (m, 2H), 5.17 (dd, *J* = 3.6, 6.5 Hz, 0.3H), 5.08 (dd, *J* = 3.6, 6.5 Hz, 0.7H), 4.84 (m, 0.3H), 4.76 (m, 0.7H), 3.67-3.69 (m, 1H), 3.50-3.62 (m, 1H), 3.34-3.47 (m, 2H), 2.22-2.28 (m, 2H), 2.10-2.17 (m, 2H), 1.74-2.05 (m, 6H), 1.40 (s, 4H), 1.15 (s, 5H), 0.85-0.91 (m, 4H), 0.79 (d, *J* = 6.5 Hz, 2H).

LCMS: Análisis calculado para $C_{36}H_{45}N_7O_3$: 623; encontrado: 624 $(M+H)^+$.

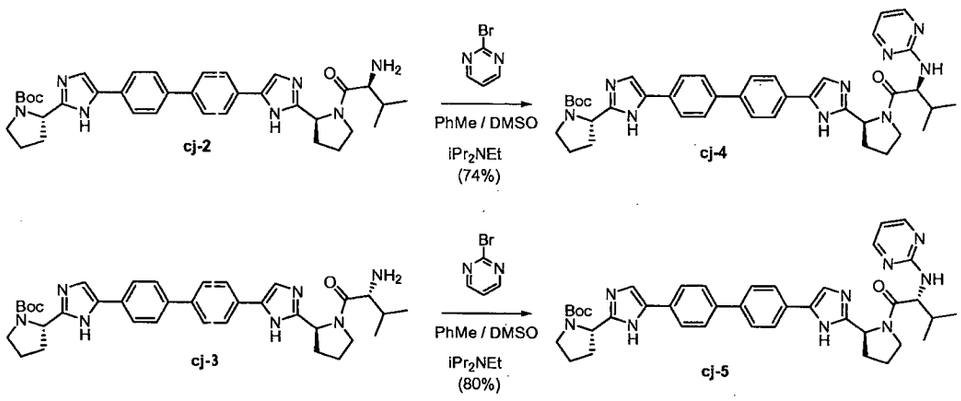
Preparación de 2-(5-(4'-(2-((*S*)-1-((*R*)-2-amino-3-metilbutanoil)pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-carboxilato de (*S*)-*ter*-butilo (cj-3)



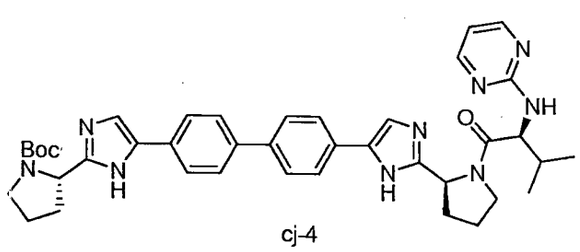
2-(5-(4'-(2-((*S*)-1-((*R*)-2-Amino-3-metilbutanoil)pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-carboxilato de (*S*)-*ter*-butilo (cj-3) se preparó usando el mismo método que el usado para preparar cj-2 para dar una espuma incolora (1.15 g, 76%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 12.17 (s, 0.35H), 12.04 (s, 0.65H), 11.89 (s, 0.65H), 11.81 (s, 0.35H), 7.78-7.83 (m,

3H), 7.60-7.71 (m, 5H), 7.43-7.52 (m, 2H), 5.22-5.25 (m, 0.4H), 5.05-5.07 (m, 0.6H), 4.83-4.86 (m, 0.5H), 4.72-4.78 (m, 0.5H), 3.78-3.84 (m, 1H), 3.49-3.64 (m, 2H), 3.35-3.43 (m, 2H), 2.19-2.32 (m, 1H), 2.04-2.17 (m, 3H), 1.95-2.04 (m, 2H), 1.76-1.90 (m, 3H), 1.40 (s, 4H), 1.15 (s, 5H), 0.85-0.91 (m, 4H), 0.67 (d, J = 6.5 Hz, 1H), 0.35 (d, J = 6.5 Hz, 1H). LCMS: Análisis calculado para $C_{36}H_{45}N_7O_3$: 623; encontrado: 624 $(M+H)^+$.

Ejemplos cj-4 y cj-5



Preparación de 2-(5-(4'-(2-((*S*)-1-((*S*)-3-metil-2-(pirimidin-2-ilamino)butanoil)pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-carboxilato de (*S*)-*ter*-butilo (cj-4)



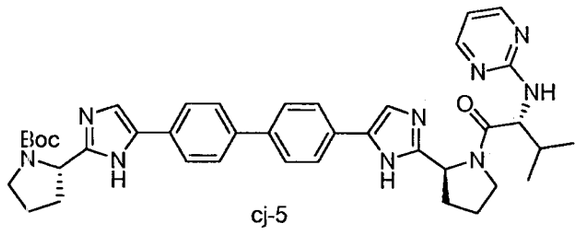
cj-4

Una mezcla de 2-(5-(4'-(2-((*S*)-1-((*S*)-2-amino-3-metilbutanoil)pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-carboxilato de (*S*)-*ter*-butilo (cj-2) (0.45 g, 0.72 mmoles), 2-bromopirimidina (0.37 g, 2.34 mmoles) e iPr_2Net (0.20 mL, 1.18 mmoles) en tolueno-DMSO (4:1, 5 mL) se calentó a 90°C durante la noche. Los volátiles se removieron al vacío y el residuo se purificó mediante HPLC preparativa (YMC Pack C-18, 30X100 mm/MeCN-H_2O-TFA). El compuesto del título (0.56 g, 74%), como su sal TFA, se obtuvo como un cristal amarillo-anaranjado.

^1H RMN (400 MHz, DMSO-d_6) δ 14.56 (br s, 2H), 8.28 (d, *J* = 5.0 Hz, 1H), 8.12-8.20 (m, 2H), 7.94-7.97 (m, 3H), 7.83-7.91 (m, 5H), 7.06 (d, *J* = 8.1 Hz, 1H), 6.62 (app t, *J* = 5.0 Hz, 1H), 4.99-5.10 (m, 2H), 4.50 (app t, *J* = 7.7 Hz, 1H), 4.07-4.12 (m, 2H), 3.83-3.87 (m, 1H), 3.56-3.62 (m, 1H), 3.40-3.47 (m, 2H), 2.36-2.41 (m, 1H), 1.94-2.22 (m, 6H), 1.40 (s, 4H), 1.17 (s, 5H), 0.88 (app t, *J* = 6.5 Hz, 6H).

LCMS: Análisis calculado para $C_{40}H_{47}N_9O_3$: 701; encontrado: 702 $(M+H)^+$.

Preparación de 2-(5-(4'-(2-((*S*)-1-((*R*)-3-metil-2-(pirimidin-2-ilamino)butanoil)pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-carboxilato de (*S*)-*ter*-butilo (cj-5)



cj-5

La sal TFA del compuesto del título se preparó siguiendo el mismo método que el usado para preparar cj-4 para dar un sólido amarillo claro (0.375 g, 59%).

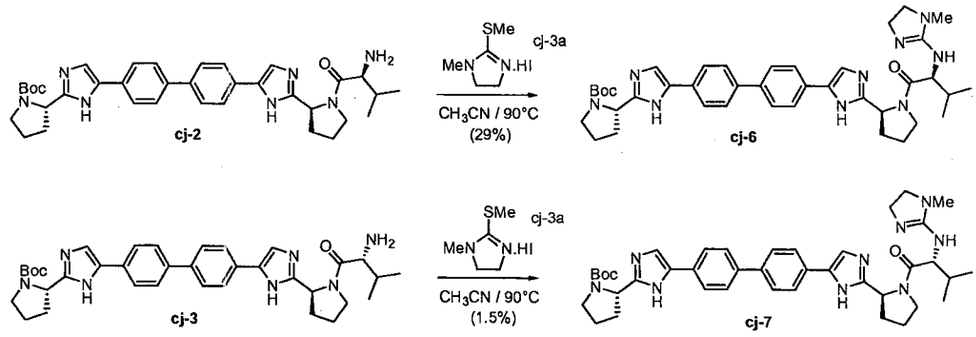
^{1}H RMN (400 MHz, DMSO-d_6) δ 14.67 (br s, 2H), 8.30 (d, *J* = 4.3 Hz, 1H), 8.04-8.19 (m, 2H), 7.84-7.96 (m, 8H), 6.88 (d, *J* = 8.6 Hz, 1H), 6.61 (app t, *J* = 4.5 Hz, 1H), 5.17 (dd, *J* = 4.4, 8.0 Hz, 1H), 5.00-5.07 (m, 1H), 4.67 (dd, *J* = 7.3, 8.1 Hz, 1H), 3.91-3.96 (m, 1H), 3.70-3.75 (m, 1H), 3.56-3.62 (m,1 H), 3.42-3.45 (m, 1H), 2.39-2.43 (m, 2H), 2.04-2.16 (m, 5H), 1.94-1.97 (m, 2H), 1.40 (s, 4H), 1.17 (s, 5H), 0.95 (d, *J* = 6.6 Hz, 2.5H), 0.91 (d, *J* = 6.6 Hz, 2.5H), 0.86 (d, *J* = 6.6 Hz, 0.5H), 0.81 (d, *J* = 6.6 Hz, 0.5H).

LCMS: Análisis calculado para $C_{40}H_{47}N_9O_3$: 701;

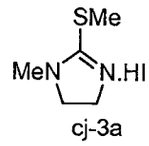
000647

encontrado: 702 $(M+H)^+$.

Ejemplos cj-6 y cj-7



Preparación de yodhidrato de 1-metil-2-(metiltio)-4,5-dihidro-1*H*-imidazol



cj-3a

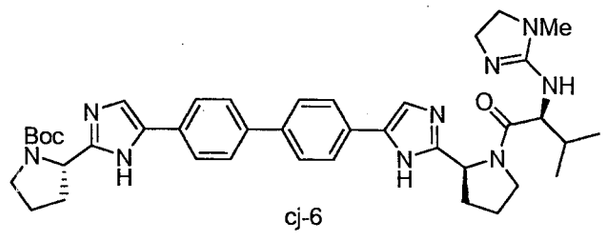
El compuesto del título se preparó de acuerdo con: Kister, J.; Assef, G.; Dou, H. J.-M.; Metzger, *J. Tetrahedron* 1976, *32*, 1395. De esta manera, una solución de *N*-metiletilendiamina (10.8 g, 146 mmoles) en EtOH-H_2O (1:1, 90 mL) se precalentó a 60°C y se añadió por goteo CS_2 (9.0 mL, 150 mmoles). La mezcla resultante se calentó a 60°C durante 3 horas y después se añadió lentamente HCl concentrado (4.7 mL). La temperatura se elevó a 90°C y se continuó agitando durante 6 horas. Después de que la mezcla enfriada se había almacenado a -20°C, se filtró y el sólido resultante se secó al vacío para dar 1-metilimidazolidin-2-tiona (8.43 g, 50%) como un sólido beige.

^{1}H RMN (400 MHz, $CDCl_3$) δ 5.15 (s, br, 1H), 3.67-3.70 (m, 2H), 3.53-3.58 (m, 2H), 3.11 (s, 3H).

A una suspensión de 1-metilimidazolidin-2-tiona (5.17 g, 44.5 mmoles) en acetona (50 mL) se le añadió MeI (2.9 mL, 46.6 mmoles). La solución se dejó agitar a temperatura ambiente durante 4 horas y el sólido resultante se filtró rápidamente y luego se secó al vacío para dar yodhidrato de 1-metil-2-(metiltio)-4,5-dihidro-1*H*-imidazol (8.79 g, 77%) como un sólido beige.

^{1}H RMN (400 MHz, $CDCl_3$) δ 9.83 (s, br, 1H), 3.99-4.12 (m, 4H), 3.10 (s, 3H), 2.99 (s, 3H).

Preparación de 2-(5-(4'-(2-((*S*)-3-metil-2-(1-metil-4-5-dihidroimidazol-2-ilamino)butanoil)pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-carboxilato de (*S*)-*ter*-butilo (cj-6)



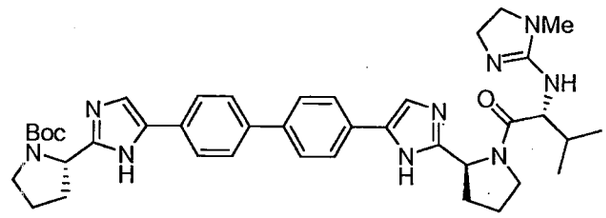
cj-6

Una mezcla de 2-(5-(4'-(2-((*S*)-1-((*S*)-2-amino-3-metilbutanoil)pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)-pirrolidin-1-carboxilato de (*S*)-*ter*-butilo (cj-2) (0.280 g, 0.448 mmoles) y yodhidrato de 1-metil-2-(metiltio)-4,5-dihidro-1*H*-imidazol (cj-3a) (0.121 g, 0.468 mmoles) en CH_3CN (5mL) se calentó a 90°C durante 12

horas. Otros 0.030 g de yodhidrato de 1-metil-2-(metiltio)-4,5-dihidro-1*H*-imidazol (cj-3a) fueron añadidos y se continuó calentando durante 12 horas más. La mezcla de reacción pura se purificó directamente mediante HPLC preparativa (Luna C-18/MeCN-H_2O-TFA) para dar la sal TFA del compuesto del título (0.089 g) como un sólido amarillo claor el cual se usó como tal en las etapas subsecuentes.

LCMS: Análisis calculado para $C_{40}H_{51}N_9O_3$: 705; encontrado: 706 $(M+H)^+$.

Preparación de 2-(5-(4'-(2-((*S*)-1-((*R*)-3-metil-2-(1-metil-4,5-dihidroimidazol-2-ilamino)butanoil)pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*ter*-butilo (cj-7)



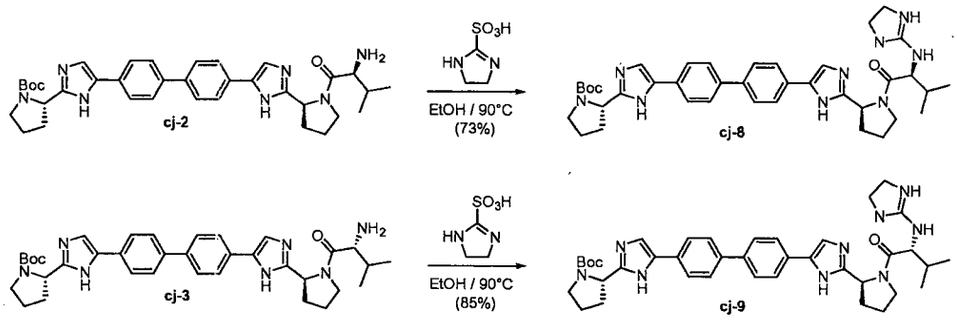
cj-7

El compuesto del título se preparó a partir de cj-3 de acuerdo con el método descrito para la síntesis de cj-6, excepto que la mezcla de reacción se purificó inicialmente mediante HPLC preparativa (YMC-Pack 25X250 mm/MeCN-H_2O-NH_4OAc) y luego se volvió a purificar mediante HPLC preparativa (Luna fenil-hexil//MeCN-H_2O-NH_4OAc). Esto dio el producto deseado (0.005 g) como una espuma que se usó como tal en las etapas

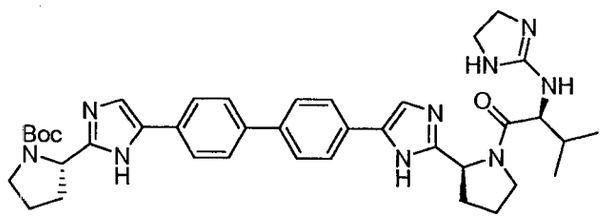
subsecuentes.

LCMS: Análisis calculado para $C_{40}H_{51}N_9O_3$: 705; encontrado: 706 $(M+H)^+$.

Ejemplos cj-8 y cj-9



Preparación de 2-(5-(4'-(2-((*S*)-1-((*S*)-3-metil-2-(3,4-dihidroimidazol-2-ilamino)butanoil)pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-carboxilato de (*S*)-*ter*-butilo (cj-8)



cj-8

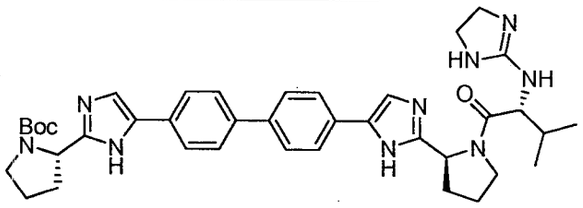
Una mezcla de 2-(5-(4'-((*S*)-1-((*S*)-2-amino-3-metilbutanoil)pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-carboxilato de (*S*)-*ter*-butilo (cj-2) (0.298 g, 0.480 mmoles), ácido 4,5-dihidro-1*H*-imidazol-2-sulfónico (AstaTech) (0.090 g, 0.60 mmoles) e iPr_2Net (0.083 mL, 0.48 mmoles) en EtOH (4 mL) se calentó a 100°C durante 12 h. La mezcla enfriada se evaporó hasta la

sequedad y el residuo se purificó mediante HPLC preparativa (Luna 5u C18/MeCN-H_2O-TFA, x2) para dar la sal TFA del compuesto del título (0.390 g, 73%) como un sólido amarillo claro.

^{1}H RMN (400 MHz, DMSO-d_6) δ 14.66 (br s, 2H), 8.51 (br s, 1H), 8.20 (d, *J* = 10.1 Hz, 2H), 8.10 (br s, 1H), 7.82-7.91 (m, 7H), 7.30 (br s, 1H), 5.12 (t, *J* = 7.1 Hz, 1H), 4.97-5.05 (m, 2H), 4.37 (dd, *J* = 4.3, 10.1 Hz, 2H), 3.82-3.86 (m, 2H), 3.73-3.77 (m, 2H), 3.59 (s, 4H), 3.39-3.48 (m, 2H), 2.15-2.25 (m, 2H), 1.93-2.07 (m, 5H), 1.40 (s, 4H), 1.17 (s, 5H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.69 (br s, 3H).

LCMS: Análisis calculado para $C_{39}H_{49}N_9O_3$: 691; encontrado: 692 $(M+H)^+$.

Preparación de 2-(5-(4'-(2-((*S*)-1-((*R*)-3-metil-2-(3,4-dihidroimidazol-2-ilamino)butanoil)pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-carboxilato de (*S*)-*ter*-butilo (cj-9)



cj-9

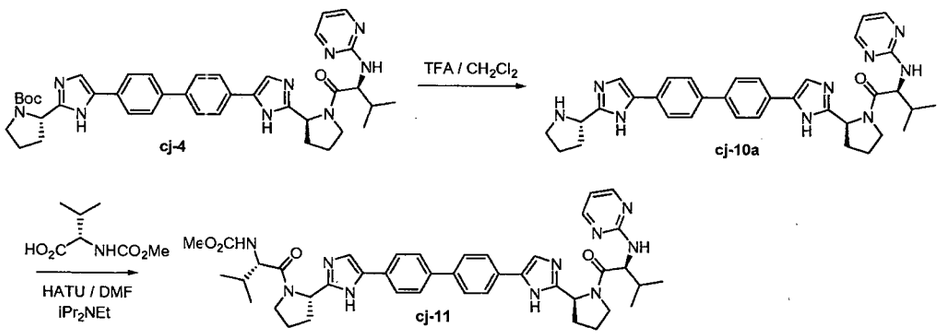
El compuesto del título se preparó a partir de cj-3 de acuerdo con el mismo método que el usado para preparar cj-8 para dar la sal TFA (0.199 g, 57%) como un cristal amarillo.

000652

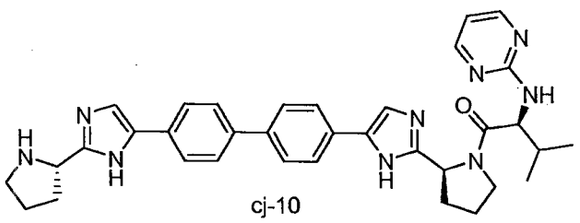
^{1}H RMN (400 MHz, DMSO-d_6) δ 14.58 (br s, 4H), 8.23 (d, *J* = 9.6 Hz, 1H), 8.11 (s, 1H), 7.87-7.89 (m, 6H), 7.25 (br s, 1H), 5.17-5.20 (m, 1H), 4.96-5.04 (m, 1H), 4.37 (dd, *J* = 5.5, 9.6 Hz, 1H), 3.91-3.95 (m, 2H), 3.37-3.46 (m, parcialmente obscurecido por H_2O, 4H), 2.39-2.42 (m, parcialmente obscurecido por solvente, 2H), 2.01-2.09 (m, 4H), 1.94-1.98 (m, 2H), 1.40 (s, 3H), 1.17 (s, 6H), 0.95 (d, *J* = 6.5 Hz, 2.5 H), 0.85 (d, *J* = 6.5 Hz, 2.5 H), 0.66 (d, *J* = 7.0 Hz, 0.5H), 0.54 (d, *J* = 6.5 Hz, 0.5H).

LCMS: Análisis calculado para $C_{39}H_{49}N_9O_3$: 691; encontrado: 692 $(M+H)^+$.

Ejemplo cj-11



Preparación de (*S*)-3-metil-2-(pirimidin-2-ilamino)-1-((*S*)-2-(5-(4'-(2-((*S*)-pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-il)butan-1-ona (cj-10a)

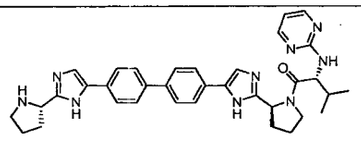


Etapa 1: Una solución de la sal TFA de 2-(5-(4'-(2-((*S*)-1-((*S*)-3-metil-2-(pirimidin-2-ilamin)butanoil)pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-carboxilato de (*S*)-*ter*-butilo (cj-4) (0.208 g, 0.199 mmoles) en una mezcla de CH_2Cl_2 (4 mL) y TFA (3 mL) se agitó a temperatura ambiente durante 1.5 horas. Los solventes se removieron después al vacío y el residuo se purificó mediante HPLC preparativa (Luna 5u C18/MeCN-H_2O-TFA) para dar la sal TFA del compuesto del título (0.391 g) como una goma anaranjada.

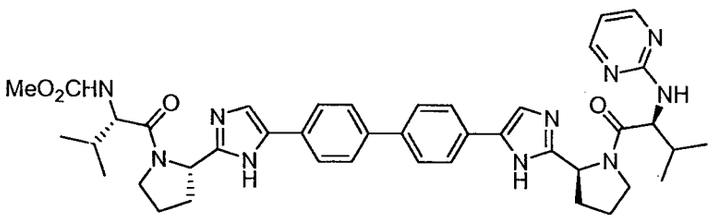
^{1}H RMN (400 MHz, DMSO-d_6) δ 14.53 (br s, 3H), 9.52-9.57 (m, 2H), 8.98-9.04 (m, 2H), 8.28 (d, *J* = 4.6 Hz, 2H), 8.13 (br s, 1H), 7.79-7.91 (m, 7H), 7.07 (d, *J* = 8.1 Hz, 1H), 6.62 (app t, *J* = 4.8 Hz, 1H), 5.07 (t, *J* = 7.1 Hz, 1H), 4.72-4.78 (m, 2H), 4.48-4.51 (m, 1H), 4.08-4.12 (m, 2H), 3.28-3.36 (m, 2H), 2.37-2.42 (m, 2H), 1.97-2.22 (m, 6H), 0.88 (app t, *J* = 4.5 Hz, 6H).

LCMS: Análisis calculado para $C_{35}H_{39}N_9O$: 601; encontrado: 602 $(M+H)^+$.

En forma similar, el siguiente ejemplo se preparó de acuerdo con el método representativo anterior.

Ejemplo	*Estructura*	*LCMS*
cj-10a (de cj-3)		LCMS: Anal. Calcd. para: $C_{35}H_{39}N_9O$: 601; encontrado: 602 $(M+H)^+$.

Preparación de ((1*S*)-2-metil-1-((2*S*)-2-(5-(4'-(2-((2*S*)-1-(*N*-2-pirimidinil-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo (cj-11)



cj-11

((1*S*)-2-metil-1-(((2*S*)-2-(5-(4'-(2-((2*S*)-1-(N-2-primidinil-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo

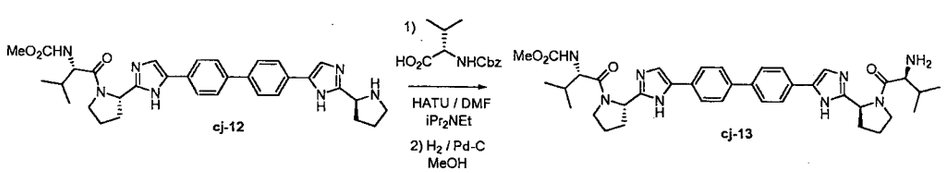
Etapa 2: A una solución de la sal TFA de (*S*)-3-metil-2-(pirimidin-2-ilamino)-1-((*S*)-2-(5-(4'-(2-((*S*)-pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-il)butan-1-ona (cj-10) (0.208 g, 0.197 mmoles) en DMF (4 mL) se le añadió

iPr_2Net (0.20 mL, 1.15 mmoles), ácido (*S*)-2-(metoxicarbonilamino)-3-metilbutanoico (0.049 g, 0.28 mmoles) y HATU (0.105 g, 0.276 mmoles). La solución se agitó durante 1.5 horas a temperatura ambiente, se diluyó con MeOH (2 mL) y se purificó directamente mediante HPLC preparativa (Luna 5u C18/MeCN-H_2O-NH_4OAc). Este material se volvió a purificar mediante cromatografía por vaporización (SiO_2/2-10% de MeOH-CH_2Cl_2) para dar un sólido que se liofilizó a partir de CH_3CN-H_2O para dar el compuesto del título (48.6 mg, 32%) como un sólido incoloro.

^1H RMN (400 MHz, DMSO-d_6) δ 11.78 (br s, 1H), 8.28 (d, *J* = 4.5 Hz, 1H), 7.76-7.79 (m, 4H), 7.66-7.69 (m, 4H), 7.48-7.51 (m, 2H), 7.29 (d, *J* = 8.6 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.60 (app t, *J* = 4.5 Hz, 1H), 5.03-5.09 (m, 2H), 4.48 (t, *J* = 8.1 Hz, 1H), 3.99-4.08 (m, 2H), 3.78-3.85 (m, 2H) 3.53 (s, 3H), 2.12-2.21 (m, 4H), 1.87-2.05 (m, 7H), 0.83-0.97 (m, 12H).

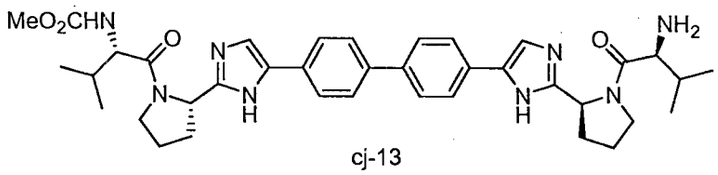
LCMS: Análisis calculado para $C_{42}H_{50}N_{10}O_4$: 758; encontrado: 759 $(M+H)^+$.

Ejemplo cj-13



000656

Preparación de (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-amino-3-metilbutanoil)pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (cj-13)



cj-13

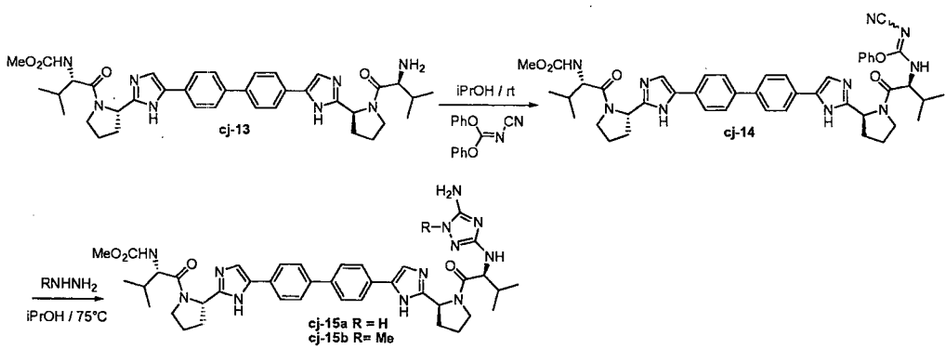
A una solución de (*S*)-3-metil-1-oxo-1-((*S*)-2-(5-(4'-(2-((*S*)-pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-il)butan-2-ilcarbamato de metilo (cj-12) (1.16 g, 1.99 mmoles), Z-Val-OH (0.712 g, 2.83 mmoles) e iPr_2Net (0.70 mL, 5.42 mmoles) en DMF (40 mL) se le añadió HATU (1.10 g, 2.89 mmoles) en porciones. La mezcla se dejó agitar a temperatura ambiente durante 1 hora y luego se vertió en hielo-agua (400 mL) y se dejó reposar durante 20 minutos. La mezcla se filtró y el sólido se lavó con agua fría y se dejó secar al aire durante la noche para dar el intermediario Z-protegido. LCMS: Análisis calculado para $C_{46}H_{54}N_8O_6$: 814; encontrado: 815 $(M+H)^+$.

El sólido obtenido se disolvió en MeOH (80 mL), 10% de Pd-C (1.0 g) se añadió y la mezcla se hidrogenó a temperatura ambiente y presión atmosférica durante 3 horas. La mezcla se filtró después y el filtrado se concentró al vacío. El residuo resultante se purificó mediante cromatografía por vaporización

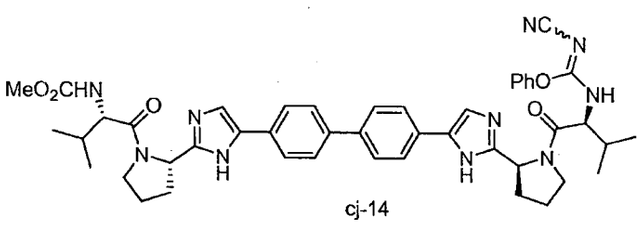
(SiO_2/5-20% de MeOH-CH_2Cl_2) para dar el compuesto del título (1.05 g, 77%) como una espuma incolora. ^{1}H RMN (400 MHz, DMSO-d_6) δ 11.75 (s, 1H), 7.75-7.79 (m, 3H), 7.61-7.67 (m, 5H), 7.49 (s, 1H), 7.26-7.28 (m, 1H), 5.05-5.09 (m, 2H), 4.03-4.09 (m, 2H), 3.77-3.80 (m, 1H), 3.66-3.70 (m, 1H), 3.52 (s, 3H), 3.40-3.47 (m, 2H), 2.21-2.26 (m, 1H), 2.10-2.17 (m, 3H), 1.81-2.02 (m, 6H), 0.77-0.92 (m, 12H).

LCMS: Análisis calculado para $C_{38}H_{48}N_8O_4$: 680; encontrado: 681 $(M+H)^+$.

Ejemplo cj-15



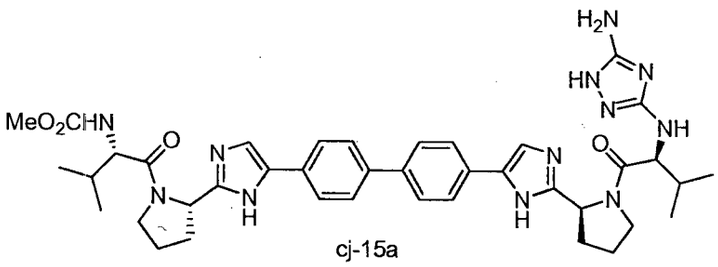
Preparación de (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-((*Z*/*E*)-(cianoimino)(fenoxi)metilamino)-3-metilbutanoil)pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (cj-14)



Una mezcla de (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-amino-3-metilbutanoil)pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (cj-13) (0.329 g, 0.527 mmoles) y cianocarbonimidato de difenilo (0.128 g, 0.537 mmoles) en iPrOH (10 mL) se agitó a temperatura ambiente durante 12 h. El sólido resultante se filtró y se secó al aire para dar el compuesto del título (0.187 g, 43%) como un sólido color crema. Este material se usó como tal en la siguiente etapa sin purificación adicional.

LCMS: Análisis calculado para $C_{46}H_{52}N_{10}O_5$: 824; encontrado: 825 $(M+H)^+$.

Preparación de ((1*S*)-1-(((2*S*)-2-(5-(4'-(2-((2*S*)-1-(*N*-(5-amino-1-metil-1*H*-1,2,4-triazol-3-il)-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1*H*-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (cj-15a, R = H)



cj-15a

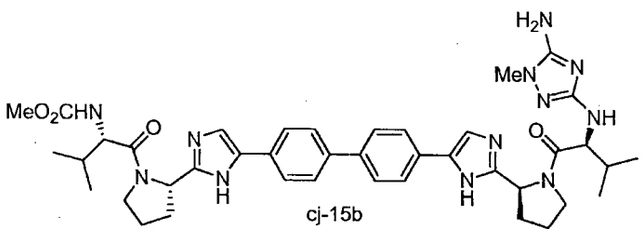
Una solución de (*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-((*Z/E*)-(cianoimino)(fenoxi)metilamino)-3-metilbutanoil)pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-

1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (cj-14) (0.074 g, 0.090 mmoles) e hidrazina hidratada (0.05 mL, 0.88 mmoles) en iPrOH (2 mL) se calentó a 75°C durante 7 h. El solvente se removió después al vacío y el residuo se purificó mediante HPLC preparativa (Luna 5u C18/MeCN-H_2O-NH_4OAc) para dar una espuma que se liofilizó a partir de CH_3CN-H_2O para dar el compuesto del título (0.032 g, 46%) como un sólido incoloro.

^{1}H RMN (400 MHz, DMSO-d_6) δ 12.17 (s, 1H), 11.75 (m, 2H), 10.66-10.84 (m, 2H), 7.76-7.79 (m, 3H), 7.62-7.74 (m, 4H), 7.49-7.51 (m, 1H), 7.24-7.29 (m, 2H), 5.28-5.32 (m, 1H), 5.05-5.08 (m, 2H), 4.04-4.09 (m, 3H), 3.87-3.94 (m, 2H), 3.72-3.81 (m, 2H), 3.53 (s, 3H), 2.09-2.17 (m, 2H), 1.90-2.02 (m, 6H), 0.81-0.99 (m, 12H).

LCMS: Análisis calculado para $C_{40}H_{50}N_{12}O_4$: 762; encontrado: 763 $(M+H)^+$.

Preparación de (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-(5-amino-1-metil-1*H*-1,2,4-triazol-3-ilamino)-3-metilbutanoil)pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (cj-15b, R = Me)



cj-15b

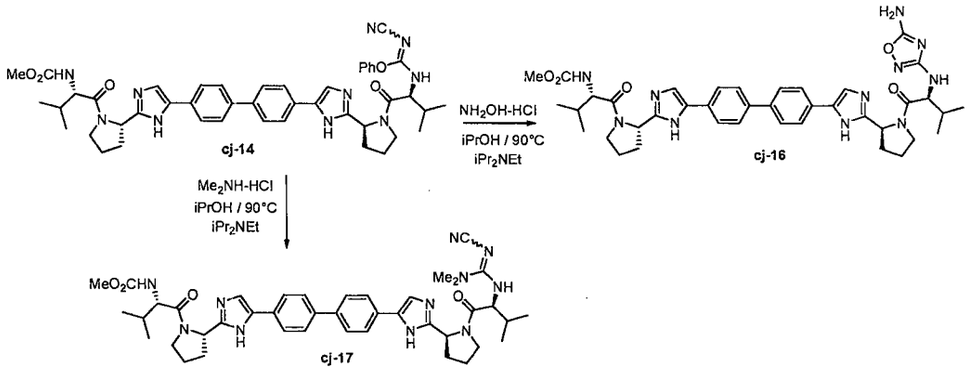
Una solución de (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-((*Z/E*)-(cianoimino)(fenoxi)metilamino)-3-metilbutanoil)pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (cj-14) (0.105 g, 0.128 mmoles) y N-metilhidrazina (0.010 mL, 0.188 mmoles) en iPrOH (2 mL) se calentó a 75°C durante 3 h. Se añadió una segunda porción de N-metilhidrazina (0.010 mL, 0.188 mmoles) y se continuó calentando durante 7 h. Los volátiles se removieron después al vacío y el residuo se purificó mediante HPLC preparativa (Luna 5u C18/MeCN-H_2O-NH_4OAc) para dar una espuma que se purificó más mediante cromatografía por vaporización (SiO_2/0-20% de MeOH-CH_2Cl_2). El material resultante se liofilizó a partir de CH_3CN-H_2O para dar el compuesto del título (0.029 g, 29%) como un sólido incoloro.

^{1}H RMN (400 MHz, DMSO-d_6) δ 13.79 (s, 0.4H), 12.19 (s, 1H), 11.76 (m, 1.6H), 7.77-7.85 (m, 4H), 7.62-7.71 (m, 4H), 7.49-7.51 (m, 1H), 7.24-7.29 (m, 1H), 6.31 (d, *J* = 9.1 Hz, 0.5 H), 6.09 (d, *J* = 9.1 Hz, 1.5 H), 5.87 (s, 1H), 5.34-5.36 (m, 1H), 5.04-5.08 (m, 2H), 4.89 (s, 1H), 4.75 (s, 2H), 3.53 (s, 3H), 2.10-2.17 (s, 3H), 1.94-2.02 (m, 6H), 0.81-0.98 (m, 12H).

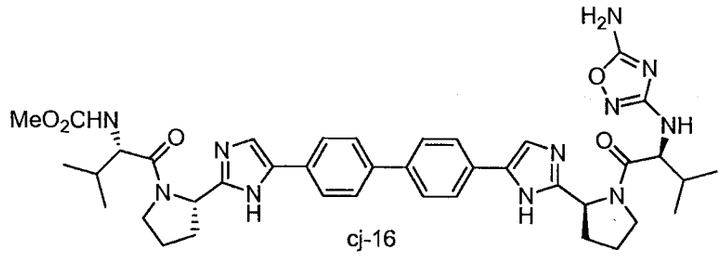
LCMS: Análisis calculado para $C_{41}H_{52}N_{12}O_4$: 776; encontrado: 777 $(M+H)^+$.

HRMS: Análisis calculado para $C_{41}H_{52}N_{12}O_4$: 776.4234; encontrado: 777.4305 $(M+H)^+$.

Ejemplos cj-16 y cj-17



Preparación de ((1*S*)-1-(((2*S*)-2-(5-(4'-(2-((2*S*)-1-(*N*-(5-amino-1,2,4-oxadiazol-3-il)-L-valil)-2-pirrolidinil)-1*H*-imidazol-5-il)-4-bifenilil)-1*H*-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (cj-16)

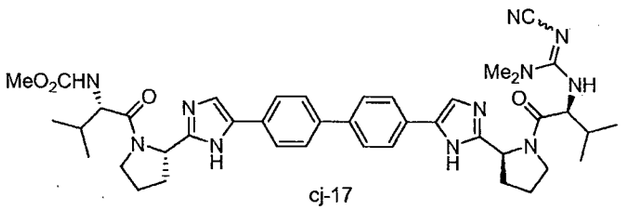


Una solución de (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-((*Z/E*)-(cianoimino)(fenoxi)metilamino)-3-metilbutanoil)pirrolidin-2-il)-1*H*-imidazol-5-

il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (cj-14) (0.120 g, 0.205 mmoles) y clorhidrato de hidroxilamina (0.0213 g, 0.307 mmoles) en iPrOH (5 mL) se calentó a 75°C durante 3 h. Se añadió una segunda porción de clorhidrato de hidroxilamina (0.0213 g, 0.307 mmoles) y se continuó calentando durante 7 h. Los volátiles se removieron después al vacío y el residuo se purificó mediante HPLC preparativa (Luna 5u C18/MeCN-H_2O-NH_4OAc) para dar una espuma que se purificó más mediante cromatografía por vaporización (SiO_2/5% de MeOH-CH_2Cl_2). La cera incolora resultante se liofilizó a partir de CH_3CN-H_2O para dar el compuesto del título (0.0344 g, 22%) como un sólido incoloro.

^1H RMN (400 MHz, DMSO-d_6) δ 12.18-12.22 (m, 1H), 11.80 (s, 1H), 11.75 (s, 1H), 8.03-8.06 (m, 1H), 7.77 (app d, *J* = 8.1 Hz, 2H), 7.62-7.73 (m, 4H), 7.50 (dd, *J* = 2.0, 5.5 Hz, 1H), 7.24-7.29 (m, 2H), 5.69 (s, 1H), 5.06-5.11 (m, 2H), 4.14 (t, *J* = 8.6 Hz, 1H), 4.06 (no resuelto dd, *J* = 8.0, 8.6 Hz, 1H), 3.78-3.90 (m, 3H), 3.53 (s, 3H), 3.01 (br s, 2H), 2.10-2.19 (m, 3H), 1.90-2.04 (m, 5H), 0.81-0.96 (m, 12H). LCMS: Análisis calculado para $C_{40}H_{49}N_{11}O_5$: 763; encontrado: 764 $(M+H)^+$.

Preparación de ((1*S*)-1-(((2*S*)-2-(5-(4'-(2-((2*S*)-1-(N-(ciano(dimetil)carbamimidoil)-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1*H*-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (cj-17)



cj-17

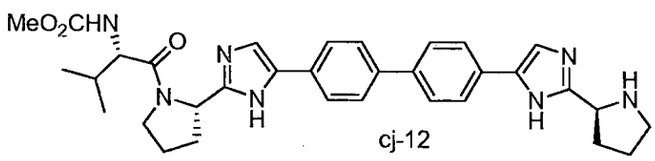
Una solución de (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-((*Z/E*)-(cianoimino)(fenoxi)metilamino)-3-metilbutanoil)pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (cj-14) (0.115 g, 0.198 mmoles) y clorhidrato de dimetilamina (0.0257 g, 0.315 mmoles) en iPrOH (5 mL) se calentó a 90°C durante 12 h. Se añadió una segunda porción de clorhidrato de dimetilamina (0.0257 g, 0.315 mmoles) y se continuó calentando durante 48 h. Los materiales volátiles fueron después removidos al vacío y el residuo se purificó mediante HPLC preparativa (Luna 5u C18/MeCN-H_2O-NH_4OAc) y luego se volvió a purificar mediante cromatografía por vaporización (SiO_2/5% de MeOH-CH_2Cl_2). La cera incolora resultante fue liofilizada a partir de CH_3CN-H_2O para dar el compuesto del título (0.0318 g, 21%) como un sólido incoloro.

^{1}H RMN (400 MHz, DMSO-d_6) δ 12.22 (m, 0.6H), 11.81

(s, 1H), 11.75 (s, 1H), 12.17-12.22 (m, 0.5H), 11.99-12.04 (m, 0.5H), 11.75-11.81 (m, 1H), 7.76-7.79 (m, 3H), 7.62-7.73 (m, 5H), 7.50 (t, *J* = 2.0 Hz, 1H), 7.23-7.29 (m, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 5.06-5.08 (m, 2H), 4.47 (t, *J* = 8.1 Hz, 2H), 4.06 (no resuelto dd, *J* = 8.0, 8.6 Hz, 1H), 3.84-3.90 (m, 2H), 3.76-3.82 (m, 3H), 3.53 (s, 3H), 3.00 (s, 6H), 2.11-2.20 (m, 3H), 1.90-2.04 (m, 5H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.89-0.91 (m, 6H), 0.84 (d, *J* = 6.5 Hz, 3H).

LCMS: Análisis calculado para $C_{42}H_{53}N_{11}O_4$: 775; encontrado: 776 $(M+H)^+$.

Preparación de (*S*)-3-metil-1-oxo-1-((*S*)-2-(5-(4'-(2-((*S*)-pirrolidin-2-il)-1*H*-imidazol-5-il)bifenil-4-il)-1*H*-imidazol-2-il)pirrolidin-1-il)butan-2-ilcarbamato de metilo (cj-12)



cj-12

Sintetizado a partir del intermediario 28d y *Extremo*-51 como en el ejemplo 28e, seguido por la remoción de Boc con TFA/CH_2Cl_2 y la formación de la base libre con resina MCX.

^{1}H RMN (400 MHz, MeOH-d_4) δ 7.79-7.82 (m, 3H), 7.65-7.75 (m, 5H), 7.48 (s, 1H), 7.32 (s, 1H), 5.19 (dd, *J* = 5.5, 5.7 Hz, 1H), 4.75 (t, *J*7.8 Hz, 1H), 4.25 (d, *J* = 7.3 Hz, 1H), 3.88-4.04 (m, 2H), 3.67 (s, 3H), 3.35-3.51 (m, 3H), 2.43-2.51

(m, 1H), 2.02-2.38 (m, 7H), 0.97 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H).

LCMS: Análisis calculado para $C_{33}H_{39}N_7O_3$: 581; encontrado: 582 $(M+H)^+$.

Sección OL

Condiciones de LC:

Condición 1: Solvente A: 5% de acetonitrilo/95% de agua/10 mmoles de acetato de amonio; solvente B: 95% de acetonitrilo/5% de agua/10 mmoles de acetato de amonio; columna: Phenomenex GEMINI 5u C18 4.6 x 5.0 mm; longitud de onda: 220 nM; velocidad de flujo: 4 ml/min; 0% de B a 100% de B durante 3 minutos con un tiempo de retención de 1 min.

Condición 2: Solvente A: 5% de acetonitrilo/95% de agua/10 mmoles de acetato de amonio; solvente B: 95% de acetonitrilo/5% de agua/10 mmoles de acetato de amonio; columna: Phenomenex GEMINI 5u C18 4.6 x 5.0 mm; longitud de onda: 220 nM; velocidad de flujo: 4 ml/min; 0% de B a 100% de B durante 2 minutos con un tiempo de retención de 1 min.

Condición 3: Solvente A: 5% de acetonitrilo/95% de agua/10 mmoles de acetato de amonio; solvente B: 95% de acetonitrilo/5% de agua/10 mmoles de acetato de amonio; columna: Phenomenex GEMINI 5u C18 4.6 x 5.0 mm; longitud de onda: 220 nM; velocidad de flujo: 4 ml/min; 0% de B a 100% de B durante 4 minutos con un tiempo de retención de 1 min.

Condición 4: Solvente A: 10% de MeOH/90% de

agua/0.1% de TFA; Solvente B: 90% de MeOH/10% de agua/0.1% de TFA; columna: Phenomenex 10u C18 3.0x5.0 mm; longitud de onda: 220 nM; velocidad de flujo: 4 ml/min; 0% de B a 100% de B durante 4 minutos con un tiempo de retención de 1 min.

Condición 5: Solvente A: 5% de acetonitrilo/95% de agua/10 mmoles de acetato de amonio; solvente B: 95% de acetonitrilo/5% de agua/10 mmoles de acetato de amonio; columna: Phenomenex GEMINI 5u C18 4.6 x 5.0 mm; longitud de onda: 220 nM; velocidad de flujo: 4 ml/min; 0% de B a 100% de B durante 9 minutos con un tiempo de retención de 1 min.

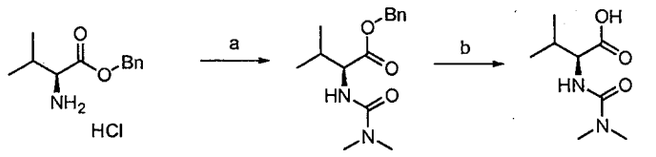
Condición 6: Solvente A: 10% de MeOH/90% de agua/0.2% de H_3PO_4; solvente B: 90% de MeOH/10% de agua/0.2% de H_3PO_4; columna: Phenomenex 5u C18 4.6 x 50 mm; longitud de onda: 220 nM; velocidad de flujo: 1.5 ml/min; 0% de B a 100% de B durante 14 minutos con un tiempo de retención de 3 min.

Condición 7: Solvente A: 10% de MeOH/90% de agua/0.1% de TFA; solvente B: 90% de MeOH/10% de agua/0.1% de TFA; columna: Phenomenex 10u C18 3.0 x 5.0 mm; longitud de onda: 220 nM; velocidad de flujo: 4 ml/min; 0% de B a 100% de B durante 3 minutos con un tiempo de retención de 1 minuto.

Condición 8: Solvente A: 10% de MeOH/90% de agua/0.1% de TFA; solvente B: 90% de MeOH/10% de agua/0.1% de TFA; columna: Phenomenex 10u C18 3.0 x 5.0 mm; longitud de onda: 220 nM; velocidad de flujo: 4 ml/min; 0% de B a 100% de B durante 2 minutos con un tiempo de retención de 1 minuto.

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Extremos experimentales:

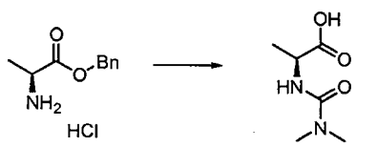


Intermediario Extremo OL-1 Extremo OL-2

Etapa a: Cloruro de dimetilcarbamoilo (0.92 mL, 10 mmoles) se añadió lentamente a una solución de clorhidrato de 2-amino-3-metilbutanoato de (S)-bencilo (2.44 g; 10 mmoles) y base de Hunig (3.67 mL, 21 mmoles) en THF (50 mL). La suspensión blanca resultante se agitó a temperatura ambiente durante la noche (16 horas) y se concentró bajo presión reducida. El residuo se dividió entre acetato de etilo y agua. La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró bajo presión reducida. El aceite amarillo resultante se purificó mediante cromatografía por vaporización, eluyendo con acetato de etilo:hexanos (1:1). Las fracciones recolectadas fueron concentradas al vacío proporcionando 2.35 g (85%) del intermediario Extremo OL-1 como un aceite transparente. ^{1}H RMN (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: Análisis calculado para $[M+H]^+$ $C_{16}H_{22}N_2O_3$: 279.17; encontrado 279.03.

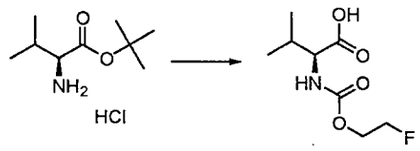
Etapa b: Al intermediario Extremo OL-1 (2.35 g;

8.45 mmoles) en 50 ml de MeOH se le añadió Pd/C (10%; 200 mg) y la suspensión negra resultante se enjuagócon N_2 (3x) y se puso bajo 1 atmósfera de H_2. La mezcla se agitó a temperatura ambiente durante la noche y se filtró a través de un filtro de microfibra para remover el catalizador. La solución transparente resultante se concentró después bajo presión reducida para obtener 1.43 g (89%) de Extremo OL-2 como una espuma blanca, la cual se usó sin purificación adicional. ^{1}H RMN (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: Análisis calculado para $[M+H]^+$ $C_8H_{17}N_2O_3$: 1898.12; encontrado 189.04.



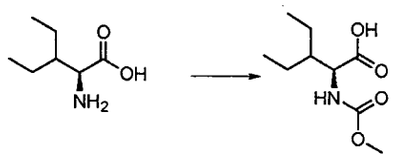
Extremo OL-3

Extremo OL-3 fue preparado a partir de clorhidrato de 2-aminopropanoato de (S)-bencilo de acuerdo con el método descrito para Extremo OL-2. ^{1}H RMN (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: Análisis calculado para $[M+H]^+$ $C_6H_{13}N_2O_3$: 161.09; encontrado 161.00.



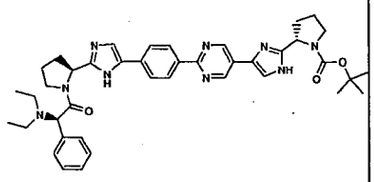
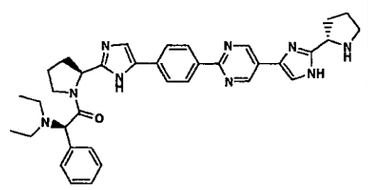
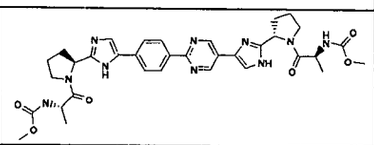
Extremo OL-4

Extremo OL-4 fue preparado a partir de clorhidrato de 2-amino-3-metilbutanoato de (S)-*ter*-butilo y cloroformiato de 2-fluoroetilo de acuerdo con el método descrito para *Extremo*-47. ^{1}H RMN (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).

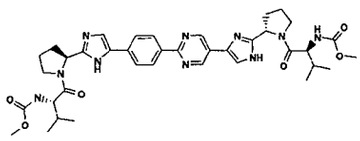
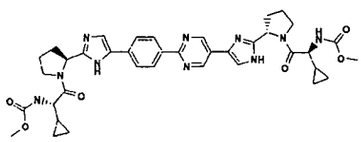


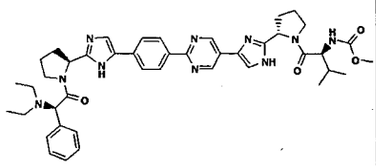
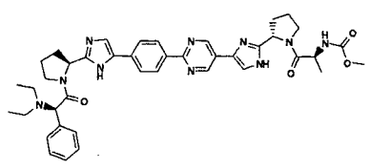
Extremo OL-5

Extremo OL-5 se preparó a partir de (S)-dietilalanina y cloroformiato de metilo de acuerdo con el método descrito para *Extremo*-51. ^{1}H RMN (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; MS: Análisis calculado para $[M+H]^+$ $C_9H_{18}NO_4$:204.12; encontrado 204.02.

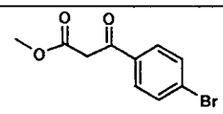
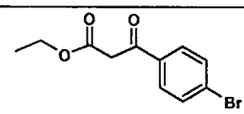
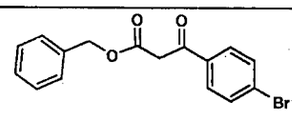
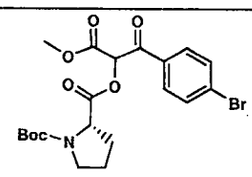
Número de Ejemplo	*Nombre del Compuesto*	*Heterociclos con Extremos Nuevos*	*Datos Analíticos (Cond 1: 3 min gradiente, 4 min corrida; Cond 2: 2 min gradiente, 3 min corrida)*
D71	(2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-(dietilamino)-2-feniłacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-5-pirimidinil)-1H-imidazol-2-il)-1-pirrolidinilcarboxilato de ter-butilo	 Preparado de 152i-1 (en lugar de 148e) y Extremo-2 usando condiciones experimentales delineadas en el Ejemplo 148	t_R = 1.82 min, (97.7%), (Cond 1) LRMS: Anal. Calcd. para: $C_{41}H_{50}N_9O_3$ 716.40; encontrado: 716.44 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{41}H_{50}N_9O_3$ 716.4037; encontrado: 716.4056 $(M+H)^+$.
D72	(1R)-N,N-dietil-2-oxo-1-fenil-2-((2S)-2-(5-(4-(5-(2-((2S)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirimidinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil) etanamina	 Preparado de entrada 71 (en lugar de 152j-27) usando condiciones experimentales delineadas en el Ejmeplo 152k-1.	t_R = 1.56 min, (~95.3%, tiene saliente), (Cond 1) LRMS: Anal. Calcd. para: $C_{36}H_{42}N_9O$ 616.35; encontrado: 616.37 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{36}H_{42}N_9O$ 616.3512; encontrado: 616.3540 $(M+H)^+$.
D73	((1S)-2-((2S)-2-(5-(4-(2-((2S)-1-(N-		t_R = 1.52 min, (96.2%), (Cond 1)

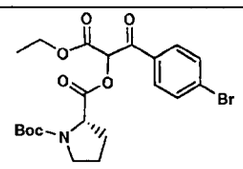
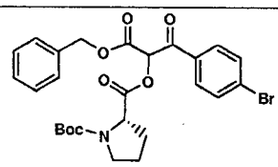
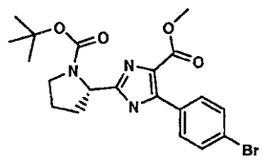
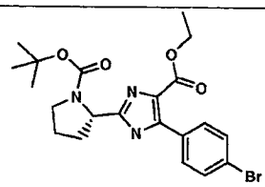
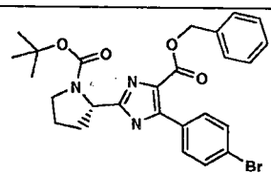
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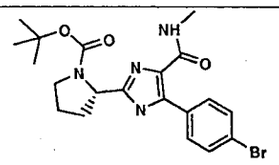
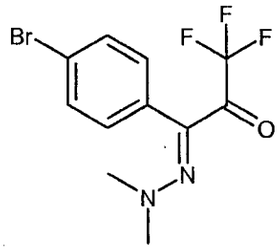
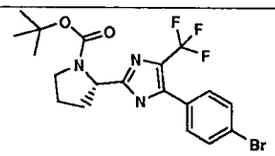
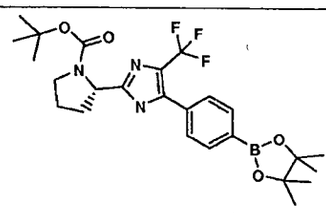
	(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirimidinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	Preparado de 152h-1 (en lugar de 148e) y Extremo-52 usando condiciones experimentales delineadas en el Ejemplo 148	LRMS: Anal. Calcd. para: $C_{34}H_{41}N_{10}O_6$ 685.32; encontrado: 685.21 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{34}H_{41}N_{10}O_6$ 685.3211; encontrado: 685.3196 $(M+H)^+$.
D74	((1S)-1-(((2S)-2-(5-(2-(4-(2-((2S)-1-((2S)-2-((metoxicarbonil) amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-5-pirimidinil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil) carbamato de metilo	 Preparado de 152h-1 (en lugar de 148e) y Extremo-51 usando condiciones experimentales delineadas en el Ejemplo 148	t_R = 2.09 min, (95%), (Cond 1) LRMS: Anal. Calcd. para: $C_{38}H_{49}N_{10}O_6$ 741.38; encontrado: 741.26 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{38}H_{49}N_{10}O_6$ 741.3837; encontrado: 741.3824 $(M+H)^+$.
D75	((1S)-1-ciclopropil-2-((2S)-2-(5-(2-(4-(2-((2S)-1-((2S)-2-ciclopropil-2-((metoxicarbonil) amino)acetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-5-pirimidinil)-1H-	 Preparado de 152h-1 (en lugar de 148e) y Extremo-54b usando condiciones experimentales delineadas en el Ejemplo 148	t_R = 1.98 min, (95%), (Cond 1) LRMS: Anal. Calcd. para: $C_{38}H_{45}N_{10}O_6$ 737.35; encontrado: 737.22 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{38}H_{45}N_{10}O_6$ 737.3524; encontrado:

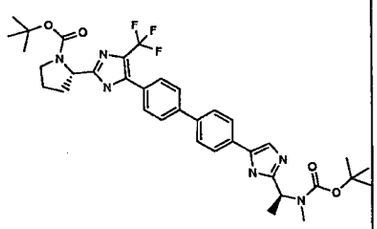
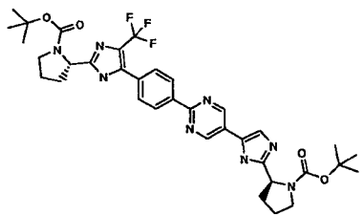
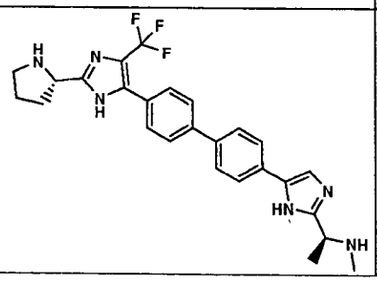
	imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo		737.3555 $(M+H)^+$.
D76	((1S)-1-(((2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-5-pirimidinil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil) carbamato de metilo	 Preparado a partir de entrada D72 (en lugar de 148e) y Extremo-51 usando condiciones experimentales delineadas en el Ejemplo 148	t_R = 1.69 min, (95%), (Cond 1) LRMS: Anal. Calcd. para: $C_{43}H_{53}N_{10}O_4$ 773.43; encontrado: 773.30 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{43}H_{53}N_{10}O_4$ 773.4251; encontrado: 773.4280 $(M+H)^+$.
D77	((1S)-2-((2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)1H-imidazol-5-il)fenil)-5-pirimidinil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	 Preparado a partir de entrada D72 (en lugar de 148e) y Extremo-52 usando condiciones experimentales delineadas en el Ejemplo 148	t_R = 1.81 min, (97.5%), (Cond 1) LRMS: Anal. Calcd. para: $C_{41}H_{49}N_{10}O_4$ 745.39; encontrado: 745.27 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{41}H_{49}N_{10}O_4$ 745.3938; encontrado: 745.3939 $(M+H)^+$.

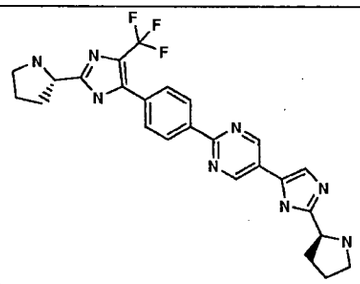
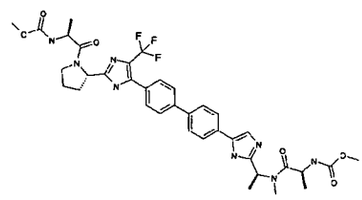
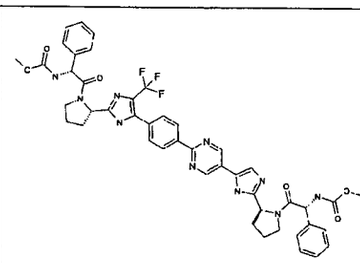
Sección J

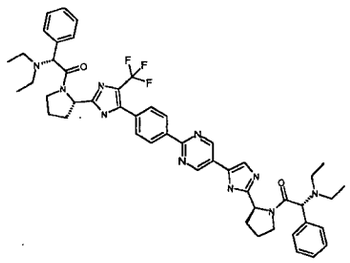
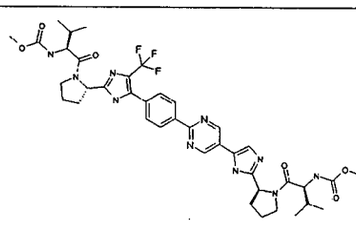
Número de Ejemplo	*Nombre del Compuesto*	*Estructura*	*Datos Analíticos*
J.1a		 Preparado de 4-bromoacetofenona y carbonato de dimetilo de Bioorg.Med.Chem.Lett (2001)11, 641	t_R = 1.7 min, (Cond 2); LCMS: $C_{10}H_9BrO_3$ encontrado: 257 $(M+H)^+$.
J.1b		 Preparado de 4-bromoacetofenona y carbonato de dietilo de Bioorg.Med.Chem.Lett (2001)11, 641.	t_R = 1.9 min, (Cond 2); LCMS: $C_{11}H_{11}BrO_3$ encontrado: 271 $(M+H)^+$.
J.1c		 Preparado de 4-bromoacetofenona y carbonato de dibencilo de Bioorg.Med.Chem.Lett (2001)11, 641.	t_R = 2.1min, (Cond 2); LCMS: $C_{16}H_{13}BrO_3$ encontrado: 332 $(M+H)^+$.
J1		 Preparado de entrada J.1a (en lugar de J.1b) y prolina usando condiciones experimentales en el Ejemplo J2.	t_R = 2.2min, (Cond 2); LCMS: $C_{20}H_{24}BrNO_7$ encontrado: 470 $(M+H)^+$.

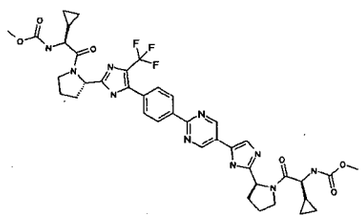
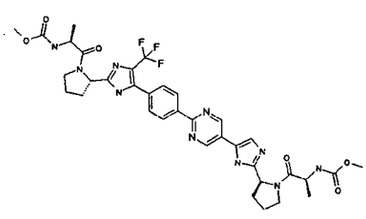
J2		 Preparado de entrada J.1b y prolina usando condiciones experimentales en el Ejemplo J2.	t_R = 2.2min, (Cond 2); LCMS: $C_{21}H_{26}BrNO_7$ encontrado: 484 $(M+H)^+$.
J3		 Preparado de entrada J.1c (en lugar de J.1b) y prolina usando condiciones experimentales en el Ejemplo J2.	t_R = 2.3min, (Cond 2); LCMS: $C_{26}H_{28}BrNO_7$ encontrado: 546 $(M+H)^+$.
J4		 Preparado de entrada J.1 y (en lugar de J.2) usando condiciones experimentales en el Ejemplo J2.	t_R = 1.84 min, (100%) (Cond 2); LRMS: Anal. Calcd. para: $C_{20}H_{24}BrN_3O_4$; 450.10; encontrado: 450.13 and 452.13 $(M+H)^+$.
J5		 Preparado de entrada J2 usando condiciones experimentales en J5.	t_R = 1.93 min, (99%) (Cond 2); Reportado en J5.
J6		 Preparado de entrada J3 (en lugar	t_R = 2.1 min, (93%) (Cond 2); LRMS: Anal. Calcd. para: $C_{26}H_{29}BrN_3O_4$

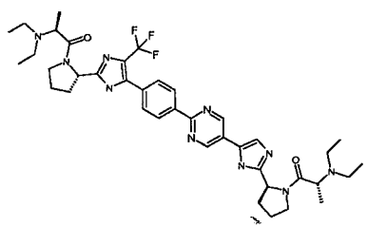
		de entrada J1) usando condiciones experimentales en J5.	526.13;encontrado: 526.16 y 528.16 $(M+H)^+$.
J7		 Preparado de entrada J5 usando condiciones experimentales en J7.	t_R = 1.7 min, (100%) (Cond 2); Reportado en J7.
J32		 Preparado de 4-bromobenzaldehído de acuerdo con el procedimiento descrito en J.Org.Chem. (1988), 53, 129.	t_R = 1.96 min, (96%) (Cond 2); LRMS: Anal. Calcd. para: $C_{11}H_{11}BrF_3N_2O$ 323.00;encontrado: 323.05 y 325.05 $(M+H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.58 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 3.06 (s, 6H).
J32.a		 Preparado de entrada J32 usando condiciones experimentales en J32.a	t_R = 2.19 min, (96%) (Cond 2); Reportado en J32.a
J32.b		 Preparado de entrada J32.a	t_R = 2.3 min, (73%) (Cond 2); LCMS: $C_{25}H_{34}BF_3N_3O_4$ encontrado: 508 $(M+H)^+$.

		(en lugar de 1b) usando condiciones experimentales delineadas en el Ejemplo 1, etapa c.	
J33.a	(2S)-2-(5-(4'-(2-((1S)-1-((ter-butoxicarbonil)(metil)amino)etil)-1H-imidazol-5-il)-4-bifenilil)-4-(trifluorometil)-1H-imidazol-2-il)-1-pirrolidincarboxilato de ter-butilo	 Preparado de entrada J32.a (en lugar de 152e-1) y 1-8c usando condiciones experimentales delineadas en el Ejemplo 152g-1.	t_R = 1.97 min, (97%) (Cond 2); LRMS: Anal. Calcd. para: $C_{36}H_{44}F_3N_6O_4$ 681.34; encontrado: 681.31 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{36}H_{44}F_3N_6O_4$ 681.3376; encontrado: 681.3383 $(M+H)^+$.
J34.a	(2S)-2-(5-(4-(5-(2-((2S)-1-(ter-butoxicarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirimidinil)fenil)-4-(trifluorometil)-1H-imidazol-2-il)-1-pirrolidincarboxilato de ter-butilo	 Preparado de entrada J32.b (en lugar de 152e-1) y 152d-1 usando condiciones experimentales delineadas en el Ejemplo 152g-1.	t_R = 1.97 min, (93%) (Cond 2); LRMS: Anal. Calcd. para: $C_{35}H_{42}F_3N_8O_4$ 695.33; encontrado: 695.28 $(M+H)^+$.
J35.a			LCMS: $C_{26}H_{28}F_3N_6$ encontrado: 481 $(M+H)^+$.

		Preparado de entrada J33.a (en lugar de 152j-27) usando condiciones experimentales delineadas en el Ejemplo 152k-1.	
J36.a		 Preparado de entrada J34.a (en lugar de 152j-27) usando condiciones experimentales delineadas en el Ejemplo 152k-1.	t_R = 1.45 min, (Cond 2); LCMS: $C_{25}H_{26}F_3N_8$ encontrado: 495 $(M+H)^+$.
J42.a	((1S)-2-((2S)-2-(5-(4'-(2-((1S)-1-((N-(metoxicarbonil)-L-alanil)(metil)amino) etil)-1H-imidazol-5-il)-4-bifenilil)-4-(trifluorometil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	 Preparado de entrada J35.a (en lugar de 148e) y Extremo-52 usando condiciones experimentales delineadas en el Ejemplo 148.	t_R = 1.69 min, (100%) (Cond 2); LRMS: Anal. Calcd. para: $C_{36}H_{42}F_3N_8O_6$ 739.32; encontrado: 739.31 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{36}H_{42}F_3N_8O_6$ 739.3179; encontrado: 739.3195 $(M+H)^+$.
J46	((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-((metoxicarbonil) amino)-2-fenilacetil) -2-		t_R = 1.82 min, (98%) (Cond 2); LRMS: Anal. Calcd. para: $C_{45}H_{44}F_3N_{10}O_6$ 877.34; encontrado:

	pirrolidinil)-1H-imidazol-5-il)-2-pirimidinil)fenil)-4-(trifluorometil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	Preparado de entrada J34.a (en lugar de 148e) y Extremo-4 usando condiciones experimentales delineadas en el Ejemplo 148	877.29 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{45}H_{44}F_3N_{10}O_6$ 877.3397; encontrado: 877.3403 $(M+H)^+$.
J47	(1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirimidinil)fenil)-4-(trifluorometil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dietil-2-oxo-1-feniletanamina	 Preparado de entrada J34.a (en lugar de 148e) y Extremo-2 usando condiciones experimentales delineadas en el Ejemplo 148	t_R = 1.58 min, (97%) (Cond 2); LRMS: Anal. Calcd. para: $C_{49}H_{56}F_3N_{10}O_2$ 873.44; encontrado: 873.40 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{49}H_{56}F_3N_{10}O_2$ 873.4540; encontrado: 873.4536 $(M+H)^+$.
J48	((1S)-1-(((2S)-2-(5-(2-(4-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-4-(trifluorometil)-1H-imidazol-5-il)fenil)-5-	 Preparado de entrada J34.a (en lugar de 148e) y Extremo-51 usando condiciones experimentales delineadas en el Ejemplo 148	t_R = 1.85 min, (99%) (Cond 2); LRMS: Anal. Calcd. para: $C_{39}H_{48}F_3N_{10}O_6$ 809.37; encontrado: 809.37 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{39}H_{48}F_3N_{10}O_6$

	pirimidinil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo		809.3710; encontrado: 809.3683 $(M+H)^+$.
J49	((1S)-1-ciclopropil-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2S)-2-((metoxicarbonil) amino)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirimidinil)fenil)-4-(trifluorometil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo	 Preparado de entrada J34.a (en lugar de 148e) y Extremo-54b usando condiciones experimentales delineadas en el Ejemplo 148	t_R = 1.75 min, (100%) (Cond 2); LRMS: Anal. Calcd. para: $C_{39}H_{44}F_3N_{10}O_6$ 805.34; encontrado: 805.34 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{39}H_{44}F_3N_{10}O_6$ 805.3397; encontrado: 805.3384 $(M+H)^+$.
J50	((1S)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirimidinil)fenil)-4-(trifluorometil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	 Preparado de entrada J34.a (en lugar de 148e) y Extremo-52 usando condiciones experimentales delineadas en el Ejemplo 148	t_R = 1.61 min, (94%) (Cond 2); LRMS: Anal. Calcd. para: $C_{35}H_{40}F_3N_{10}O_6$ 753.31; encontrado: 753.31 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{35}H_{40}F_3N_{10}O_6$ 753.3084; encontrado: 753.3099 $(M+H)^+$.

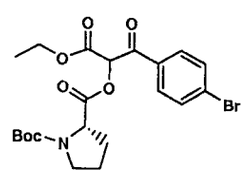
J51	(2R)-1-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-(dietilamino) propanoil)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirimidinil)fenil)-4-trifluorometil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dietil-1-oxo-2-propanamina	 Preparado de entrada J34.a (en lugar de 148e) y Extremo 70b usando condiciones experimentales delineadas en el Ejemplo 148	t_R = 1.41 min, (92%) (Cond 2); LRMS: Anal. Calcd. para: $C_{39}H_{52}F_3N_{10}O_2$ 749.42; encontrado: 749.37 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{39}H_{52}F_3N_{10}O_2$ 749.4227; encontrado: 749.4223 $(M+H)^+$.

Cond 1: Condiciones de LCMS: Phenomenex-Luna 4.6 x 50 mm S10, 0 a 100% de B durante 3 minutos, 4 minutos de tiempo de detención, 4 mL/min, 220 nm, A: 10% de MeOH-90% de H2O-0.1% de TFA; B: 90% de MeOH-10% de H2O-0.1% de TFA.

Cond. 2: Condiciones de LCMS: Phenomenex-Luna 4.6 x 50 mm S10, 0 a 100% de B durante 2 minutos, 3 minutos de tiempo de detención, 4 mL/min, 220 nm, A: 10% de MeOH-90% de H2O-0.1% de TFA; B: 90% de MeOH-10% de H2O-0.1% de TFA.

Ejemplo J2

(2S)-2-(1-(4-bromofenil)-3-etoxi-1,3-dioxopropan-2-il) pirrolidin-1,2-dicarboxilato de 1-ter-butilo



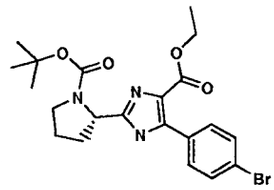
J2

El 3-(4-bromofenil)-3-oxopropanoato de etilo (15 g, 55 mmoles) se disolvió en CH_2Cl_2 (600 mL) y se añadió NBS recién recristalizado (9.8 g, 55 mmoles) y la solución se agitó 18 horas. La mezcla de reacción se lavó con solución de $NaHCO_3$, salmuera, y se secó ($MgSO_4$), se filtró y se concentró para dar un residuo que no se purificó. 2-Bromo-3-(4-bromofenil)-3-oxopropanoato de etilo (16.5 g, 48 mmoles) y N-Boc-L-prolina (10 g, 48 mmoles) se recogieron en acetonitrilo (450 mL) y base de Hunig (16 mL, 95 mmoles) se añadió y la solución se agitó 18 horas. El solvente se removió mediante evaporación giratoria y el residuo se recogió en acetato de etilo, se lavó con HCl 0.1 N y salmuera. ^{1}H RMN (300 MHz, DMSO-d_6) δ 7.95 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 6.68-6.65 (m, 1H), 4.39-4.30 (m, 1H), 4.21-4.12 (m, 2H), 2.27-2.21 (m, 1H), 2.0-1.95 (m, 1H), 1.90-1.76 (m, 2H), 1.39 (s, 2H), 1.31 (s, 9H), 1.11 (t, J = 7.3 Hz, 3H).

LRMS: Análisis calculado para $C_{21}H_{26}BrNO_7$ 484.09; encontrado: 410.08 $(M+H)^+$.

Ejemplo J5

5-(4-bromofenil)-2-(1-(ter-butoxicarbonil)pirrolidin-2-il)-1H-imidazol-4-carboxilato de (S)-etilo

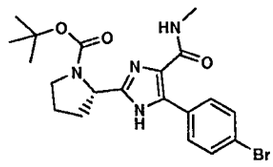


J5

Una botella de presión de 1 L se cargó con (2S)-2-(1-(4-bromofenil)-3-etoxi-1,3-dioxopropan-2-il) 1,2-dicarboxilato de 1-*ter*-butilo J2 (7 g, 35 mmoles) y 11 g de NH_4OAc en 125 mL de xileno, y la reacción se calentó a 140°C durante 3.5 horas. Después de haber sido enfriada, la solución se dividió entre acetato de etilo y agua. La capa orgánica se concentró y el residuo resultante se aplicó a un cartucho de gel de sílice Biotage 40 m y se eluyó con un gradiente de 20-100% de acetato de etilo/hexanos para dar 3 g (45%). ^1H RMN (300 MHz, $CDCl_3$) δ 12.75 (br, s, 7.82), (br, s, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 4.96-4.92 (m, 1H), 4.23 (q, *J* = 6.6 Hz, 2H), 3.68-3.50 (m, 1H), 3.40-3.32 (m, 1H), 2.19-2.15 (m, 1H), 1.99-1.89 (m, 3H), 1.48/1.13 (s, 9H), 1.23 (t, *J* = 7.3 Hz, 3H). LRMS: Análisis calculado para $C_{21}H_{26}BrN_3O_4$ 464.12; encontrado: 464.15 y 466.15 $(M+H)^+$.

Ejemplo J7

2-(5-(4-bromofenil)-4-(metilcarbamoil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-ter-butilo



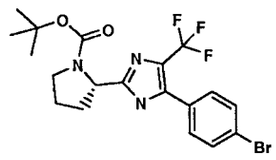
J7

5-(4-Bromofenil)-2-(1-(*ter*-butoxicarbonil)pirrolidin-2-il)-1H-imidazol-4-carboxilato de (S)-etilo (1 g, 2.1 mmoles) se disolvió en metilamina 2M en MeOH (35 mL) y se calentó en un recipiente de presión a 70°C durante 48 horas. La mezcla de reacción se concentró y el residuo se aplicó a un cartucho en gel de sílice Biogate 25 m y fue eluido con un gradiente de 10-100% de acetato de etilo/hexanos para dar 556 mg (57%). ^{1}H RMN (300 MHz, DMSO-d_6) δ 12.5 (br.s, 1H), 7.86-7.82 (m, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.7 Hz, 2H), 4.83-4.70 (m, 1H), 3.69-3.52 (br.s, 1H), 3.42-3.32 (m, 1H), 2.71 (d, 4.8 Hz, 3H), 2.30-1.78 (m, 4H), 1.19-1.14 (m, 9H).

LRMS: Análisis calculado para $C_{20}H_{26}BrN_4O_3$ 449.12; encontrado: 449.15 y 451.14 $(M+H)^+$.

Ejemplo J32.a

2-(5-(4-bromofenil)-4-(trifluorometil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-ter-butilo

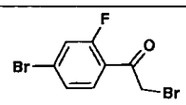
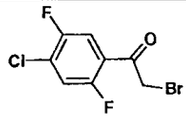
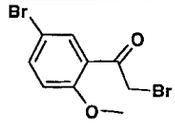


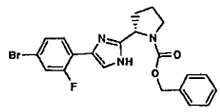
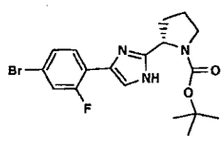
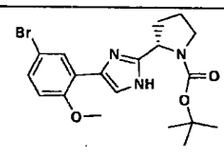
J32.a

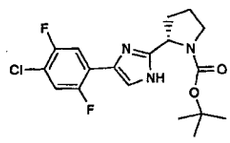
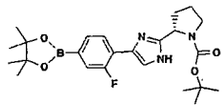
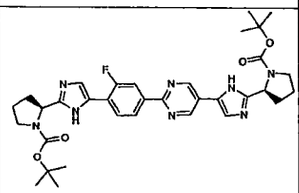
3-(4-Bromofenil)-3-(2,2-dimetilhidrazono)-1,1,1-trifluoropropan-2-ona (2.0 g, 6.2 mmoles) se suspendió en ácido sulfúrico 5N (60 mL) y se calentó a 45°C durante 6 h. La temperatura se elevó a 85°C durante 2 horas y después del enfriamiento se formó un precipitado. Este material que se aisló mediante filtración para dar 1-(4-bromofenil)-3,3,3-trifluoropropan-1,2-diona 1.6 g (92%) como un sólido amarillo. La diona (1.6 g, 5.7 mmoles) se recogió en metanol (30 mL), N-(*ter*-butoxicarbonil)-L-prolina (1 g, 5.0 mmoles) se añadió, seguido por la adición de solución de hidróxido de amonio al 28% (10 mL). La reacción se agitó a temperatura ambiente durante 18 horas, se vertió en diclorometano (200 mL), se lavó con agua y se secó con $MgSO_4$. La filtración, concentración y aplicación a un cartucho Biotage de 40 M, elución de gradiente con 5%-30% de acetato de etilo/hexanos, dio J32.a 1.3 g(50%). ^1H RMN (300 MHz, DMSO-d_6) δ 12.88 (br.s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 4.84-4.70 (m, 1H), 3.57-3.49 (m, 1H), 3.39-3.29 (m, 1H),

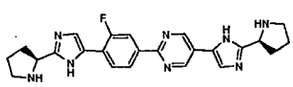
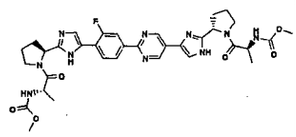
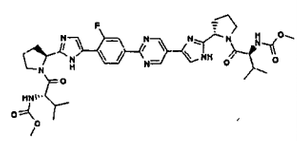
2.31-2.20 (m, 1H), 1.98-1.78 (m, 3H), 1.39/1.13 (m, 9H). LRMS: Análisis calculado para $C_{19}H_{20}BrF_3N_3O_2$ 458.07; encontrado: 458.06 y 460.06 $(M-H)^-$. HRMS: Análisis calculado para $C_{19}H_{22}BrF_3N_3O_2$ 460.0847; encontrado: 460.0866 y 462.0840 $(M+H)^+$.

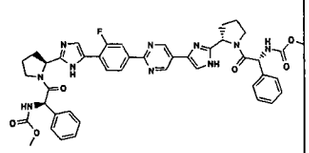
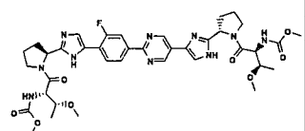
Sección D

Entrada	*Nombre del Compuesto*	*Estructura*	***Datos*
D1		 Preparado de 1-(4-bromo-2-fluorofenil) etanona (Vendedor: Marshalton 50043) usando condiciones de bromación delineadas en D5.	t_R = 2.65 min, (86.7%) LCMS: Anal. Calcd. para: $C_8H_{15}BrFO$ 296.88; encontrado: 296.91 $(M+H)^+$.
D2		 Preparado de 1-(4-cloro-2,5-difluorofenil)etanona (Vendedor: Oakwood products, 001626) usando condiciones de bromación delineadas en D5.	t_R = 2.66 min, (80%) LCMS: Anal. Calcd. para: $C_8H_4BrClFO$ 270.92; encontrado: ND $(M+H)^+$.
D3			t_R = 2.57 min, (95%) LCMS: Anal. Calcd. para:

		Preparado de 2-bromo-1-(5-bromo-2-metoxifenil) etanona (Andersh et al., Synth. Comm. 2000, 30 (12), 2091-98) usando condiciones de bromación delineadas en D5.	$C_9H_9BrO_2$ 228.99; encontrado: 229.00 $(M+H)^+$.
D4		 Preparado de entrada D1 y CBz-L-prolina (en lugar de Boc-L-prolina usando condiciones experimentales delineadas en D5.	t_R = 2.38 min, (95.0%) LRMS: Anal. Calcd. para: $C_{19}H_{20}{}^{79}BrFN_3O_2$ 444.07; encontrado: 444.04 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{19}H_{20}{}^{79}BrFN_3O_2$ 444.0721; encontrado: 444.0736 $(M+H)^+$
D5		 Condiciones experimentales en D5.	t_R = 2.27min, (95%) LRMS: Anal. Calcd. para: $C_{18}H_{22}BrFN_3O_2$ 410.09 y 412.08; encontrado: 410.08 y 412.08 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{18}H_{22}{}^{79}BrFN_3O_2$ 410.0879; encontrado: 410.0893 $(M+H)^+$.
D6		 Preparado de entrada D3 (en lugar de entrada D1) usando condiciones experimentales	t_R = 2.26 min, (95%) LRMS: Anal. Calcd. para: $C_{19}H_{25}BrN_3O_3$ 422.11 y 424.11; encontrado: 422.10 y 424.10 $(M+H)^+$.

		delineadas en D5.	HRMS: Anal. Calcd. para: $C_{19}H_{25}{}^{79}BrN_3O_3$ 422.1079; encontrado: 422.1089 $(M+H)^+$.
D7		 Preparado de entrada D2 en lugar de entrada D1) usando condiciones experimentales delineadas en experimento anexo.	t_R = 2.28 min, (95%) LRMS: Anal. Calcd. para: $C_{18}H_{21}ClF_2N_3O_2$ 384.13; encontrado: 384.13 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{18}H_{21}ClF_2N_3O_2$ 384.1290; encontrado: 384.1301 $(M+H)^+$.
D8		 Preparado de entrada D5 (en lugar de 1b) usando condiciones experimentales delineadas en el Ejemplo 1, Etapa c.	t_R = 2.62 min, (~50%) y 1.95 min (~50%, ácido borónico) LRMS: Anal. Calcd. para: $C_{24}H_{34}BFN_3O_4$ 458.26; encontrado: 458.23 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{24}H_{34}BFN_3O_4$ 458.2626; encontrado: 458.2610 $(M+H)^+$.
D13	(2S)-2-(5-(2-(4-(2-((2S)-1-(ter-butoxicarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-3-fluorofenil)-5-pirimidinil)-1H-imidazol-2-il)-1-	 Preparado de entrada D8 (en lugar de 1c) y 152b-1 usando condiciones experimentales	t_R = 2.27min, (95%) LRMS: Anal. Calcd. para: $C_{34}H_{42}FN_8O_4$ 645.33; encontrado: 645.34 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{34}H_{42}FN_8O_4$

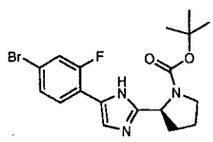
	pirrolidincarboxilato de ter-butilo	delineadas en el Ejemplo 152g-1.	645.3313; encontrado: 645.3323 $(M+H)^+$.
D32	2-(3-fluoro-4-(2-((2S)-2-pirrolidinil)-1H-imidazol-5-il) fenil)-5-(2-((2S)-2-pirrolidnil)-1H-imidazol-5-il) pirimidina	 Preparado de entrada D13 (en lugar de 152j-27) usando condiciones experimentales delineadas en el Ejemplo 152k-1.	t_R = 1.63 min, (95%) LRMS: Anal. Calcd. para: $C_{24}H_{26}FN_8$ 445.23;encontrado: 445.23 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{24}H_{26}FN_8$ 445.2264; encontrado: 445.2268 $(M+H)^+$.
D67	((1S)-2-((2S)-2-(5-(2-fluoro-4-(5-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirimidinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	 Preparado de entrada D32 (en lugar de 148e) y Cap-52 usando condiciones experimentales delineadas en el Ejemplo 148.	t_R = 1.58 min, (91.1%) LRMS: Anal. Calcd. para: $C_{34}H_{40}FN_{10}O_6$ 703.31; encontrado: 703.27 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{34}H_{40}FN_{10}O_6$ 703.3116; encontrado: 703.3101 $(M+H)^+$.
D68	((1S)-1-(((2S)-2-(5-(2-(fluoro-4-(5-(2-((2S)-1-((2S)-2-((metoxicarbonil) amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirimidinil)fenil)-	 Preparado de entrada D32 (en lugar de 148e) y Cap-51 usando condiciones experimentales delineadas en el Ejemplo 148.	t_R = 1.95 min, (99.3%) LRMS: Anal. Calcd. para: $C_{38}H_{48}FN_{10}O_6$ 759.37; encontrado: 759.30 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{38}H_{48}FN_{10}O_6$ 759.3742; encontrado: 759.3715 $(M+H)^+$.

	1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil) carbamato de metilo		
D69	((1R)-2-((2S)-2-(5-(2-(3-fluoro-4-(2-((2S)-1-((2R)-2-((metoxicarbonil) amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-5-pirimidinil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Preparado de entrada D32 (en lugar de 148e) y Extremo-4 usando condiciones experimentales delineadas en el Ejemplo 148.	t_R = 2.05 min, (99.3%) LRMS: Anal. Calcd. para: $C_{44}H_{44}FN_{10}O_6$ 827.34; encontrado: 827.27 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{44}H_{44}FN_{10}O_6$ 827.3429; encontrado: 827.3407 $(M+H)^+$.
D70	((1S,2R)-1-(((2S)-2-(5-(2-fluoro-4-(5-(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-treonil)-2-pirrolidinil)1H-imidazol-5-il)-2-pirimidinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metoxipropil) carbamato de metilo	 Preparado de entrada D32 (en lugar de 148e) y Extremo-86 usando condiciones experimentales delineadas en el Ejemplo 148.	t_R = 1.79 min, (93.0%) LRMS: Anal. Calcd. para: $C_{38}H_{48}FN_{10}O_8$ 791.36; encontrado: 791.31 $(M+H)^+$. HRMS: Anal. Calcd. para: $C_{38}H_{48}FN_{10}O_8$ 791.3641; encontrado: 791.3636 $(M+H)^+$.

** Condiciones de LCMS: Phenomenex-Luna 4.6 x 50 mm S10, 0 a 100% de B durante 3 minutos, 4 minutos de tiempo de detención, 4 mL/min, 220 nm, A = 10% de MeOH-90% de H2O-0.1% de TFA; B: 90% de MeOH-10% de H2O-0.1% de TFA.

Ejemplo D5

2-(5-(4-bromo-2-fluorofenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-ter-butilo



D5

Se añadió bromuro (0.54 mL, 10.6 mmoles) por goteo a una solución fría (0°C) de 4-bromo-2-fluoroacetofenona (2.30 g, 10.6 mmoles) en dioxano (80 mL) y tetrahidrofurano (80 mL). La mezcla se agitó durante 1 hora a 0°C y se calentó a temperatura ambiente durante 15 h. La mezcla se diluyó con acetato de etilo, se lavó con solución saturada de $NaHCO_3$, solución de tiosulfato de sodio al 5% y salmuera antes de secar (Na_2SO_4). Se aisló 2-bromo-1-(4-bromo-2-fluorofenil)etanona (D1) como una película incolora que se solidificó después de una concentración adicional al alto vacío. Este sólido se disolvió en acetonitrilo anhidro (50 mL) y se trató con N-Boc-L-prolina (2.28 g, 10.6 mmoles) y diisopropiletilamina (1.85 mL, 10.6 mmoles). Después de haber sido agitado durante 3 horas a temperatura ambiente, el solvente se removió al vacío y el residuo se dividió entre

acetato de etilo y agua. La fase orgánica se lavó con ácido clorhídrico 0.1 N, solución saturada de $NaHCO_3$ y salmuera antes del secado (Na_2SO_4), filtración y concentración. Este residuo se recogió en xilenos (50 mL) y se trató hasta NH_4OAc (4.1 g, 53.0 mmoles). La mezcla se calentó a 140°C durante 2 horas en un matraz de tapa con rosca y de paredes gruesas antes de que fuera enfriada a la temperatura ambiente, se diluyó con acetato de etilo y se lavó con solución saturada de $NaHCO_3$ y salmuera antes de secar (Na_2SO_4) y de la concentración. La purificación del residuo mediante cromatografía por vaporización Biogate™ en gel de sílice (columna 65M, pre-equilibrio con 16% de B para 1,800 mL seguido por una elución con gradiente con 16% de B a 16% de B para 450 mL, 16% de B a 50% de B para 2199 ml y finalmente 50% de B a 100% de B para 2199 mL) dio el compuesto del título (D5) (3.61 g, 83%) como un aceite color parduzco/caramelo. Una pequeña porción (40 mg) del compuesto del título se purificó más mediante HPLC preparativa (20% de B a 100% de B durante 14 minutos en donde B es 10 mM de NH_4OAc en 10:90 de H_2O/ACN y A es 10 mM de NH_4OAc en 95:5 de H_2O/CAN usando una columna Phenomenex-Gemini 30 x 100 mm S10 que fluya a 40 mL/min) para dar el compuesto del título puro (31.8 mg) como un sólido blanco.

^1H RMN (500 MHz, DMSO-d_6) δ 12.13-11.95 (m, 1H), 7.94 (br s, 1H), 7.54 (d, J = 10.7 Hz, 1H), 7.42 (d, J = 7.9

Hz, 1H), 7.36-7.34 (m, 1H), 4.86-4.77 (2m, 1H), 3.54 (m, 1H), 3.38-3.32 (m, 1H), 2.28-2.14 (2m, 1H), 2.05-1.78 (2m, 3H), 1.39 y 1.14 (2s, 9H).

HPLC Phenomenex LUNA C-18 4.6 x 50 mm, 0 a 100% de B durante 3 minutos, 1 minuto de tiempo de retención, A = 90% de agua, 10% de metanol, 0.1% de TFA, B = 10% de agua, 90% de metanol, 0.1% de TFA, RT = 2.27 min, 95% de índice de homogeneidad.

LRMS: Análisis calculado para $C_{18}H_{22}BrFN_3O_2$ 410.09 y 412.09; encontrado: 410.08 y 412.08 $(M+H)^+$.

RRMS: Análisis calculado para $C_{18}H_{22}BrFN_3O$ 410.0879; encontrado: 410.0893 $(M+H)^+$.

Sección M: Las condiciones de LC fueron las siguientes:

Condición 1

Columna = Phenomenex-Luna 3.0X 50 mm S10

% B de inicio = 0

% B final = 100

Tiempo gradiente = 2 min

Tiempo de detención = 3 min

Velocidad de flujo = 4 mL/min

Longitud de onda = 220 nm

Solvente A = 0.1% de TFA en 10% de metanol/90% de H_2O

Solvente B = 0.1% de TFA en 90% de metanol/10% de

H_2O

Condición 2

Columna = Phenomenex-Luna 4.6X50 mm S10

% B de inicio = 0

% B final = 100

Tiempo gradiente = 2 min

Tiempo de detención = 3 min

Velocidad de flujo = 5 mL/min

Longitud de onda = 220 nm

Solvente A = 0.1% de TFA en 10% de metanol/90% de H_2O

Solvente B = 0.1% de TFA en 90% de metanol/10% de H_2O

Condición 3

Columna = HPLC XTERRA C18 3.0 x 50 mm S7

% B de inicio = 0

% B final = 100

Tiempo gradiente = 3 min

Tiempo de detención = 4 min

Velocidad de flujo = 4 mL/min

Longitud de onda = 220 nm

Solvente A = 0.1% de TFA en 10% de metanol/90% de H_2O

Solvente B = 0.1% de TFA en 90% de metanol/10% de H_2O

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Condición M1

Columna = Luna 4.6X 50 mm S10

% B de inicio = 0

% B final = 100

Tiempo gradiente = 3 min

Tiempo de detención = 4 min

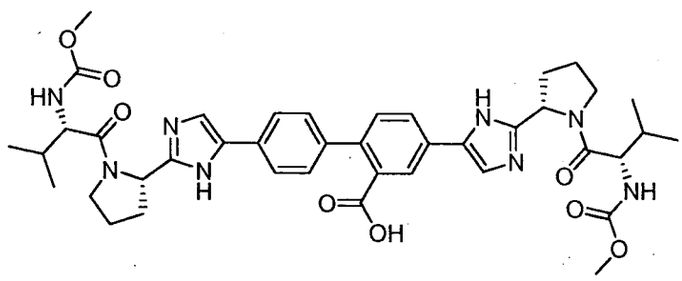
Velocidad de flujo = 4 mL/min

Solvente A = 95% de H_2O: 5% de CH_3CN, 10 mm de acetato de amonio

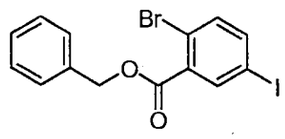
Solvente B = 5% de H_2O: 95% de CH_3CN; 10 mm de acetato de amonio.

Ejemplo M114

ácido 4,4'-bis(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-2-bifenilcarboxílico



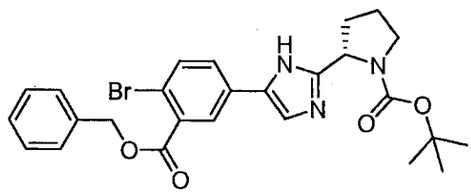
Ejemplo M114, etapa a



DMF (20 mL) se añadió a una mezcla de $KHCO_3$ (1.84 g, 18.4 mmoles) y ácido 2-bromo-5-yodobenzoico (4.99 g, 15.3

mmoles) y la mezcla resultante se agitó durante 15 minutos. Se añadió bromuro de bencilo (2.4 mL, 20.2 mmoles) por goteo durante 5 minutos y se continuó agitando a la condición ambiente durante ~ 20 horas. La mayoría del componente volátil fue removido al vacío y el residuo se dividió entre CH_2Cl_2 (50 mL) y agua (50 mL), y la capa orgánica se lavó con agua (50 mL), se secó $MgSO_4$), se filtró y se concentró. El material crudo resultante se purificó con cromatografía por vaporización (7% de EtOAc/hexanos) para dar el éster M114a como un aceite viscoso incoloro (6.01 g). ^{1}H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 8.07 (d, J = 2.0, 1H), 7.81 (dd, J = 8.4, 2.1, 1H), 7.53 (d, J = 8.4, 1H), 7.48 (m, 2H), 7.43-7.34 (m, 3H), 5.34 (s, 2H). LC (Cond. 1): RT = 2.1 min; LC/MS: Análisis calculado para $[M+Na]^+$ $C_{14}H_{10}BrINaO_2$: 438.88; encontrado 438.83.

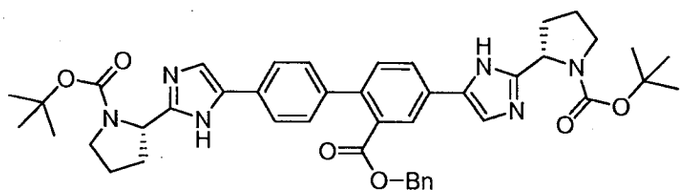
Ejemplo M114, etapas b-d



El éster M114 fue elaborado al éster M114d al emplear un protocolo de tres etapas empleado en la síntesis del bromuro 121c a partir de 1-bromo-4-yodo-2-metilbenceno. M114d: ^{1}H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.04/11.97 (br s, 1H), 8.12 (d, J = 2.0, 0.92 H), 7.99 (app br s,

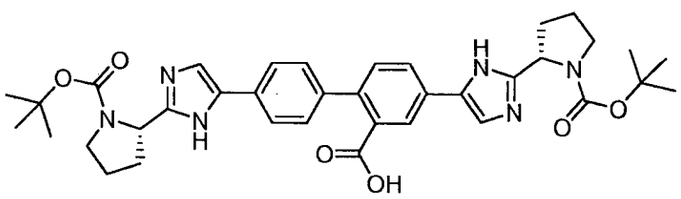
0.08H), 7.81 (dd, J = 8.3, 2.0, 0.92H), 7.74-7.62 (m, 2.08H), 7.50 (app br d, J = 7.0, 2H), 7.44-7.35 (m, 3H), 5.38 (s, 2H), 4.79 (m, 1H); 3.52 (app br s, 1H), 3.36 (m, 1H), 2.24-1.79 (m, 4H), 1.39/5.11 (dos s, 9H). LC (Cond. 1): RT = 1.66 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{26}H_{29}BrN_3O_4$: 526.13; encontrado 526.16.

Ejemplo M114, etapa e



El éster M114e se preparó a partir del bromuro M114d y el boronato 1c de acuerdo con la preparación del dímero 1d. ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.18/12.00/11.91/11.83 (cuatro br s, 2H), 8.11-7.03 (m, 14H), 5.10 (s, 2H), 4.85-4.78 (m, 2H), 3.55 (app br s, 2H), 3.37 (m, 2H), 2.29-1.80 (m, 8H), 1.41/1.16 (dos s, 18H). LC (Cond. 1): RT = 1.54 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{51}N_6O_6$: 759.59; encontrado 759.63.

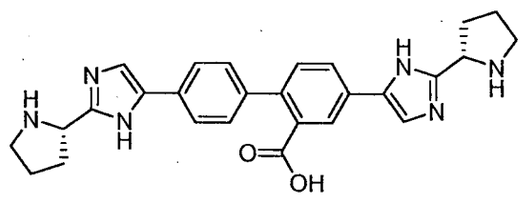
Ejemplo M114, etapa f



Una mezcla de éster bencílico M114e (1.005 g, 1.325 mmoles) y 10% de Pd/C (236 mg) en MeOH (20 mL) se agitó bajo un balón de H_2 durante 5 horas. La mezcla de reacción se

trató después con una mezcla 1:1 de MeOH y CH_2Cl_2, se filtró a través de una almohadilla de tierra diatomácea (Celite®-521), y el filtrado se evaporó giratoriamente para dar el ácido M114f (840 mg), contaminado con Ph_3PO el cual es un residuo de la etapa de acoplamiento de Suzuki. ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.17/11.98/11.89/11.81 (cuatro app br s, 2H), 8.04-7.31 (m, 9H), 4.85-4.78 (m, 2H), 3.55 (app br s, 2H), ~3.37 (m, 2H, traslapado con señal de agua) 2.27-1.84 (m, 8H), 1.41/1.16 (dos s, 18H). LC (Cond. 1): RT = 1.37 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{37}H_{45}N_6O_6$: 699.34; encontrado 699.53.

Ejemplo M114, etapa g



HCl/dioxano 4N (8.0 mL) y CH_2Cl_2 (2.0 mL) se añadieron secuencialmente al carbamato M114f (417 mg, 0.623 mmoles), la mezcla se agitó vigorosamente 5.5 horas, y luego el componente volátil se removió al vacío para dar la sal HCl (.4x) de la pirrolidina M114g (487 mg), contaminada con impureza de Ph_3PO. ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz) después de intercambio de D_2O: δ 8.23 (d, J = 1.7, 1H), 8.09-8.04 (m, 3H), 7.92 (d, J = 8.3, 2H), 7.53 (d, J = 8.1, 1H), 7.48 (d, J = 8.3, 2H), 5.00 (app br t, J = 8.3, 1H), 4.90 (app br t, J = 8.4, 1H), 3.6-3.3 (m, 4H), 2.5-1.99 (m, 8H).

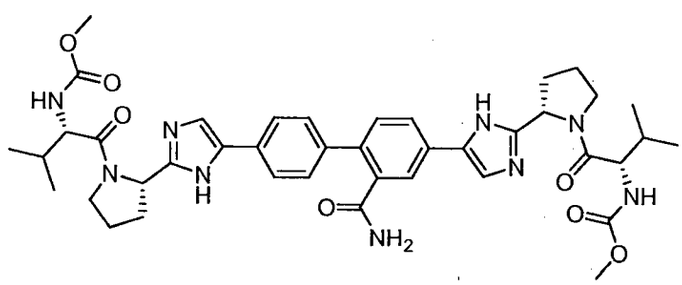
LC (Cond. 1): RT = 0.92 min; LC/MS: análisis calculado para $[M+H]^+$ $C_{27}H_{29}N_6O_2$: 469.24; encontrado 469.31.

Ejemplo M114

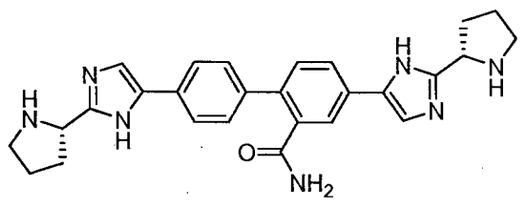
HATU (79.9 mg, 0.21 mmoles) se añadió a una solución en DMF (3.0 mL) de la pirrolidina M114g.4HCl (80 mg, 0.13 mmoles), *Extremo*-51 (92.4 mg, 0.527 mmoles) e *i*-Pr_2EtN (160 µL, 0.919 mmoles), y la mezcla de reacción se agitó a condición ambiente durante 2 horas. El componente volátil se removió al vacío y el residuo se purificó con una combinación de MCX (lavado con MeOH; elución con NH_3 2.0 M/MeOH) y una HPLC de fase inversa ($CH_3CN/H_2O/NH_4OAc$) para dar la sal ácido acético de ejemplo M114. LC (Cond. 1): RT = 1.20 min; >98 de índice de homogeneidad. LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{51}N_8O_8$: 783.3830; encontrado 783.3793.

Ejemplo M118

((1S)-1-(((2S)-2-(5-(2'-carbamoil-4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo



Ejemplo M118, etapa a



Et_3N (300 µL, 2.15 mmoles) se añadió a una mezcla del ácido M114f (198.3 mg, 0.297 mmoles), HOBt (94.2 mg, 0.697 mmoles), EDCI (0.66 mmoles), NH_4Cl (101 mg, 1.89 mmoles) en DMF (8.0 mL) y se agitó durante 17 horas a condición ambiente. La mezcla de reacción se filtró a través de un filtro de 0.45 µm, el componente volátil se removió al vacío y el residuo se dividió entre CH_2Cl_2 y agua. La capa orgánica se concentró y el material crudo resultante se purificó con una HPLC de fase inversa ($MeOH/H_2O/TFA$).

El producto anterior se trató con 25% de TFA/CH_2Cl_2 (4.0 mL) y la mezcla de reacción se agitó durante 2.5 horas a condición ambiente. El componente volátil se removió al vacío y el residuo se hizo base libre (MCX; lavado con MeOH; elución con NH_3 2.0 M/MeOH) para dar la amida M118a (67.2 mg). ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 11.83 (br s, 2H), 7.81-7.80 (m, 2H), 7.73 (d, J = 8.3, 2H), 7.65 (br s, 1H), 7.52 (br S, 1H), 7.44 (br s, 1H), 7.41 (d, J = 8.3, 2H), 7.36 (d, J = 8.3, 1H), 7.31 (br s, 1H), 4.16 (app t, J = 7.2, 2H), 3.00-2.94 (m, 2H), 2.88-2.82 (m, 2H), 2.10-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.83-1.66 (m, 4H). LC (Cond. 1): RT = 0.89 min; >95 de índice de homogeneidad. LC/MS: Análisis

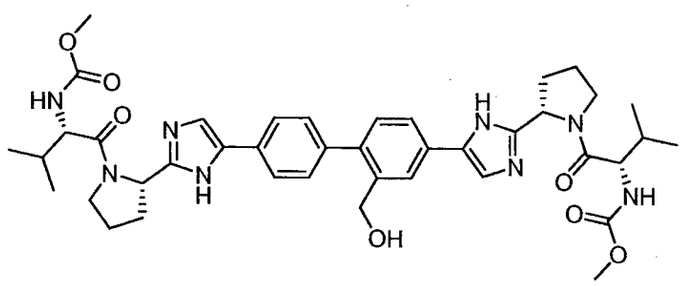
calculado para $[M+H]^+$ $C_{27}H_{30}N_7O$: 468.25; encontrado 468.24.

Ejemplo M118

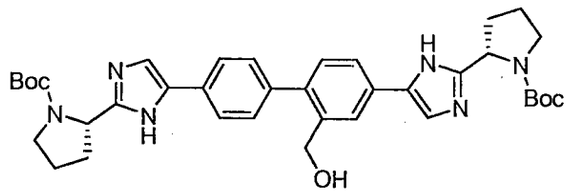
La sal TFA del ejemplo M118 se preparó a partir del intermediario M118a y *Extremo*-51 de acuerdo con el procedimiento descrito para el ejemplo 1. LC (Cond. 1): RT = 1.16 min; 97% de índice de homogeneidad. LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{52}N_9O_7$: 782.40; encontrado 782.40. HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{52}N_9O_7$: 782.3990; encontrado 782.3979.

Ejemplo M119

((1S)-1-(((2S)-2-(5-(2-(hidroximetil)-4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo



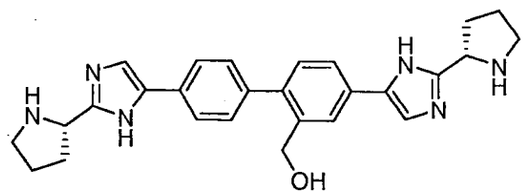
Ejemplo M119, etapa a



DIBAL-H (8.0 mL de 1.0 M/CH_2Cl_2, 8.0 mmoles) se añadió por goteo a una solución enfriada en hielo-agua en

CH_2Cl_2 (20 mL) de éster bencílico M114e (1.216 g, 1.60 mmoles), y la mezcla de reacción se agitó durante 1 hora, se añadió DIBAL-H adicional (0.5 mL de 1.0 M/CH_2Cl_2, 0.5 mmoles) y se continuó agitando durante ~2.5 horas. La reacción se enfrió rápidamente con un exceso de solución saturada de NH_4Cl y la mezcla se diluyó con agua y se extrajo con CH_2Cl_2 (3x). La fase orgánica combinadas se secó ($MgSO_4$), se filtró y se concentró al vacío. El material crudo resultante se purificó con una Biotage (100 g de gel de sílice; 2-6% de MeOH/EtOAc) para dar el alcohol M119a como una espuma blanquecina &10 mg). ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.23 (br s, 0.19 H), 12.17 (br s, 0.19H), 11.89 (br s, 0.81H), 11.82 (br s, 0.81H), 7.97 (s, 0.81H), 7.84 (s, 0.19H), 7.78 (d, J = 8.1, 1.62H), 7.69-7.20 (m, 6.38H), 5.21-5.15 (m, 1H), 4.86-4.78 (m, 2H), 4.49-4.45 (m, 2H), ~3.54 (m, 2H), 3.40-3.34 (m, 2H), 2.30-1.80 (m, 8H), 1.41/1.17 (dos s, 18H). LC (Cond. 1): RT = 1.36 min. LC/MS: Análisis calculado para $[M+H]^+$ $C_{37}H_{47}N_6O_5$: 655.36; encontrado 655.34.

Ejemplo M119, etapa b



25% de TFA/CH_2Cl_2 (3.0 mL) se añadió al carbamato M119a (105 mg, 0.160 mmoles) y la mezcla se agitó a temperatura ambiente durante 4.5 horas. El componente

volátil se removió al vacío y el residuo se hizo base libre (MCX; lavado con MeOH; elución con NH_3 2.0M/MeOH) para dar la pirrolidina M119b, contaminada con su derivado trifluoroacetilado de regioquímica desconocida. La muestra se disolvió en MeOH (1.5 mL) y se trató con NaOH 1.0 M/H_2O (300 µL, 0.3 mmoles) y la mezcla se agitó durante 2.75 horas. Después se sometió directamente a purificación MCX (lavado con MeOH; elución con NH_3 2.0M/MeOH) para dar M119b como una película de sólido blanco (63.8 mg). ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 11.82 (br s, 2H), 7.96 (s, 1H), 7.77 (d, *J* = 8.0, 2H), 7.66 (d, *J* = 8.0, 1H), 7.46 (br s, 1H), 7.42 (br s, 1H), 7.36 (d, *J* = 8.0, 2H), 7.21 (d, *J* = 8.0, 1H), 5.16 (app br s, 1H), 4.46 (s, 2H), 4.16 (app t, *J* = 7.1, 2H), 3.00-2.82 (dos m, 4H; existe una señal de línea de base amplia en esta región a partir de la pirrolidina NH que no fue incluida en la integración), 2.10-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.83-1.67 (m, 4H). LC (Cond. 1): RT = 0.78 min. LC/MS: Análisis calculado para $[M+H]^+$ $C_{27}H_{31}N_6O$: 455.26; encontrado 455.27.

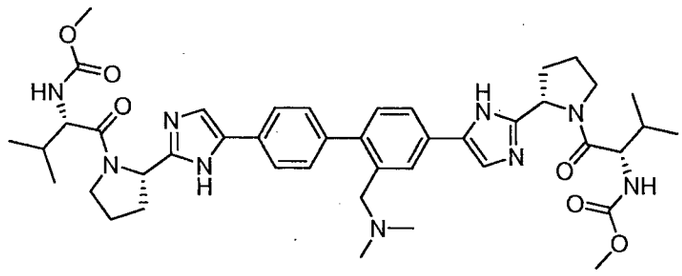
Ejemplo M119

El ejemplo M119 se preparó a partir de M119b y *Extremo*-51 de acuerdo con el procedimiento descrito para e ejemplo 1, con la excepción de que una HPLC de

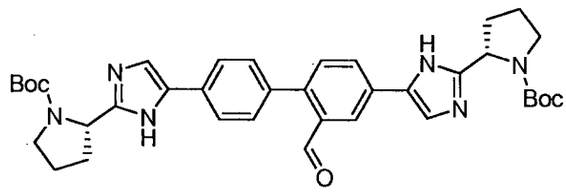
fase inversa con sistema de solvente de ACN/H_2O/NH_4OAc se empleó para la etapa de purificación. LC (Cond. 1): RT = 1.15 min; 98% de índice de homogeneidad. CL/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{53}N_8O_7$: 769.40; encontrado 769.40. HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{53}N_8O_7$: 769.4037; encontrado 769.4023.

Ejemplo M120

((1S)-1-(((2S)-2-(5-(2-((dimetilamino)metil)-4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo



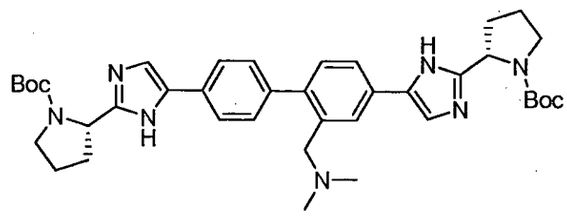
Ejemplo M120, etapa a



CH_2Cl_2 (6.0 mL) se añadió a una mezcla del alcohol M119a (501 mg, 0.765 mmoles), TPAP (29.1, 0.083 mmoles) y *N*-óxido de 4-metilmorfolina (135.8

mg, 1.159 mmoles), y la mezcla heterogénea resultante se agitó vigorosamente a condición ambiente durante 14.5 horas. Se añadieron TPAP adicionales (11.0 mg, 0.031 mmoles) y *N*-óxido de 4-metilmorfolina (39 mg, 0.33 mmoles) y se continuó agitando durante 24 horas más. La mezcla se filtró a través de tierra diatomácea (Celite®), el filtrado se evaporó giratoriamente y el material crudo resultante se purificó con una Biotage (2% de MeOH/EtOAc) para dar el aldehído M120a como un aceite viscoso amarillo (195.6 mg). LC (Cond. 1): RT = 1.37 min. LC/MS: Análisis calculado para $[M+H]^+$ $C_{37}H_{45}N_6O_5$: 653.35; encontrado 653.40.

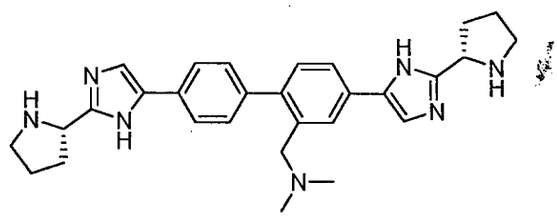
Ejemplo M120, etapa b



$NaCNBH_3$ (33 mg, 0.50 mmoles) se añadió en un lote a una solución en MaOH (3.0 ML) del aldehído M120a (195.6 mg, 0.30 mmoles) y Me_2NH (200 µL de 40% de solución en H_2O), y la mezcla de reacción se agitó durante 4 horas. El componente volátil se removió al vacío y el residuo se purificó con una cromatografía de vaporización (la muestra se cargó como una malla

de gel de sílice; 3-15% de $MeOH/CH_2Cl_2$) para dar la amina M120b como una espuma blanquecina (120 mg). LC (Cond. 1): RT = 1.32 min. LC/MS: Análisis calculado para $[M+H]^+$ $C_{39}H_{52}N_7O_4$: 682.41; encontrado 682.42.

Ejemplo M120, etapa c



El carbamato M120b se convirtió en M120c al emplear el protocolo descrito para la preparación de 1e a partir de 1d. ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 11.82 (br s, 2H), 7.87 (s, 1H), 7.77 (d, J = 8.0, 2H), 7.65 (d, J = 7.8, 1H), 7.45/7.43 (traslapado dos br s, 2H), 7.37 (d, J = 7.8, 2H), 7.21 (d, J = 7.8, 1H), 4.87 (m, 0.1H), 4.17 (m, 1.90), ~3.3 (señal de Me_2NCH_2 traslapado con agua), 3.01-2.94 (m, 2H), 2.89-2.83 (m, 2H), 2.10 (s, 6H), 2.10-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.81-1.67 (m, 4H). LC (Cond. 1): RT = 0.79 min. LC/MS: Análisis calculado para $[M+H]^+$ $C_{29}H_{36}N_7$: 482.30; encontrado 482.35.

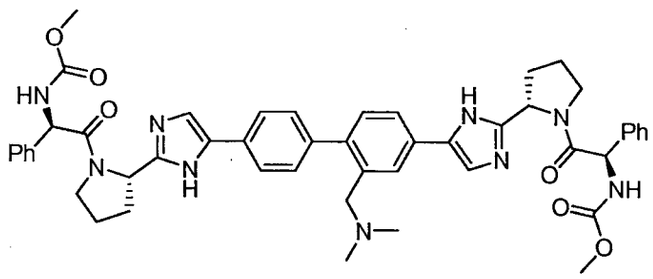
Ejemplo M120

La sal TFA del ejemplo M120 se preparó a

partir de la pirrolidina M120c y *Extremo*-51 de acuerdo con el procedimiento descrito para el ejemplo 1. LC (Cond. 1): RT = 1.06 min; 96% de índice de homogeneidad. LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{58}N_9O_6$: 796.45; encontrado 796.48. HRMS: Análisis calculado para $[M+H]^+$ $C_{43}H_{58}N_9O_6$: 796.4510; encontrado 796.4515.

Ejemplo M121

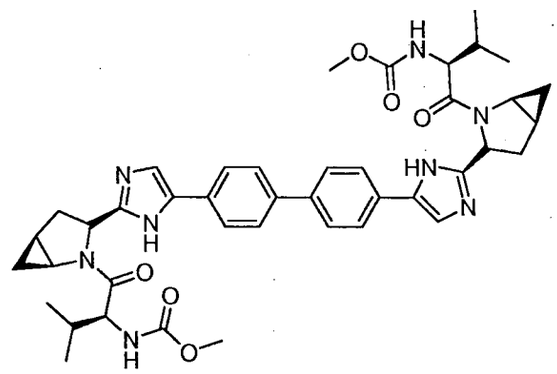
((2-((dimetilamino)metil)-4,4'-bifenildiil)bis(1H-imidazol-5,2-diil)2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))biscarbamato de dimetilo



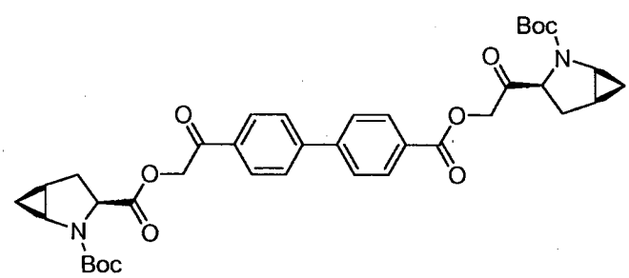
La sal TFA del ejemplo M121 se preparó a partir de M120c y *Extremo*-4 de acuerdo con el procedimiento descrito para el ejemplo 1. LC (Cond. 1): RT = 1.15 min; >98% de índice de homogeneidad. LC/MS: Análisis calculado para $[M+H]^+$ $C_{49}H_{54}N_9O_6$: 796.45; encontrado 864.46. HRMS: Análisis calculado para $[M+H]^+$ $C_{49}H_{54}N_9O_6$: 864.4197; encontrado 864.4222.

Ejemplo M122

((1S)-1-(((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo



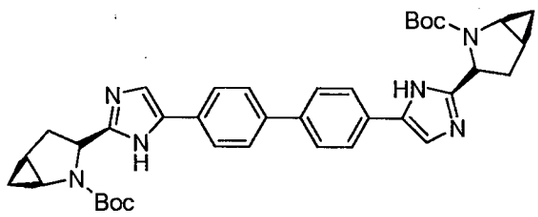
Ejemplo M122, etapa a



Diisopropiletilamina (1.81 mL, 10.4 mmoles) se añadió lentamente a una solución en acetonitrilo (20 mL) de ácido (1S,3S,5S)-2-(*ter*-butoxicarbonil)-2-azabiciclo[3.1.0]hexan-3-carboxílico (2.36 g, 10.4 mmoles) y (2-(4'-(2-bromoacetil)bifenil-4-il)-2-oxoetil)bromonio (2.0 g, 5.05 mmoles), y la mezcla de reacción se agitó a condiciones ambiente durante 16 horas. El solvente se

evaporó y el residuo se dividió entre acetato de etilo y agua (1:1, 40 mL cada uno). La capa orgánica se lavó con $NaHCO_3$ saturado (2 x 10 mL), salmuera, se secó (Na_2SO_4), se filtró y se concentró al vacío para dar el cetoéster M122a (3.58 g) como un aceite ámbar viscoso, el cual se solidificó después de su almacenamiento en un refrigerador. ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 8.20 (m, 4H), 7.97 (d, J = 8.5, 4H), 5.71-5.48 (m, 4H), 4.69 (m, 2H), 3.44 (m, 2H), 3.3 (m, 2H), 2.76-2.67 (m, 2 H), 2.27 (m, 2H), 1.60 (m, 2H), 1.44/1.38 (dos s, 18H), 0.78 (m, 2H), 0.70 (m, 2H). LC (Cond. 1): RT = 1.70 min; LC/MS: el ión molecular no fue recogido.

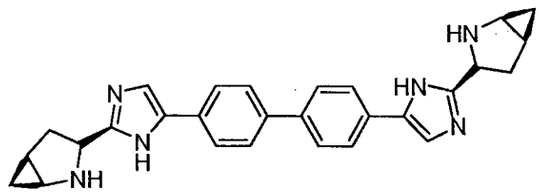
Ejemplo M122, etapa b



Acetato de amonio (2.89 g, 37.5 mmoles) se añadió a una solución en tolueno (20 mL) del cetoéster M122a (2.58 g, 3.75 mmoles), y la mezcla resultante se calentó a 120°C durante 4.5 horas, mientras el agua que se forma con una instalación Dean-Stark se somete a destilación azeotrópica. La mezcla de reacción se enfrió a la temperatura ambiente y el componente volátil se removió al vacío. Se añadió solución saturada de $NaHCO_3$ (10 mL) al sólido y la mezcla se agitó durante 30 minutos, y el sólido se filtró, se secó al

vacío y se sometió a una purificación Biotage (28-100% de EtOAc/hexanos) para dar el imidazol M122b como un sólido amarillo claro (0.6 g). LC (Cond. 1): RT = 1.52 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{45}N_6O_4$: 649.35; encontrado 649.78.

Ejemplo M122, etapa c



HCl 4N en dioxano (5 mL) se añadió a una solución en dioxano enfriada con agua helada (16 mL) del carbamato M122b (0.8 g, 1.2 mmoles), el baño de hielo-agua se retiró y la mezcla se agitó a condición ambiente durante 4 horas. Grandes trozos de sólido que se formaron durante la reacción fueron rotos con una espátula. La remoción del componente volátil al vacío dio la pirrolidina M122c (.4 HCl) como un sólido amarillo (0.73 g). ^{1}H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 7.90 (d, J = 8.3, 4H), 7.84 (br s, 2H), 7.79 (d, J = 8.3, 4H), 5.24 (m, 2H), 3.38 (m, 2H), 2.71 (m, 2H), ~2.50 (2H, traslapado con señal de solvente), 1.93 (m, 2H), 1.38 (m, 2H), 0.96 (m, 2H). LC (Cond. 1): RT = 1.03 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{28}H_{29}N_6$: 449.25; encontrado 449.59.

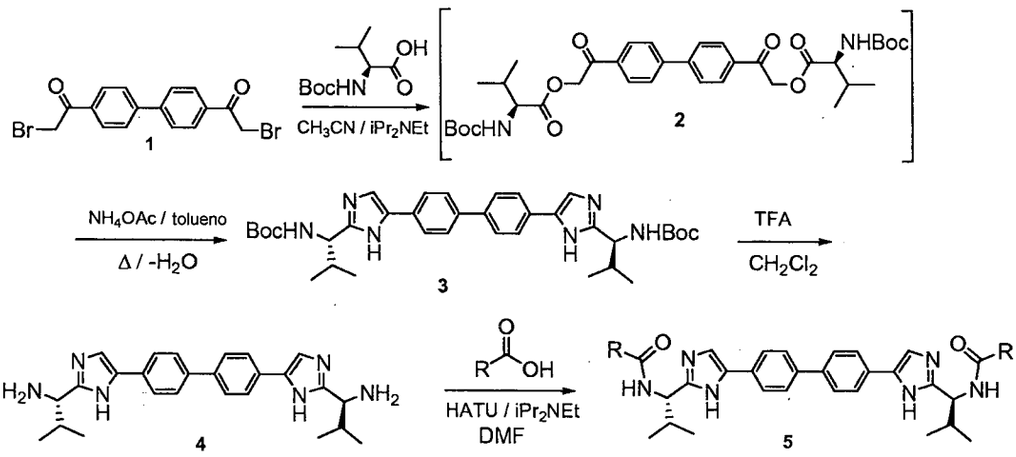
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Ejemplo M122

La sal TFA del ejemplo M122 se preparó a partir de M122c y *Extremo*-51 de acuerdo con el procedimiento descrito para el ejemplo 1. LC (Cond. 1): RT = 1.34 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{51}N_8O_6$: 763.39; encontrado 763.73.

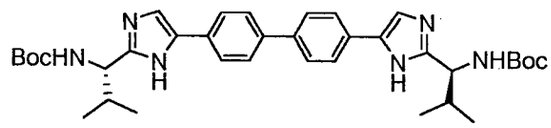
Sección R

Esquema de reacción 1



Ejemplo R1

(1S,1'S)-1,1'-(5,5'-(bifenil-4,4'-diil)bis(1H-imidazol-5,2-diil)bis(2-metilpropan-1,1-diil)dicarbamato de ter-butilo (3)

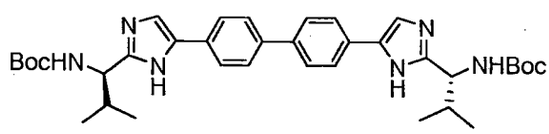


Una solución de 1,1'-(bifenil-4,4'-diil)bis(2-bromoetanona) (1) (5.14 g, 18.4 mmoles) y N-Boc-L-valina (8.00 g, 36.8 mmoles) en CH_3CN seco (40 mL) se trató con

iPr_2Net (7.05 mL, 40.5 mmoles) y la solución se dejó agitar a la temperatura ambiente durante la noche. El solvente se removió al vacío y la suspensión resultante se dividió entre EtOAc y H_2O. Las capas se separaron y la fase acuosa se extrajo con EtOAc. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron al vacío. El residuo se suspendió en tolueno (100 mL) y se añadió NH_4OAc (14.2 g, 184.2 mmoles). La mezcla se calentó a reflujo durante 16 horas con la remoción azeotrópica de H_2O (Dean-Stark). La mezcla se enfrió a la temperatura ambiente y se concentró hasta la sequedad al vacío. El residuo se purificó en cromatografía en columna (biotage) eluyendo con 0 a 40% de CH_3CN en CH_2Cl_2 y luego 10% de MeOH en CH_2Cl_2 para dar el compuesto del título (5.77 g, 50%) como una espuma amarilla. ^1H RMN (500 MHz, DMSO-d_6) δ 11.77-11.93 (m, 2H), 7.80 (s, br, 4H), 7.66-7.68 (m, 4H), 7.53 (s, br, 2H), 6.89 (d, J = 7.7 Hz, 2H), 4.43 (app t, J = 8.2 Hz, 2H), 2.05-2.11 (m, 2H), 1.38 (s, 18H), 0.90 (d, J = 6.6 Hz, 6H), 0.78 (d, J = 6.6 Hz, 6H). LCMS: Análisis calculado para $C_{36}H_{48}N_6O_4$: 628; encontrado: 629 $(M+H)^+$.

Ejemplo R2

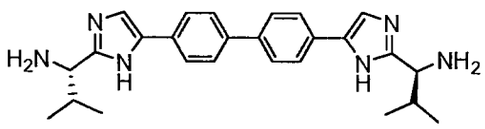
(1R,1'R)-1,1'-(5,5'-(bifenil-4,4'-diil)bis(1H-imidazol-5,2-diil))bis(2-metilpropan-1,1-diil)dicarbamato de ter-butilo



El compuesto del título se preparó de acuerdo con el método del ejemplo R1 iniciando con 1,1'-(bifenil-4,4'-diil)bis(2-bromoetanona) (1) y N-Boc-D-valina. LCMS: Análisis calculado para $C_{36}H_{48}N_6O_4$: 628; encontrado: 629 $(M+H)^+$.

Ejemplo R3

(1S,1'S)-1,1'-(5,5'-(bifenil-4,4'-diil)bis(1H-imidazol-5,2-diil))bis(2-metilpropan-1-amina)

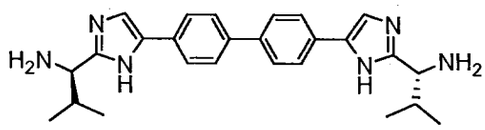


A una solución de (1R,1'R)-1,1'-(5,5'-(bifenil-4,4'-diil)bis(1H-imidazol-5,2-diil))bis(2-metilpropan-1,1-diil)dicarbamato de *ter*-butilo (1.00g, 1.59 mmoles) en CH_2Cl_2 (30 mL) se le añadió TFA (20 mL) y la solución se dejó agitar a la temperatura ambiente durante 5 h. Los solventes se removieron al vacío, el residuo se disolvió en CH_2Cl_2: MeOH (1:1) (alrededor de 10 mL) y se absorbió sobre un cartucho de intercambio catiónico MCX (Oasis). La resina se lavó con MeOH y el material deseado se liberó mediante elución con NH_3 en MeOH (2M). Los solventes se removieron al vacío para dar el compuesto del título (0.622 g, 91%) como una espuma amarilla que fue lo suficientemente pura para usarse en etapas subsecuentes. ^1H RMN (300 MHz, CD_3OD) δ 7.76 (app d, J = 8.4 Hz, 4H), 7.68 (app d, J = 8.4 Hz, 4H), 7.38 (s, 2H),

3.77 (d, J = 7.3 Hz, 2H), 2.07 (sept, J = 7.0 Hz, 2H), 1.03 (d, J = 7.0 Hz, 6H), 0.88 (d, J = 7.0 Hz, 6H). LCMS: Análisis calculado para $C_{26}H_{32}N_6$: 428; encontrado: 429 $(M+H)^+$.

Ejemplo R4

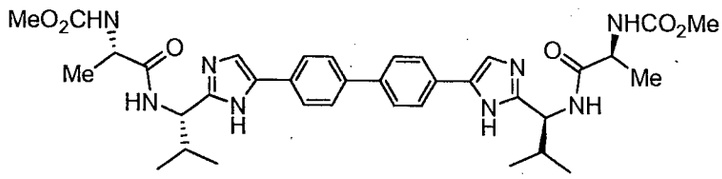
(1R,1'R)-1,1'-(5,5'-(bifenil-4,4'-diil)bis(1H-imidazol-5,2-diil))bis(2-metilpropan-1-amina)



El compuesto del título se preparó de acuerdo con el método dado en el ejemplo R3 iniciando con (1R,1'R)-1,1'-(5,5'-(bifenil-4,4'-diil)bis(1H-imidazol-5,2-diil))bis(2-metilpropan-1,1-diil)dicarbamato de *ter*-butilo. LCMS: Análisis calculado para $C_{26}H_{32}N_6$: 428; encontrado: 429 $(M+H)^+$.

Ejemplo R5

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1S)-2-metil-1,1-propandiil)imino((2S)-1-oxo-1,2-propandiil)))biscarbamato de dimetilo

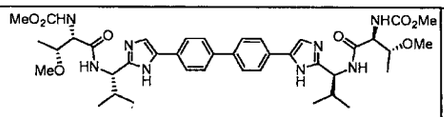
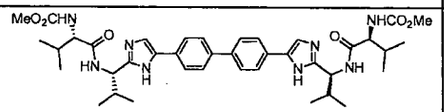
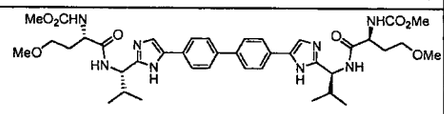
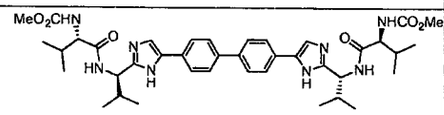


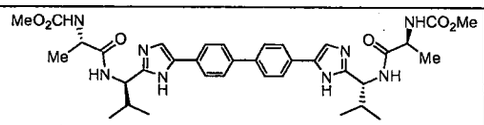
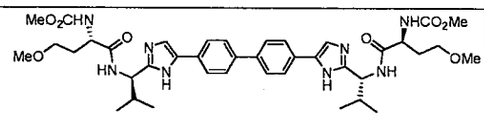
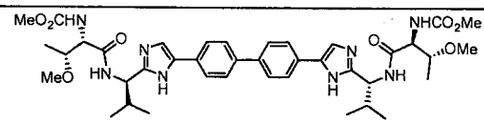
Una solución de (1S,1'S)-1,1'-(5,5'-(bifenil-4,4'-diil)bis(1H-imidazol-5,2-diil))bis(2-metilpropan-1-amina) (120 mg, 0.280 mmoles), ácido (S)-2-

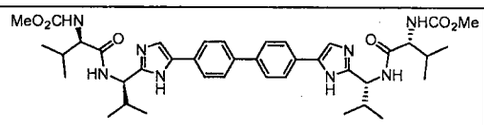
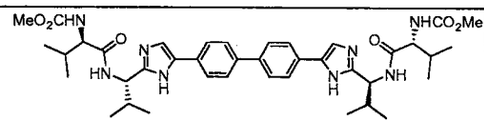
(metoxicarbonilamin)propanoico (124 mg, 0.840 mmoles) e iPr_2Net (0.489 mL, 2.80 mmoles) en DMF (5 mL) se trató con HATU (426 mg, 1.12 mmoles) y la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se dividió entre H_2O y EtOAc, las capas se separaron y la fase acuosa se extrajo con EtOAc. Las capas orgánicas combinadas se concentraron al vacío y se purificaron mediante cromatografía en columna (Biotage, 25S eluyendo con 0 a 40% de CH_3CN en CH_2Cl_2 y luego 10% de MeOH en CH_2Cl_2. Las fracciones adecuadas fueron concentradas al vacío y el residuo se purificó mediante HPLC preparativa (CH_3CN-H_2O-TFA). Dos purificaciones subsiguientes mediante HPLC preparativa (CH_3CN-H_2O-NH_4OAc) seguidas por una HPLC preparativa final (CH_3CN-H_2O-TFA) dieron la sal TFA del compuesto del título (4.9 mg, 2%) como un sólido incoloro. ^1H RMN (300 MHz, CD_3OD) δ 7.89 (s, 2H), 7.86 (s, 8H), 4.87 (d, = 8.5 Hz, 2H), 4.19 (q, J = 7.0 Hz, 2H), 3.65 (s, 6H), 1.33 (d, J = 7.0 Hz, 6H), 1.14 (d, J = 7.0 Hz, 6H), 0.96 (d, J = 7.0 Hz, 6H). LCMS: Análisis calculado para $C_{36}H_{46}N_8O_6$: 686; encontrado: 687 $(M+H)^+$.

Tabla 1A

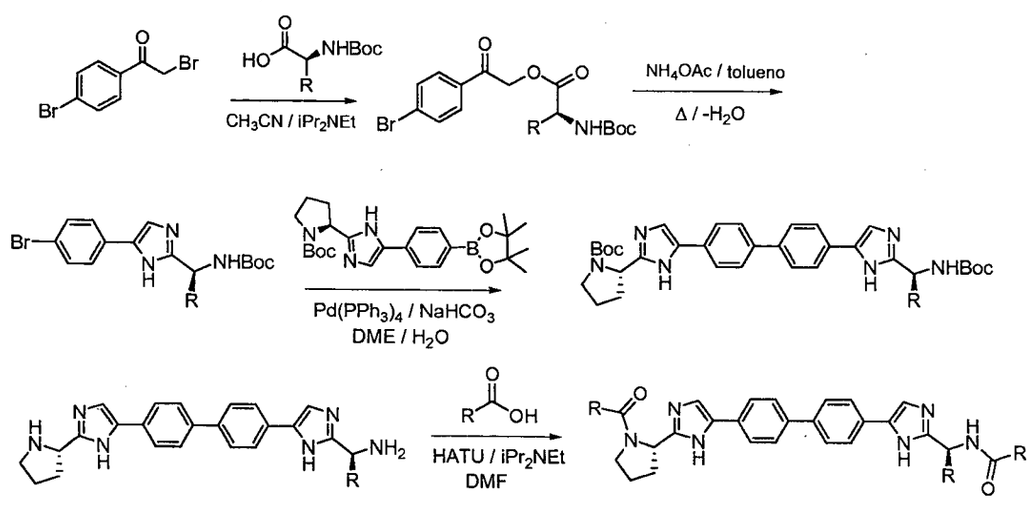
Los siguientes compuestos se prepararon de manera similar iniciando con la amina adecuada y el aminoácido sustituto.

Ejemplo	*Nombre del Compuesto*	*Estructura*	*Datos Analíticos*
Ejemplo R6	(4,4'-bifenildiilbis (1H-imidazol-4,2-diil((1S)-2-metil-1,1-propandiil) imino((2S,3R)-3-metoxi-1-oxo-1,2-butandiil)) biscarbamato de dimetilo		LCMS: Anal. Calcd. para: $C_{40}H_{54}N_8O_8$: 774; encontrado: 775 $(M+H)^+$.
Ejemplo R7	(4,4'-bifenildiilbis (1H-imidazol-4,2-diil((1S)-2-metil-1,1-propandiil) imino((2S)-3-metil-1-oxo-1,2-butandiil)) biscarbamato de dimetilo		LCMS: Anal. Calcd. para: $C_{40}H_{54}N_8O_6$: 742; encontrado: 743 $(M+H)^+$.
Ejemplo R8	(4,4'-bifenildiilbis (1H-imidazol-4,2-diil((1S)-2-metil-1,1-propandiil) imino((2S)-4-metoxi-1-oxo-1,2-butandiil)) biscarbamato de dimetilo		LCMS: Anal. Calcd. para: $C_{40}H_{54}N_8O_8$: 774; encontrado: 775 $(M+H)^+$.
Ejemplo R9	(4,4'-bifenildiilbis (1H-imidazol-4,2-diil((1R)-2-metil-1,1-		LCMS: Anal. Calcd. para: $C_{40}H_{54}N_8O_6$: 742; encontrado: 743 $(M+H)^+$.

	propandiil)imino ((2S)-3-metil-1-oxo -1,2-butandiil))) biscarbamato de dimetilo		
Ejemplo R10	(4,4'-bifenildiilbis (1H-imidazol-4,2-diil ((1R)-2-metil-1,1-propandiil)imino ((2S)-1-oxo-1,2-propandiil))) biscarbamato de dimetilo		LCMS: Anal. Calcd. para: $C_{36}H_{46}N_8O_6$: 686; encontrado: 687 $(M+H)^+$.
Ejemplo R11	(4,4'-bifenildiilbis (1H-imidazol-4,2-diil ((1R)-2-metil-1,1-propandiil)imino ((2S)-4-metoxi-1-oxo-1,2-butandiil))) biscarbamato de dimetilo		LCMS: Anal. Calcd. para: $C_{40}H_{54}N_8O_8$: 774; encontrado: 775 $(M+H)^+$.
Ejemplo R12	(4,4'-bifenildiilbis (1H-imidazol-4,2-diil ((1R)-2-metil-1,1-propandiil)imino ((2S,3R)-3-metoxi-1 -oxo-1,2-butandiil))) biscarbamato de dimetilo		LCMS: Anal. Calcd. para: $C_{40}H_{54}N_8O_8$: 774; encontrado: 775 $(M+H)^+$.

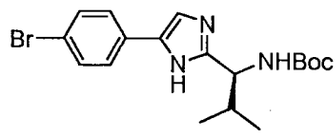
Ejemplo R13	(4,4'-bifenildiilbis (1H-imidazol-4,2-diil ((1R)-2-metil-1,1-propandiil)imino ((2R)-3-metil-1-oxo-1,2-butandiil)) biscarbamato de dimetilo		Anal. Calcd. para: $C_{40}H_{54}N_8O_6$: 742; encontrado: 743 $(M+H)^+$.
Ejemplo R14	(4,4'-bifenildiilbis (1H-imidazol-4,2-diil ((1S)-2-metil-1,1-propandiil)imino ((2R)-3-metil-1-oxo-1,2-butandiil)) biscarbamato de dimetilo		Anal. Calcd. para: $C_{40}H_{54}N_8O_6$: 742; encontrado: 743 $(M+H)^+$.

Esquema de reacción 2



Ejemplo R15

1-(5-(4-bromofenil)-1H-imidazol-2-il)-2-metilpropilcarbamato de (S)-ter-butilo

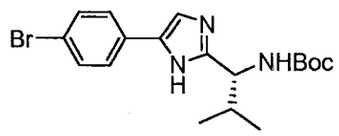


Una solución de 2-bromo-1-(4-bromofenil)etanona (6.23 g, 22.3 mmoles) y N-Boc-L-valina (5.00 g, 23.0 mmoles) en CH_3CN seco (30 mL) se trató con iPr_2Net (4.40 mL, 25.3 mmoles) y la solución se dejó agitar a temperatura ambiente durante la noche. El solvente se removió al vacío y la suspensión resultante se dividió entre EtOAc y H_2O. Las capas se separaron y la fase acuosa se extrajo con EtOAc. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron al vacío para dar un aceite amarillo. LCMS: Análisis calculado para $C_{18}H_{24}BrNO_5$: 413,415; encontrado: 412,414 $(M-H)^-$. El residuo se suspendió en tolueno (60 mL) y se añadió NH_4OAc (8.61 g, 111.7 mmoles). La mezcla se calentó a reflujo durante 16 horas con remoción azeotrópica de H_2O (Dean-Stark). La mezcla se enfrió a temperatura ambiente y se concentró hasta la sequedad al vacío. El residuo se purificó mediante cromatografía en columna (biotage) eluyendo

con 10% de MeOH en CH_2Cl_2 para dar el compuesto del título (8.55 g, 94%) como una espuma amarilla. ^1H RMN (500 MHz, CD_3OD) δ 7.84 (s, 1H), 7.66 (app d, J = 8.9 Hz, 2H), 7.64 (app d, J = 8.9 Hz, 2H), 4.65 (d, J = 7.7 Hz, 1H), 2.23-2.27 (m, 1H), 1.42 (s, 9H), 1.07 (d, J = 6.5 Hz, 3H), 0.93 (d, J = 6.5 Hz, 3H). LCMS: Análisis calculado para $C_{18}H_{24}BrN_3O_2$: 393, 395; encontrado: 394, 396 $(M+H)^+$.

Ejemplo R16

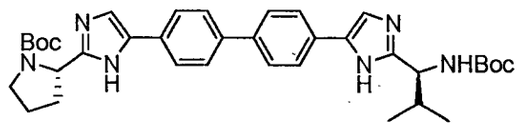
1-(5-(4-bromofenil)-1H-imidazol-2-il)-2-metilpropilcarbamato de (R)-ter-butilo



El compuesto del título se preparó iniciando a partir de 2-bromo-1-(4-bromofenil)etanona y N-Boc-D-valina usando el método dado en el ejemplo 15. ^1H RMN (500 MHz, CD_3OD) δ 7.83 (s, 1H), 7.68 (app d, J = 8.7 Hz, 2H), 7.64 (app d, J = 8.7 Hz, 2H), 4.65 (d, J = 7.3 Hz, 1H), 2.22-2.26 (m, 1H),1.42 (s, 9H), 1.08 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H). LCMS: Análisis calculado para $C_{18}H_{24}BrN_3O_2$: 393, 395; encontrado: 394,396 $(M+H)^+$.

Ejemplo R17

2-(5-(4'-(2-((S)-1-(ter-butoxicarbonilamino)-2-metilpropil)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-ter-butilo



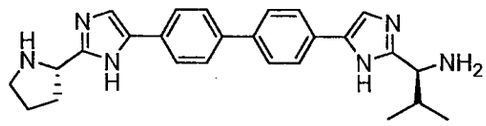
Una solución de 1-(5-(4-bromofenil)-1H-imidazol-2-il)-2-metilpropilcarbamato de (S)-*ter*-butilo (2.00 g, 5.07 mmoles), 2-(5-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*ter*-butilo (2.23 g, 5.07 mmoles) y $NaHCO_3$ (1.49 g, 17.8 mmoles) en DME (50 mL) y agua (15 mL) se desgasificó al evacuar y volver a llenar con N_2.

Se añadió tetrakis(trifenilfosfina)paladio(0) (0.293 g, 0.254 mmoles) y la mezcla de reacción se calentó durante la noche a 100°C. La mezcla se enfrió a la temperatura ambiente y se removió el DME al vacío. El residuo se dividió entre H_2O y EtOAc y las capas se separaron. La fase acuosa se extrajo con EtOAc y las capas orgánicas combinadas se concentraron hasta la sequedad al vacío y se purificaron mediante cromatografía en columna (Biotage) eluyendo con un gradiente de 0 a 40% de CH_3CN en CH_2Cl_2 y luego 0 a 10% de MeOH en CH_2Cl_2. El compuesto del título (2.05 g, 65% de rendimiento) se obtuvo como una espuma

café. Este material se usó como tal en etapas subsecuentes. LCMS: Análisis calculado para $C_{36}H_{46}N_6O_4$: 626; encontrado: 627 $(M+H)^+$.

Ejemplo R17A

(S)-2-metil-1-(5-(4'-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)propan-1-amina

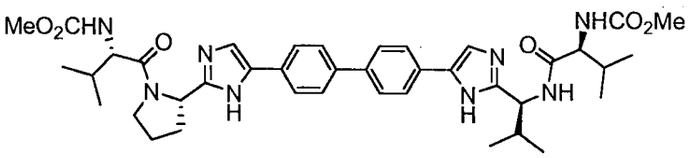


A una solución de 2-(5-(4'-(2-((S)-1-(*ter*-butoxicarbonilamino)-2-metilpropil)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*ter*-butilo (2.05 g, 3.27 mmoles) en CH_2Cl_2 (20 mL) se le añadió TFA (5 mL, 64.9 mmoles) y la solución se dejó agitar durante 2 h. Los solventes se removieron al vacío, el residuo se disolvió en CH_2Cl_2: MeOH (1:1) (alrededor de 10 mL) y se absorbió sobre un cartucho de intercambio catiónico MCX (Oasis).La resina se lavó con MeOH y el material deseado se liberó mediante elución con NH_3 en MeOH (2M). Los solventes se removieron al vacío para dar el compuesto del título (0.622 g, 91%) como una espuma amarilla que fue lo suficientemente pura para usarse en etapas subsecuentes. ^1H RMN (500 MHz,

CD_3OD) δ 7.85-7.88 (m, 4H), 7.75 (m, app d, J = 8.2 Hz, 4H), 7.70 (app d, J = 5.8 Hz, 2H), 4.96 (t, J = 8.2 Hz, 1H), 4.30 (d, J = 8.5 Hz, 1H), 3.54-3.57 (m, 1H), 3.47-3.52 (m, 1H), 2.55-2.62 (m, 1H), 2.38-2.46 (m, 1H), 2.28-2.36 (m, 1H), 2.15-2.24 (m, 1H), 1.17 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H). LCMS: Análisis calculado para $C_{26}H_{30}N_6$: 426; encontrado: 427 $(M+H)^+$.

Ejemplo R18

N^2-(metoxicarbonil)-N-((1S)-1-(4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-metilpropil)-L-valinamida

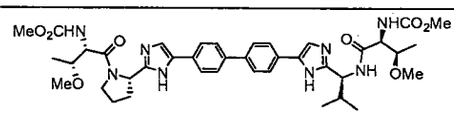
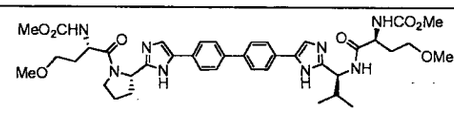


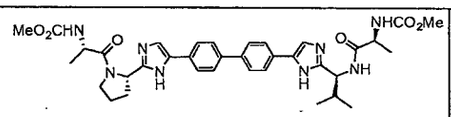
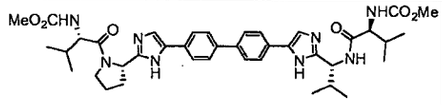
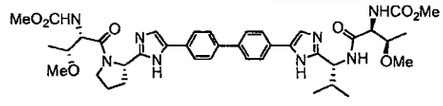
Un matraz de 50 mL de un solo cuello equipado con un agitador magnético se cargó con (S)-2-metil-1-(5-(4'-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)propan-1-amina (80 mg, 0.188 mmoles) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (99 mg, 0.563 mmoles) en DMF (5 mL) y DIEA (0.328 mL, 1.875 mmoles) fue añadido. A esta solución se le añadió HATU (285 mg, 0.750 mmoles) y la reacción se dejó agitar

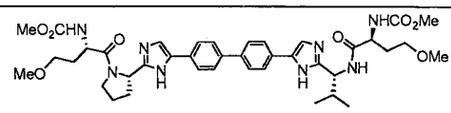
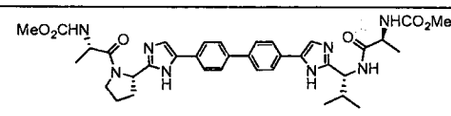
durante 4 horas a temperatura ambiente. La mezcla de reacción se dividió entre H_2O y EtOAc, las capas se separaron y la fase acuosa se extrajo con EtOAc. Las capas orgánicas combinadas se concentraron al vacío y se purificaron mediante cromatografía en columna (Biotage, 25S) eluyendo con 0 a 40% de CH_3CN en CH_2Cl_2 y luego 10% de MeOH en CH_2Cl_2. Las fracciones adecuadas se concentraron al vacío y el residuo se purificó mediante HPLC preparativa (CH_3CN-H_2O-TFA) y luego una purificación subsecuente mediante HPLC preparativa (CH_3CN-H_2O-NH_4OAc) dio el compuesto del título (31.8 mg, 23%) como un sólido incoloro. ^1H RMN (500 MHz, CD_3OD) δ 7.71 (m, 4H), 7.64-7.67 (m, 4H), 7.35 (s, 1H), 7.32 (s, 1H), 5.33-5.34 (m, 0.2H), 5.17 (dd, J = 7.6, 5.5 Hz, 0.8 H), 4.77 (d, J = 9.2 Hz, 1H), 4.22 y 4.10 (d, J = 7.6 Hz, 1H, relación de rotámeros 4:1), 3.97-4.01 (m, 1), 3.94 (d, J = 7.0 Hz, 1H), 3.84-3.89 (m, 1H), 3.64 (s, 6H), 2.28-2.35 (m, 1H), 2.18-2.27 (m, 3H), 1.98-2.08 (m, 3H), 1.05 (d, J = 6.7 Hz, 3H), 0.98 y 0.94 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 6.7 Hz, 6H), 0.88 (d, J = 6.7 Hz, 3H), 0.86 (d, J = 6.7 Hz, 3H). LCMS: Análisis calculado para $C_{40}H_{52}N_8O_6$: 740; encontrado: 741 $(M+H)^+$.

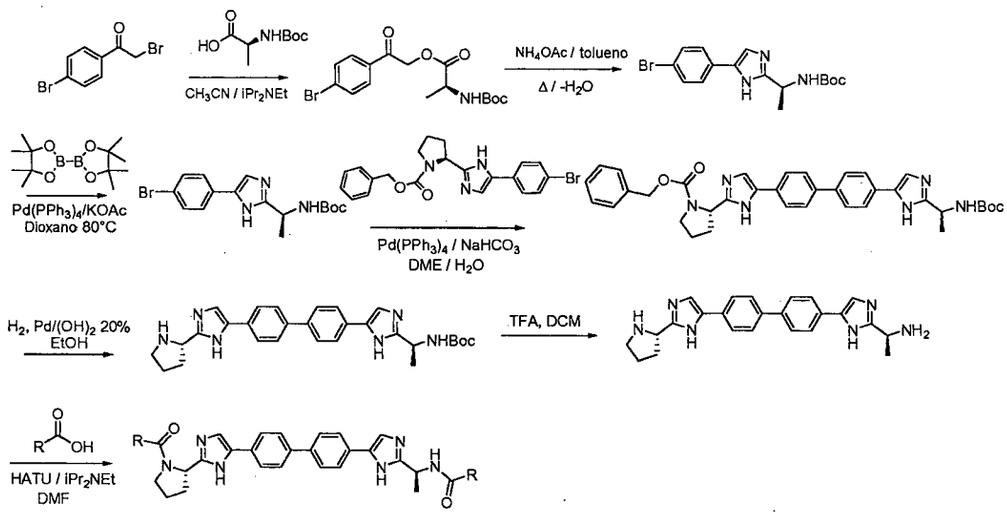
Tabla 2A

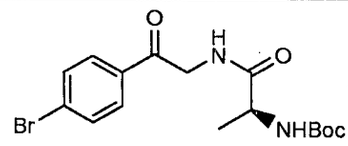
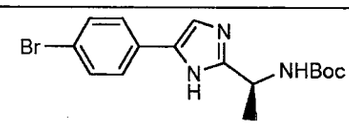
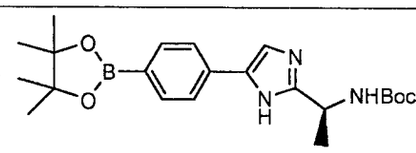
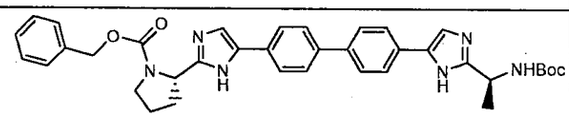
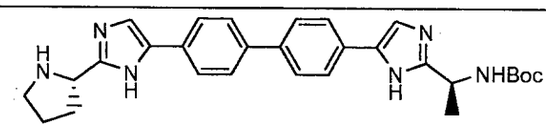
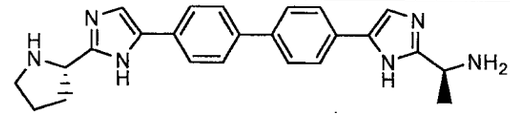
Los siguientes compuestos se prepararon de manera similar iniciando con la amina adecuada y el aminoácido sustituto.

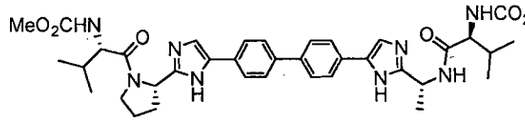
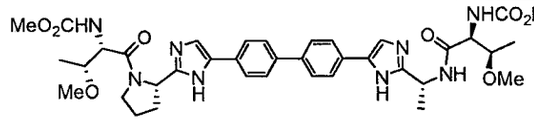
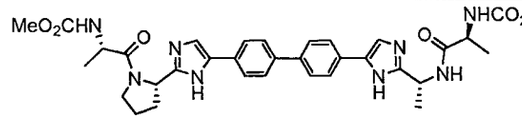
Ejemplo	*Nombre del Compuesto*	*Estructura*	*Datos Analíticos*
Ejemplo R19	((1S,2R)-2-metoxi-1-(((2S)-2-(4-(4'-(2-((1S)-1-((N-(metoxicarbonil)-O-metil-L-treonil) amino)-2-metilpropil) -1H-imidazol-4-il)-4 -bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil) propil)carbamato de metilo		LCMS: Anal. Calcd. para: $C_{40}H_{52}N_8O8$: 772 encontrado: 773 $(M+H)^+$.
Ejemplo R20	((1S)-3-metoxi-1-(((2S)-2-(4-(4'-(2-((1S)-1-((N-(metoxicarbonil)-O-metil-L-homoseril) amino)-2-metilpropil) -1H-imidazol-4-il)-4 -bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil) propil)carbamato de metilo		LCMS: Anal. Calcd. para: $C_{40}H_{52}N_8O8$: 772 encontrado: 773 $(M+H)^+$.

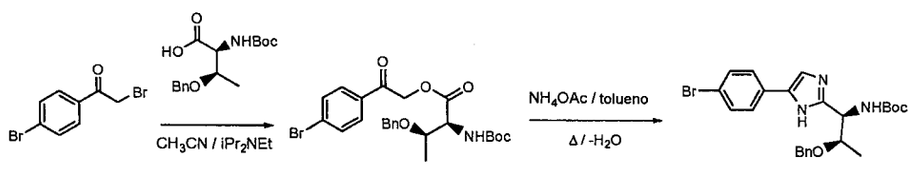
Ejemplo R21	((1S)-2-((2S)-2-(4-(4'-(2-((1S)-1-((N-(metoxicarbonil)-L-alanil)amino)-2-metilpropil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil) carbamato de metilo		LCMS: Anal. Calcd. para: $C_{36}H_{44}N_8O_6$: 684; encontrado: 685 $(M+H)^+$.
Ejemplo R22	N^2-(metoxicarbonil)-N-((1R)-1-(4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-metilpropil)-L-valinamida		LCMS: Anal. Calcd. para: $C_{40}H_{52}N_8O_6$: 740; encontrado: 741 $(M+H)^+$.
Ejemplo R23	((1S,2R)-2-metoxi-1-(((2S)-2-(4-(4'-(2-((1R)-1-((N-(metoxicarbonil)-O-metil-L-treonil)amino)-2-metilpropil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)propil) carbamato de metilo		LCMS: Anal. Calcd. para: $C_{40}H_{52}N_8O_8$: 772 encontrado: 773 $(M+H)^+$.

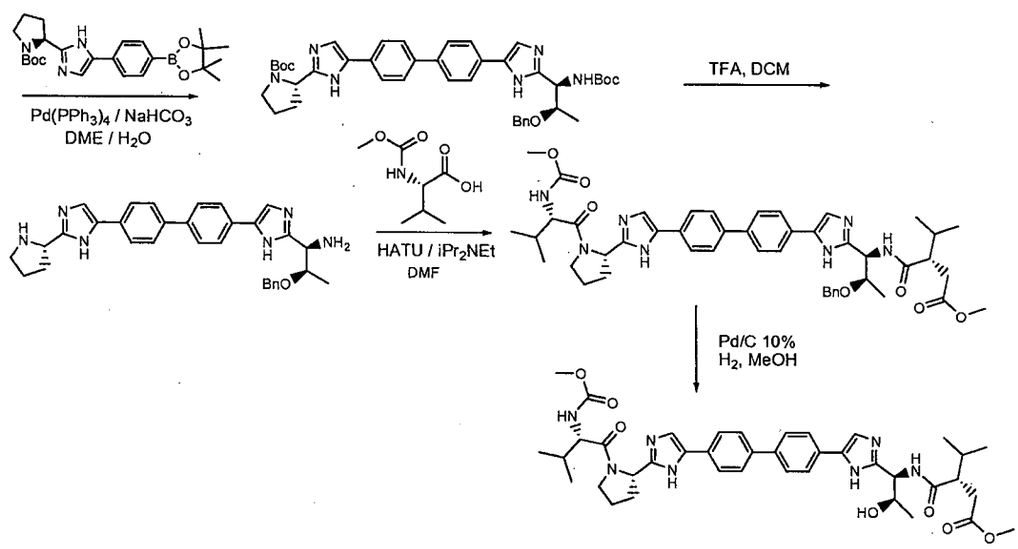
Ejemplo R24	((1S)-3-metoxi-1-(((2S)-2-(4-(4'-(2-((1R)-1-((N-(metoxicarbonil)-O-metil-L-homoseril) amino)-2-metilpropil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol -2-il)-1-pirrolidinil) carbonil)propil) carbamato de metilo		LCMS: Anal. Calcd. para: $C_{40}H_{52}N_8O_8$: 772; encontrado: 773 $(M+H)^+$.
Ejemplo R25	((1S)-2-((2S)-2-(4-(4'-(2-((1R)-1-((N-(metoxicarbonil)-L-alanil)amino)-2-metilpropil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol -2-il)-1-pirrolidinil)-1 -metil-2-oxoetil) carbamato de metilo		LCMS: Anal. Calcd. para: $C_{36}H_{44}N_8O_6$: 684; encontrado: 685 $(M+H)^+$.



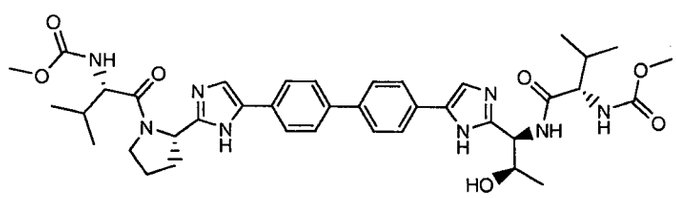
Ejemplo	*Estructura*	*Datos Analíticos*
Ejemplo A		LCMS: Anal. Calcd. para: $C_{16}H_{21}BrN_2O_4$: 385 encontrado: 386$(M+H)^+$.
Ejemplo B		LCMS: Anal. Calcd. para: $C_{16}H_{21}BrN_3O_2$: 366 encontrado: 367 $(M+H)^+$.
Ejemplo C		LCMS: Anal. Calcd. para: $C_{22}H_{32}BN_3O_4$: 413; encontrado: 414 $(M+H)^+$.
Ejemplo D		LCMS: Anal. Calcd. para: $C_{37}H_{40}N_6O_4$: 632; encontrado: 633 $(M+H)^+$.
Ejemplo E		LCMS: Anal. Calcd. para: $C_{29}H_{34}N_6O_2$: 498 encontrado: 499 $(M+H)^+$.
Ejemplo F		LCMS: Anal. Calcd. para: $C_{24}H_{26}N_6$: 398; encontrado: 399 $(M+H)^+$.

Ejemplo R26		LCMS: Anal. Calcd. para: $C_{38}H_{48}N_8O_6$: 712; encontrado: 713 $(M+H)^+$.
Ejemplo R27		LCMS: Anal. Calcd. para: $C_{38}H_{48}N_8O_8$: 744; encontrado: 745 $(M+H)^+$.
Ejemplo R28		LCMS: Anal. Calcd. para: $C_{34}H_{40}N_8O_6$: 756; encontrado: 757 $(M+H)^+$.

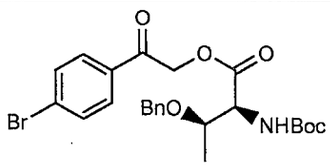
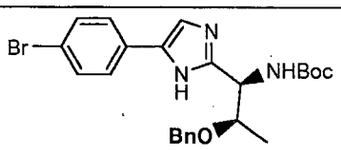
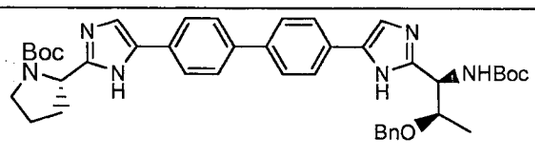
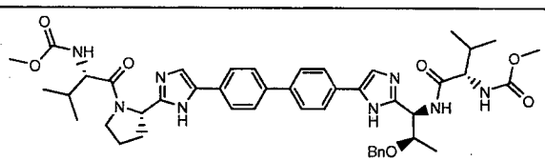
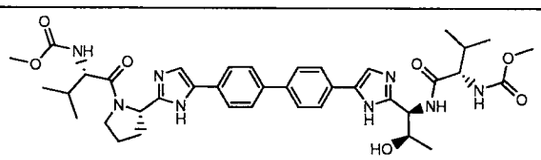




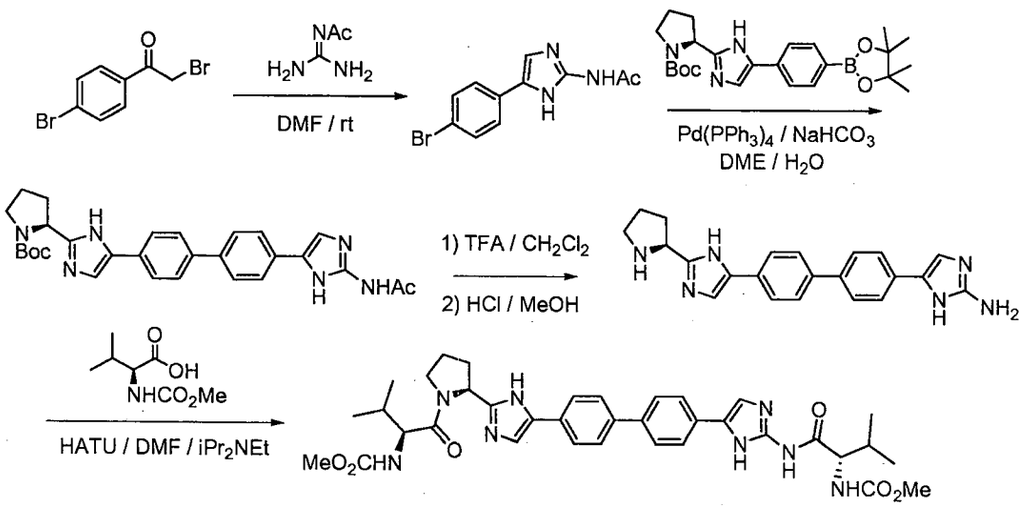
Ejemplo R29



Un matraz de 50 mL de un solo cuello equipado con un agitador magnético se cargó con un compuesto del ejemplo E (150 mg, 180 mmoles) en metanol (5 mL). A esta solución se le añadió una suspensión de paladio en carbón 10% (100 mg) en metanol (2 mL). La mezcla se purgó con 4.22 kg/cm^2 (60 psi) de hidrógeno. La mezcla se agitó en un par durante la noche a temperatura ambiente. El contenido del reactor se analizó mediante LC-MS y mostró una conclusión del 20%. Una suspensión de hidróxido de paladio en carbón 20% (100 mg) en ácido acético (2 mL) fue añadida. La mezcla se purgó con hidrógeno y se agitó en un agitador Parr con 60 psi de hidrógeno durante el fin de semana. La reacción se filtró a través de una almohadilla de Celite y el filtrado se evaporó al vacío. El residuo se purificó mediante HPLC preparativa (CH_3CN-H_2O-TFA) para dar el compuesto (ejemplo 29), 32 mg, 23% de rendimiento como un sólido blanco. LCMS: Análisis calculado para $C_{39}H_{50}N_8O_7$: 742; encontrado: 743 $(M+H)^+$.

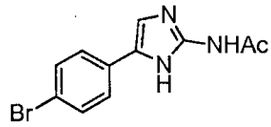
Ejemplo	*Estructura*	*Datos Analíticos*
Ejemplo G		LCMS: Anal. Calcd. para: $C_{24}H_{28}BrNO_6$: 506 encontrado: Sin ionización $(M+H)^+$.
Ejemplo H		LCMS: Anal. Calcd. para: $C_{24}H_{28}BrN_3O_3$: 486 encontrado: 487 $(M+H)^+$.
Ejemplo I		LCMS: Anal. Calcd. para: $C_{42}H_{50}BN_6O_5$: 718 encontrado: 719 $(M+H)^+$.
Ejemplo J		LCMS: Anal. Calcd. para: $C_{46}H_{56}N_8O_7$: 832; encontrado: 833 $(M+H)^+$.
Ejemplo R29		LCMS: Anal. Calcd. para: $C_{46}H_{56}N_8O_7$: 742 encontrado: 743 $(M+H)^+$.

Esquema de reacción 3



Ejemplo R30

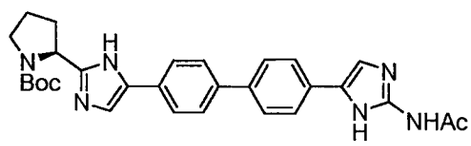
N-(5-(4-bromofenil)-1H-imidazol-2-il)acetamida



Una mezcla de 2-bromo-1-(4-bromofenil)etanona (2.00 g, 7.20 mmoles) y acetilguanidina (2.18 g, 21.6 mmoles) en DMF (40 mL) se agitó a temperatura ambiente durante 48 horas. La solución se concentró hasta la sequedad al vacío y el sólido café resultante fue de suficiente pureza para usarse en la siguiente etapa. LCMS: Análisis calculado para $C_{11}H_{10}BrN_3O$: 279, 281; encontrado: 280, 282 $(M+H)^+$.

Ejemplo R31

2-(5-(4'-(2-acetamido-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-ter-butilo

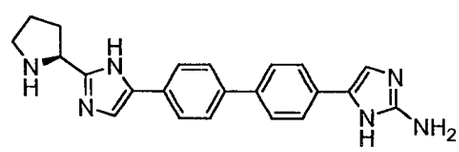


Una mezcla de N-(5-(4-bromofenil)-1H-imidazol-2-il)acetamida (0.604 g, 2.16 mmoles), 2-(5-(4-(4,4,5,5'-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*ter*-butilo (0.950 g, 2.16 mmoles), $NaHCO_3$ (0.636 g, 7.57 mmoles) en DME (20 mL) y H_2O (5 mL) se desgasificó al evacuar y volver a llenar con N_2 (X3). A esta solución se le añadió $Pd(PPh_3)_4$ (0.125 g, 0.11 mmoles)

y la suspensión se calentó a 125°C durante 24 h. La mezcla se evaporó hasta la sequedad al vacío y el residuo se purificó mediante cromatografía en columna (Biotage) eluyendo con un gradiente de 0 a 10% de MeOH en CH_2Cl_2. El material se purificó después mediante HPLC preparativa (CH_3CN-H_2O-NH_4OAc) para dar el compuesto del título como un sólido incoloro. 7.76 (app dd, J = 8.4, 2.2 Hz, 4H), 7.69 (app d, J = 8.4 Hz, 2H), 7.66 (app d, J = 8.4 Hz, 2H), 7.45 (s, 1H), 7.23 (s, 1H), 3.66-3.72 (m, 1H), 3.48-3.53 (s, 1H), 2.34-2.46 (m, 1H), 2.18 (s, 3H), 1.96-2.10 (m, 3H), 1.46, 1.25 (s, 9H, rotámeros, relación 1:2). LCMS: Análisis calculado para $C_{29}H_{32}N_6O_3$: 512; encontrado: 513, 282 $(M+H)^+$.

Ejemplo R32

(S)-5-(4'-(2-(pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-amina



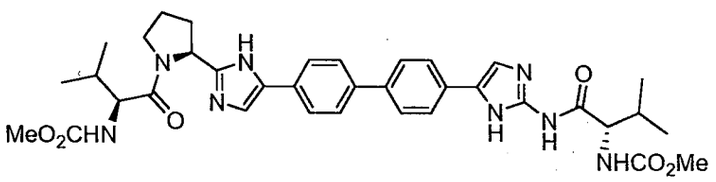
Etapa 1. Una solución de 2-(5-(4'-(2-acetamido-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*ter*-butilo (55.0 mg, 0.11 mmoles) en CH_2Cl_2 (5 mL) y TFA (1 mL) se dejó agitar a temperatura ambiente durante 3 horas. La mezcla de reacción se concentró al vacío para dar la sal TFA del compuesto del título (55.0 mg) la cual se llevó directamente a la siguiente etapa. LCMS:

Análisis calculado para $C_{24}H_{24}N_6O$: 412; encontrado: 413 $(M+H)^+$.

Etapa 2. El aceite café de la etapa 1 se suspendió en 25% de HCl concentrado en MeOH (10 mL) y se calentó a reflujo durante 3 horas. Después se removieron los materiales volátiles bajo presión reducida y el residuo se purificó mediante HPLC preparativa (CH_3CN-H_2O-TFA) para dar la sal TFA del compuesto del título (20 mg, 42%). LCMS: Análisis calculado para $C_{22}H_{22}N_6$: 370; encontrado: 371 $(M+H)^+$.

Ejemplo R33

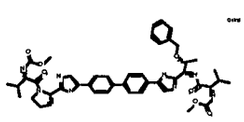
(S)-2-metoxicarbonilamin-N-(5-(4'-(2-((S)-1-((S)-2-metoxicarbonilamin-3-metilbutanoil)pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)-3-metilbutanamida



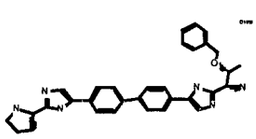
A una solución de sal de ácido (S)-5-(4'-(2-(pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-amina (20 mg, 0.04 mmoles), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (25 mg, 0.14 mmoles) e iPr_2Net (0.09 mL, 0.53 mmoles) en DMF (5 mL) se le añadió HATU (54 mg, 0.14 mmoles). La solución se dejó agitar durante 3 horas y luego se vertió en H_2O. La mezcla se concentró hasta la sequedad al vacío y el residuo se purificó mediante HPLC preparativa (CH_3CN-H_2O-TFA) dando el compuesto

del título y recuperando material de partida. El material de partida recuperado se volvió a someter a las condiciones de reacción y se purificó como arriba. Los dos lotes de producto fueron después purificados mediante HPLC preparativa (CH_3CN-H_2O-NH_4OAc) para dar el compuesto del título como un sólido pardo (18 mg, 76%). ^1H RMN (400 MHz, CD_3OD) δ 7.80-7.88 (m, 9H), 7.56 (s, 1H), 5.24 (app t, J = 7.6 Hz, 1H), 4.23 (d, J = 7.1 Hz, 1H), 4.18 (d, J = 6.6 Hz, 1H), 4.08-4.13 (m, 1H), 3.83-3.90 (m, 1H), 3.68 (s, 3H), 3.65 (s, 3H), 2.54-2.63 (m, 1H), 2.17-2.30 (m, 4H), 2.01-2.09 (m, 1H). LCMS: Análisis calculado para $C_{36}H_{44}N_8O_6$: 684; encontrado: 685 $(M+H)^+$.

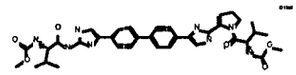
Los siguientes ejemplos se prepararon como se describió en los ejemplos anteriores usando los materiales de partida adecuados:



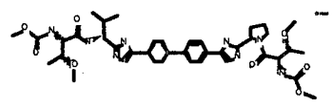
Ejemplo R34



Ejemplo R35



Ejemplo R36



Ejemplo R37

Actividad biológica

Se utilizó un ensayo de replicón de HCV en la presente invención, y se preparó, llevó a cabo y validó según se describe en PCT/US2006/022197 de propiedad común y en O'Boyle et al., *Antimicrob Agents Chemother.* **2005** Apr;49(4):1346-53.

Células de replicón 1b-377-neo de HCV fueron usadas para probar la serie de compuestos actualmente descrita así como células resistentes al compuesto A debido a una mutación Y2065H en NS5A (descrita en la solicitud PCT/US2006/022197). Se determinó que los compuestos probados tenían más de 10 veces menos actividad inhibitoria en células resistentes al compuesto A que las células tipo silvestre indicando un mecanismo de acción relacionado entre las dos series de compuestos. Así, los compuestos de la presente invención pueden ser efectivos para inhibir la función de la proteína NS5A de HCV y se entiende que son efectivos en combinaciones como las descritas

previamente en la solicitud PCT/US2006/022197 y WO/04014852 de propiedad común. Además, los compuestos de la presente invención pueden ser efectivos contra el genotipo 1b de HCV. Se debe entender que los compuestos de la presente invención pueden inhibir varios genotipos de HCV. La tabla 2 muestra los valores EC50 de compuestos representativos de la presente invención contra el genotipo 1b de HCV. En una modalidad, los compuestos de la presente invención son activos contra los genotipos 1a, 1b, 2a, 2b, 3a, 4a y 5a. Las escalas de EC50 contra 1b de HCV son las siguientes: A = 1-10 μM; B = 100-999 nM; C = 1-99 nM; y D = 1-999 pM.

Los compuestos de la presente invención pueden inhibir HCV mediante mecanismos además de o aparte de la inhibición de NS5A. En una modalidad los compuestos de la presente invención inhiben el replicón de HCV y en otra modalidad los compuestos de la presente invención inhiben NS5A.

Tabla 2

Ejemplo	Escala
1	D
24-4e	C
24-4f	B
24-4g	A
25-1	D
25-2	D
25-3	D
25-4	D
25-5	D
25-6	C
25-7	C
25-8	D
24-4h	D
120-9	D
120	D
120-5	C
120-6	C
120-7	D
120-8	C
103-3	D
103-4	D
103-1	D
103-2	D
103-5	D
103-6	C
103-8	D
103-7	D
151 isómero 1	C
151 isómero 2	B
152j-9	C
152j-10	C
152j-1	C
152j-2	D
153c-5	C
153c-6	C
153c-2	C
153c-1	C
152j-7	C
152j-8	D
153c-3	A
153c-4	A
152j-11	D
152j-12	D
152j-15	D
152j-28	D
152j-13	C
152j-14	C
152j-19	D
152j-16	D

Ejemplo	Escala
152j-3	D
152j-20	C
152j-17	D
152j-18	D
152j-3	D
152j-5	D
152j-6	D
152l-2	D
152l-1	D
152j-24	D
152j-23	D
153c-7	C
152j-22	D
24-18-2	D
24-18-1	D
24-18-4	D
24-18-5	D
24-18-6	D
24-18-3	D
152j-21	D
152l-3	D
131.1-2	D
131.1-1	D
24-4a	D
120-1	D
120-2	D
120-3	D
120-4	D
24-10	D
24-9	D
24-8	D
24-11	C
24-12	C
11	C
24-16	D
24-18	D
24-17	D
24-15	C
24-13	B
24-14	C
24-4b	C
24-4c	D
24-4d	D
148	C
149	D
150	C
24-5	D
24-6	D
24-7	D

Ejemplo	Escala
24-1	D
24-2	D
24-3	D
28-1	D
28-2	D
28-3	D
28-4	D
28-5	D
84-1	D
84-2	D
84-3	D
84-4	D
84-7	C
84-10	C
84-12	D
84-14	C
84-15	C
84-17	D
84-18	C
84-19	C
84-20	C
84-24	D
84-26	D
84-27	D
84-28	D
84-32	D
84-33	D
84-34	C
84-35	D
84-36	D
84-38	D
84-39	D
84-40	D
84-44	D
84-46	D
84-47	D
84-48	D
84-49	D
84-50	D
84-51	D
84-52	D
84-53	D
84-54	D
84-55	D
84-56	D
84-57	D
84-58	D
84-59	D
84-60	D

Ejemplo	Escala
84-61	D
84-62	D
84-63	D
84-64	D
84-65	C-D
84-66	C-D
84-67	D
84-68	C
84-69	D
84-70	C
84-71	C
84-72	C
84-73	C
84-74	D
84-75	C
84-76	D
84-77	D
84-78	D
84-79	D
84-80	D
84-81	D
84-82	D
84-83	D
84-84	D
84-85	D
84-86	D
84-87	D
94-1	D
94-2	C
94-3	D
94-6	C-D
94-9	D
94-10	D
94-12	C
94-13	D
94-17	D
94-19	D
94-20	C
94-24	D
94-25	D
94-26	D
94-27	C
94-30	D
94-32	C
94-33	C
94-34	C
94-36	D
94-37	C
94-38	D
94-42	D

Ejemplo	Escala
94-44	D
94-45	D
94-46	D
94-47	D
94-48	D
94-49	D
94-50	D
94-51	D
94-52	D
94-53	D
94-54	D
94-55	D
94-56	D
107-1	D
107-2	D
107-3	D
107-4	D
107-5	D
107-6	D
107-7	D
107-8	D
107-9	D
107-10	D
107-11	D
107-12	D
107-13	D
107-14	D
107-15	D
107-16	D
107-17	D
107-18	D
107-19	D
107-20	D
107-21	D
107-22	D
107-23	D
107-24	D
107-25	D
107-26	D
107-27	D
107-28	D
107-29	D
107-30	D
107-31	D
107-32	D
107-33	D
107-34	D
107-35	D
107-36	D
107-37	D

Ejemplo	Escala
107-38	D
107-39	D
107-40	D
107-41	D
107-42	D
107-43	D
107-44	D
2	D
3	D
4	D
5	C
6	C
7	D
8	D
24-23	D
9	C
10	C
11	C
12	C
13	C
14	B
15	C
16	C
17	D
18	D
19	D
20	C
21	D
22	D
23	D
24	C
25	D
26	C
27	C
28	C
29	D
30	C
31	D
32	C
33	D
34	D
35	D
36	D
37	D
38	D
39	D
40	D
41	D
42	D
43	D

44	D
45	D
46	D
47	D
48	D
49	D
50	B
51	D
52	D
53	D
54	D
55	D
56	D
57	D
58	D
59	D
60	D
61	D
62	D
63	D
64	D
65	C
67	D
68	D
69	D
70	C
71	D
72	C
73	D
74	D
75	D
76	D
77	D

78	D
79	D
80	D
81	D
82	D
83	D
84	D
85	D
86	D
87	D
88	D
89	D
90	D
91	D
92	D
93	D
94	D
95	D
96	D
97	D
98	D
99	D
100	D
101	D
102	D
103	D
104	D
105	D
106	D
107	D
108	D
109	C
110	D
111	D

112	D
113	D
114	D
115	D
116	D
117	D
118	D
119	D
120	D
121	D
122	D
123	D
124	D
125	D
126	D
127	D
128	D
129	D
130	D
131	D
132	D
133	C
134	D
135	D
136	D
138	D
139	D
140	D
141	D
142	C
143	D
144	D
145	D

146	D
147	D
LS2	C
LS3	C
LS4	C
LS16	C
LS6	B
LS11	A
LS14	D
LS20	D
LS21	D
LS22	D
LS23	D
LS24	D
LS25	D
LS26	D

LS27 D'mero 1	D
LS27 D'mero 2	D
LS36	D
LS37	D
F5	D
F6	D
F7	D
F8	D
F14	D
F15	D
F16	D
F17	D
F20	B
F21	B

F22	B
F25	D
F26	C
F27	C
F28	C
F29	C
F30	C
F32	B
F33	B
F34	C
F35	B
F37	B
F38	D
F39 Diastereómeros	D

F41	D
F43	D
F48	D
F49	C
F51	D
F52	D
F53	D
F54	D
F55	D
F56	D
F57	D
F58	D
F60	D
F61	C
F62	C
F63	D
F64	C
F65	B
F66	C
F67	C
F69	B
F70	B
F71	D
cj-48	B
cj-49	C
cj-50	D
cj-51	D
cj-52	D
cj-53	D
cj-54	D
cj-55	D
cj-56	D
cj-57	D
cj-58	D
cj-59	D
cj-60	D
cj-61	D
cj-62	D
cj-63	D
cj-64	D
cj-65	D
cj-66	D
cj-67	D
cj-68	D
cj-69	D
cj-70	D
cj-71	D
cj-72	D
cj-73	D
cj-74	C
cj-75	D

cj-76	D
cj-77	D
cj-78	D
cj-79	D
cj-80	D
cj-81	D
cj-82	D
cj-83	D
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cj-86	D
cj-87	D
cj-88	D
cj-89	D
cj-90	D
cj-91	D
cj-92	C
cj-93	D
cj-94	D
cj-95	D
cj-96	D
cj-97	D
cj-98	D
cj-99	D
cj-100	D
cj-101	D
cj-102	D
cj-103	D
cj-104	D
cj-105	D
cj-106	D
cj-107	D
cj-108	D
cj-109	D
cj-110	D
cj-111	D
cj-112	D
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cj-114	D
cj-115	D
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cj-117	D
cj-118	D
cj-119	D
cj-120	D
cj-121	D
cj-122	D
cj-45	D
cj-41	D
cj-47	C
cj-43	D

cj-44	D
cj-40	D
cj-46	D
cj-42	D
cj-36	D
cj-37	D
cj-38	D
cj-39	D
cj-32	D
cj-33	D
cj-34	D
cj-35	C
cj-136	D
cj-137	C
cj-138	A
cj-139	C
cj-140	B
cj-141	A
cj-142	A
cj-143	A
cj-144	D
cj-145	C
cj-146	B
cj-147	C
cj-148	C
cj-149	C
cj-150	C
cj-151	C
cj-152	C
cj-153	D
cj-154	D
cj-155	C
cj-156	D
cj-126	D
cj-127	C
cj-128	D
cj-129	D
cj-130	D
cj-131	C
cj-132	B
cj-133	C
cj-134	C
cj-135	C
cj-125	C
cj-15c	D
cj-20c	D
cj-20b	D
cj-20a	D
cj-17	D
cj-16	D
cj-20d	D

cj-20	D
cj-15a	D
cj-15	D
cj-15d	D
cj-11n	C
cj-11o	C
cj-11p	D
cj-11m	C
cj-11h	D
cj-11i	D
cj-11j	D
cj-11k	D
cj-11e	A
cj-11f	C
cj-11g	C
cj-11d	D
cj-11b	D
cj-11	D
cj-11a	D
cj-11c	D
JG-3	D
JG-4	C
JG-5	D
JG-6	C
JG-7	D
JG-8	D
JG-9	D
JG-10	C
JG-12	D
JG-13	C
JG-14	D
JG-15	D
JG-16	D
JG-17	D
OL-1	D
OL-2	D
OL-3	C
OL-4	D

OL-5	D
OL-6	D
OL-7	D
OL-8	D
OL-9	D
OL-10	D
OL-11	D
OL-12	D
OL-13	D
OL-19	D
OL-20	C
OL-21	D
D73	D
D74	D
D75	D
D76	D
D77	D
J16	D
J17	D
J18	D
J19	D
J20	D
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J22	D
J23	D
J24	D
J25	D
J26	D
J27	D
J28	C
J29	D
J30	C
J31	D
J37	D
J38	D
J39	D
J40	D
J41	D
J42	D
J42.a	D
J45	D
J46	D
J47	D
J48	D
J49	D
J50	D
J51	C
D33	D
D34	D
D35	D
D36	D

D37	D
D38	D
D39	D
D40	D
D41	D
D42	D
D43	D
D44	D
D45	D
D46	D
D47	D
D48	D
D49	D
D50	D
D51	D
D52	D
D53	D
D54	D
D55	D
D56	D
D57	D
D58	D
D59	D
D60	D
D61	D
D62	D
D63	D
D64	D
D65	D
D66	D
D67	D
D68	D
D69	D
D70	D
M1	>A
M2	C
M3	C
M4	B
M5	A
M6	A
M7	>A
M8	A
M9	B
M10	>A
M11	C
M12	C
M13	B
M14	B
M15	B
M16	A
M17	B

M18	A
M19	>A
M21	C
M22	A
M23	C
M24	C
M25	C
M26	B
M27	C
M28	A
M28-2	B
M29	>A
M30	C
M31	C
M32	B
M33	C
M34	C
M35	C
M36	C
M37	C
M38	C
M39	C
M40	C
M41	C
M42	C
M43	C
M44	B
M45	C
M46	C
M47	C
M48	C
M49	C
M50	C
M51	C
M52	C
M53	C
M54	C
M55	C
M56	C
M57	C

M58	C
M59	C
M60	C
M61	C
M62	C
M63	C
M64	C
M65	C
M66a	B
M66b	B
M66x	C
M67a	B
M67b	B
M68	B
M69	B
M70	C
M71	C
M72	C
M73	B
M74	C
M75	C
M76	C
M77	C
M78	C
M79	C
M80	C
M81	B
M82	C
M83	C
M84	C
M85	C
M86	C
M87	C
M88	C
M89	C
M90	A
M91	C
M91x	C
M91y	B
M92	A

M93	C
M94	C
M95	C
M96	B
M97	C
M98	C
M99	C
M100	C
M101	B
M102	C
M103	B
M104	B
M105	C
M106	C
M107	C
M108	C
M109	C
M110	C
M111	A
M112	C
M113	C
M114	>A
M115	>A
M116	>A
M117	>A
M118	>A
M119	B
M120	B
M121	B
M122	C
M123	A
M124	C
M125	C
M126	C
M127	C
M128	C
M129	A
M130	C

R26	D
R27	D
R28	D
R34	D
R35	B
R29	D

R36	D
R20	D
R37	D
R33	C

Será evidente para alguien capacitado en la técnica que la presente invención no está limitada a los anteriores ejemplos ilustrativos, y que puede ser incorporada en otras formas específicas sin alejarse de los atributos esenciales de la misma. Se desea por lo tanto que los ejemplos sean considerados en todos aspectos como ilustrativos y no como restrictivos, haciéndose referencia a las reivindicaciones anexas, más que a los anteriores ejemplos, y todos los cambios que estén dentro del significado y alcance de equivalencia de las reivindicaciones se intenta por lo tanto que sean abarcados en las mismas.

Los compuestos de la presente invención pueden inhibir HCV mediante mecanismos además de u otros que inhibición de NS5A. En una modalidad los compuestos de la presente invención inhiben replicón de HCV y en otra modalidad los compuestos de la presente invención inhiben NS5A. Los compuestos de la presente invención pueden inhibir varios genotipos de HCV.

REIVINDICACIONES

1. Un compuesto caracterizado porque se selecciona de

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1S)-2-metil-1,1-propandiil)imino((2S)-1-oxo-1,2-propandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1S)-2-metil-1,1-propandiil)imino((2S,3R)-3-metoxi-1-oxo-1,2-butandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1S)-2-metil-1,1-propandiil)imino((2S)-3-metil-1-oxo-1,2-butandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1S)-2-metil-1,1-propandiil)imino((2S)-4-metoxi-1-oxo-1,2-butandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1R)-2-metil-1,1-propandiil)imino((2S)-3-metil-1-oxo-1,2-butandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1R)-2-metil-1,1-propandiil)imino((2S)-1-oxo-1,2-propandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1R)-2-metil-1,1-propandiil)imino((2S)-4-metoxi-1-oxo-1,2-butandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1R)-2-

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metil-1,1-propandiil)imino((2S,3R)-3-metoxi-1-oxo-1,2-butandiil))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1R)-2-metil-1,1-propandiil)imino((2R)-3-metil-1-oxo-1,2-butandiil))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1S)-2-metil-1,1-propandiil)imino((2R)-3-metil-1-oxo-1,2-butandiil))biscarbamato de dimetilo;

N^2-(metoxicarbonil)-N-((1S)-1-(4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-metilpropil)-L-valinamida;

((1S,2R)-2-metoxi-1-(((2S)-2-(4-(4'-(2-((1S)-1-((N-(metoxicarbonil)-O-metil-L-treonil)amino)-2-metilpropil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo;

((1S)-3-metoxi-1-(((2S)-2-(4-(4'-(2-((1S)-1-((N-(metoxicarbonil)-O-metil-L-homoseril)amino)-2-metilpropil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo;

((1S)-2-((2S)-2-(4-(4'-(2-((1S)-1-((N-(metoxicarbonil)-L-alanil)amino)-2-metilpropil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo;

N^2-(metoxicarbonil)-N-((1R)-1-(4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-4-il)-

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4-bifenilil)-1H-imidazol-2-il)-2-metilpropil)-L-valinamida;

((1S,2R)-2-metoxi-1-(((2S)-2-(4-(4'-(2-((1R)-1-((N-(metoxicarbonil)-O-metil-L-treonil)amino)-2-metilpropil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo;

((1S)-3-metoxi-1-(((2S)-2-(4-(4'-(2-((1R)-1-((N-(metoxicarbonil)-O-metil-L-homoseril)amino)-2-metilpropil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo;

((1S)-2-((2S)-2-(4-(4'-(2-((1R)-1-((N-(metoxicarbonil)-L-alanil)amino)-2-metilpropil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1S)-2-metil-1,1-propandiil)imino((2S)-1-oxo-1,2-propandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1S)-2-metil-1,1-propandiil)imino((2S,3R)-3-metoxi-1-oxo-1,2-butandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1S)-2-metil-1,1-propandiil)imino((2S)-3-metil-1-oxo-1,2-butandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1S)-2-metil-1,1-propandiil)imino((2S)-4-metoxi-1-oxo-1,2-butandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1R)-2-metil-1,1-propandiil)imino((2S)-3-metil-1-oxo-1,2-butandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1R)-2-metil-1,1-propandiil)imino((2S)-1-oxo-1,2-propandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1R)-2-metil-1,1-propandiil)imino((2S)-4-metoxi-1-oxo-1,2-butandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1R)-2-metil-1,1-propandiil)imino((2S,3R)-3-metoxi-1-oxo-1,2-butandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1R)-2-metil-1,1-propandiil)imino((2R)-3-metil-1-oxo-1,2-butandiil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((1S)-2-metil-1,1-propandiil)imino((2R)-3-metil-1-oxo-1,2-butandiil)))biscarbamato de dimetilo;

N^2-(metoxicarbonil)-N-((1S)-1-(4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-metilpropil)-L-valinamida;

((1S,2R)-2-metoxi-1-(((2S)-2-(4-(4'-(2-((1S)-1-((N-(metoxicarbonil)-O-metil-L-treonil)amino)-2-metilpropil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo;

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((1S)-3-metoxi-1-(((2S)-2-(4-(4'-(2-((1S)-1-((N-(metoxicarbonil)-O-metil-L-homoseril)amino)-2-metilpropil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo;

((1S)-2-((2S)-2-(4-(4'-(2-((1S)-1-((N-(metoxicarbonil)-L-alanil)amino)-2-metilpropil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo;

N^2-(metoxicarbonil)-N-((1R)-1-(4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-metilpropil)-L-valinamida;

((1S,2R)-2-metoxi-1-(((2S)-2-(4-(4'-(2-((1R)-1-((N-(metoxicarbonil)-O-metil-L-treonil)amino)-2-metilpropil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo;

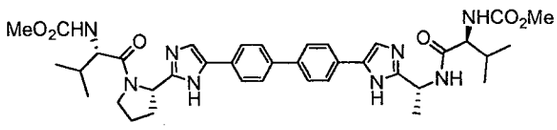
((1S)-3-metoxi-1-(((2S)-2-(4-(4'-(2-((1R)-1-((N-(metoxicarbonil)-O-metil-L-homoseril)amino)-2-metilpropil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo; y

((1S)-2-((25)-2-(4-(4'-(2-((1R)-1-((N-(metoxicarbonil)-L-alanil)amino)-2-metilpropil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo;

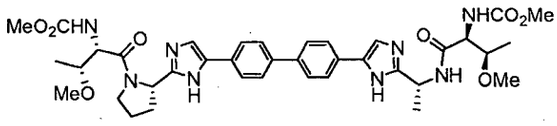
o una sal farmacéuticamente aceptable del mismo.

2. Un compuesto caracterizado porque se selecciona

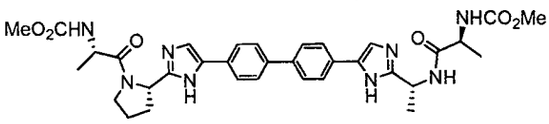
de


MeO2CHN
NHCO2Me
NH
N
H

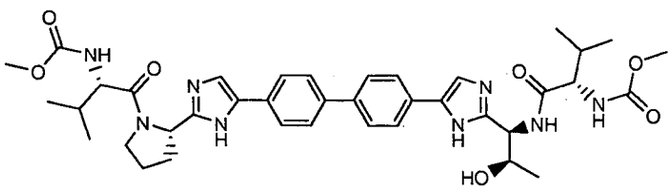
;


MeO2CHN
NHCO2Me
MeO
OMe
NH
N
H

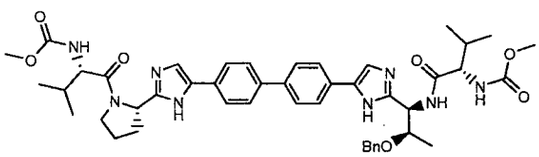
;


MeO2CHN
NHCO2Me
NH
N
H

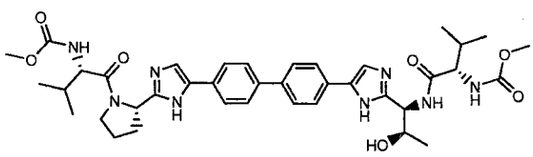
;


O
NH
N
H
HO

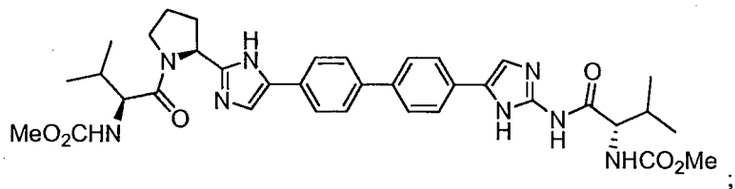
;


O
NH
N
H
BnO

;

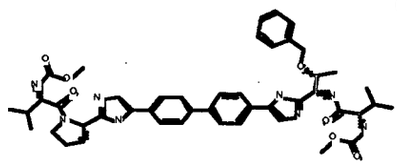

O
NH
N
H
HO

;

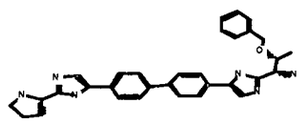


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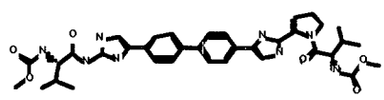
Quiral



Quiral

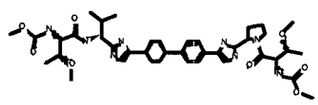


Quiral



; y

Quiral



o una sal farmacéuticamente aceptable del mismo.

3. Una composición caracterizada porque comprende el compuesto de conformidad con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, y un portador farmacéuticamente aceptable.

4. La composición de conformidad con la reivindicación 3, caracterizada porque comprende además uno o dos compuestos adicionales que tienen actividad anti-HCV.

5. La composición de conformidad con la reivindicación 4, caracterizada porque al menos uno de los compuestos adicionales es un interferón o una ribavirina.

6. La composición de conformidad con la reivindicación 5, caracterizada porque el interferón se selecciona de interferón alfa 2b, interferón alfa pegilado, interferón de consenso, interferón alfa 2A, e interferón linfoblastoide tau.

7. La composición de conformidad con la reivindicación 4, caracterizada porque al menos uno de los compuestos adicionales se selecciona de interleucina 2, interleucina 6, interleucina 12, un compuesto que mejora el desarrollo de una respuesta a células T auxiliares tipo 1, ARN de interferencia, ARN antisentido, Imiqimod, ribavirina, un inhibidor de inosín 5'-monofosfato deshidrogenasa, amantadina, y rimantadina.

8. La composición de conformidad con la reivindicación 4, caracterizada porque al menos uno de los

compuestos adicionales es efectivo para inhibir la función de un objetivo seleccionado de metaloproteasa de HCV, serina proteasa de HCV, polimerasa de HCV, helicasa de HCV, proteína NS4B de HCV, entrada de HCV, ensamble de HCV, salida de HCV, proteína NS5A de HCV e IMPDH para el tratamiento de una infección por HCV.

9. Una composición caracterizada porque comprende el compuesto de conformidad con la reivindicación 2, o una sal farmacéuticamente aceptable del mismo, y un portador farmacéuticamente aceptable.

10. La composición de conformidad con la reivindicación 9, caracterizada porque comprende además uno o dos compuestos adicionales con actividad anti-HCV.

11. La composición de conformidad con la reivindicación 10, caracterizada porque al menos uno de los compuestos adicionales es un interferón o una ribavirina.

12. La composición de conformidad con la reivindicación 11, caracterizada porque el interferón se selecciona de interferón alfa 2b, interferón alfa pegilado, interferón de consenso, interferón alfa 2A, e interferón linfoblastoide tau.

13. La composición de conformidad con la reivindicación 10, caracterizada porque al menos uno de los compuestos adicionales se selecciona de interleucina 2, interleucina 6, interleucina 12, un compuesto que mejora el

desarrollo de una respuesta a células T auxiliares tipo 1, ARN de interferencia, ARN antisentido, Imiqimod, ribavirina, un inhibidor de inosín 5'-monofosfato deshidrogenasa, amantadina, y rimantadina.

14. La composición de conformidad con la reivindicación 10, caracterizada porque al menos uno de los compuestos adicionales es efectivo para inhibir la función de un objetivo seleccionado de metaloproteasa de HCV, serina proteasa de HCV, polimerasa de HCV, helicasa de HCV, proteína NS4B de HCV, entrada de HCV, ensamble de HCV, salida de HCV, proteína NS5A de HCV e IMPDH para el tratamiento de una infección por HCV.

15. Un método para tratar una infección por HCV en un paciente, caracterizado porque comprende administrar al paciente una cantidad terapéuticamente efectiva del compuesto de conformidad con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo.

16. El método de conformidad con la reivindicación 15, caracterizado porque comprende además la administración de uno o dos compuestos adicionales que tienen actividad anti-HCV antes, después o simultáneamente con el compuesto de conformidad con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo.

17. El método de conformidad con la reivindicación 16, caracterizado porque al menos uno de los compuestos

adicionales es un interferón o una ribavirina.

18. El método de conformidad con la reivindicación 17, caracterizado porque el interferón se selecciona de interferón alfa 2b, interferón alfa pegilado, interferón de consenso, interferón alfa 2A, e interferón linfoblastoide tau.

19. El método de conformidad con la reivindicación 16, caracterizado porque al menos uno de los compuestos adicionales se selecciona de interleucina 2, interleucina 6, la interleucina 12, un compuesto que mejora el desarrollo de una respuesta a células T auxiliares tipo 1, ARN de interferencia, ARN antisentido, Imiqimod, ribavirina, un inhibidor de inosín 5'-monofosfato deshidrogenasa, amantadina, y rimantadina.

20. El método de conformidad con la reivindicación 16, caracterizado porque al menos uno de los compuestos adicionales es efectivo para inhibir la función de un objetivo seleccionado de metaloproteasa de HCV, serina proteasa de HCV, polimerasa de HCV, helicasa de HCV, proteína NS4B de HCV, entrada de HCV, ensamble de HCV, salida de HCV, proteína NS5A de HCV e IMPDH para el tratamiento de una infección por HCV.

21. Un método para tratar una infección por HCV en un paciente, caracterizado porque comprende administrar al paciente una cantidad terapéuticamente efectiva del compuesto

de conformidad con la reivindicación 2, o una sal farmacéuticamente aceptable del mismo.

22. El método de conformidad con la reivindicación 21, caracterizado porque comprende además la administración de uno o dos compuestos adicionales que tienen actividad anti-HCV antes, después o simultáneamente con el compuesto de conformidad con la reivindicación 2, o una sal farmacéuticamente aceptable del mismo.

23. El método de conformidad con la reivindicación 22, caracterizado porque al menos uno de los compuestos adicionales es un interferón o una ribavirina.

24. El método de conformidad con la reivindicación 23, caracterizado porque el interferón se selecciona de interferón alfa 2b, interferón alfa pegilado, interferón de consenso, interferón alfa 2A, e interferón linfoblastoide tau.

25. El método de conformidad con la reivindicación 22, caracterizado porque al menos uno de los compuestos adicionales se selecciona de interleucina 2, interleucina 6, la interleucina 12, un compuesto que mejora el desarrollo de una respuesta a células T auxiliares tipo 1, ARN de interferencia, ARN antisentido, Imiqimod, ribavirina, un inhibidor de inosín 5'-monofosfato deshidrogenasa, amantadina, y rimantadina.

26. El método de conformidad con la reivindicación

22, caracterizado porque al menos uno de los compuestos adicionales es efectivo para inhibir la función de un objetivo seleccionado de metaloproteasa de HCV, serina proteasa de HCV, polimerasa de HCV, helicasa de HCV, proteína NS4B de HCV, entrada de HCV, ensamble de HCV, salida de HCV, proteína NS5A de HCV e IMPDH para el tratamiento de una infección por HCV.

RESUMEN DE LA INVENCIÓN

La presente invención se refiere a composiciones de (4,4'-diimidazolil)bifenilos y a métodos para el tratamiento del virus de la hepatitis C (VHC). También se describen composiciones farmacéuticas que contienen estos compuestos y métodos para el uso de estos compuestos en el tratamiento de infección por VHC.

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

PODER OTORGADO POR BRISTOL-MYERS SQUIBB COMPANY

APOSTILLA

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA

2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR:
SALLY B. HANSEN

3. QUIEN ACTÚA EN CALIDAD DE NOTARIO PÚBLICO DE NUEVA JERSEY

4. LLEVA EL SELLO DE:
SALLY B. HANSEN, NOTARIO

CERTIFICADO

5. EN TRENTON, NUEVA JERSEY

6. EL 28 DE JUNIO DE 2007

7. POR BRADLEY ABELOW, TESORERO DE NUEVA JERSEY

8. N° A295716

9. SELLO (APARECE ADHERIDO SELLO DORADO)

10. FIRMA (FIRMADO) BRADLEY ABELOW

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 el 30 de mayo de 2007

(Firmado) Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Sen

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06 AGO 2007
Eduardo Duran Gomez
NOTARIO 38 DE BOGOTÁ D.C

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

CERTIFICACIÓN NOTARIAL

Texto en inglés y en español mediante el cual el suscrito Notario certifica el 30 de mayo de 2007 la existencia legal de la sociedad **BRISTOL-MYERS SQUIBB COMPANY** así como las funciones y firma de su representante autorizado Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior) para lo cual se basó en los documentos relacionados en inglés en el punto 6 de la certificación los cuales se traducen aquí al español, a saber:

Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.

Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado mayo 24, 2005.

[Firmado] SALLY B. HANSEN, Notario Público

[Sello en tinta que dice: "SALLY B. HANSEN. Notario Público de Nueva Jersey. Mi comisión vence el 6 de junio de 2010"]

[Aparece sello realzado]

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

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JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
SALLY B HANSEN

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
SALLY B HANSEN, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

6. THE 28TH DAY OF JUNE 2007

7. BY: Bradley Abelow, NEW JERSEY TREASURER

8. NO. A295716

9. SEAL/STAMP:

10. SIGNATURE

Bradley Abelow

AUTENTICACION DE COPIA DE ORIGINAL
COMO NOTARIO TRECE Y ORDENADO CIRCULO DE BOGOTA D.C.
CERTIFICO QUE PREVIO EL COTEJO RESPECTIVO LA
PRESENTE COPIA CORRESPONDE TEXTO A LA VISTA

06 AGO 2010

NOTARIO TRECE DE BOGOTA, D.C.

BAKER & MCKENZIE

Raisbeck, Lara, Rodriguez & Ruedy
Av. 82 No. 10 - 62 6th Floor
Bogotá, Colombia

NIT: 860.066.640-3
Tel: +57 1 634 1500
Fax: +57 1 376 2211
www.bakernet.com

000761

POWER OF ATTORNEY

The undersigned.

BRISTOL–MYERS SQUIBB COMPANY

domiciled in

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America

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 obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models, industrial designs, integrated circuits, layout-designs and vegetal varieties; the registration of trademarks, denominations of origin, commercial names, trade emblems, slogans and domain names; its renewal, assignments, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b)Processes of protection to the consumer, unfair competition, oppositions, cancellations, nullity, precautionary injunctions, infringement, granting of licenses, writ mandamus, the protection of trade secrets, and in general the civil, penal, an administrative processes relating to those rights. And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

I hereby ratify all actions previously taken on behalf of this company by the aforementioned attorneys with respect to the mentioned matters.

Done and subscribed in

On the 30 day of May of 2007

Signature of the person issuing the Power

Anastasia P. Winslow
Senior Patent Counsel

AUTENTICACION DE COPIA DE ORIGINAL
COMO NOTARIO TREINTA Y OCHO DEL CIRCULO DE BOGOTA, D.C.
CERTIFICO QUE PREVIO EL COTEJO RESPECTIVO LA
PRESENTE COPIA CONCUERDA CON EL ORIGINAL TENIDO A LA VISTA
06 AGO 2010
Eduardo Pinzón Parra
NOTARIO 38 DE BOGOTA, D.C.

PODER DE ABOGADO

La abajo firmada,

BRISTOL–MYERS SQUIBB COMPANY

domiciliada en

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 Estados Unidos de América

declara por el presente que otorga 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 obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera autoridades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, diseños industriales, esquemas de trazado de circuitos integrados y variedades vegetales; el registro de marcas, denominaciones de origen, nombres comerciales, enseñas, lemas comerciales y nombres de dominio; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Los procesos para la protección del consumidor, competencia desleal, oposiciones, cancelaciones, nulidades, medidas cautelares, infracciones, concesión de licencias, la tutela, la protección de secretos industriales, y en general procesos civiles, penales, administrativos relacionados con estos derechos. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del caso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

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 30 días del mes de mayo de 2007

Firma de la persona que firma el Poder

000762

NOTARIAL CERTIFICATION

On this 30 day of May

2007 , the undersigned Notary

CERTIFIES

1. That **Name of the person issuing the power**
Anastasia P. Winslow
of legal age and domiciled in
Princeton, NJ USA
Address, city, state, country
set his hand on the foregoing document.

2. That the grantor is to me personally known and that he/she has legal capacity to execute the instrument.

3. That the grantor has executed the foregoing document as
Senior Patent Counsel
Position of the person issuing the Power
of the judicial person **BRISTOL-MYERS SQUIBB COMPANY**

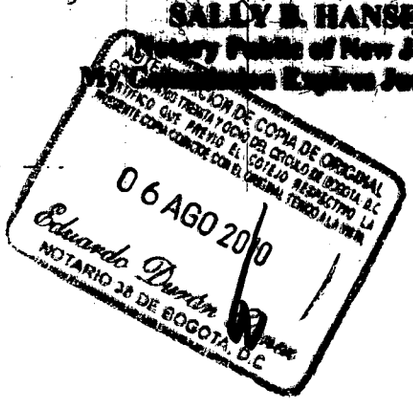
4. That the judicial person **BRISTOL-MYERS SQUIBB COMPANY**
having its home office in
Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America
is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

5. That the grantor has in fact the referred to authority and that his/her representation is legal.

6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:
(Please indicate here the documents such as the articles of incorporation, by laws or resolution from the Board of Directors and their dates, on which the notary relied to grant the certification)
- Certification executed by Sr. Vice President and General Counsel of Bristol-Myers Squibb Company on April 7, 2007
- Amended and Restated Certificate of Incorporation of Bristol-Myers Squibb Company dated May 24, 2005

Notary Public

SALLY B. HANSEN
Notary Public of New Jersey
My Commission Expires June 6, 2010



CERTIFICACION NOTARIAL

A los 30 días del mes de mayo

de 2007 , el suscrito Notario

DA FE

1 Que Anastasia P. Winslow

mayor y domiciliado en Princeton, NJ
Estados Unidos de América

suscribió de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

3 Que el otorgante ha suscrito el referido documento en su carácter de
Abogados de Patentes Senior
de la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**

4 Que la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**
con sede en
Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 Estados Unidos de América
está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se otorga el poder está comprendido entre los que constituyen su objeto social.

5 Que el otorgante tiene efectivamente la representación que ostenta y que ésta es legítima.

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:
- Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.
- Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado el 4 de mayo de 2005.

El Notario Público

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
CORREA ORDOÑEZ ALVARO
Apoderado(a) y/o Representante de
BRISTOL - MYERS SQUIBB COMPANY

REFERENCIA	Radicación No.	10 098050
	Solicitud internacional	PCT/US2008/053638
	Fecha inicio fase nacional	12/09/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	№ 12543

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. El solicitante debe presentar un nuevo titulo que permita identificar la materia de la cual trata la solicitud, ya que el titulo relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular única 5.2.9)

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Continua en la página siguiente...

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 24 SET. 2010.
adpa11