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Industria y Comercio

SUPERINTENDENCIA

PCT

INVENTARIO

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-099269 -00000-0000
Fecha: 2010-08-12 16:09:56 Dep: 2020 DIR NUEVAS CR
Tra: 11 PATENTE(YII Eve: 378 FASE NACIONAL I
Act: 411 PRESENTACION Folios: 1917

SOLICITUD

PATENTE DE INVENCION

21. **EXPEDIENTE No.** 10-099269

54. **TÍTULO** IMIDAZOLIL-BIFENIL-IMIDAZOLES COMO INHIBIDORES DEL 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 12, 2010

(FORMA P-10)

PETITORIO

00001

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-099269- -00000-0000
Fecha: 2010-08-12 16:09:56 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411, PRESENTACION Folios: 1917

Industria y Comercio
SUPERINTENDENCIA

...de radicación

FORMULARIO ÚNICO DE ...UD 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) **INVENTOR (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); 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); 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 Research 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, 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, Connecticut 06492 (US); 7 Whitney Street, North Grafton, MA 01536 (US) Nacionalidad o Domicilio: Canadá y Estados Unidos de América	

(5) **PCT (85)**

Solicitud Internacional No. PCT/US2008/053779 Fecha 13.02.2008

Publicación Internacional No. WO/2009/102325 Fecha 20.08.2009

(6) **Título (54)** IMIDAZOLIL-BIFENIL-IMIDAZOLES COMO INHIBIDORES DEL VIRUS DE LA HEPATITIS C

(7) **Clasificación Internacional (51)** C07D 403/14, A61K 31/41, A61P 31/00, C07D 405/14, C07D 417/14

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

(9) **Comprobante de pago No.** 10-63,485 – 10-63,508 – 10-54,988 – 10-63,392 **Fecha** 12-08, 2010

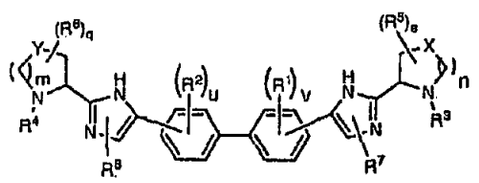
000002

(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
- [X] Arte final 12 x 12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: Extractos

(11) FIGURA CARATERISTICA

(I)



(12) Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

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

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

2010/08/12

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

000003

RECIBO OFICIAL DE CAJA : 10 - 63,485
FECHA : AGOSTO 3 DE 2010.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-099269- -00000-0000
Fecha: 2010-08-12 16:09:56 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1917

***** 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

***** 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._____

2010/014

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-099269- -00000-0000
Fecha: 2010-08-12 16:09:56 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 1917

CERTIFICACION DE EXCEDENTE : 10 - 63,508
FECHA : AGOSTO 3 DE 2010

***** 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

***** 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	7,000.00
		TOTAL : $	7,000.00

SON: SIETE 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.

2010/013

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

000005

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-099269- -00000-0000
Fecha: 2010-08-12 16:09:56 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 1917

RECIBO OFICIAL DE CAJA : 10 - 54,988
FECHA : JULIO 6 DE 2010

***** 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	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	12	MARCAS Y LEMAS COMERCIALES	114,000.00
			TOTAL : $	114,000.00

SON: CIENTO CATORCE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

2010/014

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 63,392
FECHA : AGOSTO 3 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-099269- -00000-0000
Fecha: 2010-08-12 16:09:56 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 1917

***** 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

***** 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 AFLICADO AL EXPEDIENTE No._____

Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

TARJETA ARCHIVO PROPIETARIOS

000007

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

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

(51) Clasificación Internacional: C07D 403/14, A61K 31/41, A61P 31/00, C07D 405/14, C07D 417/14

(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: 13-09-2010

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 13.02.2008
No. de solicitud: PCT/US2008/053779

(87) Publicación internacional
Fecha: 20.08.2009
N° publicación: WO/2009/102325

(54) Titulo: IMIDAZOLIL-BIFENIL-IMIDAZOLES COMO INHIBIDORES DEL VIRUS DE LA HEPATITIS C

Industria y Comercio
SUPERINTENDENCIA

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

000008

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

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

(51) Clasificación Internacional: C07D 403/14, A61K 31/41, A61P 31/00, C07D 405/14, C07D 417/14

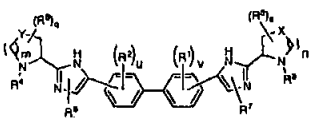
(71)Solicitante(s) **BRISTOL-MYERS SQUIBB COMPANY**

(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***

(I)



(85) Fecha límite inicio fase nacional: 13-09-2010

(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud: 13.02.2008
No. de solicitud PCT/US2008/053779

(87) Publicación internacional:
Fecha: 20.08.2009
No. Publicación: WO/2009/102325

(54) Titulo: IMIDAZOLIL-BIFENIL-IMIDAZOLES COMO INHIBIDORES DEL VIRUS DE LA HEPATITIS C

(57) Resumen: La presente descripción se refiere a compuestos, composiciones y métodos para el tratamiento de la infección por virus de hepatitis C (HCV). También se describen composiciones farmacéuticas que contienen tales compuestos y métodos para usar estos compuestos en el tratamiento de la infección por HCV.

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 403/14, A61K 31/41, A61P 31/00, C07D 405/14, C07D 417/14
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: 13-09-2010 (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: 13.02.2008 No. de PCT/US2008/053779	(87) Publicación internacional Fecha: 20.08.2009 N° publicación: WO/2009/102325

(54) Titulo: IMIDAZOLIL-BIFENIL-IMIDAZOLES COMO INHIBIDORES DEL VIRUS DE LA HEPATITIS C

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

((1S)-2-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-(N-(metoxicarbonil)-L-alanil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-1-metil-2-oxoetil)carbamato de metilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0]hexano-3,2-diil((2S)-1-oxo-1,2-butanodiil)))biscarbamato de dimetilo;

(2-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-(((metoxicarbonil)amino)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxoetil) carbamato de metilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0]hexano-3,2-diil((1S)-1-ciclopropil-2-oxo-2,1-etanediil)))biscarbamato de dimetilo;

((1R)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2R)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilopropil)carbamato de metilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0]hexano-3,2-diil((1R)-2-oxo-1-fenil-2,1-etanediil)))biscarbamato de dimetilo;

((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-acetil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilopropil)carbamato de metilo;

((1S)-2-metil-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-(5-((3aS,4S,6aR)-2-oxohexahidro-1H-tieno[3,4-d]imidazol-4-il)pentanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil-2-metilopropil)carbamato de metilo;

N-((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-acetamido-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilopropil)acetamide;

((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-((tert-butoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilopropil)carbamato de tert-butilo;

(2S)-1-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-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)-3-metil-1-oxo-2-butanamina;

N-((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-((ciclopropilcarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilopropil)ciclopropanocarbamato;

((1R)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2R)-2-((tert-butoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilopropil)carbamato de tert-butilo;

N-((1R)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2R)-2-acetamido-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilopropil)acetamide;

N,N'-(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0]hexano-3,2-diil((2S)-3-metil-1-oxo-1,2-butanodiil)))di(2-pirimidinamina);

((1S)-1-(((6S)-6-(4-(4'-(2-((6S)-5-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-azaspiro[2.4]hept-6-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-5-azaspiro[2.4]hept-5-il)carbonil)-2-metilopropil)carbamato de metilo;

((1S)-1-(((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)carbonil)-2-metilopropil)carbamato de metilo;

(2-((6S)-6-(4-(4'-(2-((6S)-5-(((metoxicarbonil)amino)acetil)-5-azaspiro[2.4]hept-6-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-5-azaspiro[2.4]hept-5-il)-2-oxoetil)carbamato de metilo;

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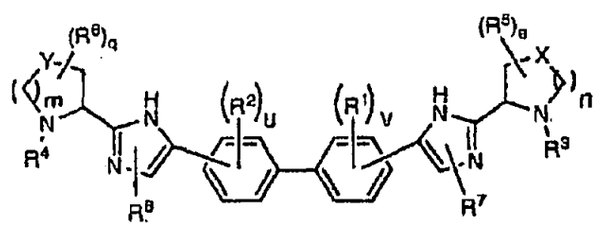
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(54) Title: IMIDAZOLYL BIPHENYL IMIDAZOLES AS HEPATITIS C VIRUS INHIBITORS

(I)



(57) Abstract: The present disclosure relates to compounds Formule (I), 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.

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IMIDAZOLYL BIPHENYL IMIDAZOLES AS 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.

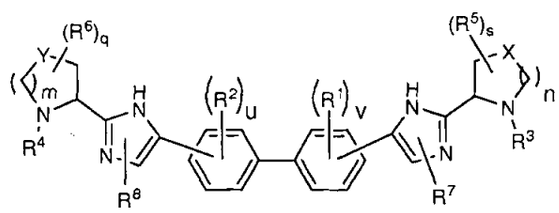
Considerable heterogeneity is found within the nucleotide and encoded amino acid sequence throughout the HCV genome. At least six major genotypes have been characterized, and more than 50 subtypes have been described. The major genotypes of HCV differ in their distribution worldwide, and the clinical 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 a first aspect the present disclosure provides a compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, wherein

m and n are independently 0, 1, or 2;

q and s are independently 0, 1, 2, 3, or 4;

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

X is selected from O, S, S(O), SO_2, CH_2, CHR^5, and $C(R^5)_2$;

provided that when n is 0, X is selected from CH_2, CHR^5, and $C(R^5)_2$;

Y is selected from O, S, S(O), SO_2, CH_2, CHR^6, and $C(R^6)_2$;

provided that when m is 0, Y is selected from CH_2, CHR^6, and $C(R^6)_2$;

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, R^9-C(O)-, and R^9-C(S)-;

each R^5 and R^6 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;

R^7 and R^8 are each independently selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, (NR^aR^b)carbonyl, and trialkylsilylalkoxyalkyl; and

each 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.

In a first embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1.

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

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

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

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

u and v are each independently 0 or 1; and

when present, R^1 and/or R^2 are halo.

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

u and v are each independently 0 or 1; and

when present, R^1 and/or R^2 are halo, wherein the halo is fluoro.

In a fifth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of X and Y is S.

In a sixth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein X and Y are each S.

In a seventh embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein X is selected from CHR^5, and $C(R^5)_2$; and Y is selected from CH_2, CHR^6, and $C(R^6)_2$.

In an eighth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^7 and R^8 are independently selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, and (NR^aR^b)carbonyl.

In a ninth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^7 and R^8 are each hydrogen.

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

q and s are independently 0, 1, or 2; and

each R^5 and R^6 is independently selected from alkyl, aryl, halo, and hydroxy, 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 an eleventh embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein

q and s are independently 0 or 1; and

when present, R^5 and/or R^6 are each halo.

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

q and s are independently 0 or 1; and

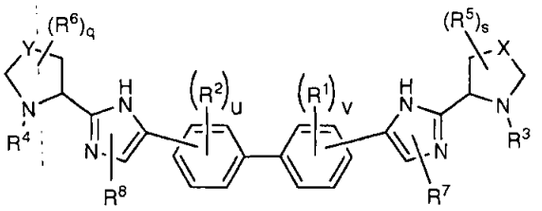
when present, R^5 and/or R^6 are each halo, wherein the halo is fluoro.

In a thirteenth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of R^3 and R^4 is hydrogen.

In a fourteenth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are each R^9-C(O)-.

In a fifteenth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein each R^9 is 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 second aspect the present disclosure provides a compound of Formula (II)



(II),

or a pharmaceutically acceptable salt thereof, wherein

q and s are independently 0, 1, or 2;

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

X is selected from S, CH_2, CHR^5, and $C(R^5)_2$;

Y is selected from S, CH_2, CHR^6, and $C(R^6)_2$;

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

R^3 and R^4 are each independently selected from hydrogen and R^9-C(O)-;

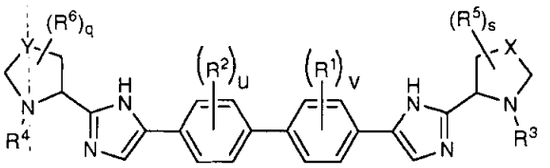
each R^5 and R^6 is independently selected from alkyl, aryl, halo, and hydroxy, wherein the alkyl can optionally form a fused three- to six-membered ring with an

adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

R^7 and R^8 are each independently selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, and (NR^aR^b)carbonyl; and

each R^9 is 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 third aspect the present disclosure provides a compound of Formula (III)



(III),

or a pharmaceutically acceptable salt thereof, wherein

q and s are independently 0, 1, or 2;

u and v are independently 0 or 1;

X is selected from CH_2, CHR^5, and $C(R^5)_2$;

Y is selected from CH_2, CHR^6, and $C(R^6)_2$;

when present, R^1 and/or R^2 are halo, wherein the halo is fluoro;

R^3 and R^4 are each R^9-C(O)-;

when present, R^5 and/or R^6 are halo, wherein the halo is fluoro; and

each 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.

In a fourth aspect the present disclosure provides a compound selected from methyl ((1S)-1-(((2S)-2-(5-(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;

(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);

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((1R,3R,5R)-3-(5-(4'-(2-((1R,3R,5R)-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;

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

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

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

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate; and

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate;

or a pharmaceutically acceptable salt thereof.

In a first embodiment of the fifth aspect the pharmaceutically acceptable salt is a dihydrochloride salt.

In a sixth 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 sixth aspect the composition further comprises one or two additional compounds having anti-HCV activity. In a second embodiment at least one of the additional compounds is an interferon or a ribavirin. In a third embodiment 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 sixth aspect the composition further comprises 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 sixth aspect the composition further comprises 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 an seventh 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 seventh 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 at least one of the additional compounds is an interferon or a ribavirin. In a third embodiment the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon,

interferon alpha 2A, and lymphoblastiod interferon tau.

In a fourth embodiment 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, 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.

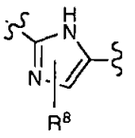
In a fifth embodiment the method further comprises administering one or two additional compounds having anti-HCV activity prior to, after or simultaneously with the compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of the additional compounds is effective to 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.

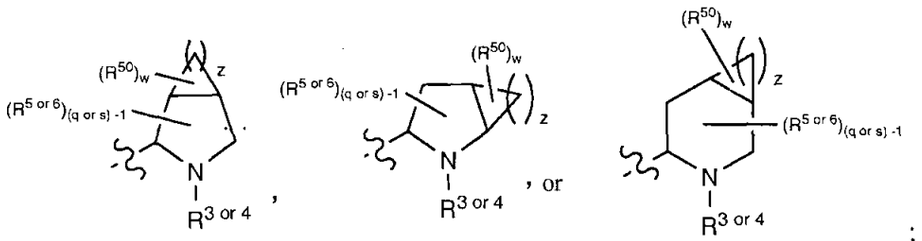
The term "alkoxyalkylcarbonyl," as used herein, refers to an alkoxyalkyl group attached to the parent molecular moiety through a carbonyl group.

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 McA	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	Serono, Geneva, Switzerland
Roferon A	Interferon	IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Intron A	Interferon	IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
Intron A and Zadaxin	Interferon	IFN-α2b/α1-thymosin	RegeneRx 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.

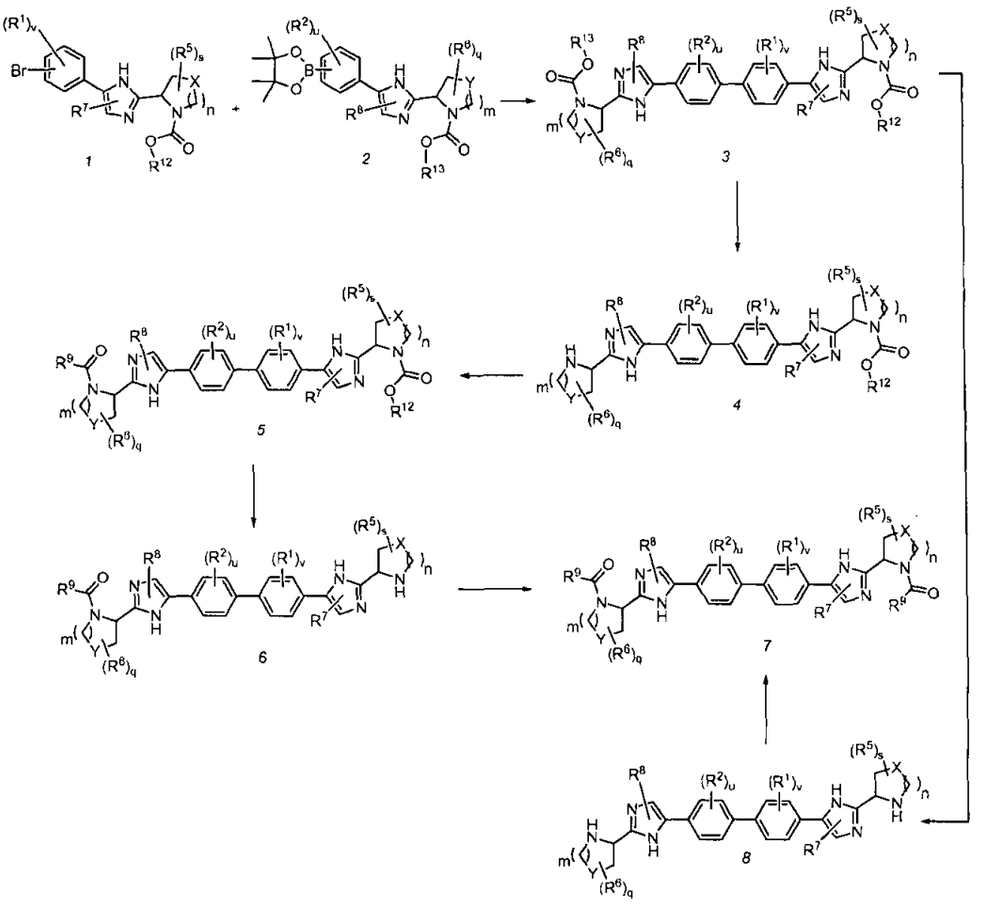
The abbreviations used in the present application, including particularly in the illustrative schemes and examples which follow, are well-known to those skilled in the art. Some of the abbreviations used are as follows:

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.

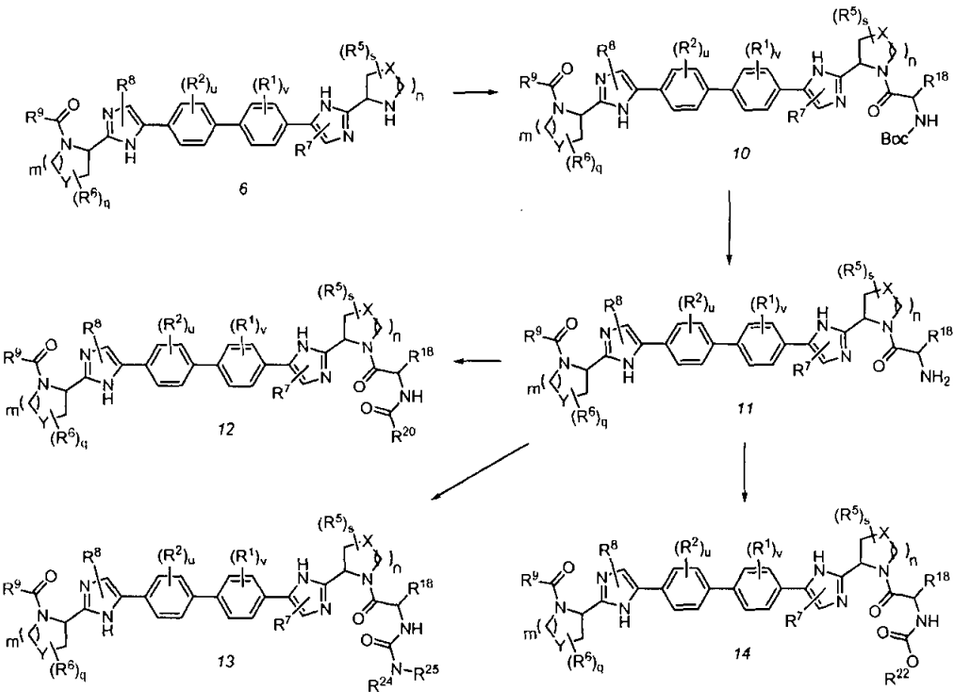
Scheme 1: Symmetric or Asymmetric Biphenyls

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.



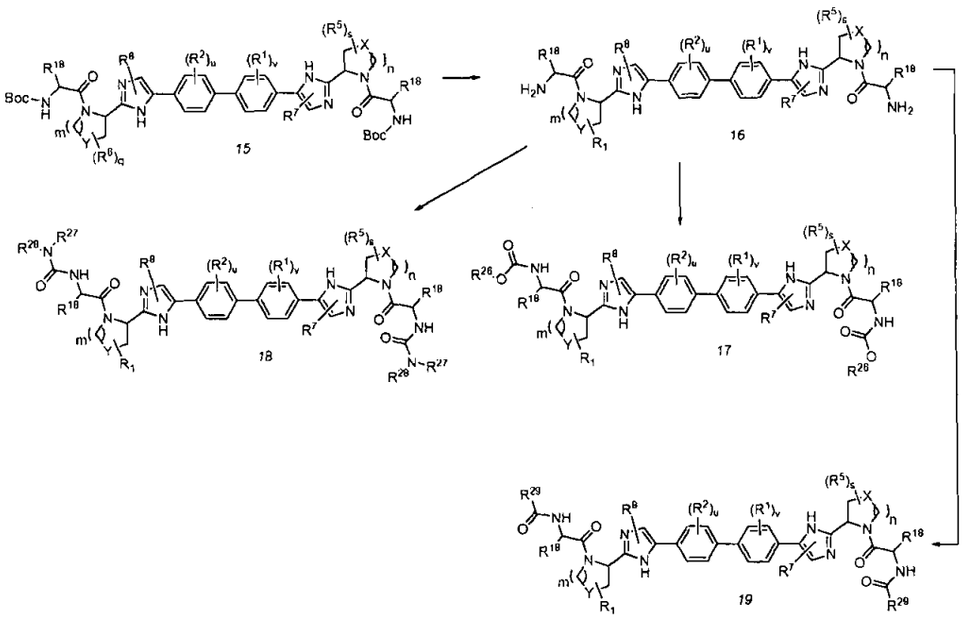
Scheme 2: Asymmetrically Capped Biphenyls

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.



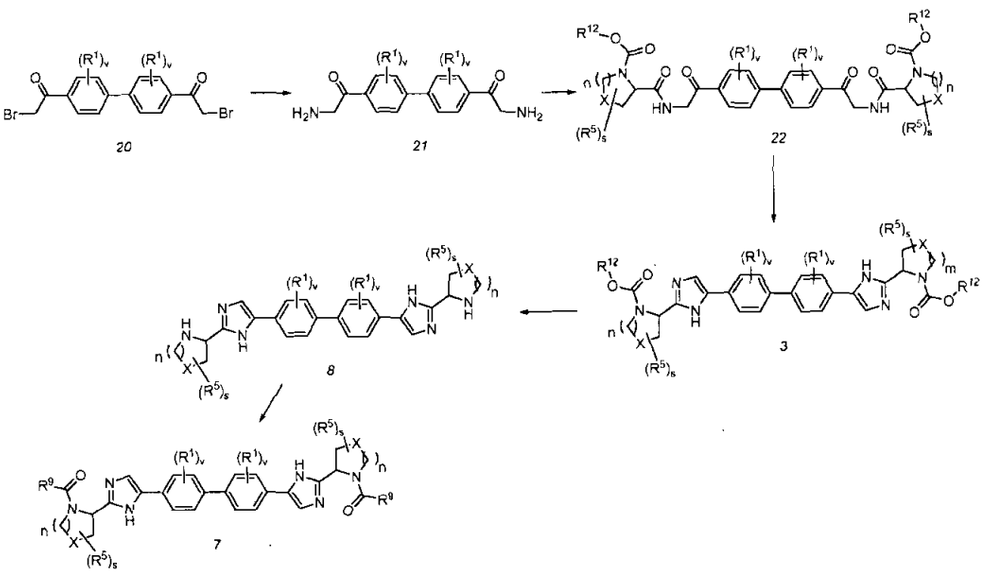
Scheme 3: Symmetric Cap Elaborated Biphenyls

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.



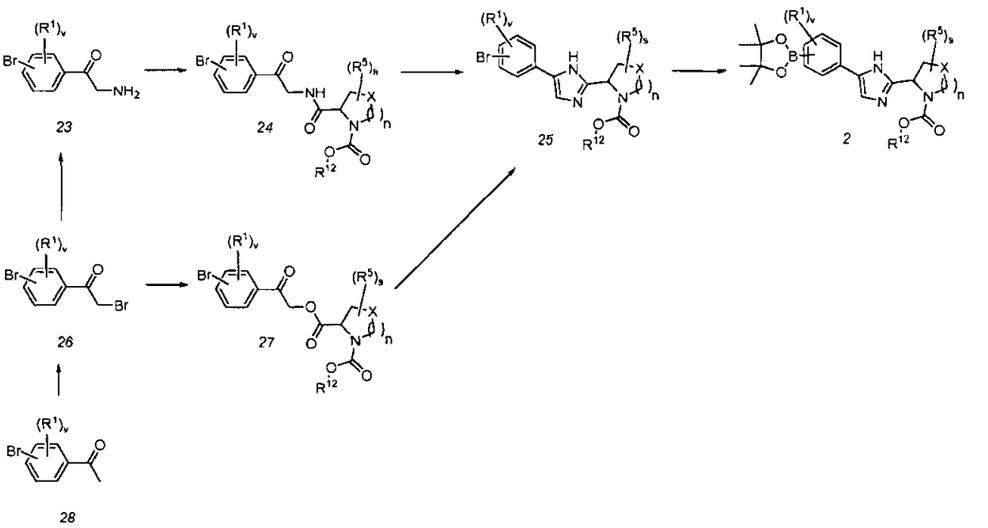
Scheme 4: Symmetric Biphenyls

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).



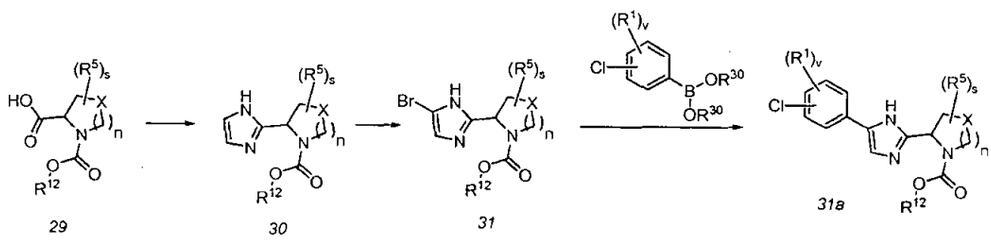
Scheme 5: Starting Materials 25 and 2

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

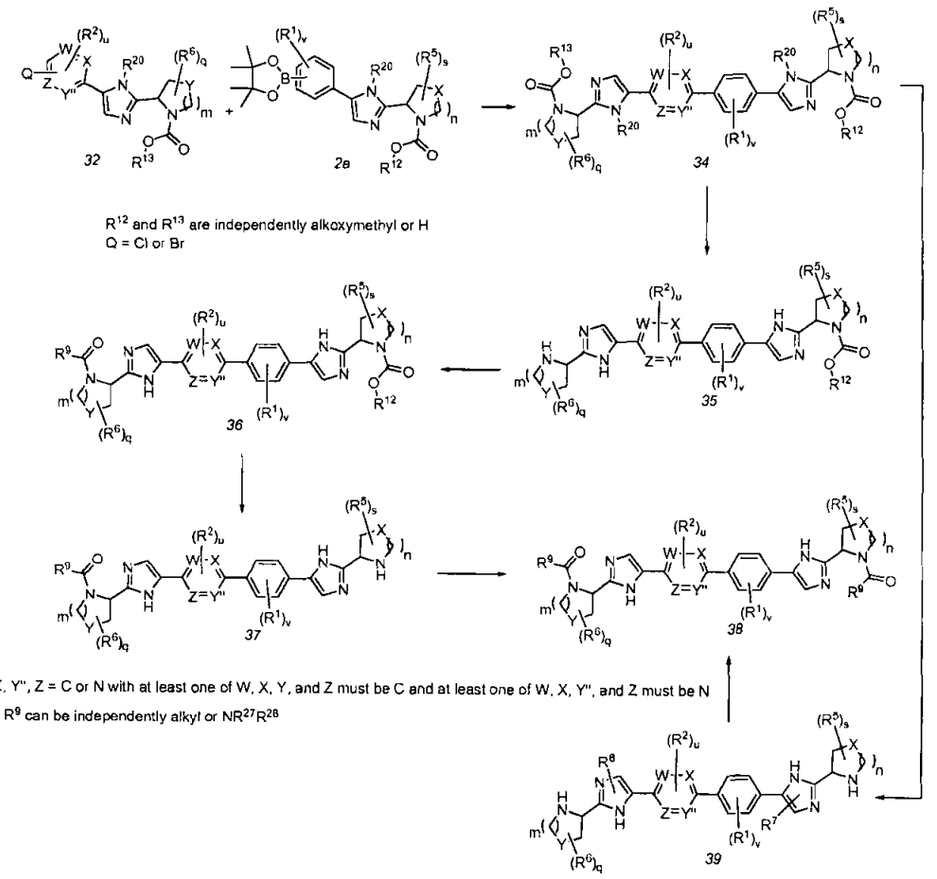
In another embodiment, starting materials such as *31a* (analogous to *25* in Scheme 5 and *1* in Scheme 1) may be prepared by reacting bromoimidazole derivatives *31* under Suzuki-type coupling conditions with a variety of chloro-substituted aryl boronic acids which can either be prepared by standard 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

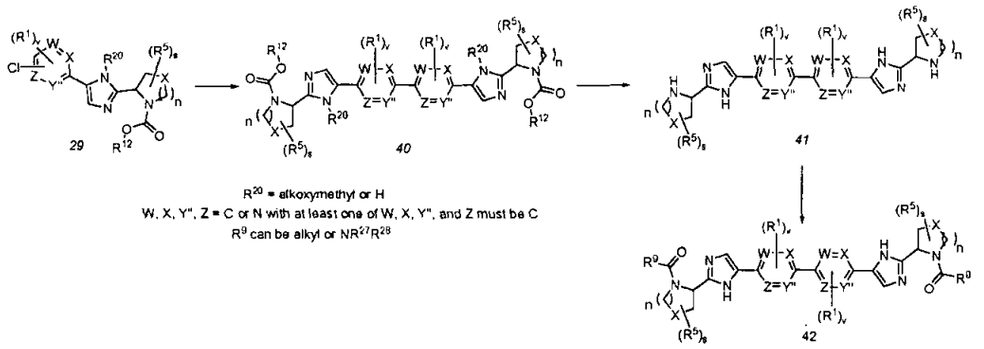
In yet another embodiment of the current disclosure, aryl halide *32* can be coupled under Suzuki-Miyaura palladium catalyzed conditions to form the heteroaryl derivative *34*. Compound *34* can be elaborated to *35* by treatment to hydrogenolytic conditions with hydrogen and a transition metal catalyst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



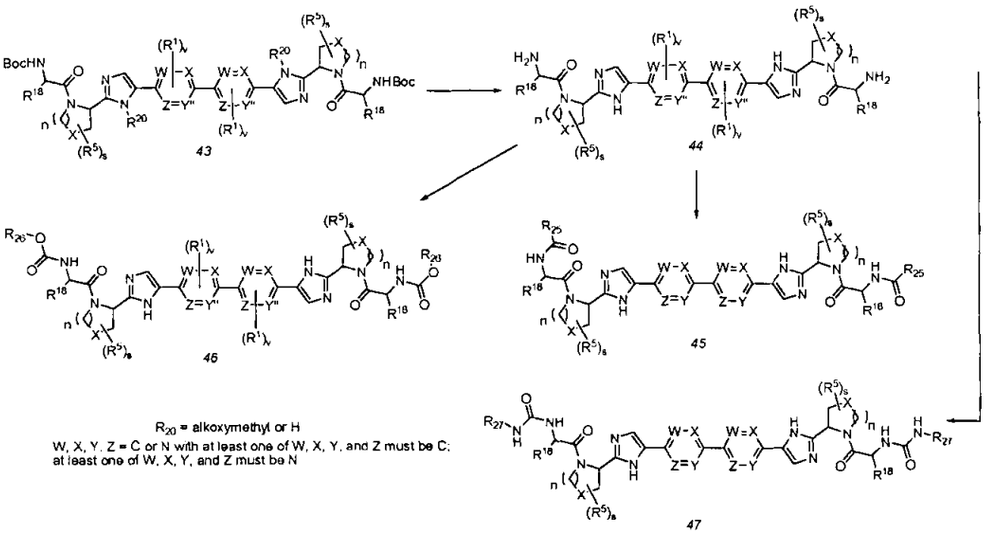
Scheme 8

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.



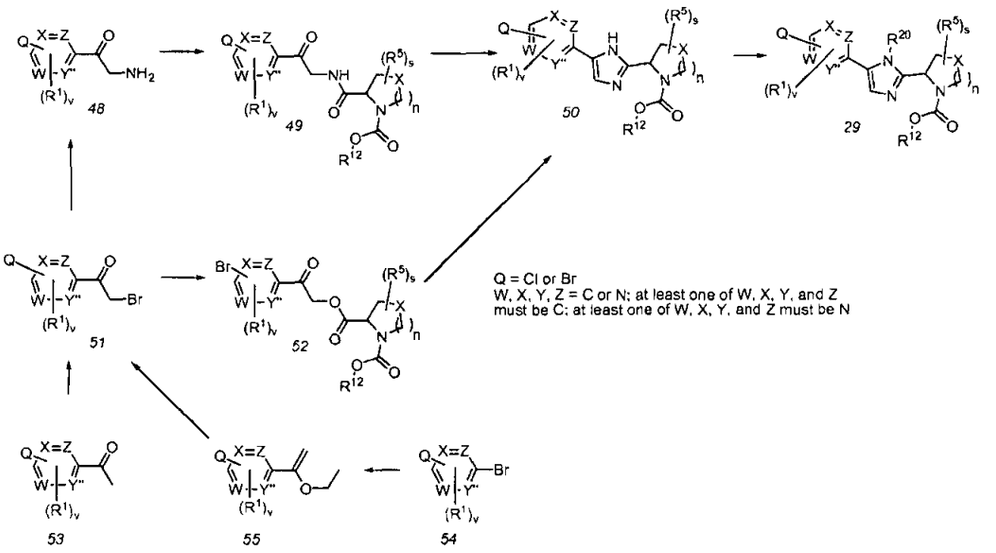
Scheme 9: Symmetric Cap Substituted Heteroaryls

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

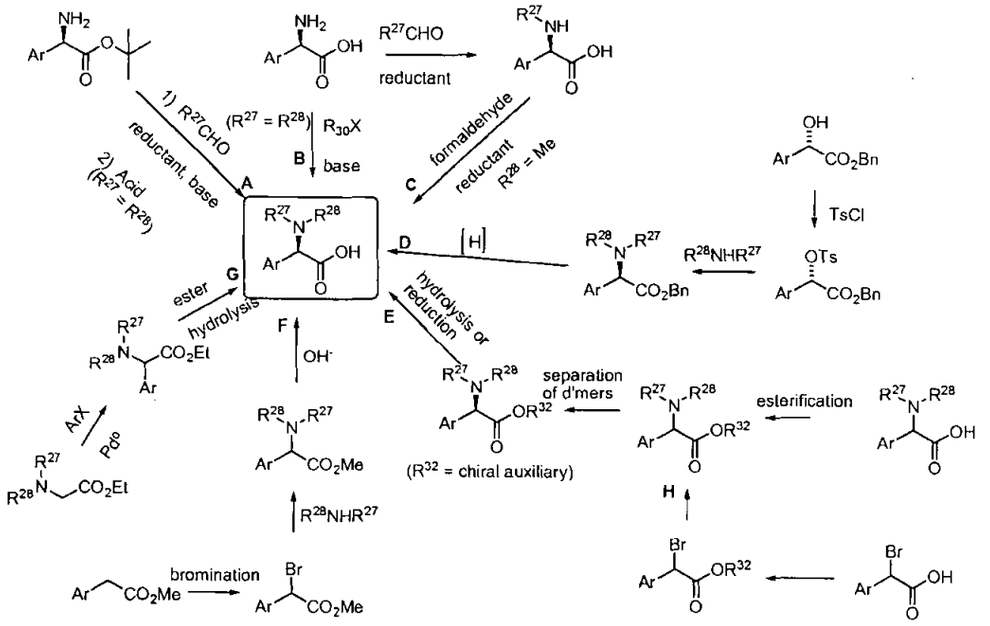
Heteroaryl bromides *54* may be reacted with a vinyl stannane such as tributyl(1-ethoxyvinyl)tin in the presence of a source of palladium such as dichlorobis(triphenylphosphine)palladium (II) to provide *55* which can be subsequently transformed into bromoketone *51 via* treatment with a source of bromonium 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,

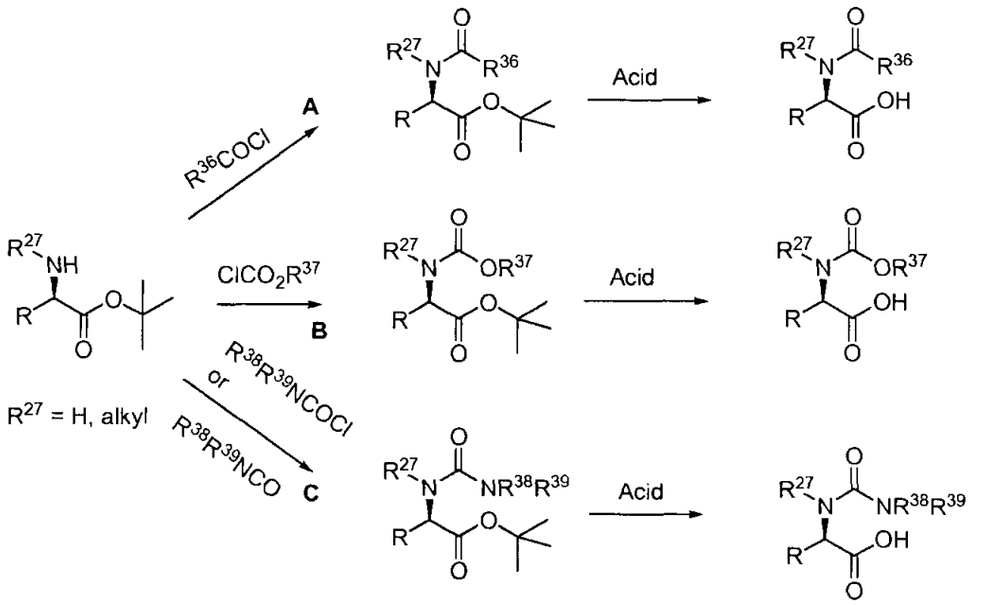
etc) followed by removal of the chiral auxiliary providing enantiomerically pure phenylglycine derivatives. Pathway H illustrates a synthetic sequence which intersects with pathway E wherein the aforementioned chiral auxiliary is installed prior to amine addition. Alternatively, an ester of an arylacetic 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

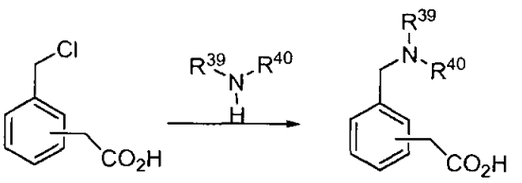
In another embodiment of the present disclosure, acylated phenylglycine derivatives may be prepared as illustrated below. Phenylglycine derivatives wherein

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

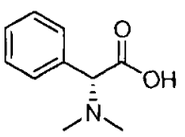
Flow rate = 4 mL/min

Solvent A: = 95% H_2O: 5% CH_3CN, 10 mm Ammonium acetate

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

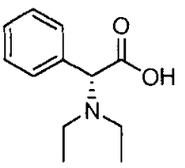
Synthesis of common caps

Cap-1



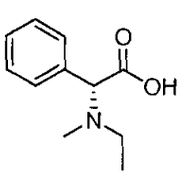
A suspension of 10% Pd/C (2.0g) in methanol (10 mL) was added to a mixture of (R)-2-phenylglycine (10g, 66.2 mmol), formaldehyde (33 mL of 37% wt. in water), 1N HCl (30 mL) and methanol (30 mL), and exposed to H_2 (60 psi) for 3 hours. The reaction mixture was filtered through diatomaceous earth (Celite®),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

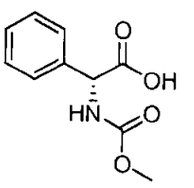


Acetaldehyde (5.0 mL, 89.1 mmol) and a suspension of 10% Pd/C (720 mg) in methanol/H_2O (4mL/1 mL) was sequentially added to a cooled (~ 15 °C) mixture of (R)-2-phenylglycine (3.096g, 20.48 mmol), 1N HCl (30 mL) and methanol (40 mL). The cooling bath was removed and the reaction mixture was stirred under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

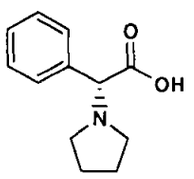


$ClCO_2Me$ (3.2 mL, 41.4 mmol) was added dropwise to a cooled (ice/water) THF (410 mL) semi-solution of (R)-tert-butyl 2-amino-2-phenylacetate/HCl (9.877 g, 40.52 mmol) and diisopropylethylamine (14.2 mL, 81.52 mmol) over 6 min, and stirred at similar temperature for 5.5 hours. The volatile component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

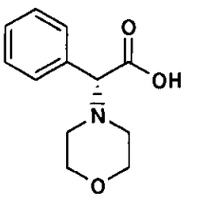
Cap-5



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

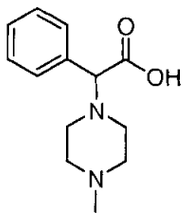
HPLC (water/methanol/TFA) to provide the TFA salt of *Cap*-5 as a semi-viscous white foam (1.0 g). ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) δ 10.68 (br s, 1H), 7.51 (m, 5H), 5.23 (s, 1H), 3.34 (app br s, 2H), 3.05 (app br s, 2H), 1.95 (app br s, 4H); RT = 0.30 min (Cond. 1); >98% homogeneity index; LC/MS: 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.

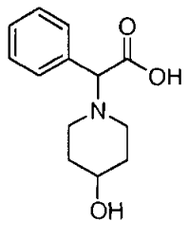
A THF (75 mL) solution of benzyl 2-phenyl-2-(tosyloxy)acetate (6.0 g, 15.1 mmol), 1-methylpiperazine (3.36 mL, 30.3 mmol) and N,N-diisopropylethylamine (13.2 mL, 75.8 mmol) was heated at 65 °C for 7 hours. The reaction was allowed to cool to ambient temperature and the volatile component was removed *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.

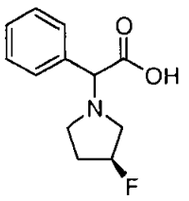
Cap-8



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.

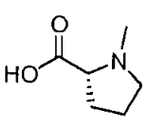
Cap-9



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): ^{1}H 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): ^{1}H 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.

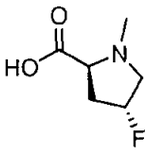
Cap-10



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

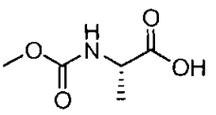
hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and concentrated *in vacuo* to provide *Cap*-10 as an off-white solid (2.15 g). ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) 3.42 (m, 1H), 3.37 (dd, *J* = 9.4, 6.1, 1H), 2.85-2.78 (m, 1H), 2.66 (s, 3H), 2.21-2.13 (m, 1H), 1.93-1.84 (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.

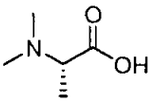
Cap-12



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),

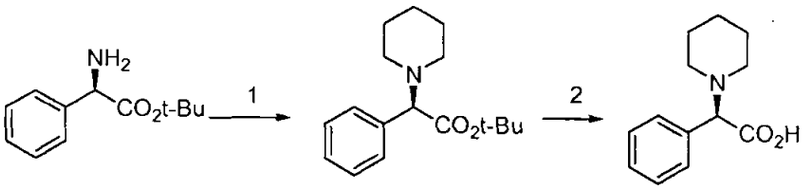
filtered, and concentrated *in vacuo* to provide a colorless oil (2.58 g). 500 mg of this material was purified by a reverse phase HPLC (H_2O/methanol/TFA) to provide 150 mg of *Cap*-12 as a colorless oil . ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) 7.44 (d, *J* = 7.3, 0.8H), 7.10 (br s, 0.2H), 3.97 (m,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



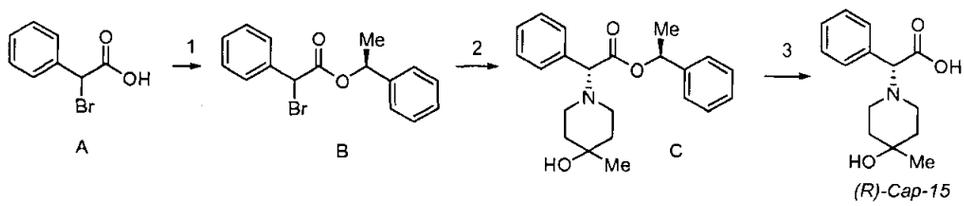
Cap-14

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

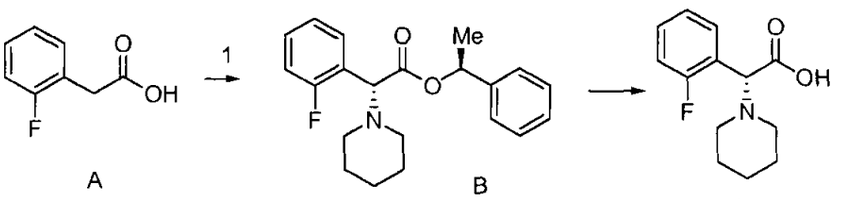
yellow oil. Flash chromatography (SiO_2/ hexane-ethyl acetate, 4:1) of this oil provided the title compound (11.64 g, 73%) as a white solid. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.53-7.17 (m, 10H), 5.95 (q, *J* = 6.6 Hz, 0.5H), 5.94 (q, *J* = 6.6 Hz, 0.5H), 5.41 (s, 0.5H), 5.39 (s, 0.5H), 1.58 (d, *J* = 6.6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



A B *(R)-Cap-16*

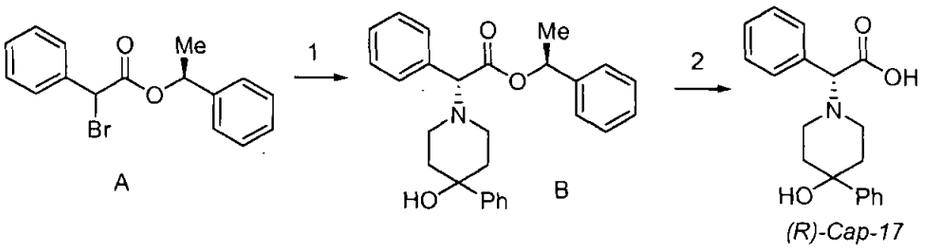
Step 1; (S)-1-Phenylethyl 2-(2-fluorophenyl)acetate: A mixture of 2-fluorophenylacetic acid (5.45 g, 35.4 mmol), (S)-1-phenylethanol (5.62 g, 46.0 mmol), EDCI (8.82 g, 46.0 mmol) and DMAP (0.561 g, 4.60 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 12 hours. The solvent was then concentrated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

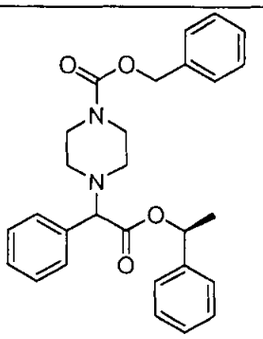


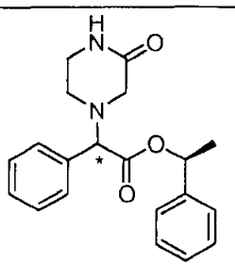
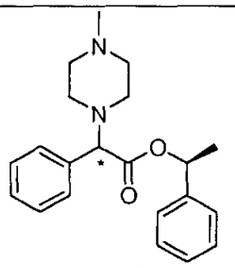
(R)-Cap-17

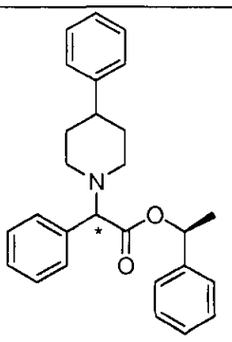
Step 1; (S)-1-Phenylethyl (R)-2-(4-hydroxy-4-phenylpiperidin-1-yl)- 2-phenylacetate: To a solution of (S)-1-phenylethyl 2-bromo-2-phenylacetate (1.50 g, 4.70 mmol) in THF (25 mL) was added triethylamine (1.31 mL, 9.42 mmol), followed by tetrabutylammonium iodide (0.347 g, 0.94 mmol). The reaction mixture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

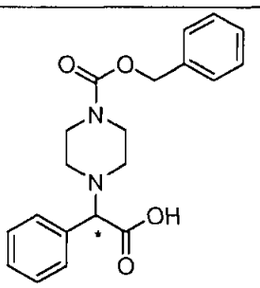
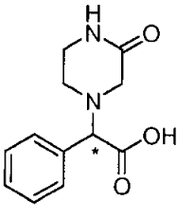
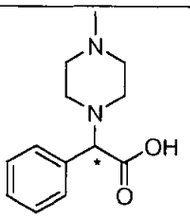
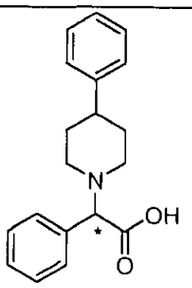
Condition 2

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

Fianl % B = 100

Gradient Time = 4 min

Flow Rate = 4 mL/min

Wavelength = 220

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

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

Condition 2

Column: Waters-Sunfire 4.6 X 50 mm S5

Start % B = 0

Fianl % B = 100

Gradient Time = 2 min

Flow Rate = 4 mL/min

Wavelength = 220

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

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

Condition 3

Column: Phenomenex 10µ 3.0 X 50 mm

Start % B = 0

Fianl % B = 100

Gradient Time = 2 min

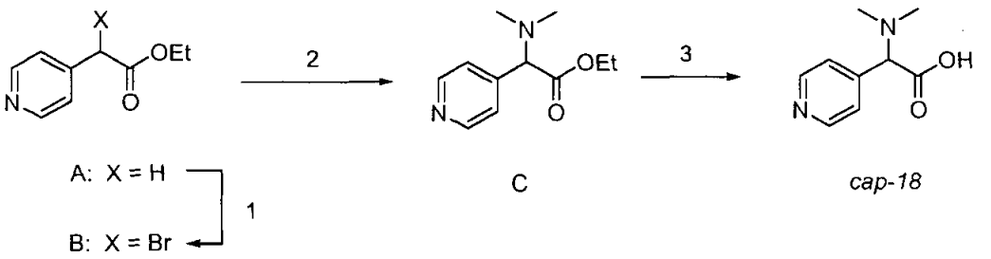
Flow Rate = 4 mL/min

Wavelength = 220

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

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

Cap-18



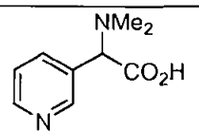
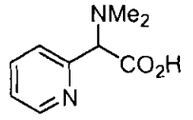
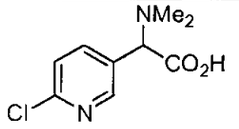
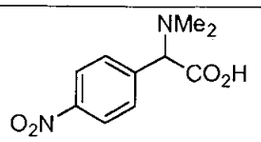
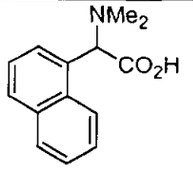
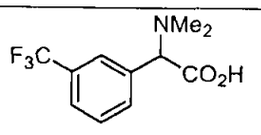
Step 1; (R,S)-Ethyl 2-(4-pyridyl)-2-bromoacetate: To a solution of ethyl 4-pyridylacetate (1.00 g, 6.05 mmol) in dry THF (150 mL) at 0 °C under argon was added DBU (0.99 mL, 6.66 mmol). The reaction mixture was allowed to warm to room temperature over 30 minutes and then it was cooled to -78 °C. To this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

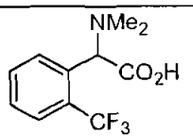
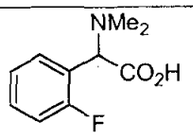
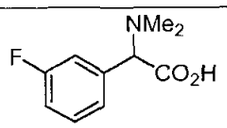
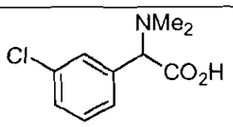
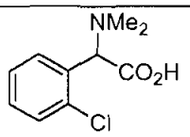
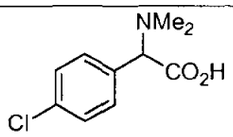
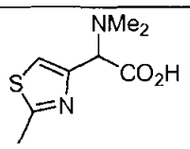
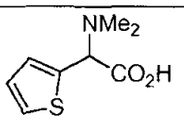
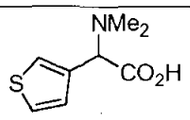
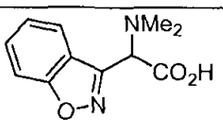
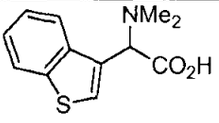
Step 2; (R,S)-Ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate: To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-bromoacetate (1.40 g, 8.48 mmol) in DMF (10 mL) at room temperature was added dimethylamine (2M in THF, 8.5 mL, 17.0 mmol). After completion of the reaction (as judged by tlc) the volatiles were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

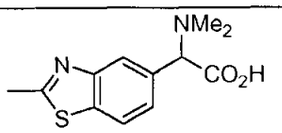
Step 3; (R,S)-2-(4-Pyridyl)-2-(N,N-dimethylamino)acetic acid: To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate (0.200 g, 0.960 mmol) in a mixture of THF-methanol-H_2O (1:1:1, 6 mL) was added powdered LiOH (0.120 g,

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).

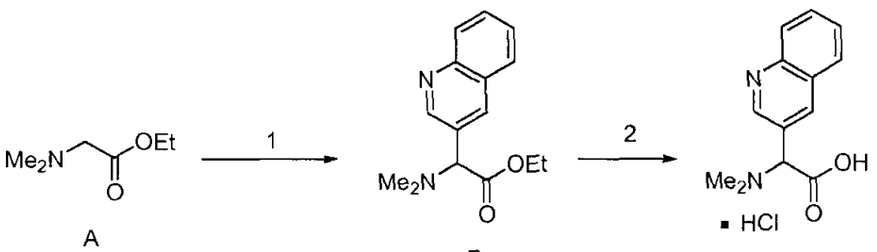
The following examples were prepared in similar fashion using the method described in Example 4;

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

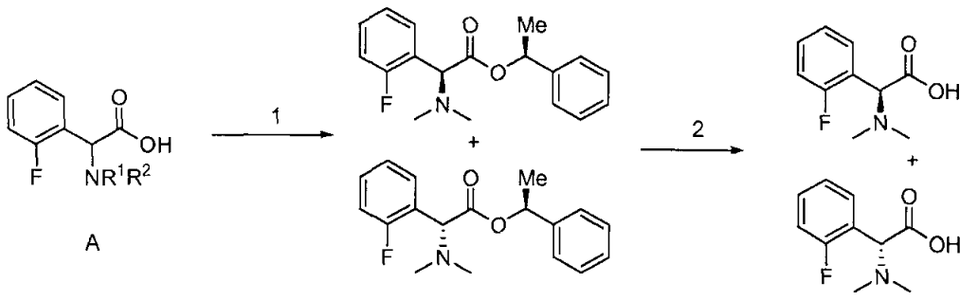


Step 1; (R,S)-Ethyl 2-(quinolin-3-yl)-2-(N,N-dimethylamino)-acetate: A mixture of ethyl N,N-dimethylaminoacetate (0.462 g, 3.54 mmol), K_3PO_4 (1.90 g, 8.95 mmol), $Pd(t\text{-}Bu_3P)_2$ (0.090 g, 0.176 mmol) and toluene (10 mL) was degassed with a stream of Ar bubbles for 15 minutes. The reaction mixture 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 $(M+H)^+$.

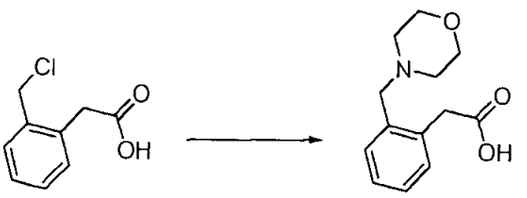
Cap-40



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 $(M+H)^+$.

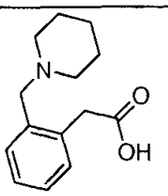
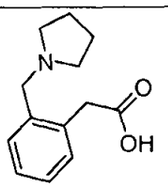
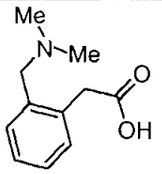
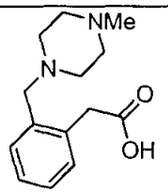
Cap-41



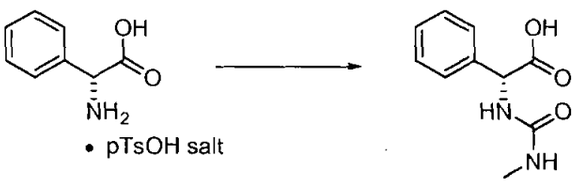
cap-41

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

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

Cap-45

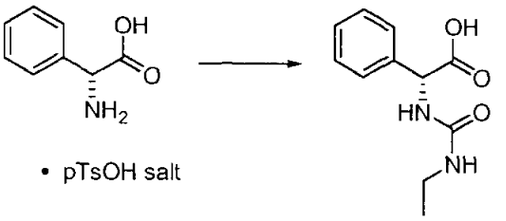


Cap-45

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

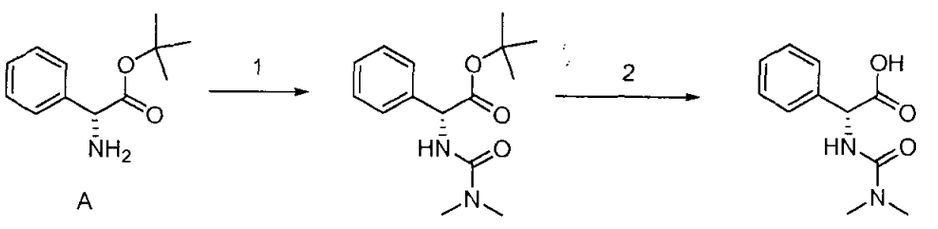


cap-46

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



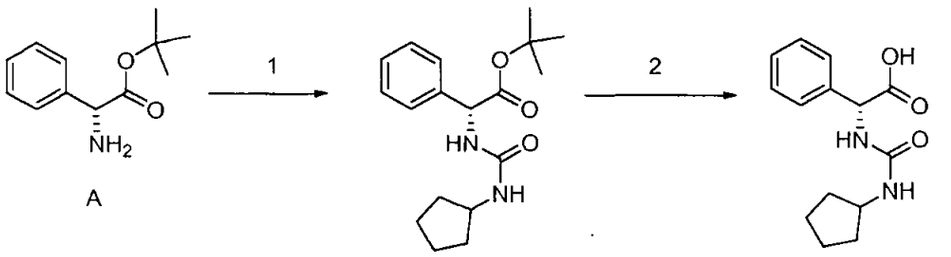
A B *Cap-47*

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

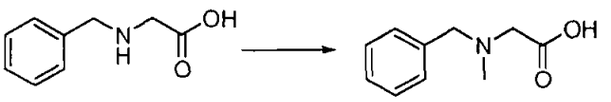


Step 1; (R)-tert-butyl 2-(3-cyclopentylureido)-2-phenylacetate: To a stirred solution of (R)-2-amino-2-phenylacetic acid hydrochloride (1.0 g, 4.10 mmol) and Hunig's base (1.0 mL, 6.15 mmol) in DMF (15 mL) was added cyclopentyl isocyanate (0.46 mL, 4.10 mmol) dropwise and over 10 minutes. After stirring 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. ^1H NMR (500 MHz, CD_3Cl-D) δ ppm 1.50 - 1.57 (m, 2H) 1.58 - 1.66 (m, 2H) 1.87 - 1.97 (m, 2H) 3.89 - 3.98 (m, 1H) 5.37 (s, 1H) 7.26 - 7.38 (m, 5H). LCMS: Anal. Calcd. for $C_{18}H_{26}N_2O_3$ 318.19 found 319.21 $(M+H)^+$; HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 4 minutes, 1 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 trietheylsilane (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%). ^1H 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.

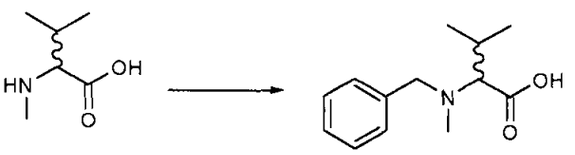
Cap-49



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. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.75 (s, 3H) 4.04 (s, 2H) 4.34 (s, 2H) 7.29 - 7.68 (m, 5H). LCMS: Anal. Calcd. for: $C_{10}H_{13}NO_2$ 179.22; Found: 180.20 $(M+H)^+$.

Cap-50

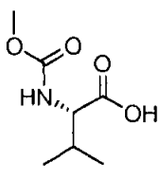


Cap-50

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,

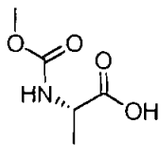
detection at 220 nm, flow rate 40 mL/min, 20 to 80% B over 6 min; A = 90% water, 10 % methanol, 0.1% TFA, B = 10% water, 90 % methanol, 0.1% TFA) to provide 2-(benzyl(methyl)amino)-3-methylbutanoic acid, TFA salt (126 mg, 19%) as a colorless wax. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.98 (d, 3H) 1.07 (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

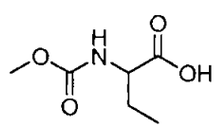
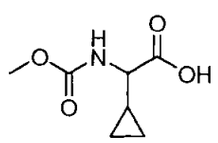
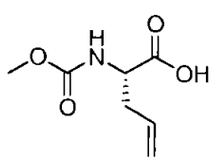
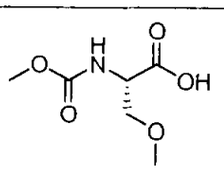
Cap-52

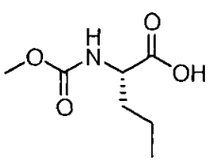
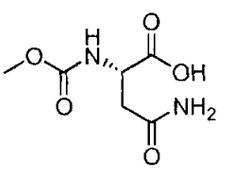
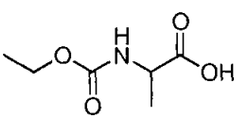
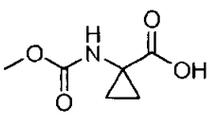
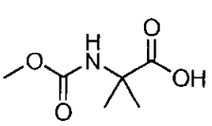


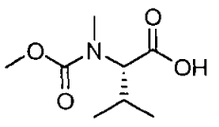
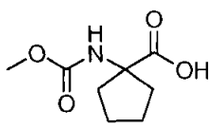
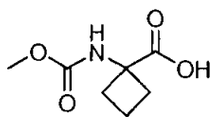
Cap-52 was synthesized from L-alanine according to the procedure described for the synthesis of *Cap*-51. For characterization purposes, a portion of the crude material was purified by a reverse phase HPLC (H_2O/MeOH/TFA) to afford *Cap*-52 as a colorless viscous oil. ^{1}H NMR (DMSO-d_6, δ= 2.5 ppm,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

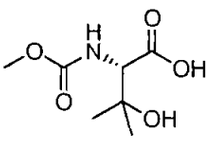
Cap-53 to -64 were prepared from appropriate starting materials according to the procedure described for the synthesis of *Cap*-51, with noted modifications if any.

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

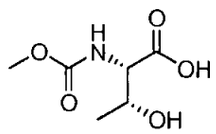


Methyl chloroformate (0.65 mL, 8.39 mmol) was added dropwise over 5 min to a cooled (ice-water) mixture of Na_2CO_3 (0.449 g, 4.23 mmol), NaOH (8.2 mL of 1M/H_2O, 8.2 mmol) and (*S*)-3-hydroxy-2-(methoxycarbonylamino)-3-methylbutanoic acid (1.04 g, 7.81 mmol). The reaction mixture was stirred for 45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

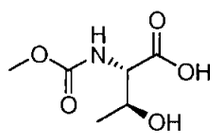
Cap-66 and -67 were prepared from appropriate commercially available starting materials by employing the procedure described for the synthesis of *Cap*-65.

Cap-66



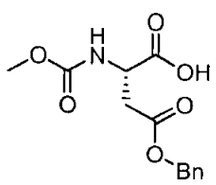
^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.58 (br s, 1H), 7.07 (d, *J* = 8.3, 0.13H), 6.81 (d, *J* = 8.8, 0.67H), 4.10-4.02 (m, 1.15H), 3.91 (dd, *J* = 9.1, 3.5, 0.85H), 3.56 (s, 3H), 1.09 (d, *J* = 6.2, 3H). [Note: only the dominant signals of NH were noted].

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]

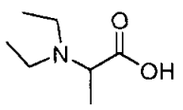
Cap-68



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.

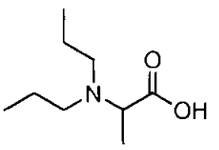
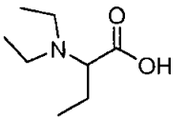
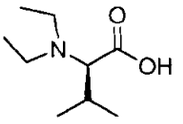
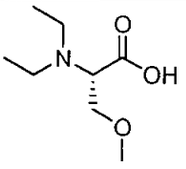
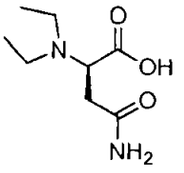
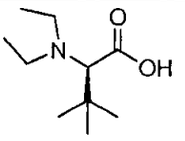
Cap-69a and -69b



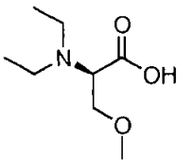
Cap-69a: (R)-enantiomer
Cap-69b: (S)-enantiomer

$NaCNBH_3$ (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).

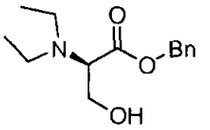
Cap-70 to -74 were prepared according to the procedure described for the synthesis of *Cap*-69 by employing appropriate starting materials.

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



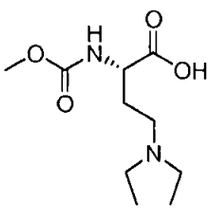
$NaBH_3CN$ (1.6 g, 25.5 mmol) was added to a cooled (ice/water bath) water (25 ml)/methanol (15 ml) solution of H-D-Ser-OBzl HCl (2.0 g, 8.6 mmol). Acetaldehyde (1.5 ml, 12.5 mmol) was added drop-wise over 5 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition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

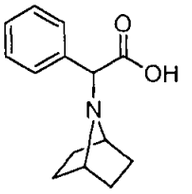


$NaCNBH_3$ (1.60 g, 24.2 mmol) was added in batches to a chilled (~15 °C) water/MeOH (12 mL each) solution of (*S*)-4-amino-2-(tert-butoxycarbonylamino) butanoic acid (2.17 g, 9.94 mmol). A few minutes later acetaldehyde (2.7 mL, 48.1 mmol) was added drop-wise over 2 min, the cooling bath was removed,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

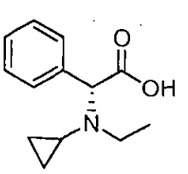
Cap-77a and -77b



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.

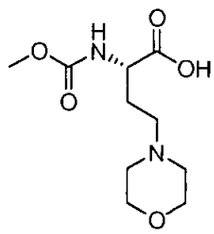
Cap-78



$NaCNBH_3$ (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



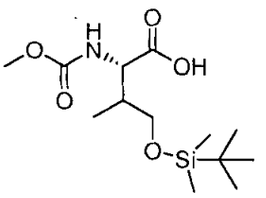
Ozone was bubbled through a cooled (-78 °C) CH_2Cl_2 (5.0 mL) solution *Cap*-55 (369 mg, 2.13 mmol) for about 50 min until the reaction mixture attained a tint of blue color. Me_2S (10 pipet drops) was added, and the reaction mixture was stirred for 35 min. The -78 °C bath was replaced with a -10 °C 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,

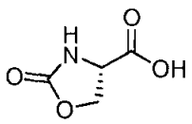
16H), 4.66 (d, J = 12.4, 1H), 4.39 (d, J = 12.4, 1H), 3.61 (dd, J = 9.9, 5.6, 1H), 3.45 (d, J = 9.5, 1H), 3.41 (dd, J = 10, 6.2, 1H), 2.55 (dd, J = 9.5, 7.3, 1H), 1.74 (m, 1H), 0.77 (s, 9H), 0.61 (d, J = 7.1, 3H), -0.06 (s, 3H), -0.08 (s, 3H).

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.

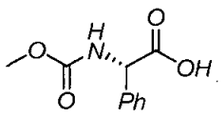
Cap-81



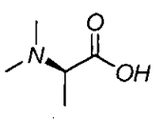
Prepared according to the protocol described by Falb et al. *Synthetic Communications* 1993, *23*, 2839.

Cap-82 to Cap-85

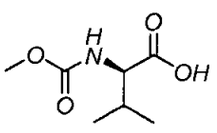
Cap-82 to *Cap*-85 were synthesized from appropriate starting materials according to the procedure described for *Cap*-51. The samples exhibited similar spectral profiles as that of their enantiomers (i.e., *Cap*-4, *Cap*-13, *Cap*-51 and *Cap*-52, respectively)



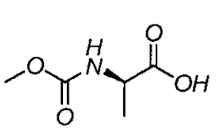
Cap-82



Cap-83

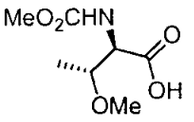


Cap-84



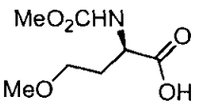
Cap-85

Cap-86



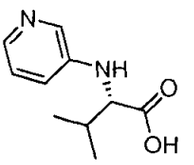
To a mixture of O-methyl-L-threonine (3.0 g, 22.55 mmol), NaOH (0.902 g, 22.55 mmol) in H_2O (15 mL) was added $ClCO_2Me$ (1.74 mL, 22.55 mmol) dropwise at 0°C. The mixture was allowed to stir for 12 h and acidified to pH 1 using 1N HCl. The aqueous phase was extracted with EtOAc and (2x250 mL) and 10%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



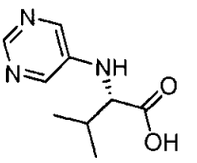
To a mixture of L-homoserine (2.0 g, 9.79 mmol), Na_2CO_3 (2.08 g, 19.59 mmol) in H_2O (15 mL) was added $ClCO_2Me$ (0.76 mL, 9.79 mmol) dropwise at 0°C. The mixture was allowed to stir for 48 h and acidified to pH 1 using 1N HCl. The aqueous phase was extracted with EtOAc and (2X250 mL) and the combined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

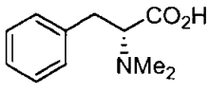
Cap-89



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

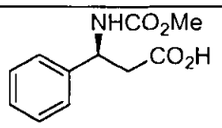
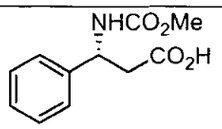
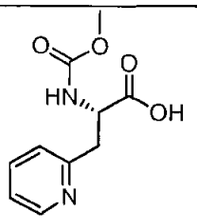
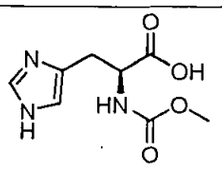
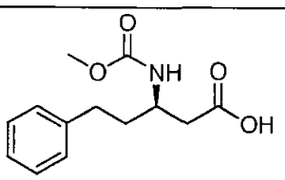
could not be estimated. The material was used as is in subsequent reactions. LCMS: Anal. Calcd. for $C_9H_{13}N_3O_2$: 195; found: 196 $(M+H)^+$.

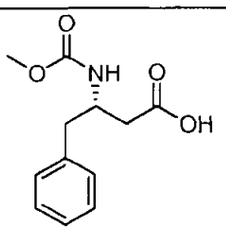
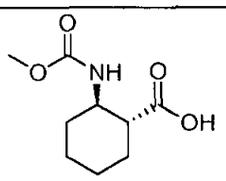
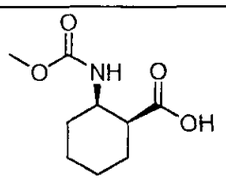
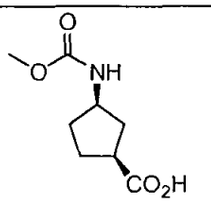
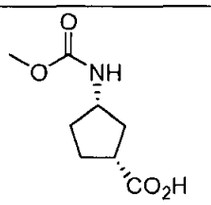
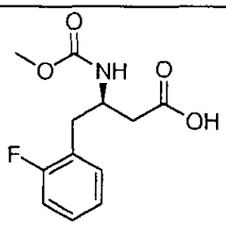
Cap–90

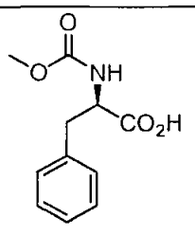
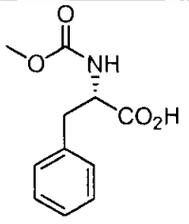
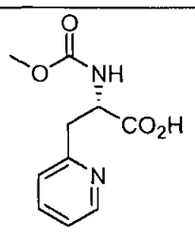
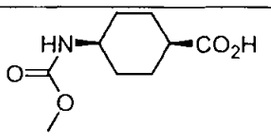
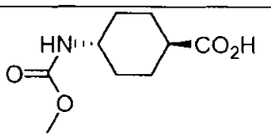
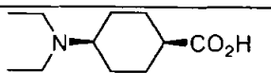


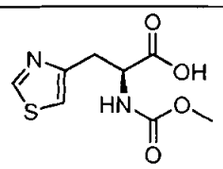
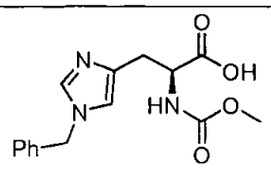
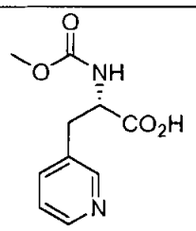
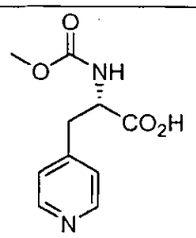
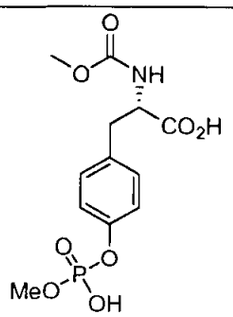
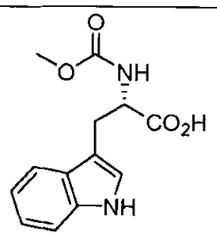
Cap-90 was prepared according to the method described for the preparation of *Cap*-1. The crude material was used as is in subsequent steps. LCMS: Anal. Calcd. for $C_{11}H_{15}NO_2$: 193; found: 192 $(M-H)^-$.

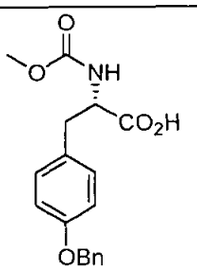
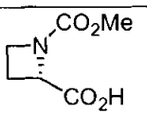
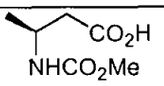
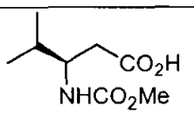
The following caps were prepared according to the method of example 51:

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 $(M+H)^+$.

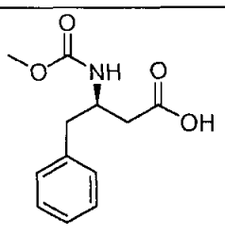
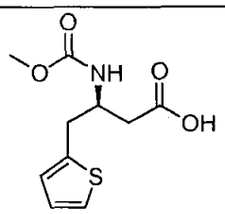
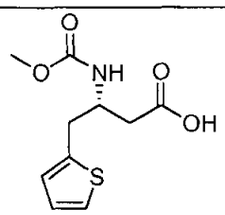
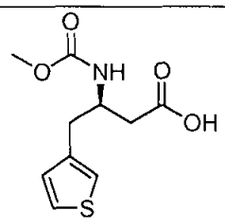
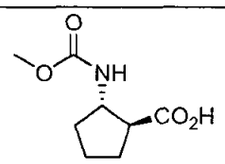
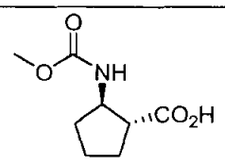
Cap-101		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$.
Cap-102		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$
Cap-103		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-104		^{1}HNMR (400 MHz, CD_3OD) δ 3.60 (s, 3H), 3.50 – 3.53 (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		^{1}HNMR (400 MHz, CD_3OD) δ 3.16 (q, J = 7.3 Hz, 4H), 2.38 - 2.41 (m, 1H), 2.28 – 2.31 (m, 2H), 1.79 – 1.89 (m, 2H), 1.74 (app, ddd J = 3.5, 12.5, 15.9 Hz, 2H), 1.46 (app

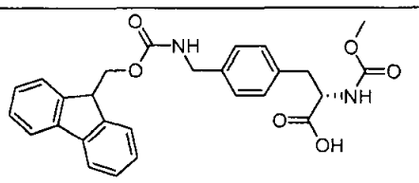
		dt J = 4.0, 12.9 Hz, 2H), 1.26 (t, J = 7.3 Hz, 6H).
Cap-107		LCMS: Anal. Calcd. for $C_8H_{10}N_2O_4S$: 230; found: 231 $(M+H)^+$.
Cap-108		LCMS: Anal. Calcd. for $C_{15}H_{17}N_3O_4$: 303; found: 304 $(M+H)^+$.
Cap-109		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-110		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-111		LCMS: Anal. Calcd. for $C_{12}H_{16}NO_8P$: 333; found: 334 $(M+H)^+$.
Cap-112		LCMS: Anal. Calcd. for $C_{13}H_{14}N_2O_4$: 262; found: 263 $(M+H)^+$.

Cap-113		LCMS: Anal. Calcd. for $C_{18}H_{19}NO_5$: 329; found: 330 $(M+H)^+$.
Cap-114		^{1}HNMR (400 MHz, $CDCl_3$) δ 4.82 – 4.84 (m, 1H), 4.00 – 4.05 (m, 2H), 3.77 (s, 3H), 2.56 (s, br, 2H)
Cap-115		^{1}HNMR (400 MHz, $CDCl_3$) δ 5.13 (s, br, 1H), 4.13 (s, br, 1H), 3.69 (s, 3H), 2.61 (d, J = 5.0 Hz, 2H), 1.28 (d, J = 9.1 Hz, 3H).
Cap-116		^{1}HNMR (400 MHz, $CDCl_3$) δ 5.10 (d, J = 8.6 Hz, 1H), 3.74 – 3.83 (m, 1H), 3.69 (s, 3H), 2.54 – 2.61 (m, 2H), 1.88 (sept, J = 7.0 Hz, 1H), 0.95 (d, J = 7.0 Hz, 6H).

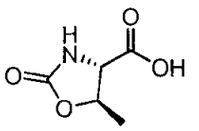
Cap-117 to Cap-123

For the preparation of 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 $(M+H)^+$.

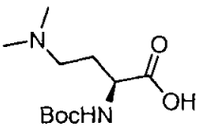
Preparation of *Cap*-124 . (4S,5R)-5-methyl-2-oxooxazolidine-4-carboxylic acid



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 $(M+H)^+$.

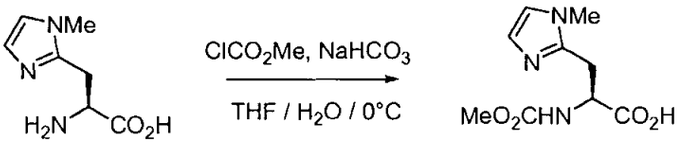
Preparation of *Cap*-125. (S)-2-(tert-butoxycarbonylamino)-4-(dimethylamino)butanoic acid.



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*

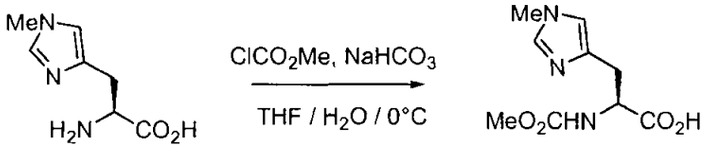
This procedure is a modification of that used to prepare *Cap*-51. To a suspension of (S)-2-amino-3-(1-methyl-1H-imidazol-2-yl)propanoic acid (0.80 g, 4.70 mmol) in THF (10mL) and H_2O (10 mL) at 0°C was added $NaHCO_3$ (0.88 g, 10.5 mmol). The resulting mixture was treated with $ClCO_2Me$ (0.40 mL, 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).



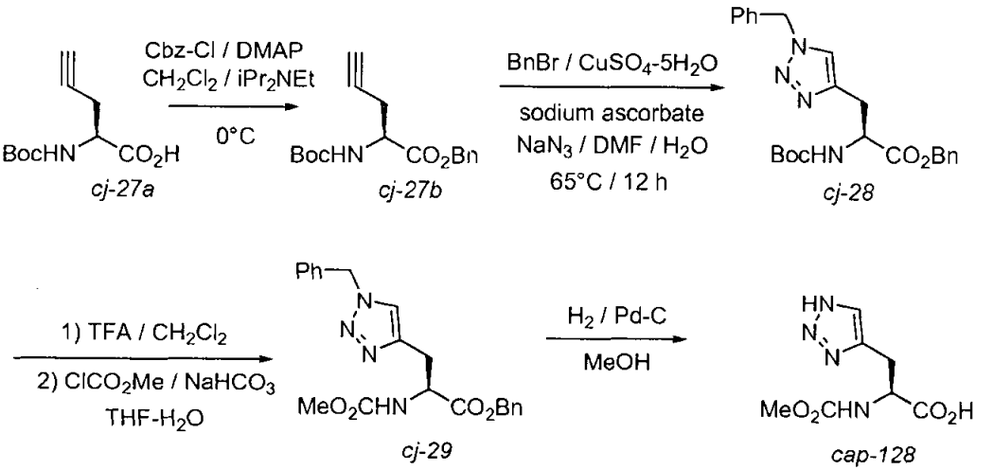
cj-26 *cap-127*

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).

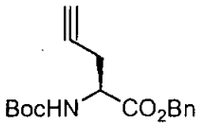
LCMS: Anal. Calcd. for $C_{17}H_{15}NO_2$: 392; found: 393 $(M+H)^+$.

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*

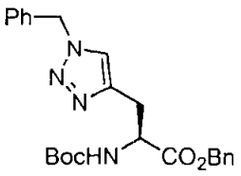
Step 1. Preparation of (S)-benzyl 2-(tert-butoxycarbonylamino)pent-4-ynoate (cj-27b).



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).

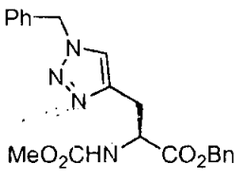


cj-28

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 $(M+H)^+$.

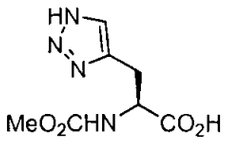
Step 2. Preparation of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(methoxycarbonylamino)propanoate (cj-29).



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).

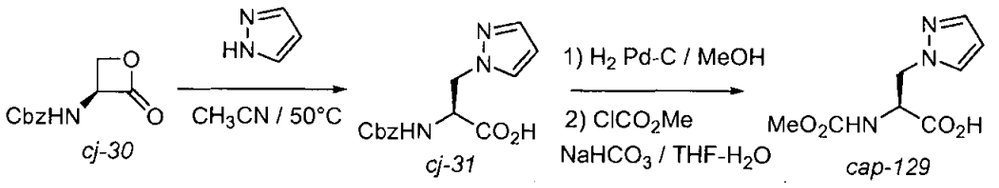


Cap-128

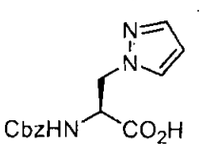
(S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(methoxycarbonylamino)propanoate (502 mg, 1.11 mmol) was hydrogenated in the presence of Pd-C (82 mg) in MeOH (5 mL) at atmospheric pressure for 12h. The mixture was filtered through diatomaceous earth (Celite®) and concentrated *in vacuo*. (S)-2-(methoxycarbonylamino)-3-(1H-1,2,3-triazol-4-yl)propanoic 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).

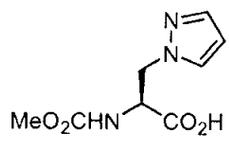


cj-31

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).

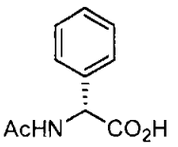


cap-129

(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.

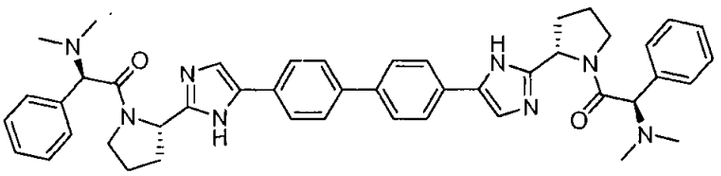
Method D: HPLC – Phenomenex C-18 4.6 x 150mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.2% H_3PO_4, B = 90% methanol 10% water 0.2% H_3PO_4

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.

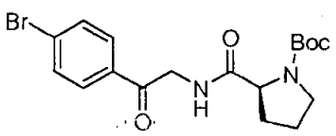
Method F: LCMS-Luna C-18 3.0 x 50mm, 0 to 100% B over 7.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate.

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)



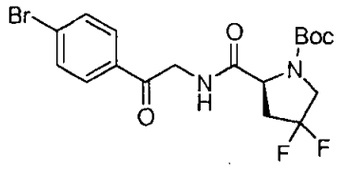
Example 1, Step a



1a

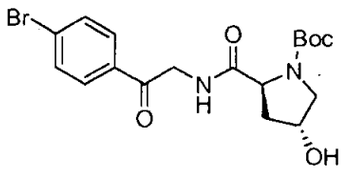
N,N-Diisopropylethylamine (18 mL; 103.3 mmol) was added dropwise, over 15 minutes, to a heterogeneous mixture of *N*-Boc-L-proline (7.139 g, 33.17 mmol), HATU (13.324 g, 35.04 mmol), the HCl salt of 2-amino-1-(4-bromophenyl)ethanone (8.127 g, 32.44 mmol), and DMF (105 mL), and stirred at ambient condition 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.



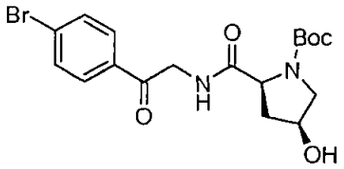
1-1a

^{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

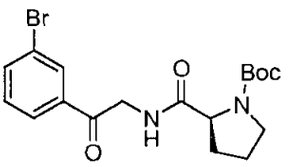
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm (8.25 1H, s), 7.91 (2H, d, *J*=8.24Hz), 7.75 (2H, d, *J*=8.24 Hz), 4.98 (1H, s), 4.59-4.63 (1H, m), 4.46-4.52 (1H, m), 4.23 (1H, m), 3.37 (1H, s), 3.23-3.28 (1H, m), 2.06 (1H, m), 1.88 (1H, s), 1.38 (3H, s), 1.33 (6H, s). LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% 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

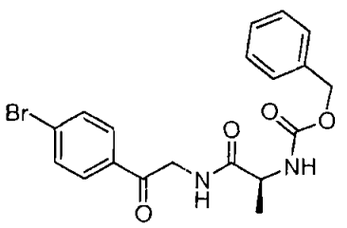
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.30 (1H, s) 7.93-7.96 (2H, m) 7.76 (2H d, *J*=8.24 Hz) 5.13 (1H, s) 4.66-4.71 (1H, m) 4.52-4.55 (1H, m) 4.17 (1H, m) 3.51 (1H,

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

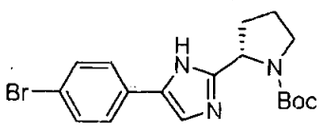
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.29-1.47 (m, 9H), 1.67-1.90 (m, 3H), 2.00-2.20 (m, 1H), 3.23-3.30 (m, 1H), 3.34-3.44 (m, 1H), 4.16 (dd, 1H), 4.57 (q, 2H), 7.51 (t, *J*=7.78 Hz, 1H), 7.86 (dd, *J*=7.93, 1.22 Hz, 1H), 7.98 (d, *J*=7.63 Hz, 1H), 8.11 (s, 1H), 8.15-8.29 (m, 1H). LC/MS $(M+Na)^+$ = 433.12/435.12.



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. ^1H 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

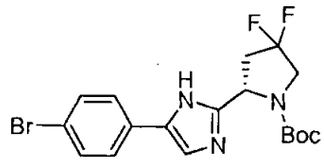
Solvent: 2% ethanol/heptane (isocratic)

Flow rate: 1 mL/min

Wavelength: either 220 or 254 nm

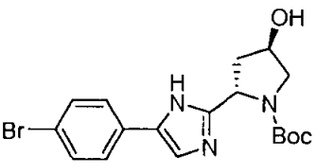
Relative retention time: 2.83 minutes (*R*), 5.34 minutes (*S*)

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



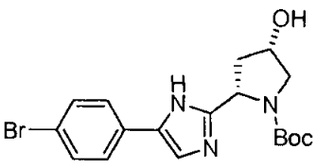
1-1b

^{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 $(M)^+$.



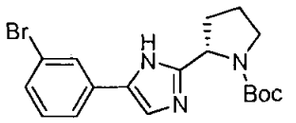
1-2b

^{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 $(M+H)^+$.



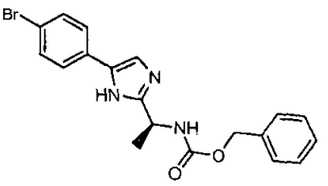
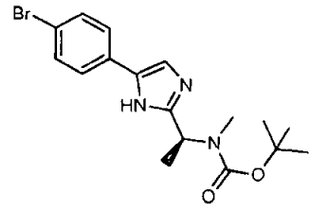
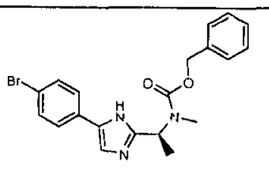
1-4b

^{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.

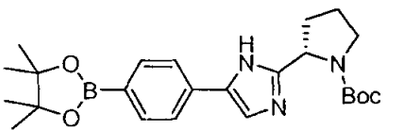
LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

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 $(M+H)^+$.

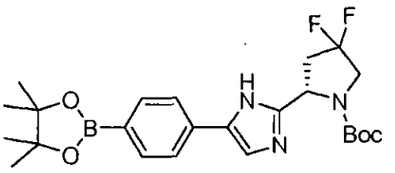
Example 1, Step c



1c

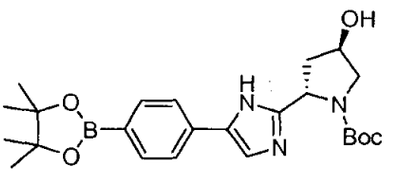
$Pd(Ph_3P)_4$ (469 mg, 0.406 mmol) was added to a pressure tube containing a mixture of bromide 1b (4.008 g, 10.22 mmol), bis(pinacolato)diboron (5.422 g, 21.35 mmol), potassium acetate (2.573g, 26.21 mmol) and 1,4-dioxane (80 mL). The reaction flask was purged with nitrogen, capped and heated with an 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.



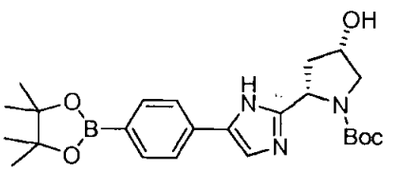
1-1c

^{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

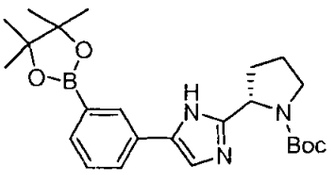
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.97 (1H, m), 7.62-7.75 (5H, m), 5.05 (1H d, *J*=3.36 Hz), 4.82 (m, 1H), 4.35 (m, 1H), 3.58 (1H, m), 2.389 (1H, s), 2.17 (1 H, m), 1.38 (3H, s), 1.30 (12H, s), 1.1 (6H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, 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 $(M+H)^+$.



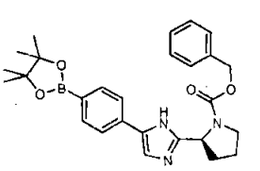
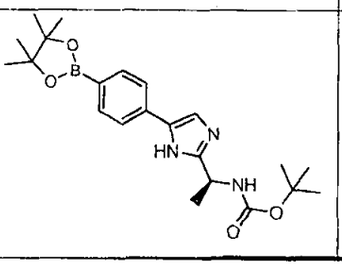
1-4c

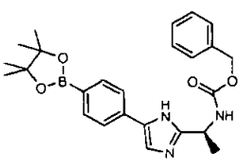
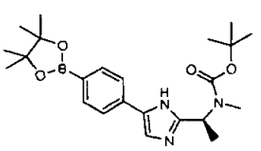
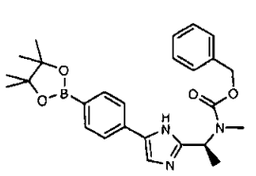
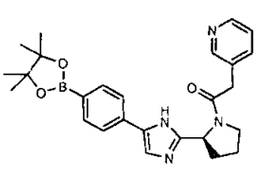
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.02-1.54 (m, 21H), 1.75-2.07 (m, 3H), 2.09-2.33 (m, 1H), 3.32-3.44 (m, 1H), 3.55 (s, 1H), 4.69-4.94 (m, 1H), 7.33 (t, *J*=7.32 Hz, 1H), 7.41-7.57 (m, 2H), 7.84 (d, *J*=7.32 Hz, 1H), 8.08 (s, 1H), 11.62-12.07 (m, 1H). LC/MS $(M+H)^+$ = 440.32.

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.

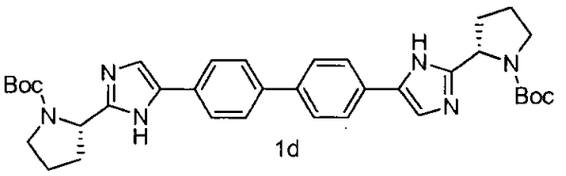
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

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

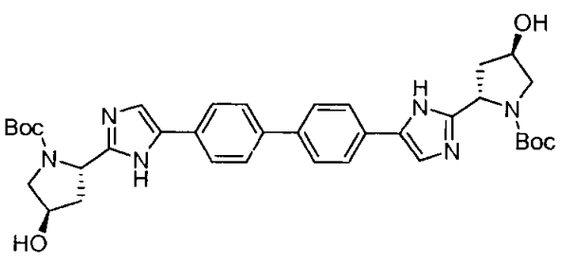
di-tert-butyl (2S,2'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))di(1-pyrrolidinecarboxylate)



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.

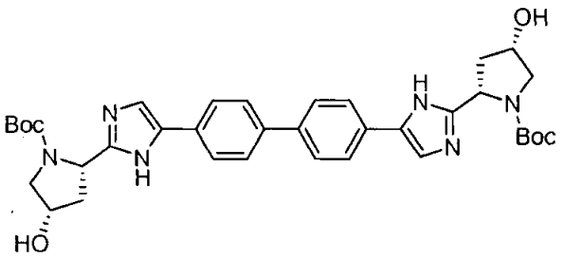
Additional symmetric analogs can be prepared in similar fashion.



1-1d

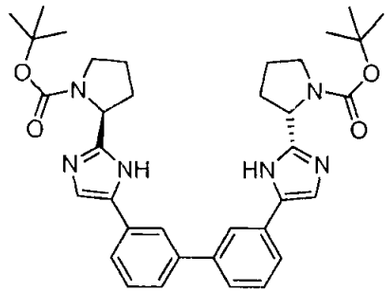
Example 1-1d was prepared using intermediates 1-2c and 1-2b. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 11.94-12.22 (2H, m) 7.53-7.82 (10H, m) 4.82-4.92 (2 H, m) 4.34-4.43 (2 H, m) 3.55-3.64 (2 H, m) 3.36 (2 H, d, *J*=11.29 Hz) 2.12-2.22 (2 H, m) 2.02-

2.11 (2 H, m) 1.40 (6 H, s) 1.14 (12 H, 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= 3.32min, Anal. Calcd. for 656.79; found 657.40 $(M+H)^+$. Nominal/LRMS – $(M+H)^+$ 657.42, $(M-H)^-$ -655.28.



1-2d

Example 1-2d was prepared using intermediates 1-3b and 1-3c. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.00-12.20 (2H, m) 7.56-7.76 (10H, m) 4.90 (1H, s) 4.82 (1H, s) 4.25-4.34 (2H, m) 3.56 (2H, s) 3.34-3.47 (2H, m) 1.97-2.13 (4H, m) 1.39 (9H, m) 1.20 (9H, 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= 3.35min, Anal. Calcd. for 656.79; found 657.30 $(M+H)^+$.

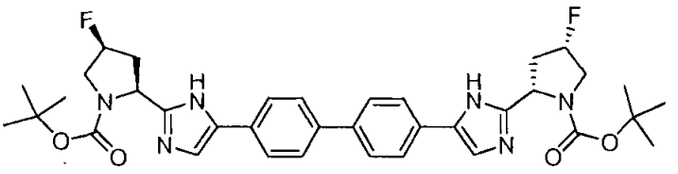


1-2d-1

tert-butyl (2S)-2-(4-(3'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate

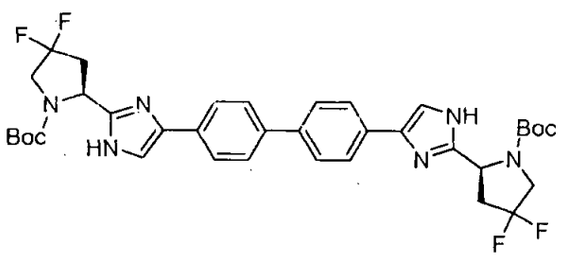
Example 1-2d-1 was prepared using intermediates 1-4c and 1-4b. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.09-1.51 (m, 18H), 1.84-2.15 (m, 6H), 2.34-2.50 (m, 2H),

3.35-3.52 (m, 2H), 3.54-3.67 (m, 2H), 5.08 (d, J=5.49 Hz, 2H), 7.68 (t, J=7.78 Hz, 2H), 7.78-7.92 (m, 4H), 8.11-8.30 (m, 4H), 14.81 (s, 2H). LC/MS $(M+H)^+$ = 625.48.



1-2d-2

Diol 1-1d (0.15g, 0.23mmol) was added as a solid to a solution of bis(2-methoxyethyl) aminosulfur trifluoride (0.1mL, 0.51mmol) in 1.0mL CH_2Cl_2 cooled to -78 °C. The reaction was stirred at -78 °C for two hours and then warmed to room temperature and stirred for 2 hours. The reaction was poured into saturated sodium bicarbonate solution and stirred until bubbling ceased. The layers were separated and the aqueous layer was extracted one time with CH_2Cl_2. The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a yellow oil. The oil was triturated with CH_2Cl_2 and pentane to provide the desired product as a tan solid (0.092g, 61%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.76-11.94 (2H, m), 7.77 - 7.85 (4 H, m), 7.66 - 7.72 (4 H, m), 7.60 - 7.66 (2 H, m, J=11.60 Hz), 5.39 (1 H, s), 5.28 (1 H, s), 5.03 (2 H, s), 3.66 - 3.79 (4 H, m), 2.61 - 2.70 (2 H, m), 2.28 - 2.38 (2 H, m), 1.42 (10 H, s), 1.24 (8 H, 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, (t_R= 3.58 min) Anal Calcd. for $C_{36}H_{42}F_2N_6O_4$ 660.70; found 661.68 $(M+H)^+$.

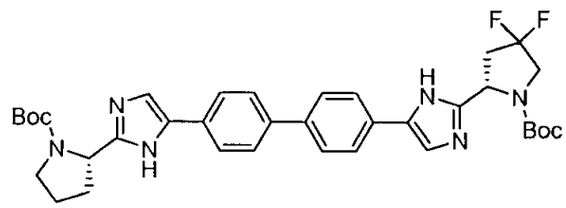


1-2d-3

Prepared from 1-1b and 1-1c in the same manner as the preparation of 1d from 1b and 1c. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.18/1.40 (two br. s., 18H),

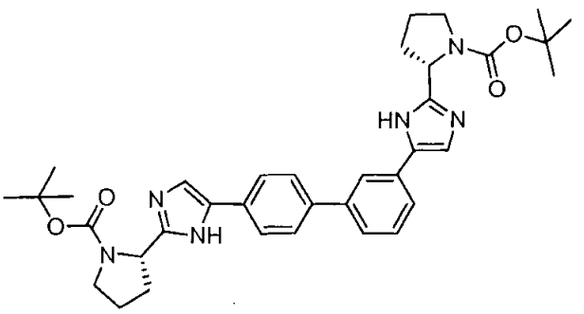
2.53 - 2.75 (m, *J*=25.94 Hz, 2H), 2.86 - 3.06 (m, 2H), 3.78 - 4.02 (m, 4H), 5.04 (br s, 2H), 7.17 – 8.24 (m, 10H), 12.07/12.37 (two br. s., 2H); HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 2 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.31 min, 99% homogeneity index. LCMS: Anal. Calcd. for $C_{36}H_{40}F_4N_6O_4$: 696.73; found: 967.64 $(M+H)^+$.

Dissymmetric compounds such as intermediate 1-3d and 1-4d can be prepared by the same method. For example, reaction of 1-1c with 1b in the same manner as described above for the preparation of 1d provided 1-3d. Similarly, reaction of 1-4c with 1b in the same manner as described above for the preparation of 1d provideed 1-4d.



1-3d

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.40/1.18 (two br s, 18H), 1.90-2.02 (m, 2H), 2.02-2.12 (m, 1H), 2.28-2.46 (m, 2H), 2.68-2.87 (m, 1H), 3.35-3.49 (m, 1H), 3.53-3.62 (m, 1H), 3.82-4.10 (m, 2H), 4.92-5.11 (m, 1H), 5.28 (s, 1H), 7.79-8.00 (m, 8H), 8.03-8.25 (m, 2H), 13.77-15.16 (m, 2H); HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.22 minutes, 99% homogeneity index. LCMS: Anal. Calcd. for $C_{36}H_{42}F_2N_6O_4$: 660.75; found: 661.98 $(M+H)^+$.



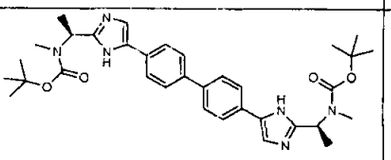
1-4d

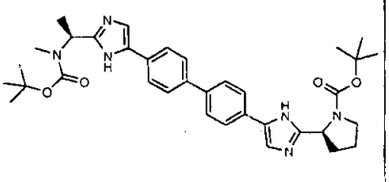
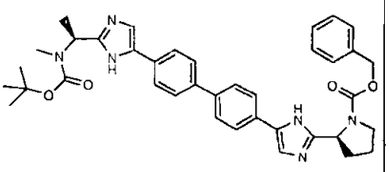
Example 1-4d was prepared from 1-4c and 1b in similar fashion to the preparation of 1d from 1b and 1c. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.99 - 1.60 (m, 18 H) 1.75 - 2.11 (m, *J*=73.24 Hz, 6 H) 2.12 - 2.32 (m, 2 H) 3.32 - 3.41 (m, 2 H) 3.56 (s, 2 H) 4.63 - 5.02 (m, 2 H) 6.98 - 8.28 (m, 10 H) 11.67 - 12.33 (m, 2 H); LC conditions: Phenomenex Luna 3.0 X 5.0mm S10, Solvent A – 0.1% TFA in 10% MeOH/90%H_2O, Solvent B - 0.1% TFA in 90% MeOH/10% H_2O, 0 to 100% B over 2min, Stop time = 3min, Flow rate = 4ml/min, Wavelength = 220nm, LC/MS $(M+H)^+$ = 625.32. Retention time = 1.438 min

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.

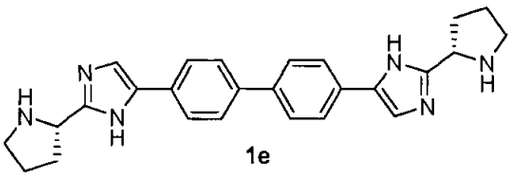
Example	*Compound Name*	*Structure*	*Characterization Data*
1-5d	di-tert-butyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S)-1,1-ethanediyl))bis(meth	 Prepared from 1-8c and 1-6b	RT = 1.64 minutes (>95%); Condition 2; LCMS: Anal. Calcd $C_{34}H_{45}N_6O_4$

	ylcarbamate)		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 $(M+H)^+$.

5

Example 1, Step e

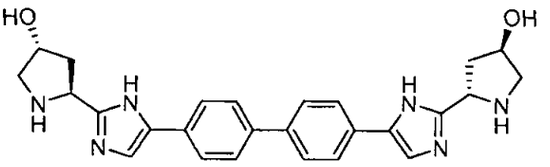
5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole)



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). ^{1}H 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 such as 1-1e to 1-4e can be prepared in a similar fashion.

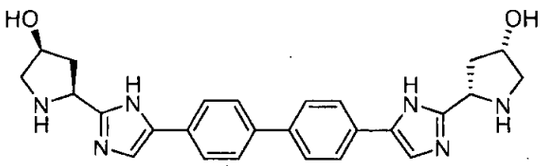


· 4 HCl

1-1e

To a solution of 1-1d (3R,3'R,5S,5'S)-tert-butyl 5,5'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(3-hydroxypyrrolidine-1-carboxylate) in 3mL dioxane was added 0.8mL of a 4.0M solution of HCl in dioxane. The reaction was stirred for 2 hours at room temperature and concentrated under reduced pressure. The resulting tan solid was dried under vacuum to give 1-1e (3R,3'R,5S,5'S)-5,5'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))dipyrrolidin-3-oltetrahydrochloride (0.55g, 100%yield). Used without further purification.^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.33 (s, 2H), 9.85 (s, 2H), 8.09 (s, 2H), 8.01 (d, J=8.24 Hz, 4H), 7.88 (d, J=8.24 Hz, 4H), 5.14 (m, 2H), 4.62 (m, 2H), 3.61 (m, 2H),

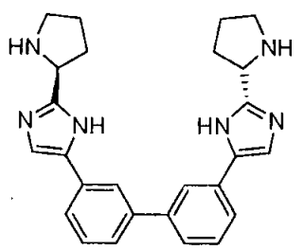
3.23 (d, *J*=11.29 Hz, 2H), 2.64 (m, 2H), 2.44 (dd, *J*=13.43, 6.71 Hz, 2H); LCMS – Waters-Sunfire C-18 4.6 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, RT= 1.35 minutes Anal. Calcd. for 456.30; found 457.25 $(M+H)^+$; Nominal/LRMS – $(M+H)^+$ 457.35.



• 4 HCl

1-2e

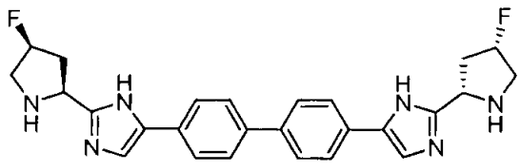
Example 1-2e was prepared in similar fashion to the method described for the preparation of 1-1e. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.32 (1 H, s) 8.01 (2 H, s) 7.97 (4 H, d, *J*=8.24 Hz) 7.86 (4 H, d, *J*=8.24 Hz) 5.01-5.10 (2 H, m) 4.52-4.60 (2 H, m) 3.36-3.45 (2 H, m) 3.25 (2 H, s) 2.60-2.68 (2 H, m) 2.40-2.48 (2 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, RT= 2.10min., Anal. Calcd. for 456.30; found 457.22 $(M+H)^+$



1-2e-1

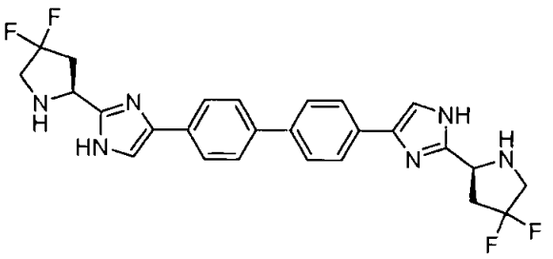
2-((2S)-2-pyrrolidinyl)-4-(3'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-biphenylyl)-1H-imidazole

Example 1-2e-1 was prepared from 1-2d-1 in similar fashion described for the preparation of 1-1e. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.74-2.44 (m, 12H), 4.83 (s, 2H), 7.37-7.72 (m, 4H), 7.74-8.03 (m, 4H), 8.10 (s, 2H), 9.14 (s, 2H), 9.81 (s, 2H). LC/MS $(M+H)^+$ = 425.30.



1-2e-2

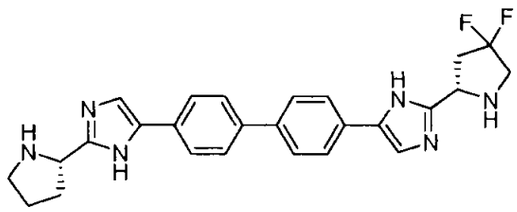
To a solution of 1-2d-2 (0.084g, 0.13mmol) in 1mL dioxane was added 0.5mL of a 4.0M solution of HCl in dioxane. The reaction was stirred for 2 hours at room temperature and concentrated under reduced pressure. The resulting tan solid was dried under vacuum to give 1-2e-2 (0.077g, 100%yield). The compound was used without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (2H, s), 7.97 (4H, d, *J*=8.55 Hz), 7.85 (4H, d, *J*=8.24 Hz), 5.63 (1H, s), 5.52 (1H, s), 5.09 - 5.17 (2H, m), 3.67 - 3.74 (2H, m), 3.63 - 3.67 (2H, m), 3.07 - 3.14 (1H, m), 2.89 - 2.96 (1H, m), 2.81 - 2.87 (2H, 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= 2.22 min) Anal Calcd. for $C_{26}H_{26}F_2N_6$ 460.53; found 461.37 $(M+H)^+$.



1-2e-3

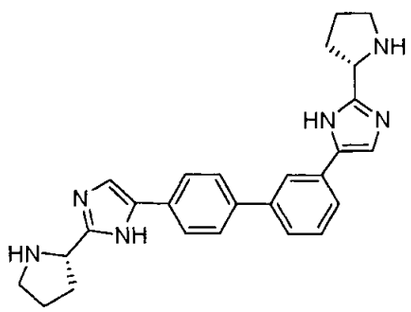
Prepared from 1-2d-3 in the same manner as the preparation of 1-1e from 1-1d. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.97 - 3.13 (m, 4H), 3.64 - 3.91 (m, 4H), 5.16 (d, *J*=6.41 Hz, 2H), 7.84 (d, *J*=7.93 Hz, 4H), 7.96 (d, *J*=7.93 Hz, 4H), 8.00 (s, 2H); HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 4 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.66 min, 92% homogeneity index. LCMS: Anal. Calcd. for $C_{26}H_{24}F_4N_6$: 496.50; found: 495.53 $(M-H)^-$.

Analogous dissymmetric compounds such as intermediates 1-3e and 1-4e can be prepared by the same method.



1-3e

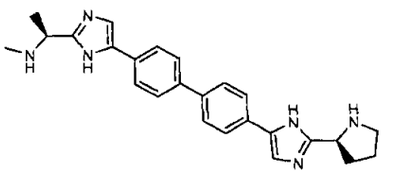
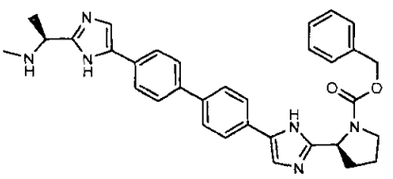
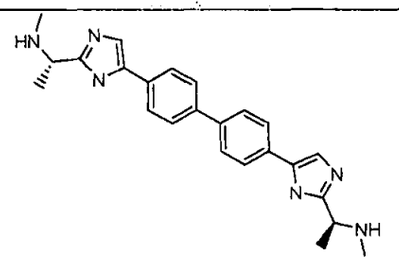
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.87-2.09 (m, 1H), 2.13-2.26 (m, 1H), 2.37-2.47 (m, 2H), 2.92-3.12 (m, 2H), 3.37 (s, 1H), 3.40-3.49 (m, 1H), 3.67-3.91 (m, 2H), 4.96-5.05 (m, 1H), 5.14 (t, *J*=8.70 Hz, 1H), 7.86 (t, *J*=9.00 Hz, 4H), 7.93-8.03 (m, 5H), 8.10 (s, 1H), 10.26/9.75 (two br s., 2H); HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 0.8622 minutes, 99% homogeneity index; LCMS: Anal. Calcd. for $C_{26}H_{26}F_2N_6$: 460.52; found: 461.45 $(M+H)^+$.



1-4e

Example 1-4e was prepared from 1-4d in similar fashion to that described for the preparation of 1-1c from 1-1d. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.90 - 2.13 (m, 2 H) 2.12 - 2.31 (m, 2 H) 2.36 - 2.60 (m, 4 H) 3.29 - 3.55 (m, 4 H) 5.00 (s, 2 H) 7.35 - 8.50 (m, 10 H) 9.76 (s, 2 H) 10.12 - 10.45 (m, 2 H). LC conditions: Phenomenex Luna 3.0 X 5.0mm S10, Solvent A – 0.1% TFA in 10% MeOH/90%H_2O, Solvent B - 0.1% TFA in 90% MeOH/10% H_2O, 0 to 100% B over 2min, Stop time = 3min, Flow rate = 4ml/min, Wavelength = 220nm, LC/MS $(M+H)^+$ = 425.28. Retention time = 0.942 min

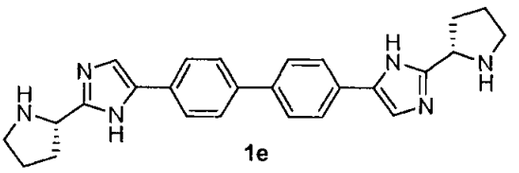
Additional analogs were prepared similarly:

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.

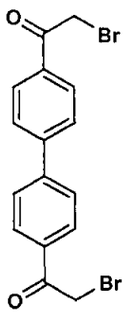
Alternative Synthesis of Example 1, Step e

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



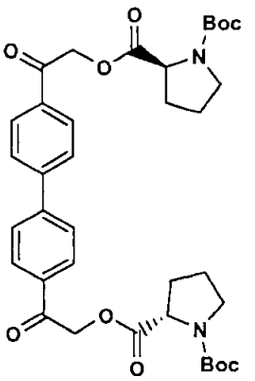
1e

Example A-1e-1



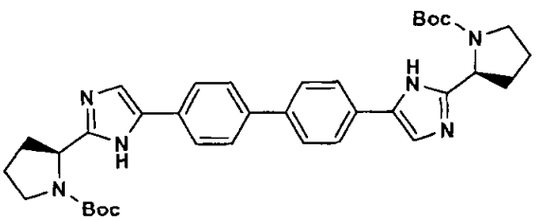
A 1 L, 3-neck round bottom flask, fitted with a nitrogen line, overhead stirrer and thermocouple was charged with 20 g (83.9 mmol, 1 equiv) 1,1'-(biphenyl-4,4'-diyl)diethanone, 200 mL CH_2Cl_2 and 8.7 mL (27.1g, 169.3 mmol, 2.02 quiv) bromine. The mixture was allowed to stir under nitrogen for about 20h under ambient conditions. The resulting slurry was charged with 200 mL CH_2Cl_2 and concentrated down to about 150 mL *via* vacuum distillation. The slurry was then solvent exchanged into THF to a target volume of 200 mL *via* vacuum distillation. The slurry was cooled to 20-25 °C over 1h and allowed to stir at 20-25 °C for an additional hour. The off-white crystalline solids were filtered and washed with 150 mL CH_2Cl_2. The product was dried under vacuum at 60 °C to provide 27.4 g (69.2 mmol, 82%) of the desired product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.85 (m, 4H), 7.60-7.50 (m, 4H), 4.26 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 145.1, 133.8, 129.9, 127.9, 30.8; IR (KBr, cm-1) 3007, 2950, 1691, 1599, 1199; Anal calcd for $C_{16}H_{12}Br_2O_2$: C, 48.52; H, 3.05; Br, 40.34. Found: C, 48.53; H, 3.03; Br, 40.53. HRMS calcd for $C_{16}H_{13}Br_2O_2$ (M + H; DCI^+): 394.9282. Found: 394.9292. mp 224-226 °C.

Example A-1e-2



A 500 mL jacketed flask, fitted with a nitrogen line, thermocouple and overhead stirrer, was charged with 20 g (50.5 mmol, 1 equiv) of Example A-1e-1, 22.8 g (105.9 moles, 2.10 equiv) 1-(*tert*-butoxycarbonyl)-L-proline, and 200 mL acetonitrile. The slurry was cooled to 20 °C followed by the addition of 18.2 mL (13.5 g, 104.4 mmol, 2.07 equiv) DIPEA. The slurry was warmed to 25 °C and allowed to stir for 3h. The resulting clear, organic solution was washed with 3 x 100 mL 13 wt% aqueous NaCl. The rich acetonitrile solution was solvent exchanged into toluene (target volume = 215 mL) by vacuum distillation until there was less than 0.5 vol% acetonitrile.

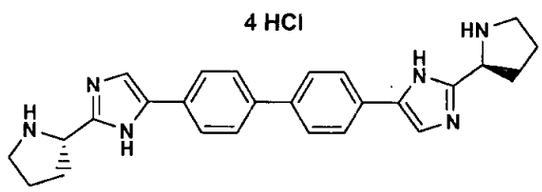
Example A-1e-3



The above toluene solution of Example A-1e-2 was charged with 78 g (1.011 moles, 20 equiv) ammonium acetate and heated to 95-100 °C. The mixture was allowed to stir at 95-100 °C for 15h. After reaction completion, the mixture was cooled to 70-80 °C and charged with 7 mL acetic acid, 40 mL n-butanol, and 80 mL of 5 vol% aqueous acetic acid. The resulting biphasic solution was split while maintaining a temperature > 50 °C. The rich organic phase was charged with 80 mL of 5 vol% aqueous acetic acid, 30 mL acetic acid and 20 mL n-butanol while

maintaining a temperature > 50 °C. The resulting biphasic solution was split while maintaining a temperature > 50 °C and the rich organic phase was washed with an additional 80 mL of 5 vol% aqueous acetic acid. The rich organic phase was then solvent exchanged into toluene to a target volume of 215 mL by vacuum distillation. While maintaining a temperature > 60 °C, 64 mL MeOH was charged. The resulting slurry was heated to 70-75 °C and aged for 1h. The slurry was cooled to 20-25 °C over 1h and aged at that temperature for an additional hour. The slurry was filtered and the cake was washed with 200 mL 10:3 toluene:MeOH. The product was dried under vacuum at 70 °C, resulting in 19.8 g (31.7 mmol, 63%) of the desired product: ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00-11.00 (s, 2H), 7.90-7.75 (m, 4H), 7.75-7.60 (m, 4H), 7.60-7.30 (s, 2H), 4.92-4.72 (m, 2H), 3.65-3.49 (m, 2H), 3.49-3.28 (m, 2H), 2.39-2.1 (m, 2H), 2.10-1.87 (m, 6H), 1.60-1.33 (s, 8H), 1.33-1.07 (s, 10H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.1, 153.8, 137.5, 126.6, 125.0, 78.9, 78.5, 55.6, 55.0, 47.0, 46.7, 33.7, 32.2, 28.5, 28.2, 24.2, 23.5; IR (KBr, cm-1) 2975, 2876, 1663, 1407, 1156, 1125; HRMS calcd for $C_{36}H_{45}N_6O_4$ (M + H; ESI$^+$): 625.3502. Found: 625.3502. mp 190-195 °C (decomposed).

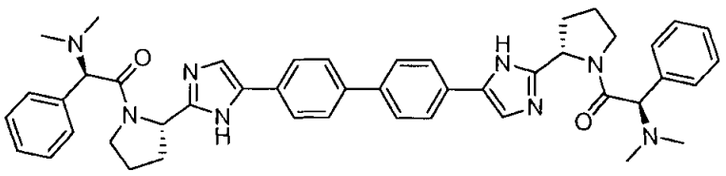
Example A-1e-4



To a 250 ml reactor equipped with a nitrogen line and overhead stirrer, 25.0 g of Example A-1e-3 (40.01 mmol, 1 equiv) was charged followed by 250 mL methanol and 32.85 mL (400.1 mmol, 10 equiv) 6M aqueous hydrogen chloride. The temperature was increased to 50 °C and agitated at 50 °C for 5h. The resulting slurry was cooled to 20-25 °C and held with agitation for ca. 18h. Filtration of the slurry afforded a solid which was washed successively with 100 ml 90% methanol/water (V/V) and 2x100 ml of methanol. The wet cake was dried in a vacuum oven at 50 °C overnight to give 18.12 g (31.8 mmol, 79.4%) of the desired product.

Recrystallization of Example A-1e-4

To a 250 ml reactor equipped with a nitrogen line and an overhead stirrer, 17.8g of crude Example A-1e-4 was charged followed by 72 mL methanol. The resulting slurry was agitated at 50 °C for 4h, cooled to 20-25 °C and held with agitation at 20-25 °C for 1h. Filtration of the slurry afforded a crystalline solid which was washed with 60 ml methanol. The resulting wet cake was dried in a vacuum oven at 50 °C for 4 days to yield 14.7 g (25.7 mmol, 82.6%) of the desired product: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.5-10.25 (br, 2H), 10.1-9.75 (br, 2H), 8.19 (s, 2H), 7.05 (d, J = 8.4, 4H), 7.92 (d, J = 8.5, 4H), 5.06 (m, 2H), 3.5-3.35 (m, 4H), 2.6-2.3 (m, 4H), 2.25-2.15 (m, 2H), 2.18-1.96 (m, 2H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 156.6, 142.5, 139.3, 128.1, 127.5, 126.1, 116.9, 53.2, 45.8, 29.8, 24.3; IR (KBr, cm^{-1}) 3429, 2627, 1636, 1567, 1493, 1428, 1028. Anal calcd for $C_{26}H_{32}N_6Cl_4$: C, 54.75; H, 5.65; Cl, 24.86; Adjusted for 1.9% water: C, 53.71; H, 5.76; N, 14.46; Cl, 24.39. Found: C, 53.74; H, 5.72; N, 14.50; Cl, 24.49; KF = 1.9. mp 240 °C (decomposed)



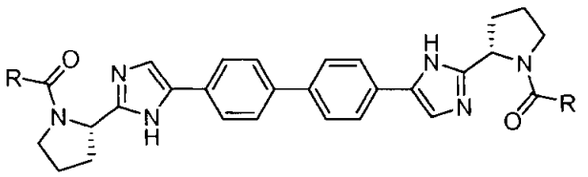
Example 1

(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)

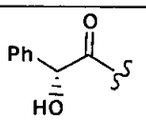
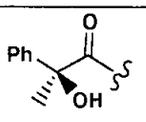
HATU (44.6 mg, 0.117 mmol) was added to a mixture of pyrrolidine 1e (22.9 mg, 0.054 mmol), diisopropylethylamine (45 μL, 0.259 mmol) and *Cap*-1 (28.1 mg, 0.13 mmol) in DMF (1.5 mL), and the resulting mixture was stirred at ambient for 90 minutes. The volatile component was removed *in vacuo*, and the 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

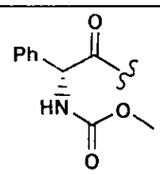
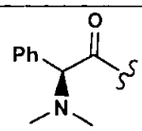
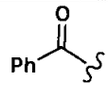
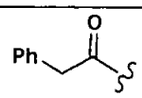
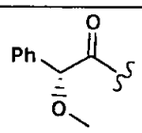
too broad to assign a chemical shift]; LC (Cond. 1): RT = 1.40 min; > 98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{51}N_8O_2$: 747.41; found 747.58

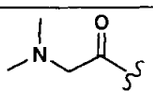
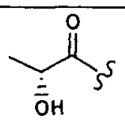
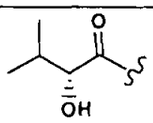
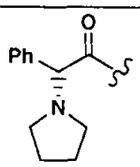
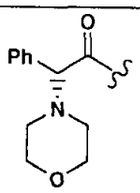
Examples 2 to 24-4d

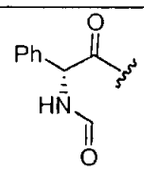
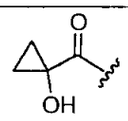
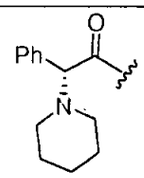
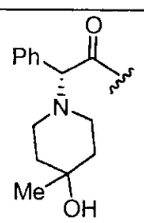


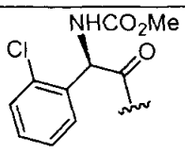
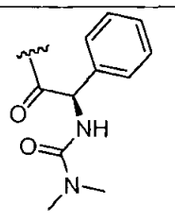
Examples 2 to 24-4h were prepared as TFA salts by substituting the respective acids for *Cap*-1 using the same method described for Example 1. Caps in the following table without a number are commercially available.

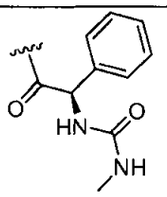
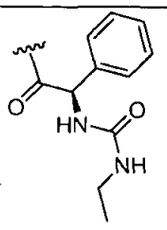
Example	*Compound Name*		*RT (LC-Cond.): % homogeneity index; MS data*
2	(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(2-oxo-1-phenylethanol)		1.55 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_6O_4$: 693.32; found 693.46; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_6O_4$: 693.3189; found 693.3182
3	(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(1-oxo-2-phenyl-2-propanol)		1.77 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_6O_4$: 721.35; found 721.52; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_6O_4$: 721.3502; found 721.3515

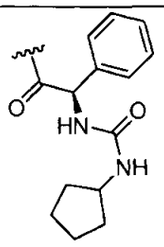
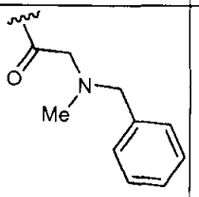
4	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 *Cap-4*	1.64 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_6$: 807.36; found 807.58
5	(1S,1'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)	 *ent of Cap-1*	1.33 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{51}N_8O_2$: 747.41; found 747.64; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{51}N_8O_2$: 747.4135; found 747.4103
6	5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-benzoyl-2-pyrrolidinyl)-1H-imidazole)		1.65 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{37}N_6O_2$: 633.30; found 633.51
7	5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-(phenylacetyl)-2-pyrrolidinyl)-1H-imidazole)		1.71 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_6O_2$: 661.33; found 661.53; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_6O_2$: 661.3291; found 661.3300
8	5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazole)		1.63 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_6O_4$: 721.35; found 721.59; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_6O_4$: 721.3502; found 721.3536

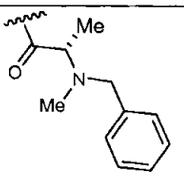
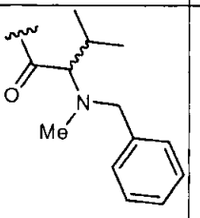
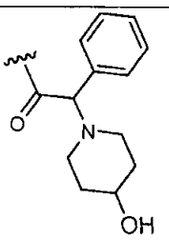
			$C_{36}H_{41}N_6O_4$: 621.3189; found 621.3191
14	2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxoethanamine)		1.27 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{43}N_8O_2$: 595.35; found 595.54; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{43}N_8O_2$: 595.3509; found 595.3503
15	(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(1-oxo-2-propanol)		1.36 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{32}H_{37}N_6O_4$: 569.29; found 569.44; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{32}H_{37}N_6O_4$: 569.2876; found 569.2872
16	(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(3-methyl-1-oxo-2-butanol)		1.51 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{45}N_6O_4$: 625.35; found 625.50; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{45}N_6O_4$: 625.3502; found 625.3517
17	5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazole)	 *Cap-5*	1.13 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{55}N_8O_2$: 799.45; found 799.67
18	4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-		1.11 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{55}N_8O_4$: 831.44; found

23	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))diformamide		1.22 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{43}N_8O_4$: 747.34; found 747.38
24	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl))dicyclopropanol		1.77 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{37}N_6O_4$: 593.29; found 593.16
24-1	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))dipiperidine	 *Cap-14*	^{1}HNMR (400 MHz, DMSO-d_6) δ 12.18 (m, 0.4H), 11.96 (m, 0.4H), 11.79 (m, 1.2H), 7.84-7.70 (m, 4H), 7.69-7.65 (m, 4H), 7.53-7.50 (m, 2H), 7.43-7.28 (m, 4H), 7.09-7.01 (m, 2H), 6.87-6.85 (m, 2H), 5.51-5.48 (m, 0.5H), 5.01-4.98 (m, 1.5H), 4.29 (m, 1.5H), 4.16 (m, 0.5H), 3.98 (m, 2H), 3.65-3.49 (m, 2H), 3.43-3.36 (m, 2H), 2.41-2.31 (m, 8H), 2.14-1.82 (m, 8H), 1.47-1.31 (m, 12H); LCMS: Anal. Calcd. for $C_{52}H_{58}N_8O_2$: 826; found: 827 $(M+H)^+$.
24-2	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(4-methyl-4-piperidinol)	 *Cap-15*	^{1}HNMR (400 MHz, DMSO-d_6) δ 12.02 (br s, 1H), 11.82 (br s, 1H), 7.90-7.79 (m, 4H), 7.79-7.65 (m, 5H), 7.55 (br s, 2H), 7.45 (d, J = 7.6 Hz, 2H), 7.39-7.25 (m, 3H),

			7.34 (d, *J* = 7.6 Hz, 2H), 7.04 (t, *J* = 7.6 Hz, 2H), 6.85 (d, *J* = 8.1 Hz, 2H), 5.15-4.96 (m, 2H), 4.31-3.96 (m, 6H), 2.35-2.20 (m, 2H), 2.05-1.94 (m, 4H), 1.94-1.81 (m, 4H), 1.50-1.35 (m, 9H), 1.35-1.20 (m, 5H), 1.09 (s, 2H), 1.05 (s, 4H); LCMS: Anal. Calcd. for $C_{54}H_{62}N_8O_4$: 886; found: 887 $(M+H)^+$.
24-3	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-1-(2-chlorophenyl)-2-oxo-2,1-ethanediyl)))biscarbamate		LCMS: Anal. Calcd. for $C_{46}H_{44}Cl_2N_8O_6$: 874; found: 875 $(M+H)^+$.
24-4a	N',N''''-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1,1-dimethylurea)	 *Cap-47*	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.89-2.00 (m, *J*=17.09, 7.02 Hz, 4H), 2.06-2.13 (m, *J*=14.95, 3.97 Hz, 3H), 2.24-2.33 (m, *J*=8.70, 6.56 Hz, 2H), 2.79-2.84 (m, 12H), 3.29 (q, 2H), 3.95-4.03 (m, 3H), 5.26 (dd, *J*=8.55, 2.14 Hz, 3H), 5.52 (d, *J*=5.80 Hz, 3H), 6.72 (d, *J*=6.10 Hz, 3H), 7.02-7.07 (m, 1H), 7.29-7.36 (m, 3H), 7.39 (t, *J*=7.17 Hz, 4H), 7.46 (d, *J*=7.02 Hz, 3H), 7.92 (s, 8H), 8.12 (s, 2H); HPLC XTERRA C-18 4.6 ×

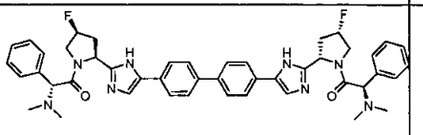
			30 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 2.13 minutes, 96% homogeneity index; LCMS: Anal. Calcd. for $C_{48}H_{53}N_{10}O_4$: 832.42; found: 833.43 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{48}H_{54}N_{10}O_4$ 833.4251; found: 833.4267 $(M+H)^+$.
24-4b	N',N'''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-methylurea)	 *Cap-45*	RT = 4.45 minutes (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); LCMS: Anal. Calcd. for $C_{46}H_{48}N_{10}O_4$ 804.95; found: 805.41 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{46}H_{49}N_{10}O_4$ 805.3938; found: 805.3929 $(M+H)^+$.
24-4c	N',N'''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-ethylurea)	 *Cap-46*	RT = 4.20 minutes (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%

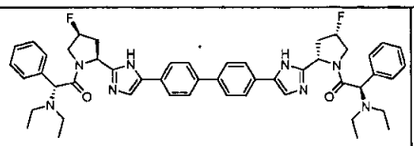
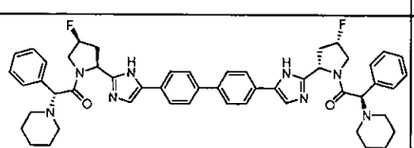
			acetonitrile, 5% water, 10mm ammonium acetate);LCMS: Anal. Calcd. for $C_{48}H_{52}N_{10}O_4$ 833.00; found: 833.48 $(M+H)^+$.
24-4d	N',N''''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-cyclopentylurea)	 *Cap-48*	RT = 4.92 minutes (Gemini 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); LCMS: Anal. Calcd. for $C_{54}H_{60}N_{10}O_4$ 912.49; found: 913.68 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{54}H_{61}N_{10}O_4$ 913.4877; found: 913.4899 $(M+H)^+$.
24-4e	2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-benzyl-N-methyl-2-oxoethanamine)	 *Cap-49*	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.97-2.43 (m, 8H), 2.64-2.91 (m, 6H), 3.45-3.63 (m, 2H), 3.62-3.76 (m, 2H), 4.14 (dd, 4H), 4.22-4.45 (m, 4H), 5.29 (s, 2H), 7.28-7.65 (m, 10H), 7.90 (s, 8H), 8.06 (s, 2H), 14.62 (s, 2H); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B =

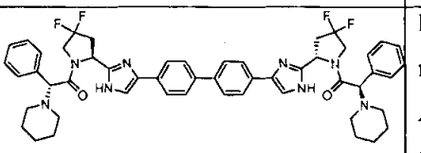
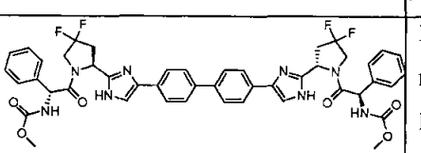
			10% water, 90% methanol, 0.2% phosphoric acid. RT = 3.06 min; LCMS: Anal. Calcd. for: $C_{46}H_{50}N_8O_2$ 746.96; Found: 747.41 $(M+H)^+$.
24-4f	(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-benzyl-N-methyl-1-oxo-2-propanamine)		RT = 2.95 minutes (99%); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{48}H_{54}N_8O_2$ 775.02; Found: 775.45 $(M+H)^+$.
24-4g	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-benzyl-N,3-dimethyl-1-oxo-2-butanamine)	 *Cap-50*	RT = 3.86 minutes (100%); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{52}H_{62}N_8O_2$ 831.13; Found: 831.51 $(M+H)^+$.
24-4h	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl(2-oxo-1-phenyl-2,1-ethanediyl)))di(4-piperidinol)	 *Cap-8*	RT = 2.86 minutes (100%); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90%

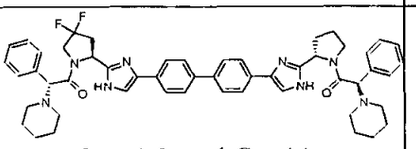
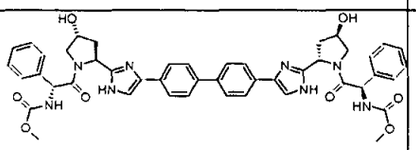
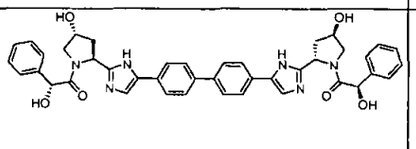
			methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{52}H_{58}N_8O_4$ 859.09; Found: 859.45 $(M+H)^+$.

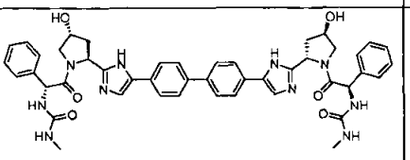
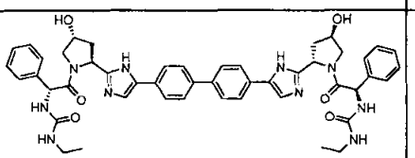
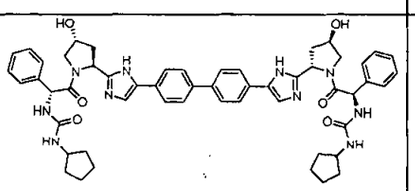
Examples 24-5 to 24-18

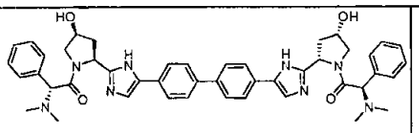
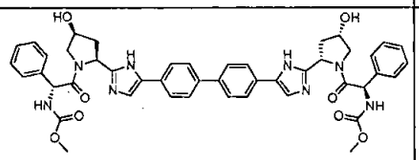
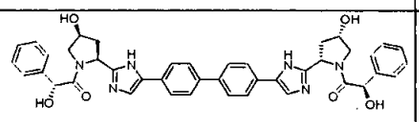
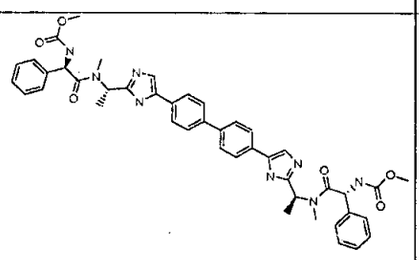
Example	*Compound Name*	*Structure*	*Data*
24-5	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4S)-4-fluoro-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))dipiperidine	 from 1-2e-2 and *Cap*-1	Gemini C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate. (RT=4.163 min); Nominal/LRMS – Calcd. for $C_{46}H_{48}F_2N_8O_2$ 782.93; found 783.40 $(M+H)^+$; Accurate/HRMS – Calcd. for $C_{46}H_{49}F_2N_8O_2$ 783.3946; 783.3934 $(M+H)^+$.

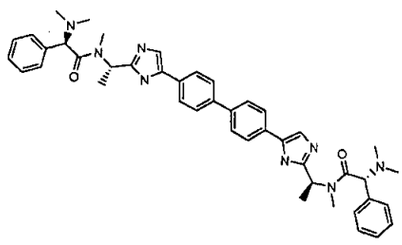
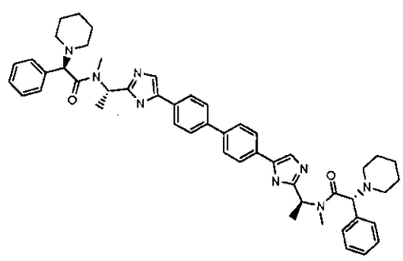
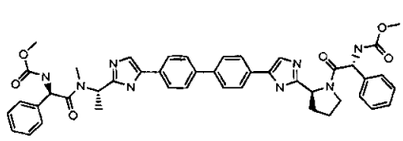
24-6	(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4S)-4-fluoro-2,1-pyrrolidinediyl)))bis(N,N-diethyl-2-oxo-1-phenylethanamine)	 from 1-2e-2 and *Cap*-2	Gemini C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate. (RT = 3.76 min); LCMS: Anal. Calcd. for $C_{50}H_{56}F_2N_8O_2$ 839.04; found: 839.49 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{50}H_{57}F_2N_8O_2$ 839.4572; found: 839.4590 $(M+H)^+$.
24-7	(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4S)-4-fluoro-2,1-pyrrolidinediyl)))bis(N,N-dimethyl-2-oxo-1-phenylethanamine	 from 1-2e-2 and *Cap*-14	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

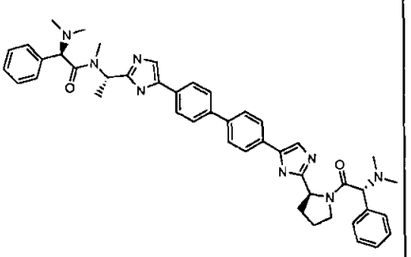
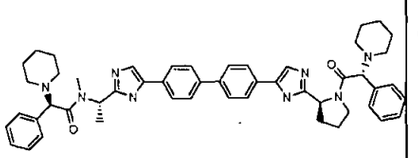
	)		acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate. RT = 3.99 min; LCMS: Anal. Calcd. for $C_{52}H_{56}F_2N_8O_2$ 863.06; found: 863.47 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{52}H_{57}F_2N_8O_2$ 863.4572; found: 863.4553 $(M+H)^+$.
24-8	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S)-4,4-difluoro-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))dipiperidine	 from 1-2e-3 and *Cap*-14	RT = 1.64 minutes, method B; LCMS: Anal. Calcd. for $C_{52}H_{54}F_4N_8O_6$: 898.43; found: 899.46 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{52}H_{55}F_4N_8O_6$ 899.4384; found: 899.4380 $(M+H)^+$.
24-9	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S)-4,4-difluoro-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscar	 from 1-2e-3 and *Cap*-4	RT = 2.62 minutes, method C; LCMS: Anal. Calcd. for $C_{46}H_{42}F_4N_8O_6$: 878.88; found: 879.81 $(M+H)^+$; HRMS: Anal. Calcd. for

	bamate		$C_{46}H_{43}F_4N_8O_6$ 879.33242; found: 879.3273 $(M+H)^+$.
24-10	1-((1R)-2-((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine	 from 1-3e and *Cap*-14.	RT = 1.54 minutes, method B; LCMS: Anal. Calcd. for $C_{52}H_{56}F_2N_8O_6$: 862.45; found: 863.46 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{52}H_{57}F_2N_8O_6$ 863.4573; found: 863.4572 $(M+H)^+$.
24-11	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 from 1-1e and *Cap*-4	RT = 8.54 minutes, method A; LCMS: Anal. Calcd. for $C_{46}H_{46}N_8O_8$ 838.93; found: 839.41 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{46}H_{47}N_8O_8$ 839.9300; found: 839.3527 $(M+H)^+$.
24-12	(3R,5S,3'R,5'S)-5,5'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))bis(1-((2R)-2-hydroxy-2-phenylacetyl)-3-	 from 1-1e and mandelic acid	RT = 6.92 minutes , method A; LCMS: Anal. Calcd. for $C_{42}H_{40}N_6O_6$ 724.81; found: 725.43 $(M+H)^+$; HRMS: Anal. Calcd. for

	pyrrolidinol)		$C_{42}H_{41}N_6O_6$ 725.3087; found: 725.3088 $(M+H)^+$.
24-13	N,N''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(3-methylurea)	 Prepared from 1-1e and *Cap*-45	RT = 3.80 minutes, method C; LCMS: Anal. Calcd. for $C_{46}H_{48}N_{10}O_6$ 836.95; found: 837.52 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{46}H_{49}N_{10}O_6$ 837.3836; found: 837.3809 $(M+H)^+$.
24-14	N',N''''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-ethylurea)	 Prepared from 1-1e and *Cap*-46	RT = 4.39 minutes, method C; LRMS: Anal. Calcd. for $C_{48}H_{52}N_{10}O_6$ 865.003; found: 865.56 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{48}H_{53}N_{10}O_6$ 865.4149; found: 865.4139 $(M+H)^+$.
24-15	N',N''''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-cyclopentylurea)	 Prepared from 1-1e and *Cap*-48	RT = 4.88 minutes, method B; LRMS: Anal. Calcd. for $C_{54}H_{60}N_{10}O_6$ 944.13; found: 945.65 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{54}H_{61}N_{10}O_6$ 945.4775; found: 945.4769 $(M+H)^+$.

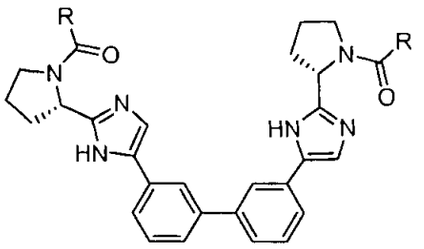
24-16	(3S,5S,3'S,5'S)-5,5'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))bis(1-((2R)-2-(dimethylamino)-2-phenylacetyl)-3-pyrrolidinol)	 Prepared from 1-2e and *Cap*-1	RT = 3.66 minutes, method D; LRMS: Anal. Calcd. for $C_{46}H_{50}N_8O_4$ 778.39 found: 779.39 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{46}H_{51}N_8O_4$ 779.4033; found: 779.4021 $(M+H)^+$.
24-17	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4S)-4-hydroxy-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 Prepared from 1-2e and *Cap*-4	RT = 5.75 minutes, method C; LRMS: Anal. Calcd. for $C_{46}H_{46}N_8O_8$ 838.93; found: 839.44 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{46}H_{47}N_8O_8$ 839.3517 found: 839.3519 $(M+H)^+$.
24-18	(3S,5S,3'S,5'S)-5,5'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))bis(1-((2R)-2-hydroxy-2-phenylacetyl)-3-pyrrolidinol)	 from 1-2e and mandelic acid	RT = 4.41 minutes, method D; LRMS: Anal. Calcd. for $C_{42}H_{40}N_6O_6$ 724.81; found: 725.13 $(M+H)^+$.
24-18-1	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S)-1,1-ethanediyl(methylimino))((1R)-2-oxo-1-phenyl-2,1-	 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

	ethanediyl)))biscarbamate		$C_{44}H_{47}N_8O_6$ 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-	 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 $(M+H)^+$.

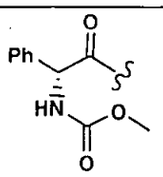
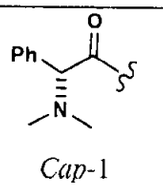
	pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		
24-18-5	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)ethyl)-N-methyl-2-phenylacetamide	 Prepared from 1-5e and *Cap*-1	RT = 1.21[1]; LRMS: Anal. 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 $(M+H)^+$.
24-18-6	(2R)-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)-2-(1-piperidinyl)acetamide	 Prepared from 1-5e and *Cap*-14	RT = 1.30[1]; LRMS: Anal. Calcd. for $C_{51}H_{58}N_8O_2$ 814.47; found: 815.48 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{51}H_{59}N_8O_2$ 815.4761 found: 815.4744 $(M+H)^+$.

[1]LC Conditions for 24-18-1 through 24-18-6: 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.

Examples 24-19 to 24-20



Example 24-19 and 24-20 were prepared as TFA salts from 1-2e-1 and the respective acids using the same method described for Example 1.

Example	*Compound Name*		*Data*
24-19	methyl ((1*R*)-2-((2*S*)-2-(4-(3'-(2-((2*S*)-1-((2*R*)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1*H*-imidazol-5-yl)-3-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-4	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.82-1.97 (m, 2H), 1.97-2.17 (m, 4H), 2.18-2.37 (m, 2H), 3.18 (d, *J*=9.77 Hz, 2H), 3.44-3.58 (m, 6H), 3.79-4.04 (m, 2H), 5.09-5.46 (m, 2H), 5.45-5.84 (m, 2H), 6.97-7.49 (m, 10H), 7.61-7.74 (m, 4H), 7.75-7.93 (m, 4H), 8.10-8.32 (m, 4H), 14.48 (app br s, 2H); RT = 1.34 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_6$: 807.36; found 807.40
24-20	(1*R*)-2-((2*S*)-2-(4-(3'-(2-((2*S*)-1-((2*R*)-2-(dimethylamino)-2-phenylacetyl)-2-	 *Cap*-1	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.71-2.32 (m, 8H), 3.33-3.68 (m, 2H), 3.89-4.16 (m,

	pyrrolidinyl)-1*H*-imidazol-5-yl)-3-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)-*N*,*N*-dimethyl-2-oxo-1-phenylethanamine		*J*=2.75 Hz, 2H), 4.96 (app br s, 12H), 5.26 (s, 2H), 5.45 (s, 2H), 7.03-7.78 (m, 12H), 7.84 (s, 4H), 8.07-8.43 (m, 4H), 9.90-10.87 (m, 2H); RT = 1.10 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{51}N_8O_2$: 747.41; found 747.45

LC conditions for 24-19 and 24-20:

Column = Phenomenex-Luna 3.0X 50 mm S10

Start %B = 0

Final %B = 100

Gradient time = 2 min

Stop time = 3 min

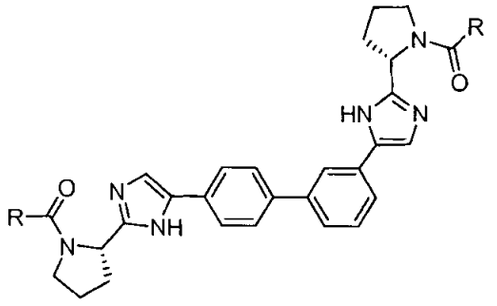
Flow Rate = 4 mL/min

Wavelength = 220 nm

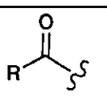
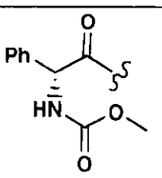
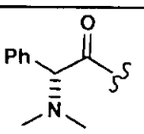
Slovent A = 0.1% TFA in 10% methanol/90%H_2O

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

Examples 24-21 to 24-22



Example 24-21 and 24-22 were prepared as TFA salts from 1-4e and the respective carboxylic acids using the same method described for Example 1.

Example	*Compound Name*		*Data*
24-21	methyl ((1*R*)-2-((2*R*)-2-(4-(3'-(2-((2*S*)-1-((2*R*)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1*H*-imidazol-4-yl)-4-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-4	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.73-2.37 (m, 8H), 3.13 (s, 2H), 3.36-4.29 (m, 8H), 5.26 (s, 2H), 5.53 (s, 2H), 6.99-8.61 (m, 22H), 14.51 (s, 2H); RT = 1.33min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_6$: 807.36; found 807.58
24-22	(1*R*)-2-((2*R*)-2-(4-(3'-(2-((2*S*)-1-((2*R*)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1*H*-imidazol-4-yl)-4-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)-*N*,*N*-dimethyl-2-oxo-1-phenylethanamine	 *Cap*-1	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.84-2.32 (m, 8H), 2.92-3.10 (m, 2H), 3.92-4.08 (m, 2H), 4.43 (app br s, 12H), 5.16-5.37 (m, 2H), 5.39-5.58 (m, 2H), 7.16-8.24 (m, 20H),

			9.60-10.46 (m, 2H); RT = 1.08 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{51}N_8O_2$: 747.41; found 747.45

LC conditions for 24-21 and 24-22:

Column = Phenomenex-Luna 3.0X 50 mm S10

Start %B = 0

Final %B = 100

Gradient time = 2 min

Stop time = 3 min

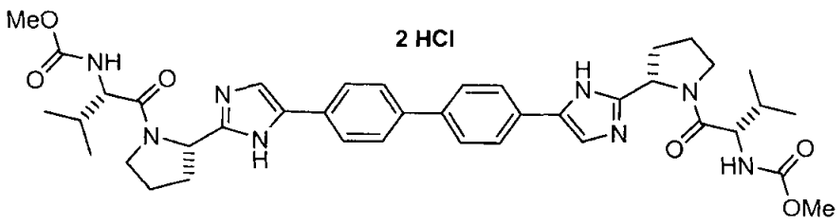
Flow Rate = 4 mL/min

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

Example 24-23



methyl ((1S)-1-(((2S)-2-(5-(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

A 50 mL flask equipped with a stir bar was sequentially charged with 2.5 mL acetonitrile, 0.344 g (2.25 mmol, 2.5 equiv) hydroxy benzotriazole hydrate, 0.374 g (2.13 mmol, 2.4 equiv) *N*-(methoxycarbonyl)-L-valine, 0.400 g (2.09 mmol, 2.4 equiv) 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride and an

additional 2.5 mL acetonitrile. The resulting solution was agitated at 20 °C for 1 hour and charged with 0.501 g (0.88 mmol, 1 equiv) Example A-1e-4. The slurry was cooled to about 0 °C and 0.45 g (3.48 mmol, 4 equiv) diisopropylethylamine was added over 30 minutes while maintaining a temperature below 10 °C. The solution was slowly heated to 15 °C over 3 hours and held at 15 °C for 16 hours. The temperature was increased to 20 °C and stirred for 3.25 hours. The resulting solution was charged with 3.3 g of 13 wt% aqueous NaCl and heated to 50 °C for 1 hour. After cooling to 20 °C, 2.5 mL of isopropyl acetate was added. The rich organic phase was washed with 2 x 6.9 g of a 0.5 N NaOH solution containing 13 wt% NaCl followed by 3.3 g of 13 wt% aqueous NaCl. The mixture was then solvent exchanged into isopropyl acetate by vacuum distillation to a target volume of 10 mL. The resulting hazy solution was cooled to 20 °C and filtered through a 0.45 μm filter. The clear solution was then solvent exchanged into ethanol by vacuum distillation with a target volume of 3 mL. 1.67 mL (2.02 mmol, 2.3 equiv) of 1.21 M HCl in ethanol was added. The mixture was then stirred at 25 °C for 15 hours. The resulting slurry was filtered and the wet cake was washed with 2.5 mL of 2:1 acetone:ethanol. The solids were dried in a vacuum oven at 50 °C to give 0.550 g (0.68 mmol, 77 %) of the desired product.

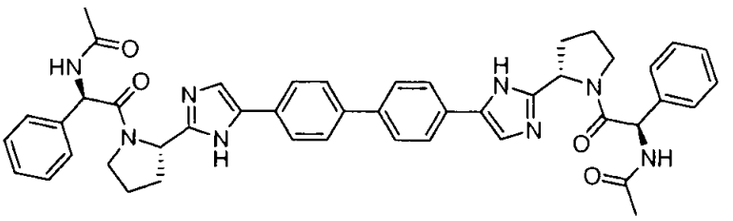
Recrystallization of Example 24-23

A solution of Example 24-23 prepared above was prepared by dissolving 0.520 g of the above product in 3.65 mL methanol. The solution was then charged with 0.078 g of type 3 Cuno Zeta loose carbon and allowed to stir for 0.25 hours. The mixture was then filtered and washed with 6 ml of methanol. The product rich solution was concentrated down to 2.6 mL by vacuum distillation. 7.8 mL acetone was added and allowed to stir at 25 °C for 15 h. The solids were filtered, washed with 2.5 mL 2:1 acetone:ethanol and dried in a vacuum oven at 70 °C to give 0.406 g (57.0%) of the desired product as white crystals: ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C): 8.02 (d, J=8.34 Hz, 4 H), 7.97 (s, 2 H), 7.86 (d, J=8.34 Hz, 4 H), 6.75 (s, 2 H), 5.27 (t, J=6.44 Hz, 2 H), 4.17 (t, J=6.95 Hz, 2 H), 3.97 - 4.11 (m, 2 H), 3.74 - 3.90 (m, 2 H), 3.57 (s, 6 H), 2.32 - 2.46 (m, 2 H), 2.09 - 2.31 (m, 6 H), 1.91 - 2.07 (m, 2 H), 0.88 (d, J=6.57 Hz, 6 H), 0.79 (d, J=6.32 Hz, 6 H); ^{13}C NMR (75 MHz, DMSO-

d_6): δ 170.9, 156.9, 149.3, 139.1, 131.7, 127.1, 126.5, 125.9, 115.0, 57.9, 52.8, 51.5, 47.2, 31.1, 28.9, 24.9, 19.6, 17.7; IR (neat, cm^{-1}): 3385, 2971, 2873, 2669, 1731, 1650. Anal. Calcd for $C_{40}H_{52}N_8O_6Cl_2$: C, 59.18; H, 6.45; N, 13.80; Cl, 8.73. Found C, 59.98; H, 6.80; N, 13.68; Cl, 8.77. mp 267 °C (decomposed). Characteristic diffraction peak positions (degrees 2θ ± 0.1) @ RT, based on a high quality pattern collected with a diffractometer (CuKα) with a spinning capillary with 2θ calibrated with a NIST other suitable standard are as follows: 10.3, 12.4, 12.8, 13.3, 13.6, 15.5, 20.3, 21.2, 22.4, 22.7, 23.7.

Example 25

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))diacetamide

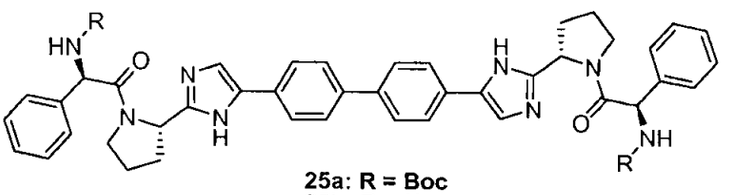


Example 25 Step a:

di-tert-butyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate

and

Example 25 Step b:



25a: R = Boc
25b: R = H

HATU (96.2 mg, 0.253 mmol) was added to a mixture of pyrrolidine 1e (52.6 mg, 0.124 mmol), diisopropylethylamine (100 μL, 0.57 mmol) and Boc-D-Phg-OH (69 mg, 0.275 mmol) in DMF (3.0 mL). The reaction mixture was stirred for 25 minutes, and then diluted with methanol and purified by a reverse phase HPLC

system (H_2O/methanol/TFA). The HPLC elute was neutralized with excess 2.0 M/NH_3 in CH_3OH and the volatile component was removed *in vacuo*. The residue was carefully partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The aqueous phase was extracted with more CH_2Cl_2 (2x). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide 25a as a film of semisolid oil (78.8 mg). LC (Cond. 1): RT = 1.99 min; >98% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{52}H_{59}N_8O_6$: 891.46; found 891.55.

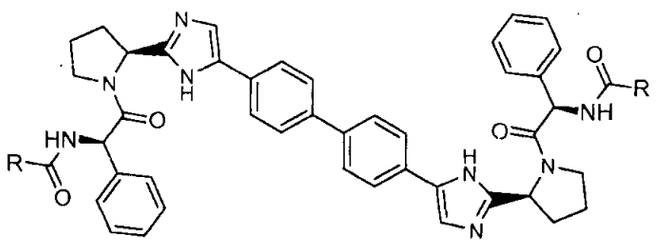
Carbamate 25a was converted to amine 25b according to the procedure described for the preparation of 1e. LC(Cond. 1): RT = 1.44 min; 97% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{43}N_8O_2$: 691.35; found 691.32

Example 25

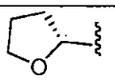
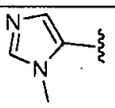
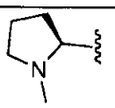
N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))diacetamide

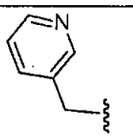
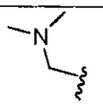
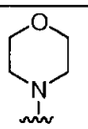
Acetic anhydride (20 µL, 0.21 mmol) was added to a DMF (1.5 mL) solution of amine 25b (29 mg, 0.042 mmol)and triethylamine (30 µL, 0.22 mmol) and stirred for 2.5 hours. The reaction mixture was then treated with NH_3/methanol (1 mL of 2 M) and stirred for an additional 1.5 hours. The volatile component was removed *in vacuo* and the residue was purified by a reverse phase HPLC system (H_2O/methanol/ TFA) to provide the TFA salt of Example 25 as a white foam (28.1 mg). LC (Cond.1): RT = 1.61 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_4$: 775.37; found 775.40; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_4$: 775.3720; found 775.3723

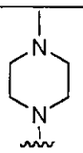
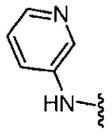
Example 25-1 to 25-5



Examples 25-1 to 25-5 were prepared from 25b and the appropriate carboxylic acid using standard amide forming conditions similar to that described for the preparation of example 1 from 1e. Examples 25-6 to 25-8 were prepared from 25b and the appropriate carbamoyl chloride or isocyanate.

Example Number	*Compound Name*	*R*	*RT (LC-Cond.); % homogeneity index; MS data*
25-1	(2R,2'R)-N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))ditetrahydro-2-furancarboxamide		RT = 5.68 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{52}H_{54}N_8O_6$: 887.06; Found: 887.58 $(M+H)^+$
25-2	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-methyl-1H-imidazole-5-carboxamide)		RT = 3.54 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{52}H_{50}N_{12}O_4$: 907.06; Found: 907.42 $(M+H)^+$
25-3	(2S,2'S)-N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(1-methyl-2-pyrrolidinecarboxamide)		RT = 3.1 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{54}H_{60}N_{10}O_4$ 913.14; Found: 913.54 $(M+H)^+$

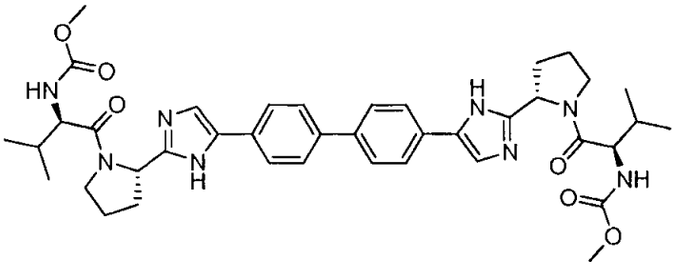
25-4	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(2-(3-pyridinyl)acetamide)		RT = 3.37 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{56}H_{52}N_{10}O_4$ 929.10 Found: 929.42 $(M+H)^+$
25-5	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(2-(dimethylamino)acetamide) (non-preferred name)		RT = 7.07 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{50}H_{56}N_{10}O_4$ 861.07 Found: 859.69 $(M+H)^+$
25-6	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))di(4-morpholinecarboxamide)		^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.86-2.18 (m, 6H), 2.23-2.39 (m, 2H), 3.20-3.40 (m, 8H), 3.40-3.61 (m, 8H), 3.90-4.19 (m, 4H), 5.27 (dd, J=8.09, 3.51 Hz, 2H), 5.37-5.63 (m, 2H), 6.92-7.11 (m, 3H), 7.30-7.45 (m, 5H), 7.44-7.56 (m, 4H), 7.83-8.04 (m, 8H), 8.15 (s, 2H), 14.29 (s, 2H); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid, RT = 6.01 minutes; LCMS: Anal. Calcd. for: $C_{52}H_{56}N_{10}O_6$ 917.09; Found:

			917.72 $(M+H)^+$
25-7	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(4-methyl-1-piperazinecarboxamide)		RT = 3.74 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{54}H_{62}N_{12}O_4$ 943.17; Found: 943.84 $(M+H)^+$
25-8	N,N''-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(3-(3-pyridinyl)urea)		^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.79-2.17 (m, 6H), 2.29 (d, *J*=9.77 Hz, 2H), 3.06-3.39 (m, 2H), 3.72-4.14 (m, 2H), 5.27 (dd, *J*=8.24, 2.75 Hz, 2H), 5.66 (d, *J*=7.02 Hz, 2H), 7.26-7.65 (m, 12H), 7.82-8.11 (m, 12H), 8.17 (s, 2H), 8.23-8.45 (m, 2H), 8.61-8.97 (m, 2H), 9.38 (s, 2H), 14.51 (s, 2H); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid, RT = 4.05 minutes; LCMS: Anal. Calcd. for: $C_{54}H_{50}N_{12}O_4$ 931.08; Found: 931.78 $(M+H)^+$.

5

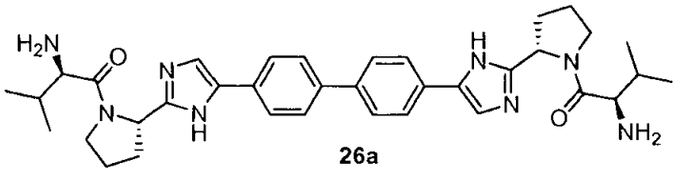
Example 26

methyl ((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate



Example 26, Step a

(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(3-methyl-1-oxo-2-butanamine)



26a

Diamine 26a was prepared starting from pyrrolidine 1e and BOC-D-Val-OH according to the procedure described for the synthesis of diamine 25b.

Example 26

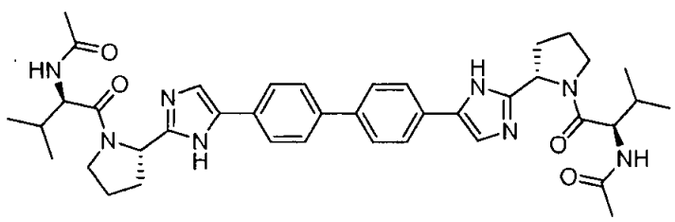
methyl ((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

Methyl chloroformate (18 μL, 0.23 mmol) was added to a THF (1.5 mL) solution of diamine 26a (30 mg, 0.048 mmol) and triethylamine (30 μL, 0.22 mmol), and the reaction mixture was stirred at ambient condition for 3 hours. The volatile components was removed *in vacuo*, and the residue was treated with NH_3/methanol (2 mL of 2 M) and stirred at ambient conditions for 15 minutes. All the volatile component was removed *in vacuo*, and the crude product was purified by reverse phase prep-HPLC (H_2O/methanol/TFA) to provide the TFA salt of Example 26 as a white solid (13.6 mg). LC (Cond.2): RT = 2.00 min; >98% homogeneity index;

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.39; found 739.67; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.3932; found 739.3966.

Example 27

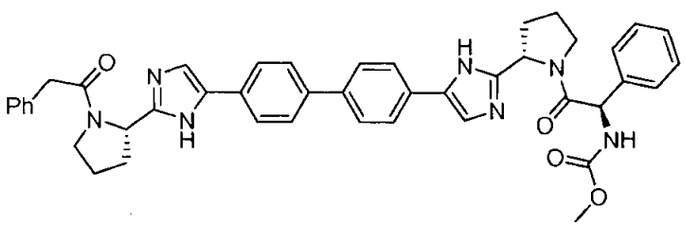
N-((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-acetamido-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)acetamide



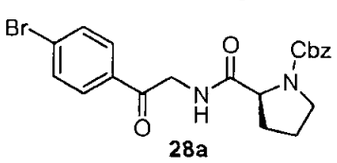
Diamine 26a was converted to Example 27 (TFA salt) according to a method described in the preparation of Example 25: LC (Cond.2): RT = 1.93min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_4$: 707.40; found 707.59; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_4$: 707.4033; found 707.4054.

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

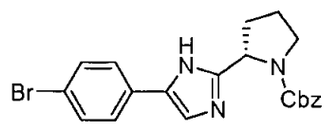


28a

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)

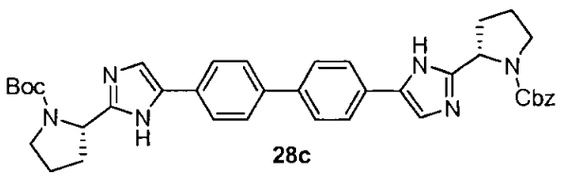
Flow rate: 1 mL/min

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)

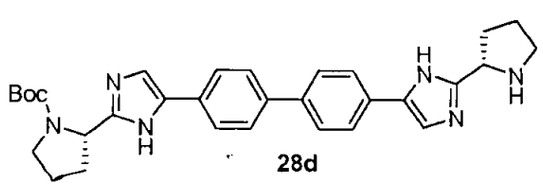


28c

$Pd(Ph_3P)_4$ (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.

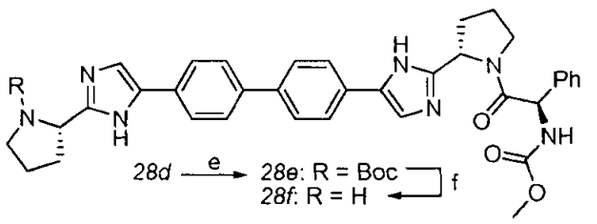
Example 28, Step e-f

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

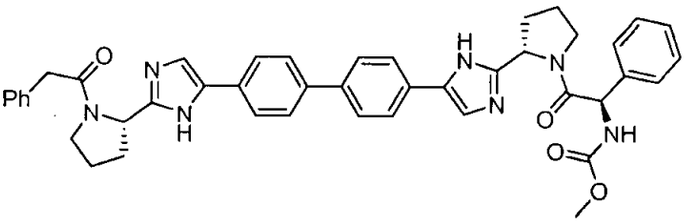


Step e: HATU (316.6 mg, 0.833 mmol) was added to a DMF (7.0 mL) solution of pyrrolidine 28d (427 mg, 0.813 mmol), *Cap*-4 (177.6 mg, 0.849 mmol) and diisopropylethylamine (0.32 mL, 1.84 mmol), and the reaction mixture was stirred for 45 minutes. The volatile component was removed *in vacuo*, and the 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

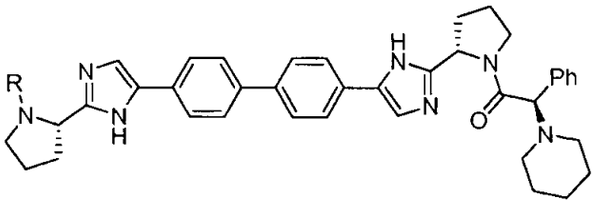
methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate



Amine 28f was converted to the TFA salt of Example 28 by employing the last step of the synthesis of Example 1. ^1H 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 28-1 to 28-4



Examples 28-1 through 28-4 (R groups shown in the table below) were prepared in similar fashion to example 28 *via* the intermediacy of intermediate 28d.

Example 28-1

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine

Cap-1 was appended, the Boc carbamate was removed with TFA or HCl , and *Cap*-14 was appended.

Example 28-2

1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine

Tetrahydrofuroic acid was appended, the Boc carbamate was removed with TFA or HCl , and *Cap*-14 was appended.

Example 28-3

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

Cap-40 was appended, the Boc carbamate was removed with TFA or HCl , and *Cap*-14 was appended.

Example 28-4

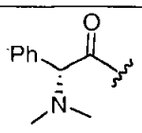
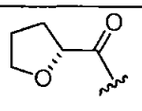
(1R)-1-(2-chlorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine

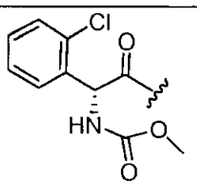
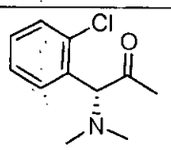
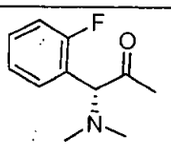
Cap-39 was appended, the Boc carbamate was removed with TFA or HCl , and *Cap*-14 was appended.

Example 28-5

(1R)-1-(2-fluorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine

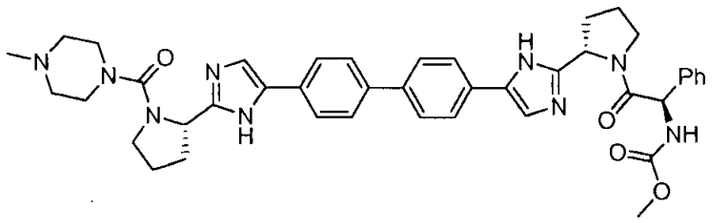
Cap-38 was appended, the Boc carbamate was removed with TFA or HCl , and *Cap*-14 was appended.

Example	*Compound Name*	*R*	*Data*
28-1	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{49}H_{54}N_8O_2$: 786; found: 787 $(M+H)^+$.
28-2	1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-		LCMS: Anal. Calcd. for

	((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine		$C_{44}H_{49}N_7O_3$: 723; found: 724 $(M+H)^+$.
28-3	methyl ((1R)-1-(2-chlorophenyl)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{49}H_{51}ClN_8O_4$: 850; found: 851 $(M+H)^+$.
28-4	(1R)-1-(2-chlorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{49}H_{53}ClN_8O_2$: 820; found: 821 $(M+H)^+$.
28-5	(1R)-1-(2-fluorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{49}H_{53}FN_8O_2$: 804; found: 805 $(M+H)^+$.

Example 29

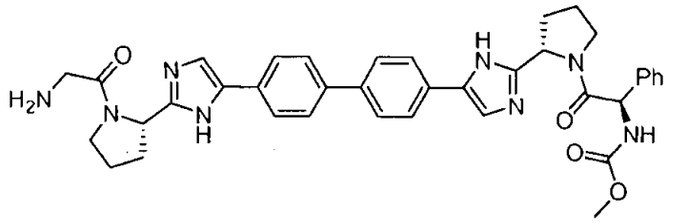
methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-methyl-1-piperazinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate



4-Methylpiperazine-1-carbonyl chloride/HCl (11.6 mg, 0.58 mmol) was added to a mixture of 28f (30 mg, 0.049 mmol), triethylamine (15 µl, 0.11 mmol) and THF (1.0 mL), and stirred at ambient conditions for 1 hour. The volatile component was removed *in vacuo*, and the residue was purified by a reverse phase HPLC (H_2O/methanol/TFA) to provide the TFA salt of Example 29 as a light yellow foam (29.3 mg). LC (Cond. 2): RT = 1.82 minutes, >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{48}N_9O_4$: 742.38; found 742.49.

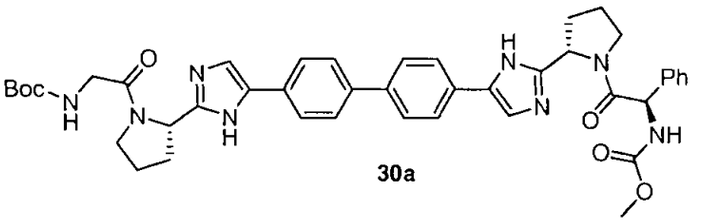
Example 30

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



Example 30, Step a

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(tert-butoxycarbonyl)glycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate



30a

Carbamate 30a was prepared from pyrrolidine 28f and Boc-Glycine by using the procedure described for the preparation of 25a from 1e. LC (Cond. 2): RT = 2.12 minutes, >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_6$: 773.38; found 773.46

Example 30

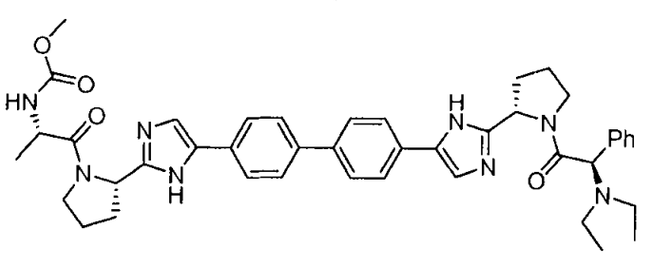
methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-glycyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate

Carbamate 30a was converted to Example 30 according to the procedure described for the preparation of 1e from 1d. LC (Cond. 2): RT = 1.81 minutes, >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{41}N_8O_4$: 673.33; found 673.43

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{41}N_8O_4$: 673.3251; found 673.3262

Example 30-1

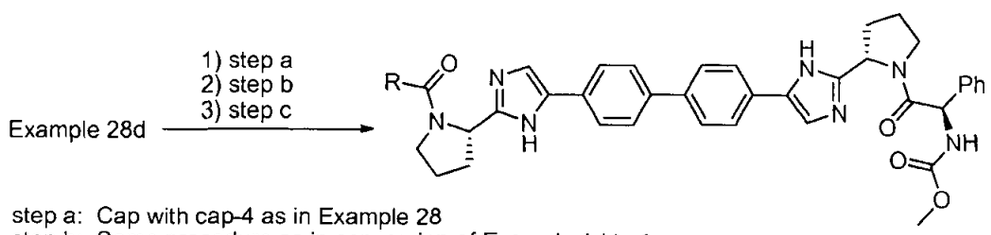
methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate



Example 30-1 was prepared in three steps from Example 28d. Step one: Append *Cap*-2 using the procedure describing the synthesis of 28e from 28d. Step two: Hydrolyze the Boc carbamate using the procedure describing the synthesis of 28f from 28e. Step three: Append *Cap*-52 using the procedure describing the synthesis of 28e from 28d. RT = 1.70 min (Cond. 1b); >95% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.40; found, 743.50. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.4033; found, 743.4053

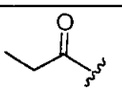
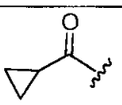
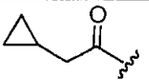
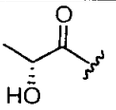
Substituting the appropriate acid chloride or carboxylic acid into Example 29 or 30, the following compounds (Example 31 to 84-87) were prepared as TFA salts.

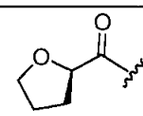
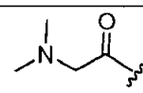
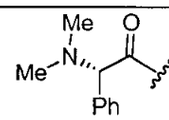
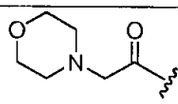
Example 31 to 84-88

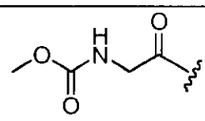
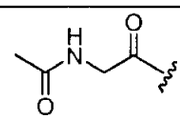
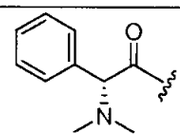
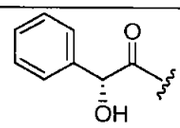


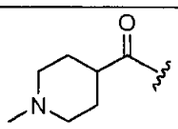
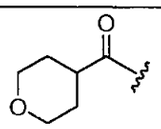
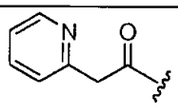
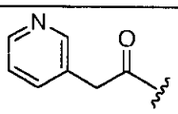
step a: Cap with cap-4 as in Example 28
step b: Same procedure as in conversion of Example 1d to 1e
step c: As in the last step of Example 1 using 1.1 equiv. of the appropriate carboxylic acid and HATU

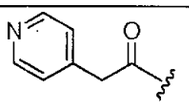
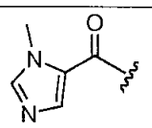
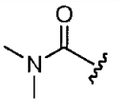
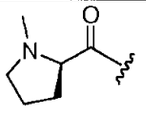
Example	*Compound Name*		*Retention time (LC-Condition); homogeneity index MS data*
31	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-acetyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.54 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{40}N_7O_4$: 658.31; found 658.42; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{40}N_7O_4$: 658.3142; found 658.3135

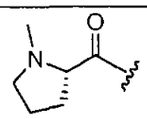
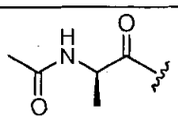
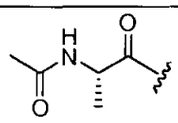
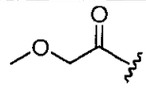
32	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-propionyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.57 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_4$: 672.33; found 672.46; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_4$: 672.3298; found 672.3299
33	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(cyclopropylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.59 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{42}N_7O_4$: 684.33; found 684.44; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{42}N_7O_4$: 684.3298; found 684.3324
34	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(cyclopropylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.61 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{42}N_7O_4$: 698.35; found 698.48; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{42}N_7O_4$: 698.3455; found 698.3489
35	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hydroxypropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.54 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_5$: 688.33; found 688.47

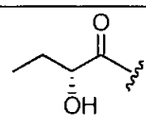
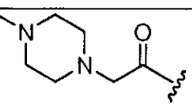
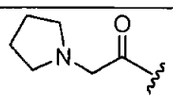
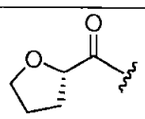
36	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.59 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}N_7O_5$: 714.34; found 714.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}N_7O_5$: 714.3404; found 714.3430
37	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dimethylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.48 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{45}N_8O_4$: 701.36; found 701.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{45}N_8O_4$: 701.3564; found 701.3553
38	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap-1*	1.20 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{49}N_8O_4$: 777.39; found 777.61; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{49}N_8O_4$: 777.3877; found 777.3909
39	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morpholinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.79 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_5$: 743.37; found 743.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_5$: 743.3669; found

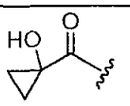
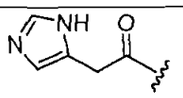
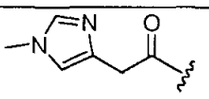
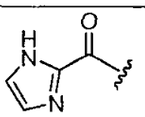
			743.3672
40	methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		1.92 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{43}N_8O_6$: 731.33; found 731.42; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{43}N_8O_6$: 731.3306; found 731.3333
41	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-acetylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.86 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{43}N_8O_5$: 715.34; found 715.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{43}N_8O_5$: 715.3356; found 715.3369
42	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.85 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{49}N_8O_4$: 777.39; found 777.56
43	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.96 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{44}N_7O_5$: 750.34; found 750.51; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{44}N_7O_5$: 750.3404; found

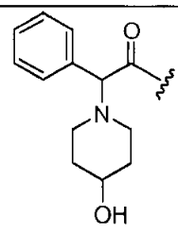
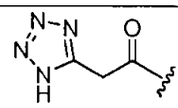
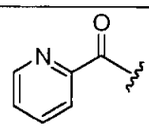
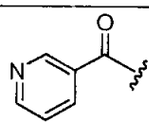
			750.3437
44	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-methyl-4-piperidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.78 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_4$: 741.39; found 741.55; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_4$: 741.3877; found 741.3893
45	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(tetrahydro-2H-pyran-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.87 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}N_7O_5$: 728.36; found 728.52; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}N_7O_5$: 728.3560; found 728.3587
46	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.80 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{43}N_8O_4$: 735.34; found 735.51; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{43}N_8O_4$: 735.3407; found 735.3416
47	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.76 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{43}N_8O_4$: 735.34; found 735.52

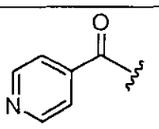
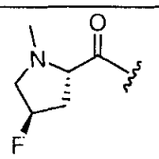
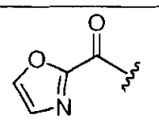
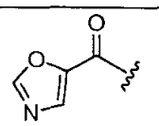
48	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.77 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{43}N_8O_4$: 735.34; found 735.50; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{43}N_8O_4$: 735.3407; found 735.3405
49	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-methyl-1H-imidazol-5-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.77 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{42}N_9O_4$: 724.34; found 724.51; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{42}N_9O_4$: 724.3360; found 724.3380
50	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(dimethylcarbamoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.91 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{43}N_8O_4$: 687.34; found 687.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{43}N_8O_4$: 687.3407; found 687.3414
51	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-methyl-D-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap-10*	1.79 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.37; found 727.34; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.3720; found

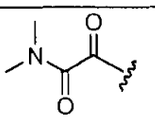
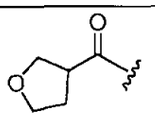
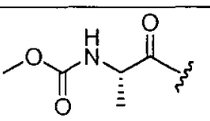
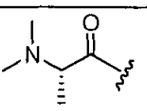
			727.3719
52	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-methyl-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *enantiomer of Cap-10*	1.77 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.37; found 727.33; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.3720; found 727.3738
53	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-acetyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.92 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_5$: 729.35; found 729.33; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_5$: 729.3513; found 729.3530
54	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-acetyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.87 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_5$: 729.35; found 729.33
55	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(methoxyacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.89 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_5$: 688.32; found 688.28; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_5$: 688.3247; found 688.3231

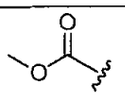
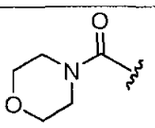
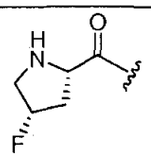
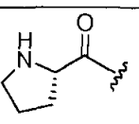
56	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hydroxybutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.91 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{44}N_7O_5$: 702.34; found 702.30; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{44}N_7O_5$: 702.3404; found 702.3393
57	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-methyl-1-piperazinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.80 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{50}N_9O_4$: 756.40; found 756.36; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{50}N_9O_4$: 756.3986; found 756.3965
58	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-pyrrolidinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.82 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.37; found 727.33; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.3720; found 727.3696
59	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.94 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{43}N_7O_5$: 714.34; found 714.24

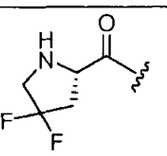
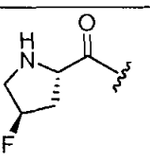
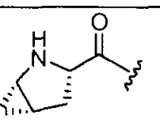
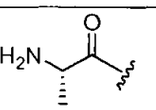
60	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-hydroxycyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.93 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{42}N_7O_5$: 700.32; found 700.23; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{42}N_7O_5$: 700.3247; found 700.3265
61	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-5-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.84 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{42}N_9O_4$: 724.34; found 724.21; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{42}N_9O_4$: 724.3360; found 724.3365
62	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-methyl-1H-imidazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.85 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{44}N_9O_4$: 738.35; found 738.22; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{44}N_9O_4$: 738.3516; found 738.3539
63	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-2-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.95 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{41}N_9O_4$: 710.32; found 710.17

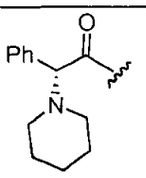
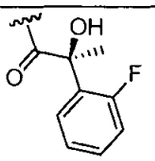
64	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-hydroxy-1-piperidinyl)(phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap-8* A single diastereomer	1.92 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{49}H_{53}N_8O_5$: 833.41; found 833.32; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{49}H_{53}N_8O_5$: 833.4139; found 833.4163
65	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-tetrazol-5-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.92 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{40}N_{11}O_4$: 726.33; found 726.22; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{40}N_{11}O_4$: 726.3265; found 726.3290
67	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-pyridinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		2.03 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_8O_4$: 721.33; found 721.31; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_8O_4$: 721.3251; found 721.3247
68	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-pyridinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.91 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_8O_4$: 721.33; found 721.31; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_8O_4$:

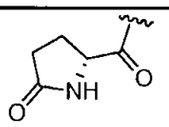
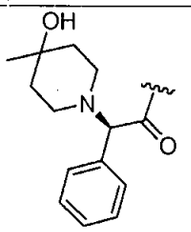
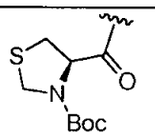
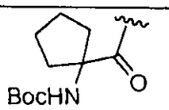
			721.3251; found 721.3226
69	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-isonicotinoyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.89 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_8O_4$: 721.33; found 721.29; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_8O_4$: 721.3251; found 721.3251
70	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4R)-4-fluoro-1-methyl-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-11	1.84 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}FN_8O_4$: 745.36; found 745.27; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}FN_8O_4$: 745.3626; found 745.3658
71	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-2-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.97 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{39}N_8O_5$: 711.30; found 711.27
72	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-5-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.95 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{39}N_8O_5$: 711.30; found 711.27; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{39}N_8O_5$: 711.3043; found

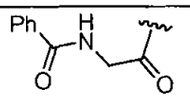
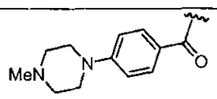
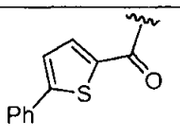
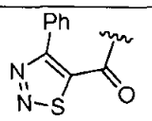
			711.3078
73	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(oxo)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.92 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{43}N_8O_5$: 715.34; found 715.40
74	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(tetrahydro-3-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.91 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}N_7O_5$: 714.34; found 714.39; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}N_7O_5$: 714.3404; found 714.3433
75	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-12	1.94 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_6$: 745.35 found 745.34; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_6$: 745.3462; found 745.3486
76	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dimethyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.80 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_4$ 715.37; found 715.35 ; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_4$ 715.3720; found 715.3737

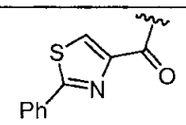
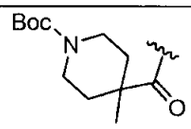
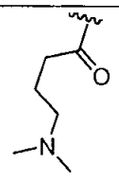
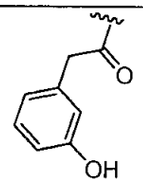
77	methyl (2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate		1.97 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{40}N_7O_5$: 674.31; found 674.66; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{40}N_7O_5$: 674.3091; found 674.3110
78	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morpholinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.95 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_5$: 729.35; found 729.40; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_5$: 729.3513; found 729.3502
79	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4S)-4-fluoro-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.80 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}FN_8O_4$: 731.84; found 731.26
80	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-L-prolyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.84 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_4$: 713.36; found 713.36; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{45}N_8O_4$: 713.3564; found 713.3563

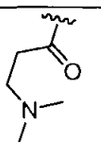
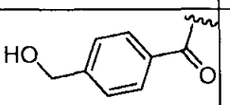
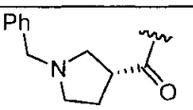
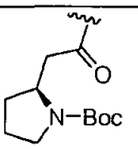
81	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4,4-difluoro-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.88 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{43}F_2N_8O_4$: 749.34; found 749.31; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{43}F_2N_8O_4$: 749.3375; found 749.3390
82	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4R)-4-fluoro-L-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.83 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}FN_8O_4$: 731.35; found 731.37; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}FN_8O_4$: 731.3470; found 731.3502
83	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1S,3S,5S)-2-azabicyclo[3.1.0]hex-3-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.82 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{45}N_8O_4$: 725.36; found 725.39; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{45}N_8O_4$: 725.3564; found 725.3574
84	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-L-alanyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.82 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{43}N_8O_4$: 687.34; found 687.32; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{43}N_8O_4$: 687.3407; found

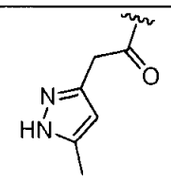
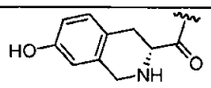
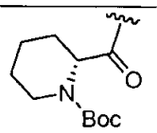
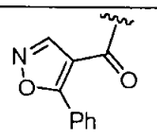
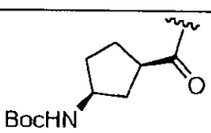
			687.3435
84-1	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate	 *Cap-14*	^{1}HNMR (400 MHz, CD_3OD) δ 7.90-7.85 (m, 9H), 7.81-7.79 (m, 1H), 7.63-7.57 (m, 5H), 7.45-7.32 (m, 6H), 5.51 (s, 1H), 5.45 (s, 1H), 5.33-5.29 (m, 2H), 4.06-4.01 (m, 2H), 3.63 (d, J = 4.04 Hz, 3H), 3.59-3.50 (m, 2H), 3.19-3.12 (m, 1H), 3.07-3.01 (m, 1H), 2.93-2.76 (m, 2H), 2.57-2.51 (m, 1H), 2.40-2.31 (m, 2H), 2.22-2.06 (m, 4H), 2.00-1.90 (m, 3H), 1.84-1.64 (m, 4H), 1.52-1.43 (m, 2H); LCMS: Anal. Calcd. for $C_{49}H_{52}N_8O_4$: 816; found: 817 $(M+H)^+$.
84-2	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(2-fluorophenyl)-2-hydroxypropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		^{1}HNMR (400 MHz, CD_3OD) δ 7.89-7.85 (m, 8H), 7.81-7.73 (2H), 7.67-7.65 (m, 1H), 7.45-7.26 (m, 7H), 7.13-7.08 (m, 1H), 6.94-6.89 (m, 0.5H), 6.72-6.67 (0.5H), 6.09-6.07 (m, 0.4H), 5.51 (s, 1H), 5.32-5.25 (m, 1.6H), 4.08-3.95 (m, 2H), 3.85-3.79 (1H), 3.64-3.63 (m, 3H), 3.56-3.49 (1H), 3.09-3.03 (m, 1H), 2.59-2.50 (m, 1H),

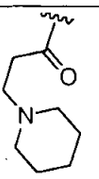
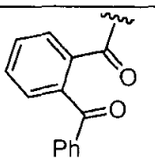
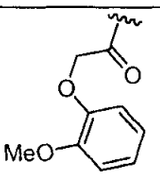
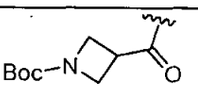
			2.42-2.33 (m, 2H), 2.21-2.00 (m, 6H), 1.82-1.74 (m, 1H), 1.66 (d, *J* = 4.55 Hz, 3H); LCMS: Anal. Calcd. for $C_{45}H_{46}FN_7O_3$: 781; found: 782 $(M+H)^+$.
84-3	methyl ((1R)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(5-oxo-D-prolyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{42}N_8O_5$: 726; found: 727 $(M+H)^+$.
84-4	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(4-hydroxy-4-methyl-1-piperidinyl)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-15	LCMS: Anal. Calcd. for $C_{50}H_{54}N_8O_5$: 846; found: 847 $(M+H)^+$.
84-5	tert-butyl (4R)-4-(((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-pyrrolidinyl)carbonyl)-1,3-thiazolidine-3-carboxylate		LCMS: Anal. Calcd. for $C_{45}H_{50}N_8O_6S$: 830; found: 831 $(M+H)^+$.
84-6	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-((tert-butoxycarbonyl)amino)cyclopentyl)carbonyl)-2-		LCMS: Anal. Calcd. for $C_{47}H_{54}FN_8O_6$: 826; found: 827 $(M+H)^+$.

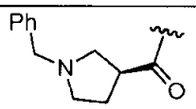
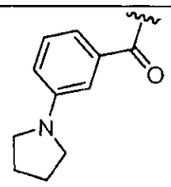
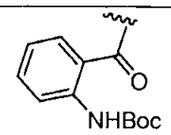
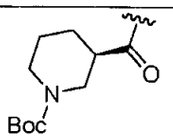
	pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		
84-7	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-benzoylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{44}FN_8O_5$: 776; found: 777 $(M+H)^+$.
84-8	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(4-methyl-1-piperazinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{51}N_9O_4$: 817; found: 818 $(M+H)^+$.
84-9	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-phenyl-2-thienyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{47}H_{43}N_7O_4S$: 801; found: 802 $(M+H)^+$.
84-10	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-phenyl-1,2,3-thiadiazol-5-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{41}N_9O_4S$: 803; found: 804 $(M+H)^+$.

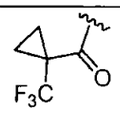
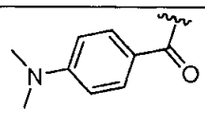
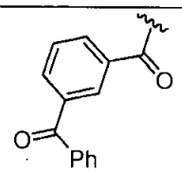
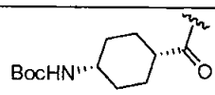
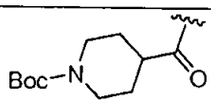
84-11	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-phenyl-1,3-thiazol-4-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{42}N_8O_4S$: 802; found: 803 $(M+H)^+$.
84-12	tert-butyl 4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-4-methyl-1-piperidinecarboxylate		LCMS: Anal. Calcd. for $C_{48}H_{56}N_8O_6$: 840; found: 841 $(M+H)^+$.
84-13	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(dimethylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{48}N_8O_4$: 728; found: 729 $(M+H)^+$.
84-14	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-hydroxyphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{43}N_7O_5$: 749; found: 750 $(M+H)^+$.

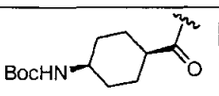
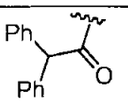
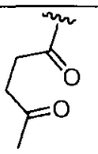
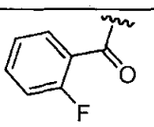
84-15	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dimethyl-beta-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{46}N_8O_4$: 714; found: 715 $(M+H)^+$.
84-16	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(hydroxymethyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{43}N_7O_5$: 749; found: 750 $(M+H)^+$.
84-17	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3R)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{50}N_8O_4$: 802; found: 803 $(M+H)^+$.
84-18	tert-butyl (2S)-2-(2-((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-pyrrolidinyl)-2-oxoethyl)-1-pyrrolidinecarboxylate		LCMS: Anal. Calcd. for $C_{47}H_{54}N_8O_6$: 826; found: 827 $(M+H)^+$.

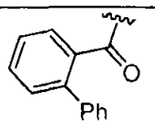
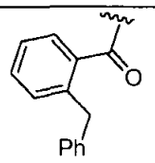
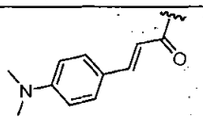
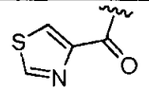
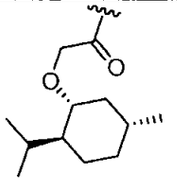
84-19	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-methyl-1H-pyrazol-3-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{43}N_9O_4$: 737; found: 738 $(M+H)^+$.
84-20	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3S)-7-hydroxy-1,2,3,4-tetrahydro-3-isoquinolinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{46}N_8O_5$: 790; found: 791 $(M+H)^+$.
84-21	tert-butyl (2R)-2-(((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-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		LCMS: Anal. Calcd. for $C_{47}H_{54}N_8O_6$: 826; found: 827 $(M+H)^+$.
84-22	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-phenyl-4-isoxazolyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{42}N_8O_5$: 786; found: 787 $(M+H)^+$.
84-23	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1R,3S)-3-((tert-butoxycarbonyl)amino)cyclop		LCMS: Anal. Calcd. for $C_{47}H_{54}N_8O_6$: 826; found: 827 $(M+H)^+$.

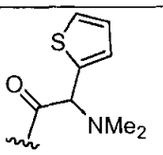
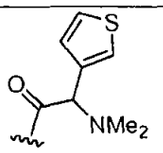
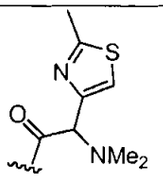
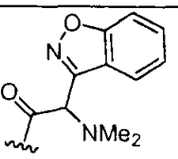
	entyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		
84-24	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-piperidinyl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{50}N_8O_4$: 754; found: 755 $(M+H)^+$.
84-25	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-benzoylbenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{50}H_{45}N_7O_5$: 823; found: 824 $(M+H)^+$.
84-26	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methoxyphenoxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_6$: 779; found: 780 $(M+H)^+$.
84-27	tert-butyl 3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-		LCMS: Anal. Calcd. for $C_{45}H_{50}N_8O_6$: 798; found: 799 $(M+H)^+$.

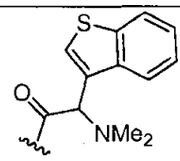
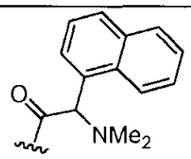
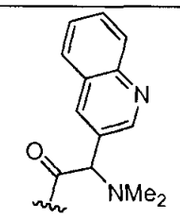
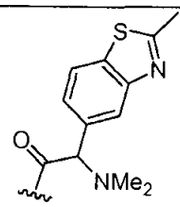
	yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate		
84-28	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3S)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{50}N_8O_4$: 802; found: 803 $(M+H)^+$.
84-29	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-pyrrolidinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{47}H_{48}N_8O_4$: 788; found: 789 $(M+H)^+$.
84-30	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-((tert-butoxycarbonyl)amino)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{50}N_8O_6$: 834; found: 835 $(M+H)^+$.
84-31	tert-butyl (3R)-3-(((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-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		LCMS: Anal. Calcd. for $C_{47}H_{54}N_8O_6$: 826; found: 827 $(M+H)^+$.

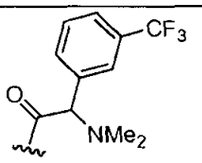
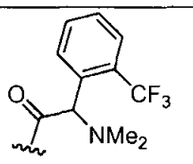
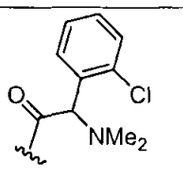
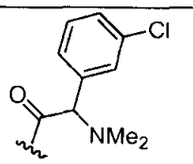
84-32	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-(trifluoromethyl)cyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{40}F_3N_7O_4$: 751; found: 752 $(M+H)^+$.
84-33	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(dimethylamino)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{46}N_8O_4$: 762; found: 763 $(M+H)^+$.
84-34	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-benzoylbenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{50}H_{45}N_7O_5$: 823; found: 824 $(M+H)^+$.
84-35	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-((tert-butoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{56}N_8O_6$: 840; found: 841 $(M+H)^+$.
84-36	tert-butyl 4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-		LCMS: Anal. Calcd. for $C_{47}H_{54}N_8O_6$: 826; found: 827 $(M+H)^+$.

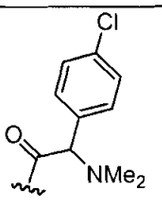
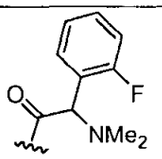
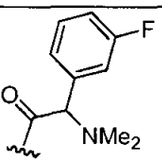
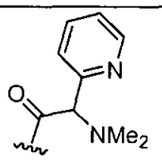
	1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		
84-37	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-((tert-butoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{56}N_8O_6$: 840; found: 841 $(M+H)^+$.
84-38	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(diphenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{50}H_{47}N_7O_4$: 809; found: 810 $(M+H)^+$.
84-39	methyl ((1R)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-oxopentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{43}N_7O_5$: 713; found: 714 $(M+H)^+$.
84-40	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-fluorobenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{43}H_{40}FN_7O_4$: 737; found: 738 $(M+H)^+$.

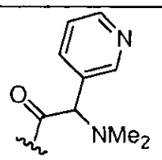
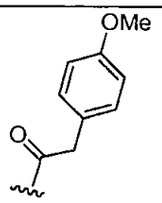
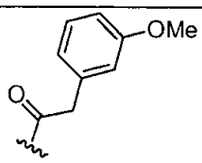
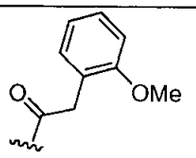
84-41	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-biphenylylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{49}H_{45}N_7O_4$: 795; found: 796 $(M+H)^+$.
84-42	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-benzylbenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{50}H_{47}N_7O_4$: 809; found: 810 $(M+H)^+$.
84-43	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2E)-3-(4-(dimethylamino)phenyl)-2-propenoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{47}H_{48}N_8O_4$: 788; found: 789 $(M+H)^+$.
84-44	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-thiazol-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{40}H_{38}N_8O_4S$: 726; found: 727 $(M+H)^+$.
84-45	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-		LCMS: Anal. Calcd. for $C_{48}H_{57}N_7O_5$: 811; found: 812 $(M+H)^+$.

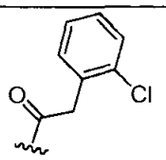
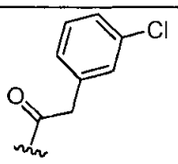
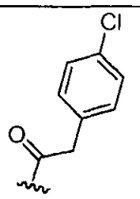
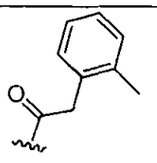
	yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		
84-46	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-thienyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-32	LCMS: Anal. Calcd. for $C_{44}H_{46}N_8O_4S$: 782; found: 782 $(M+H)^+$.
84-47	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(3-thienyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-33	LCMS: Anal. Calcd. for $C_{44}H_{46}N_8O_4S$: 782; found: 782 $(M+H)^+$.
84-48	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-methyl-1,3-thiazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-31	LCMS: Anal. Calcd. for $C_{44}H_{47}N_9O_4S$: 797; found: 798 $(M+H)^+$.
84-49	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,2-benzisoxazol-3-yl(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-	 *Cap*-34	LCMS: Anal. Calcd. for $C_{47}H_{47}N_9O_5$: 817; found: 818 $(M+H)^+$.

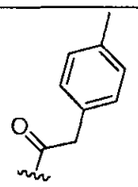
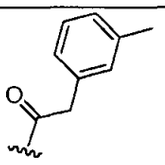
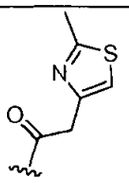
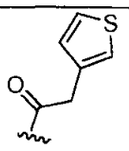
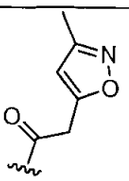
	2-oxo-1-phenylethyl)carbamate		
84-50	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-benzothiophen-3-yl(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-35	LCMS: Anal. Calcd. for $C_{48}H_{48}N_8O_4S$: 832; found: 833 $(M+H)^+$.
84-51	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(1-naphthyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-23	LCMS: Anal. Calcd. for $C_{50}H_{50}N_8O_4$: 826; found: 827 $(M+H)^+$.
84-52	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(3-quinolinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-37	LCMS: Anal. Calcd. for $C_{49}H_{49}N_9O_4$: 827; found: 828 $(M+H)^+$.
84-53	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-methyl-1,3-benzothiazol-5-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-	 *Cap*-36	LCMS: Anal. Calcd. for $C_{48}H_{49}N_9O_4S$: 847; found: 848 $(M+H)^+$.

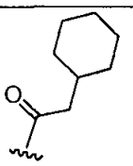
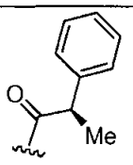
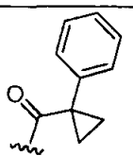
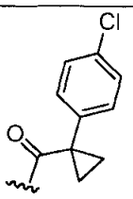
	2-oxo-1-phenylethyl)carbamate		
84-54	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(3-(trifluoromethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-24	LCMS: Anal. Calcd. for $C_{47}H_{47}F_3N_8O_4$: 844; found: 845 $(M+H)^+$.
84-55	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-(trifluoromethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-25	LCMS: Anal. Calcd. for $C_{47}H_{47}F_3N_8O_4$: 844; found: 845 $(M+H)^+$.
84-56	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-chlorophenyl)(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-29	LCMS: Anal. Calcd. for $C_{46}H_{47}ClN_8O_4$: 810; found: 811 $(M+H)^+$.
84-57	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-chlorophenyl)(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-	 *Cap*-28	LCMS: Anal. Calcd. for $C_{46}H_{47}ClN_8O_4$: 810; found: 811 $(M+H)^+$.

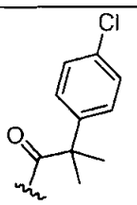
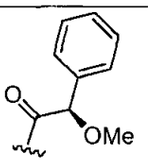
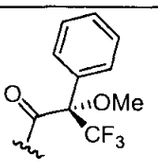
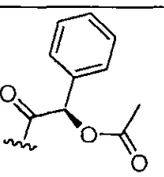
	phenylethyl)carbamate		
84-58	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-chlorophenyl)(dimethylamino) acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-30	LCMS: Anal. Calcd. for $C_{46}H_{47}ClN_8O_4$: 810; found: 811 $(M+H)^+$.
84-59	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-26	LCMS: Anal. Calcd. for $C_{46}H_{47}FN_8O_4$: 794; found: 795 $(M+H)^+$.
84-60	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(3-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-27	LCMS: Anal. Calcd. for $C_{46}H_{47}FN_8O_4$: 794; found: 795 $(M+H)^+$.
84-61	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimethylamino)(2-pyridinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-	 *Cap*-20	LCMS: Anal. Calcd. for $C_{45}H_{47}N_9O_4$: 777; found: 778 $(M+H)^+$.

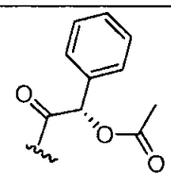
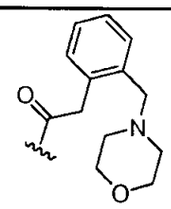
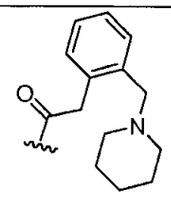
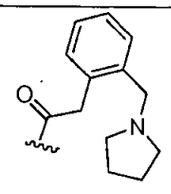
	phenylethyl)carbamate		
84-62	methyl ((1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((dimethylamino)(3-pyridinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap*-19	LCMS: Anal. Calcd. for $C_{45}H_{47}N_9O_4$: 777; found: 778 $(M+H)^+$.
84-63	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-methoxyphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_5$: 763; found: 764 $(M+H)^+$.
84-64	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-methoxyphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_5$: 763; found: 764 $(M+H)^+$.
84-65	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methoxyphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_5$: 763; found: 764 $(M+H)^+$.

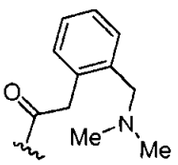
84-66	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-chlorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{42}ClN_7O_4$: 767; found: 768 $(M+H)^+$.
84-67	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-chlorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{42}ClN_7O_4$: 767; found: 768 $(M+H)^+$.
84-68	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-chlorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{42}ClN_7O_4$: 767; found: 768 $(M+H)^+$.
84-69	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methylphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_4$: 747; found: 748 $(M+H)^+$.

84-70	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-methylphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_4$: 747; found: 748 $(M+H)^+$.
84-71	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-methylphenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_4$: 747; found: 748 $(M+H)^+$.
84-72	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methyl-1,3-thiazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{42}N_8O_4S$: 754; found: 755 $(M+H)^+$.
84-73	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-thienylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{41}N_7O_4S$: 739; found: 740 $(M+H)^+$.
84-74	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-methyl-5-isoxazolyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-		LCMS: Anal. Calcd. for $C_{42}H_{42}N_8O_5$: 738; found: 739 $(M+H)^+$.

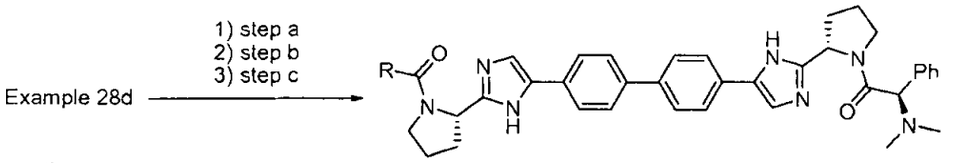
	yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		
84-75	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(cyclohexylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{49}N_7O_4$: 739; found: 740 $(M+H)^+$.
84-76	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_4$: 747; found: 748 $(M+H)^+$.
84-77	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-phenylcyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{45}N_7O_4$: 759; found: 760 $(M+H)^+$.
84-78	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-(4-chlorophenyl)cyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{44}ClN_7O_4$: 793; found: 794 $(M+H)^+$.

84-79	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-(4-chlorophenyl)-2-methylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{46}ClN_7O_4$: 795; found: 796 $(M+H)^+$.
84-80	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{45}N_7O_5$: 763; found: 764 $(M+H)^+$.
84-81	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{44}F_3N_7O_5$: 831; found: 832 $(M+H)^+$.
84-82	(1R)-2-((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-pyrrolidinyl)-2-oxo-1-phenylethyl acetate		LCMS: Anal. Calcd. for $C_{46}H_{45}N_7O_6$: 791; found: 792 $(M+H)^+$.

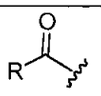
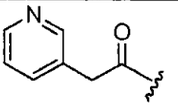
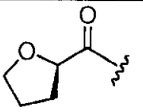
84-83	(1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl acetate		LCMS: Anal. Calcd. for $C_{46}H_{45}N_7O_6$: 791; found: 792 $(M+H)^+$.
84-84	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-(4-morpholinylmethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap-41*	LCMS: Anal. Calcd. for $C_{49}H_{52}N_8O_5$: 832; found: 833 $(M+H)^+$.
84-85	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-(1-piperidinylmethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate	 *Cap-42*	LCMS: Anal. Calcd. for $C_{50}H_{54}N_8O_4$: 830; found: 831 $(M+H)^+$.
84-86	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-(1-pyrrolidinylmethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate	 *Cap-43*	LCMS: Anal. Calcd. for $C_{49}H_{52}N_8O_4$: 816; found: 816 $(M+H)^+$.

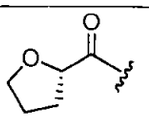
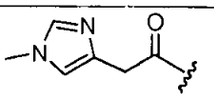
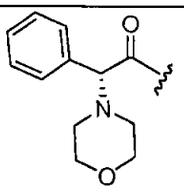
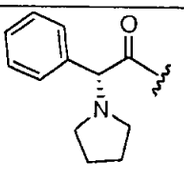
84-87	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-((dimethylamino)methyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 *Cap-44*	LCMS: Anal. Calcd. for $C_{47}H_{50}N_8O_4$: 790; found: 791 $(M+H)^+$.

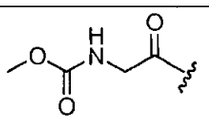
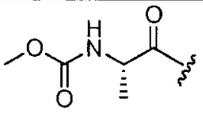
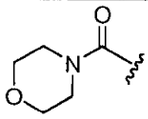
Examples 85-94

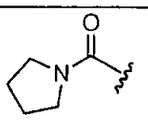
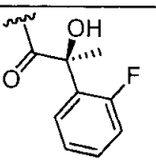


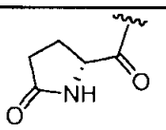
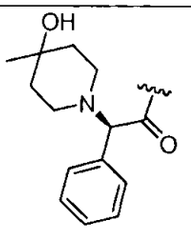
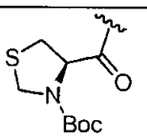
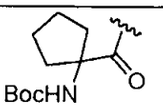
step a: Cap with cap-1 as in Example 28
step b: Same procedure as in conversion of Example 1d to 1e
step c: As in the last step of Example 1 using 1.1 equiv. of the appropriate carboxylic acid and HATU

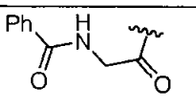
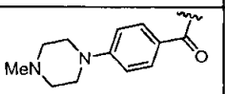
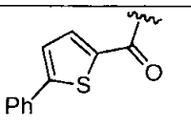
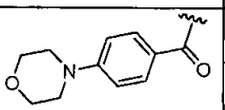
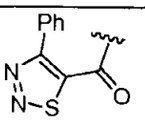
Example	*Compound Name*		*Retention time (LC-Condition); homogeneity index MS data*
85	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		1.64 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{45}N_8O_2$: 705.37; found 705.43; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{45}N_8O_2$: 705.3665; found 705.3675
86	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-		1.73 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{46}N_7O_3$: 684.37; found 684.44; HRMS: Anal.

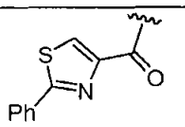
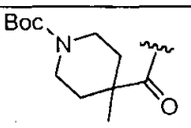
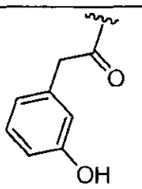
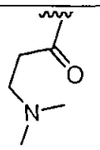
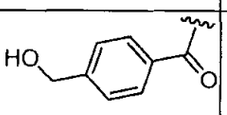
	yl)-1-pyrrolidinyl)ethanamine		Calcd. for $[M+H]^+$ $C_{41}H_{46}N_7O_3$: 684.3662; found 684.3671
87	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		1.12 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{46}N_7O_3$: 684.37; found 684.68; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{46}N_7O_3$: 684.3662; found 684.3692
88	(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-methyl-1H-imidazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine		1.66 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}N_9O_2$: 708.38; found 708.36
89	(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(4-morpholinyl)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine	 *Cap-6*	1.70 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{45}N_8O_4$: 701.36; found 701.34; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{45}N_8O_4$: 701.3564; found 701.3576
90	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-		1.80 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{53}N_8O_2$:

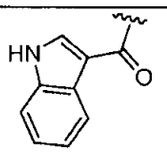
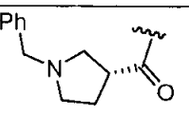
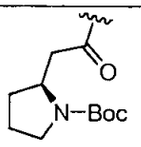
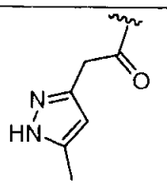
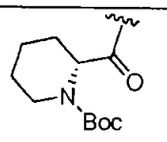
	pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine	*Cap-5*	773.43; found 773.42; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{53}N_6O_2$: 773.4291; found 773.4309
91	methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		1.66 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}N_9O_2$: 708.38; found 708.36; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{46}N_9O_2$: 708.3744; found 708.3770
92	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 *Cap-12*	1.73 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_4$: 715.37; found 715.41; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_4$: 715.3720; found 715.3729
93	(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morpholinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine		1.76 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_3$: 699.38; found 699.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_3$: 699.3771; found

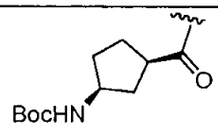
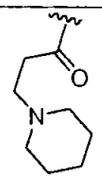
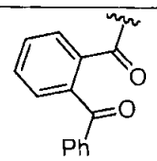
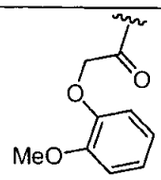
			699.3803
94	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-pyrrolidinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		1.86 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_2$: 683.38; found 683.46; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_2$: 683.3822; found 683.3835
94-1	(2S)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-(2-fluorophenyl)-1-oxo-2-propanol		^{1}HNMR (400 MHz, CD_3OD) δ 7.90-7.84 (m, 9H), 7.79-7.73 (m, 2H), 7.67-7.65 (m, 1H), 7.63-7.52 (m, 5H), 7.39-7.36 (m, 1H), 7.30-7.26 (m, 1H), 7.13-7.08 (m, 1H), 6.93-6.88 (m, 0.5H), 6.72-6.67 (m, 0.5H), 5.51 (s, 0.2H), 5.46 (s, 0.8H), 5.33-5.30 (m, 1H), 5.28-5.24 (m, 1H), 4.05-3.94 (m, 2H), 3.84-3.73 (m, 1H), 3.69-3.55 (m, 1H), 3.21-3.04 (m, 2H), 2.79 (br s, 6H), 2.39-2.33 (m, 2H), 2.21-1.93 (m, 5H), 1.65 (d, J = 4.55 Hz, 3H).; LCMS: Anal. Calcd. for $C_{45}H_{46}FN_7O_3$:

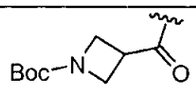
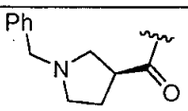
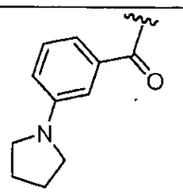
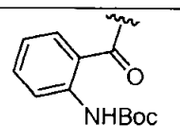
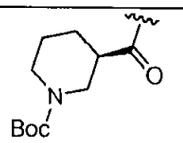
			751; found: 752 $(M+H)^+$.
94-2	(5R)-5-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-pyrrolidinone		LCMS: Anal. Calcd. for $C_{41}H_{44}N_8O_3$: 696; found: 697 $(M+H)^+$.
94-3	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)-4-methyl-4-piperidinol	 *Cap-15*	LCMS: Anal. Calcd. for $C_{50}H_{56}N_8O_3$: 816; found: 817 $(M+H)^+$.
94-4	tert-butyl (4R)-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1,3-thiazolidine-3-carboxylate		LCMS: Anal. Calcd. for $C_{45}H_{52}N_8O_4S$: 800; found: 801 $(M+H)^+$.
94-5	tert-butyl (1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate		LCMS: Anal. Calcd. for $C_{47}H_{56}FN_8O_4$: 796; found: 797 $(M+H)^+$.

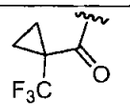
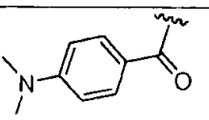
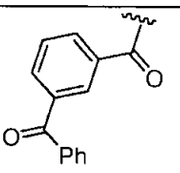
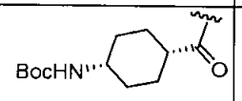
94-6	N-(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)benzamide		LCMS: Anal. Calcd. for $C_{45}H_{46}FN_8O_3$: 746; found: 747 $(M+H)^+$.
94-7	(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(4-methyl-1-piperazinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{48}H_{53}N_9O_2$: 787; found: 788 $(M+H)^+$.
94-8	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-phenyl-2-thienyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{47}H_{45}N_7O_2S$: 771; found: 772 $(M+H)^+$.
94-9	(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(4-morpholinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{47}H_{50}N_8O_3$: 774; found: 775 $(M+H)^+$.
94-10	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-phenyl-1,2,3-thiadiazol-5-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{45}H_{43}N_9O_2S$: 773; found: 774 $(M+H)^+$.

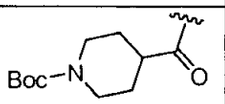
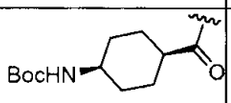
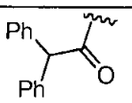
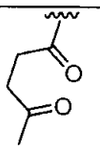
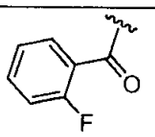
94-11	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-phenyl-1,3-thiazol-4-yl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{46}H_{44}N_8O_2S$: 772; found: 773 $(M+H)^+$.
94-12	tert-butyl 4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-4-methyl-1-piperidinecarboxylate		LCMS: Anal. Calcd. for $C_{48}H_{58}N_8O_4$: 810; found: 811 $(M+H)^+$.
94-13	3-(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)phenol		LCMS: Anal. Calcd. for $C_{44}H_{45}N_7O_3$: 719; found: 720 $(M+H)^+$.
94-14	3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-3-oxo-1-propanamine		LCMS: Anal. Calcd. for $C_{41}H_{48}N_8O_2$: 684; found: 685 $(M+H)^+$.
94-15	(4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-		LCMS: Anal. Calcd. for $C_{44}H_{45}N_7O_3$: 719; found: 720 $(M+H)^+$.

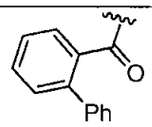
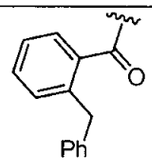
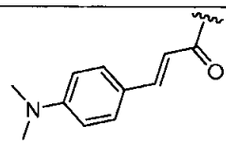
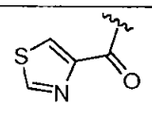
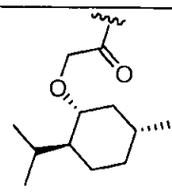
	pyrrolidinyl)carbonyl)phenyl)methanol		
94-16	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-indol-3-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{45}H_{44}N_8O_2$: 728; found: 729 $(M+H)^+$.
94-17	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3R)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{48}H_{52}N_8O_2$: 772; found: 773 $(M+H)^+$.
94-18	tert-butyl (2S)-2-(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)-1-pyrrolidinecarboxylate		LCMS: Anal. Calcd. for $C_{47}H_{56}N_8O_4$: 796; found: 797 $(M+H)^+$.
94-19	(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-methyl-1H-pyrazol-3-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{42}H_{45}N_9O_2$: 707; found: 708 $(M+H)^+$.
94-20	tert-butyl (2R)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-		LCMS: Anal. Calcd. for $C_{47}H_{56}N_8O_4$: 796; found: 797 $(M+H)^+$.

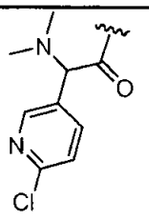
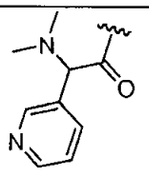
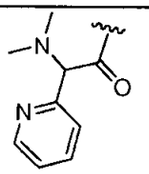
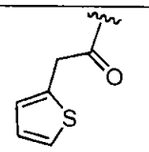
	phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		
94-21	tert-butyl ((1S,3R)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate		LCMS: Anal. Calcd. for $C_{47}H_{56}N_8O_4$: 796; found: 797 $(M+H)^+$.
94-22	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-piperidinyl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{44}H_{52}N_8O_2$: 724; found: 725 $(M+H)^+$.
94-23	(2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)(phenyl)methanone		LCMS: Anal. Calcd. for $C_{50}H_{47}N_7O_3$: 793; found: 794 $(M+H)^+$.
94-24	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methoxyphenoxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{45}H_{47}N_7O_4$: 749; found: 750 $(M+H)^+$.

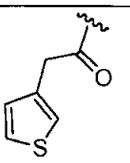
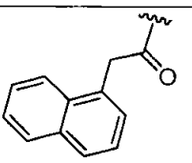
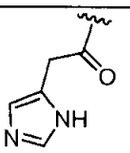
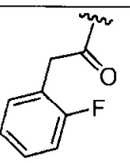
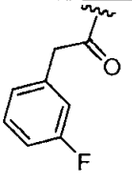
94-25	tert-butyl 3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate		LCMS: Anal. Calcd. for $C_{45}H_{52}N_8O_4$: 768; found: 769 $(M+H)^+$.
94-26	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3S)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{48}H_{52}N_8O_2$: 772; found: 773 $(M+H)^+$.
94-27	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-pyrrolidinyl)benzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{47}H_{50}N_8O_2$: 758; found: 759 $(M+H)^+$.
94-28	tert-butyl (2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{52}N_8O_4$: 804; found: 805 $(M+H)^+$.
94-29	tert-butyl (3R)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-		LCMS: Anal. Calcd. for $C_{47}H_{56}N_8O_4$: 796; found: 797 $(M+H)^+$.

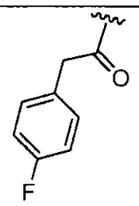
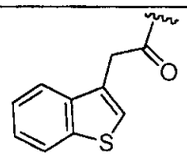
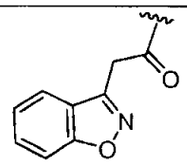
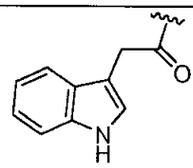
	1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		
94-30	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-(trifluoromethyl)cyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{41}H_{42}F_3N_7O_2$: 721; found: 722 $(M+H)^+$.
94-31	4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-N,N-dimethylaniline		LCMS: Anal. Calcd. for $C_{45}H_{48}N_8O_2$: 732; found: 733 $(M+H)^+$.
94-32	(3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)(phenyl)methanone		LCMS: Anal. Calcd. for $C_{50}H_{47}N_7O_3$: 793; found: 794 $(M+H)^+$.
94-33	tert-butyl (cis-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl		LCMS: Anal. Calcd. for $C_{48}H_{58}N_8O_4$: 810; found: 811 $(M+H)^+$.

	)carbamate		
94-34	'tert-butyl 4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		LCMS: Anal. Calcd. for $C_{47}H_{56}N_8O_4$: 796; found: 797 $(M+H)^+$.
94-35	tert-butyl (cis-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{58}N_8O_4$: 810; found: 811 $(M+H)^+$.
94-36	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(diphenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{50}H_{49}N_7O_2$: 779; found: 780 $(M+H)^+$.
94-37	5-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-5-oxo-2-pentanone		LCMS: Anal. Calcd. for $C_{41}H_{45}N_7O_3$: 683; found: 684 $(M+H)^+$.
94-38	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-fluorobenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-		LCMS: Anal. Calcd. for $C_{43}H_{42}FN_7O_2$: 707; found: 708 $(M+H)^+$.

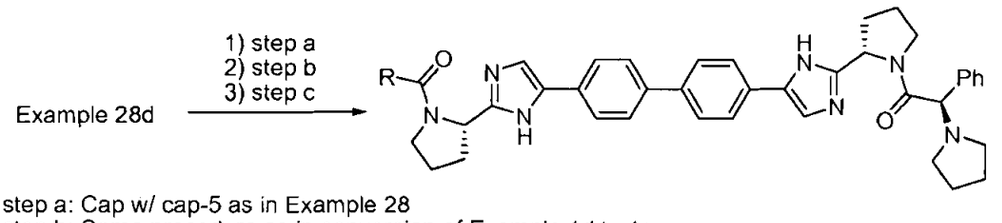
	yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		
94-39	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-biphenylylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{49}H_{47}N_7O_2$: 765; found: 766 $(M+H)^+$.
94-40	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-benzylbenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{50}H_{49}N_7O_2$: 779; found: 780 $(M+H)^+$.
94-41	4-((1E)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-propen-1-yl)-N,N-dimethylaniline		LCMS: Anal. Calcd. for $C_{47}H_{50}N_8O_2$: 758; found: 759 $(M+H)^+$.
94-42	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-thiazol-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{40}H_{40}N_8O_2S$: 696; found: 697 $(M+H)^+$.
94-43	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-		LCMS: Anal. Calcd. for $C_{48}H_{59}N_7O_3$: 781; found: 782 $(M+H)^+$.

	4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		
94-44	1-(6-chloro-3-pyridinyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxoethanamine	 *Cap-21*	LCMS: Anal. Calcd. for $C_{45}H_{48}ClN_9O_2$: 781; found: 782 $(M+H)^+$.
94-45	2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-(3-pyridinyl)ethanamine	 *Cap-19*	LCMS: Anal. Calcd. for $C_{45}H_{49}N_9O_2$: 747; found: 748 $(M+H)^+$.
94-46	2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-(2-pyridinyl)ethanamine	 *Cap-20*	LCMS: Anal. Calcd. for $C_{45}H_{49}N_9O_2$: 747; found: 748 $(M+H)^+$.
94-47	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-thienylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{42}H_{43}N_7O_2S$: 709; found: 710 $(M+H)^+$.

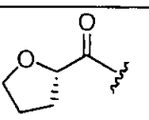
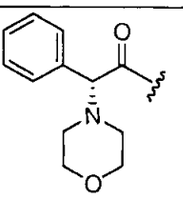
94-48	(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-thienylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{42}H_{43}N_7O_2S$: 709; found: 710 $(M+H)^+$.
94-49	(1R)-N,N-dimethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-naphthylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{48}H_{47}N_7O_2$: 753; found: 754 $(M+H)^+$.
94-50	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-5-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{41}H_{43}N_9O_2$: 693; found: 694 $(M+H)^+$.
94-51	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{44}H_{44}FN_7O_2$: 721; found: 722 $(M+H)^+$.
94-52	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{44}H_{44}FN_7O_2$: 721; found: 722 $(M+H)^+$.

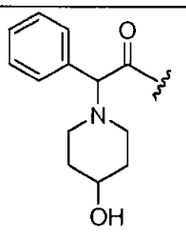
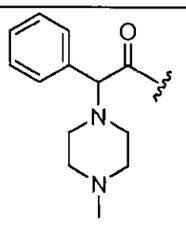
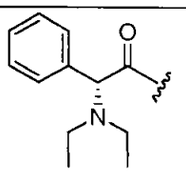
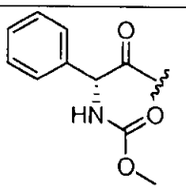
94-53	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{44}H_{44}FN_7O_2$: 721; found: 722 $(M+H)^+$.
94-54	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-benzothiophen-3-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{46}H_{45}N_7O_2S$: 759; found: 760 $(M+H)^+$.
94-55	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,2-benzisoxazol-3-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{45}H_{44}N_8O_3$: 744; found: 745 $(M+H)^+$.
94-56	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-indol-3-ylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{46}H_{46}N_8O_2$: 742; found: 743 $(M+H)^+$.

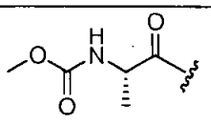
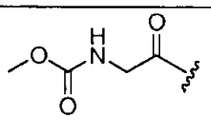
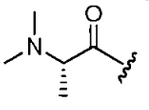
Examples 95-103



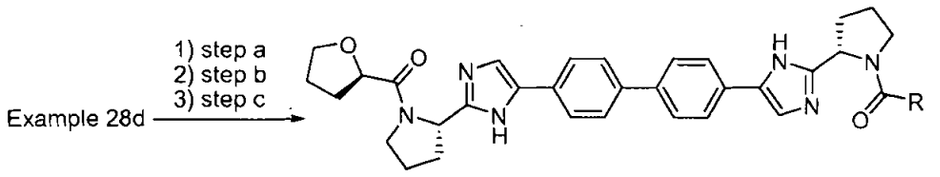
step a: Cap w/ cap-5 as in Example 28
step b: Same procedure as in conversion of Example 1d to 1e
step c: As in the last step of Example 1 using 1.1 equiv. of the appropriate carboxylic acid and HATU

Example	*Compound Name*		*Retention time (LC-Condition); homogeneity index MS data*
95	2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole		1.16 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{48}N_7O_3$: 710.38; found 710.60
96	4-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)morpholine	 *Cap-6*	1.82 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{55}N_8O_3$: 815.44; found 815.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{55}N_8O_3$: 815.4397; found 815.4395

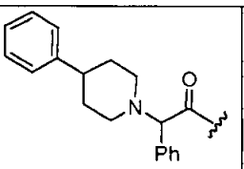
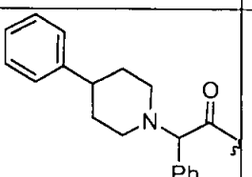
97	1-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-piperidinol	 A single diastereomer *Cap-8*	1.79 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{57}N_8O_3$: 829.46; found 829.43; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{57}N_8O_3$: 829.4554; found 829.4585
98	1-methyl-4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperazine	 A single diastereomer *Cap-17c*	1.84 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{58}N_9O_2$: 828.47; found 828.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{58}N_9O_2$: 828.4713; found 828.4722
99	(1R)-N,N-diethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine	 *Cap-2*	1.86 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{57}N_8O_2$: 801.46; found 801.44; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{57}N_8O_2$: 801.4604; found 801.4595
100	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-	 *Cap-4*	1.93 minutes (Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{51}N_8O_4$: 803.40; found 803.47 ;

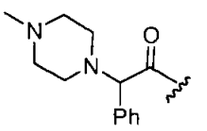
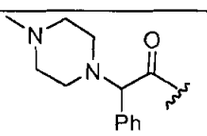
	4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		HRMS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{51}N_8O_4$: 803.4033; found 803.4058
101	methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate	 *Cap*-12	1.80 minutes (Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_4$: 741.39; found 741.33; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_4$: 741.3877; found 741.3900
102	methyl (2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		1.80 minutes (Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.37; found 727.24; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.3720; found 727.3743
103	(2S)-N,N-dimethyl-1-oxo-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-propanamine	 *Cap*-13	1.69 minutes (Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_2$: 711.41; found 711.37; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_2$: 711.4135; found 711.4154

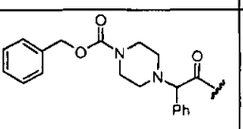
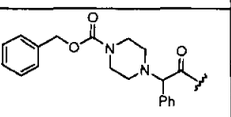
Examples 103-1 to 103-12

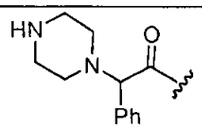
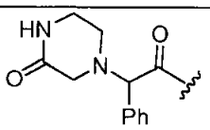
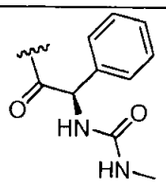


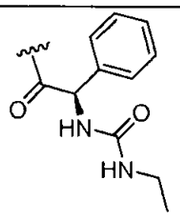
step a: Cap with (R)-2-tetrahydrofuroic acid as in Example 28
step b: Same procedure as in the conversion of Example 1d to 1e
step c: As in the last step of Example 1 using 1.1 equiv. of the appropriate carboxylic acid and HATU

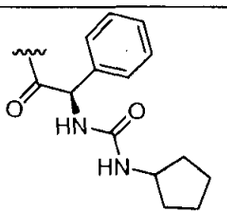
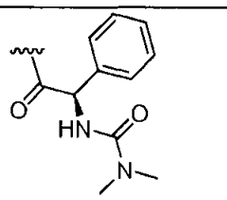
103-1	1-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-phenylpiperidine	 Diastereomer 1 *Cap-17d*	RT = 4.80 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{50}H_{53}N_7O_3$ 800.03 Found: 800.49 $(M+H)^+$
103-2	1-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-phenylpiperidine	 Diastereomer 2 *Cap-17d*	RT = 4.59 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2%

			phosphoric acid; LCMS: Anal. Calcd. for: $C_{50}H_{53}N_7O_3$ 800.03 Found: 800.48 $(M+H)^+$
103-3	1-methyl-4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperazine	 Diastereomer 1 *Cap-17c*	RT = 3.36; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{44}H_{50}N_8O_3$ 738.94 Found: 739.49 $(M+H)^+$
103-4	1-methyl-4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperazine	 Diastereomer 2 *Cap-17c*	RT = 3.47 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{44}H_{50}N_8O_3$ 738.94

			Found: 739.51 $(M+H)^+$
103-5	benzyl 4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-1-piperazinecarboxylate	 Diastereomer 1 *Cap-17a*	RT = 5.00 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{51}H_{54}N_8O_5$ 859.05 Found: 859.51 $(M+H)^+$
103-6	benzyl 4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-1-piperazinecarboxylate	 Diastereomer 2 *Cap-17a*	RT = 5.10 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{51}H_{54}N_8O_5$ 859.05 Found: 859.49 $(M+H)^+$

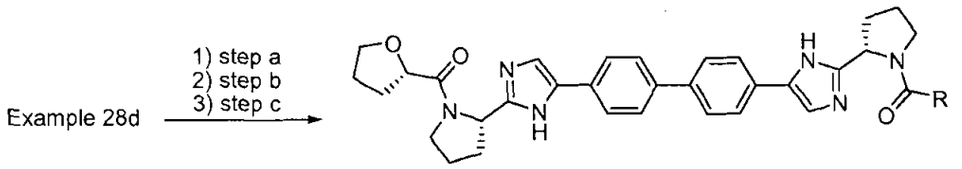
103-7	1-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperazine	 prepared by hydrogenolyzing 103-5	RT = 3.61 minutes; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{43}H_{48}N_8O_3$ 724.91 Found: 725.47 $(M+H)^+$
103-8	4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-2-piperazinone	 *Cap-17b*	RT = 3.97; HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid; LCMS: Anal. Calcd. for: $C_{43}H_{46}N_8O_4$ 738.90 Found: 739.56 $(M+H)^+$
103-9	1-methyl-3-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-		HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 4 minutes, 1 minute

	pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)urea	employed *Cap-45*	hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.81 minutes, 96% homogeneity index.; LCMS: Anal. Calcd. for $C_{41}H_{44}N_8O_4$: 712.84; found: 713.37 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{41}H_{45}N_8O_4$ 713.3564; found: 713.3564 $(M+H)^+$.
103-10	1-ethyl-3-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)urea	 employed *Cap-46*	HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.88 minutes, 95% homogeneity index; LCMS: Anal. Calcd. for $C_{42}H_{46}N_8O_4$: 726.87; found: 727.71 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{42}H_{47}N_8O_4$ 727.3720; found:

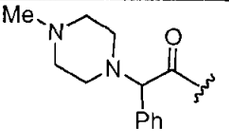
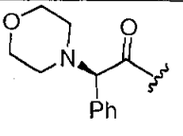
			727.3695 $(M+H)^+$.
103-11	1-cyclopentyl-3-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)urea	 employed *Cap-48*	HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 2.11 minutes, 96% homogeneity index; LCMS: Anal. Calcd. for $C_{45}H_{50}N_8O_4$: 766.93; found: 767.45 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{45}H_{51}N_8O_4$ 767.4033; found: 767.4032 $(M+H)^+$.
103-12	1,1-dimethyl-3-((1R)-2-oxo-1-phenyl-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)urea	 employed *Cap-47*	HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.87 minutes, 97% homogeneity index; LCMS: Anal. Calcd. for $C_{42}H_{46}N_8O_4$:

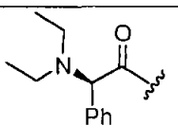
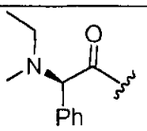
			726.87; found: 727.38 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{42}H_{47}N_8O_4$ 727.3720; found: 727.3723 $(M+H)^+$.

Examples 104-107

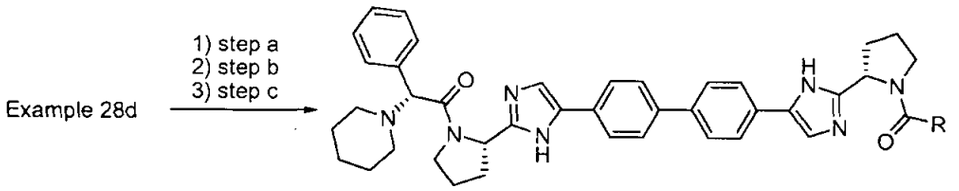


step a: Cap with (S)-2-tetrahydrofuroic acid as in Example 28
step b: Same procedure as in the conversion of Example 1d to Example 1e
step c: As in the last step of Example 1 using 1.1 equiv. of the appropriate carboxylic acid and HATU

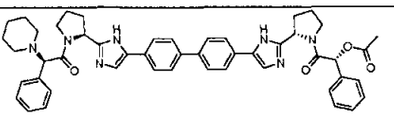
Example	*Compound Name*		*Retention time (LC-Condition); homogeneity index MS data*
104	1-methyl-4-(2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperazine	 A single diastereomer *Cap-17c*	1.12 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{51}N_8O_3$: 739.41; found 739.63; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{51}N_8O_3$: 739.4084; found 739.4054
105	4-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-	 *Cap-6*	1.13 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{48}N_7O_4$:

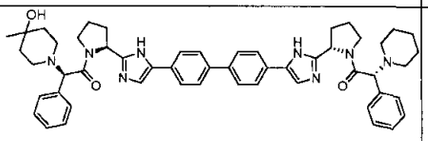
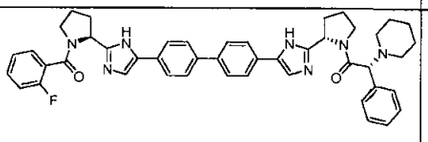
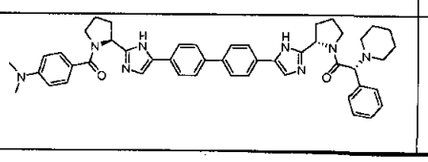
	yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)morpholine		726.38; found 726.63; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{48}N_7O_4$: 726.3768; found 726.3803
106	(1R)-N,N-diethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine	 *Cap-2*	1.12 minutes (Cond. 1); 97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{50}N_7O_3$: 712.40; found 712.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{50}N_7O_3$: 712.3975; found 712.3998
107	(1R)-N-ethyl-N-methyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine	 *Cap-3*	1.10 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{48}N_7O_3$: 698.38; found 698.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{48}N_7O_3$: 698.3819; 698.3823

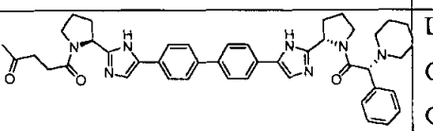
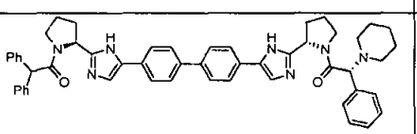
Examples 107-1 to 107-30

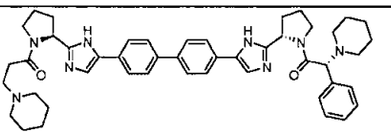
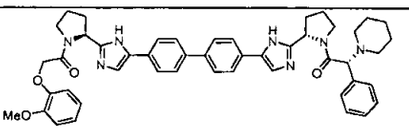
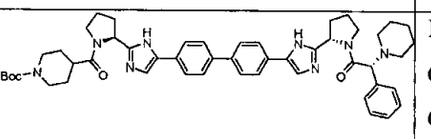


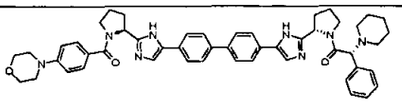
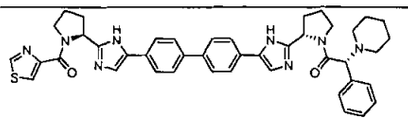
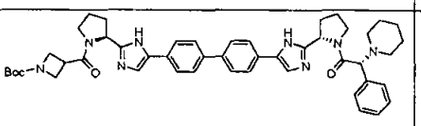
step a: Cap with cap-14 as in Example 28
step b: Same procedure as in the conversion of Example 1d to 1e
step c: As in the last step of Example 1 using 1.1 equiv. of the appropriate carboxylic acid and HATU

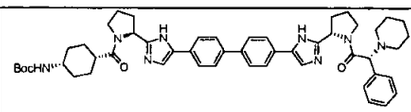
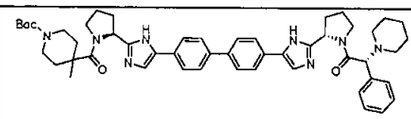
Example Number	*Compound Name*	*Structure*	*Data*
Example 107-1	(1S)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl acetate		^{1}HNMR (400 MHz, $CDCl_3$) δ 7.63-7.85 (m, 8H), 7.48- 7.54 (m, 2H), 7.26- 7.46 (m, 7H), 6.94- 7.17 (m, 3H), 6.22 and 6.18 (s, 1H, rotamers, 1:1), 5.99 and 5.68 (s, 1H, rotamers, 1:1), 5.61 and 5.54 (d, J = 7.8 Hz, 1H, rotamers, 1:1), 5.20- 5.23 and 5.10- 5.13 (m, 1H, rotamers, 1:1), 4.46 and 4.43 (s, 1H, rotamers, 1:1), 3.97-4.06 (m, 1H), 3.89- 3.93 and 3.78- 3.84 (m, 1H, rotamers, 1:1), 3.63- 3.72 and 3.46- 3.60 (m, 1H, rotamers, 1:1), 3.23-3.32 (m, 2H), 2.41-2.59 (m, 4H), 2.13- 2.26 (m, 2H), 2.11 and 2.10 (s, 3H, rotamers, 1:1), 2.05-2.09 (m, 2H), 1.97-1.98 (m, 1H), 1.82-1.90 (m, 1H), 1.58 (br s, 4H),

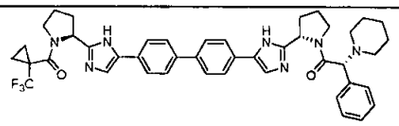
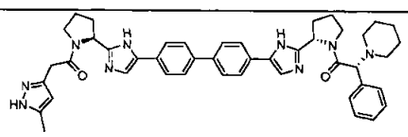
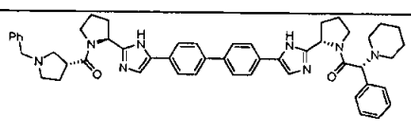
			1.45 (br s, 2H); LCMS: Anal. Calcd. for $C_{49}H_{51}N_7O_4$: 801; found: 802 $(M+H)^+$.
Example 107-2	4-methyl-1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-piperidinol		LCMS: Anal. Calcd. for $C_{53}H_{60}N_8O_3$: 856; found: 857 $(M+H)^+$.
Example 107-3	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-fluorobenzoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		LCMS: Anal. Calcd. for $C_{46}H_{56}FN_7O_2$: 747; found: 748 $(M+H)^+$.
Example 107-4	N,N-dimethyl-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-		LCMS: Anal. Calcd. for $C_{48}H_{52}N_8O_2$: 772;

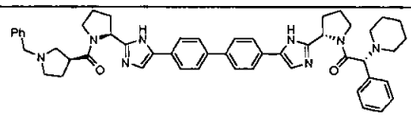
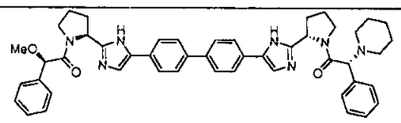
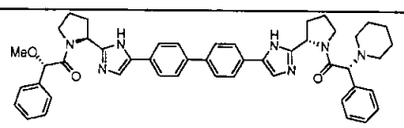
	2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)aniline		found: 773 $(M+H)^+$.
Example 107-5	5-oxo-5-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-pentanone		LCMS: Anal. Calcd. for $C_{44}H_{49}N_7O_3$: 723; found: 724 $(M+H)^+$.
Example 107-6	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(diphenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		LCMS: Anal. Calcd. for $C_{53}H_{53}N_7O_2$: 819; found: 820 $(M+H)^+$.

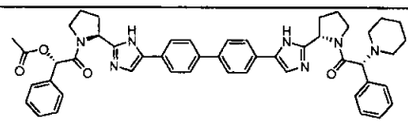
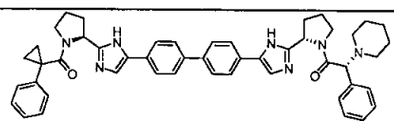
Example 107-7	1-(3-oxo-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)propyl)piperidine		LCMS: Anal. Calcd. for $C_{47}H_{56}N_8O_2$: 764; found: 765 $(M+H)^+$.
Example 107-8	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methoxyphenoxy)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		LCMS: Anal. Calcd. for $C_{48}H_{51}N_7O_4$: 789; found: 790 $(M+H)^+$.
Example 107-9	tert-butyl 4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-		LCMS: Anal. Calcd. for $C_{50}H_{60}N_8O_4$: 836; found: 837 $(M+H)^+$.

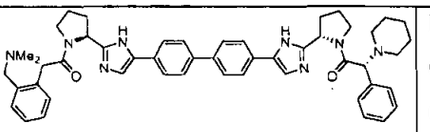
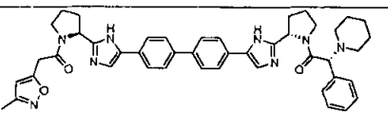
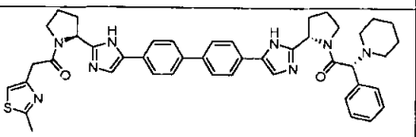
	pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		
Example 107-10	4-(4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)phenyl)morpholine		LCMS: Anal. Calcd. for $C_{50}H_{54}N_8O_3$: 814; found: 815 $(M+H)^+$.
Example 107-11	1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-thiazol-4-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine		LCMS: Anal. Calcd. for $C_{43}H_{44}N_8O_2S$: 736; found: 737$(M+H)^+$.
Example 107-12	tert-butyl 3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-		LCMS: Anal. Calcd. for $C_{48}H_{56}N_8O_4$: 808; found: 809 $(M+H)^+$.

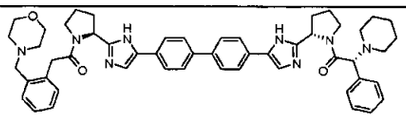
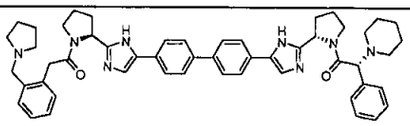
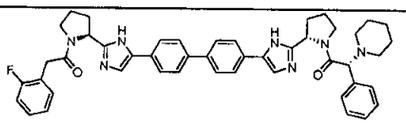
	yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate		
Example 107-13	tert-butyl (cis-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate		LCMS: Anal. Calcd. for $C_{51}H_{62}N_8O_4$: 850; found: 851 $(M+H)^+$.
Example 107-14	tert-butyl 4-methyl-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-piperidinecarboxylate		LCMS: Anal. Calcd. for $C_{51}H_{62}N_8O_4$: 850; found: 851 $(M+H)^+$.

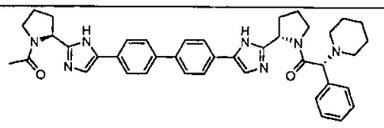
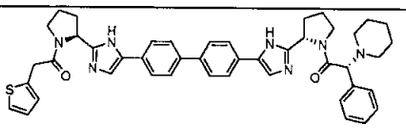
Example 107-15	1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-(trifluoromethyl)cyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine		LCMS: Anal. Calcd. for $C_{44}H_{46}F_3N_7O_2$: 761; found: 762 $(M+H)^+$.
Example 107-16	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-methyl-1H-pyrazol-3-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		LCMS: Anal. Calcd. for $C_{45}H_{49}N_9O_2$: 747; found: 748 $(M+H)^+$.
Example 107-17	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3R)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-		LCMS: Anal. Calcd. for $C_{51}H_{56}N_8O_2$: 812; found: 813 $(M+H)^+$.

	imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		
Example 107-18	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3S)-1-benzyl-3-pyrrolidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		LCMS: Anal. Calcd. for $C_{51}H_{56}N_8O_2$: 812; found: 813 $(M+H)^+$.
Example 107-19	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		LCMS: Anal. Calcd. for $C_{48}H_{51}N_7O_3$: 773; found: 774 $(M+H)^+$.
Example 107-20	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-		LCMS: Anal. Calcd. for $C_{48}H_{51}N_7O_3$: 773;

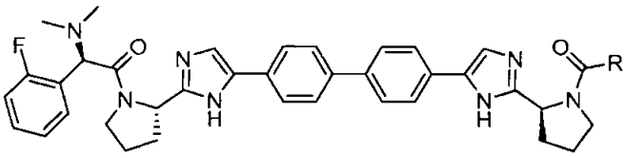
	methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		found: 774 $(M+H)^+$.
Example 107-21	(1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl acetate		LCMS: Anal. Calcd. for $C_{49}H_{51}N_7O_4$: 801; found: 802 $(M+H)^+$.
Example 107-22	1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-phenylcyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine		LCMS: Anal. Calcd. for $C_{49}H_{51}N_7O_2$: 769; found: 770 $(M+H)^+$.

Example 107-23	N,N-dimethyl-1-(2-(2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)phenyl)methanamine		LCMS: Anal. Calcd. for $C_{50}H_{56}N_8O_2$: 800; found: 801 $(M+H)^+$.
Example 107-24	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-methyl-5-isoxazolyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		LCMS: Anal. Calcd. for $C_{45}H_{48}N_8O_3$: 748; found: 749 $(M+H)^+$.
Example 107-25	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-methyl-1,3-thiazol-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-		LCMS: Anal. Calcd. for $C_{45}H_{48}N_8O_2S$: 764; found: 765 $(M+H)^+$.

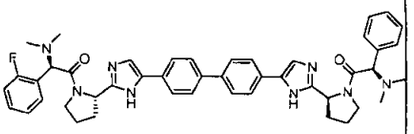
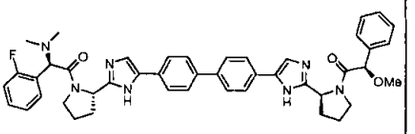
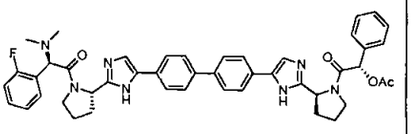
	imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		
Example 107-26	4-(2-(2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)benzyl)morpholine		LCMS: Anal. Calcd. for $C_{52}H_{58}N_8O_3$: 842; found: 843 $(M+H)^+$.
Example 107-27	1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-(1-pyrrolidinylmethyl)phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine		LCMS: Anal. Calcd. for $C_{52}H_{58}N_8O_2$: 826; found: 827 $(M+H)^+$.
Example 107-28	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-fluorophenyl)acet		LCMS: Anal. Calcd. for $C_{47}H_{48}FN_7O_2$: 800; found: 801

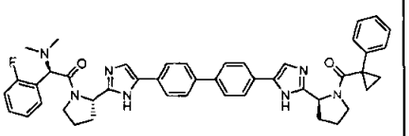
	yl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		$(M+H)^+$.
Example 107-29	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-acetyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperidine		LCMS: Anal. Calcd. for $C_{41}H_{45}FN_7O_2$: 667; found: 668 $(M+H)^+$.
Example 107-30	1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-thienylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)piperidine		LCMS: Anal. Calcd. for $C_{45}H_{47}N_7O_2S$: 749; found: 750 $(M+H)^+$.

Example 107-31 to 107-34

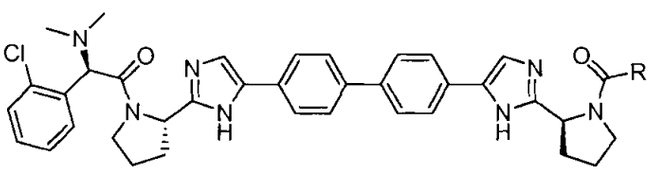


Examples 107-31 through 107-34 were prepared in similar fashion to example 28. *Cap*-38 was appended to intermediate 28d, the Boc carbamate was removed with TFA or HCl and the appropriate carboxylic acid was coupled.

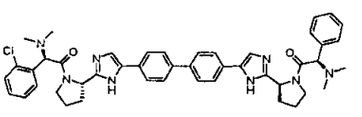
Example	*Compound Name*	*Structure*	*Data*
Example 107-31	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-(2-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{46}H_{49}FN_8O_2$: 764; found: 765 $(M+H)^+$.
Example 107-32	(1R)-1-(2-fluorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxoethanamine		LCMS: Anal. Calcd. for $C_{45}H_{46}FN_7O_3$: 751; found: 752 $(M+H)^+$.
Example 107-33	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-(2-fluorophenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-		LCMS: Anal. Calcd. for $C_{46}H_{46}FN_7O_4$: 779; found: 780

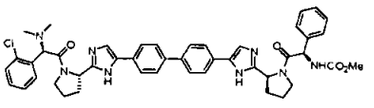
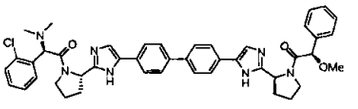
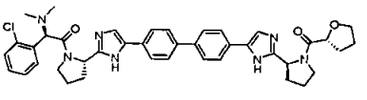
	imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl acetate		$(M+H)^+$.
Example 107-34	(1R)-1-(2-fluorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-phenylcyclopropyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{46}H_{46}FN_7O_2$: 747; found: 748 $(M+H)^+$.

Example 107-35 to 107-38

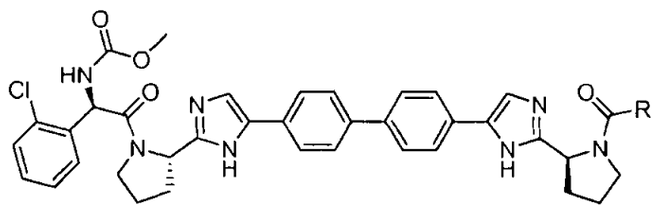


Examples 107-35 through 107-38 were prepared in similar fashion to example 28. *Cap*-39 was appended to intermediate 28d, the Boc carbamate was removed with TFA or HCl and the appropriate carboxylic acid was coupled.

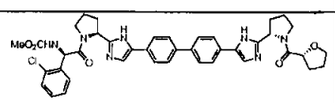
Example	*Compound Name*	*Structure*	*Data*
Example 107-35	(1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxoethanamine		LCMS: Anal. Calcd. for $C_{46}H_{49}ClN_8O_2$: 780; found: 781 $(M+H)^+$.

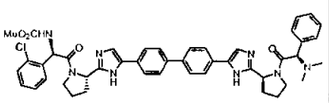
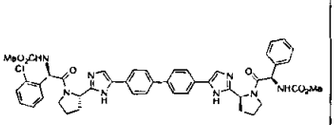
Example 107-36	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(2-chlorophenyl)-2-(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{47}ClN_8O_4$: 810; found: 811 $(M+H)^+$.
Example 107-37	(1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxoethanamine		LCMS: Anal. Calcd. for $C_{45}H_{46}ClN_7O_3$: 767; found: 768 $(M+H)^+$.
Example 107-38	(1R)-1-(2-chlorophenyl)-N,N-dimethyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		LCMS: Anal. Calcd. for $C_{41}H_{44}ClN_7O_3$: 717; found: 718 $(M+H)^+$.

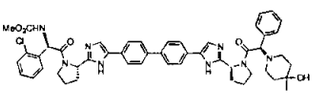
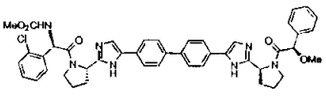
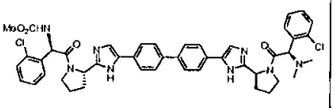
Example 107-39 to 107-43



Examples 107-39 through 107-44 were prepared in similar fashion to example 28. *Cap*-40 was appended to intermediate 28d, the Boc carbamate was removed with TFA or HCl and the appropriate carboxylic acid was coupled.

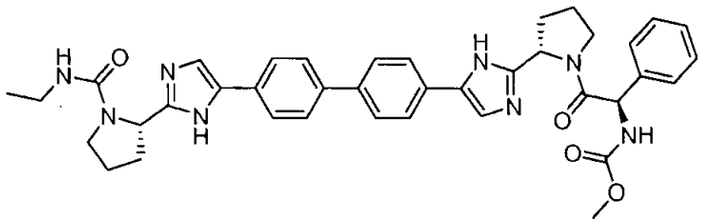
Example	*Compound Name*	*Structure*	*Data*
Example 107-39	methyl ((1R)-1-(2-chlorophenyl)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		^{1}HNMR (400 MHz, CD_3OD) δ 7.58-7.77 (m, 8H), 7.42- 7.55 (m, 2H), 7.19-7.39 (m, 4H), 5.94 and 5.89 (s, 1H, rotamers, 1:1), 5.80 and 5.61 (s, 1H, rotamers, 1:1), 5.43-5.47 and 5.35-5.38 (m, 1H, rotamers, 1:1), 5.20-5.24 (m, 1H), 5.15- 5.18 (m, 1H), 4.67-4.70 and 4.39-4.42 (m, 1H, rotamers, 1:1), 3.92-3.98 (m, 1H), 3.85-3.90 (m, 1H), 3.69-3.84 (m, 2H),

			3.64 and 3.63 (s, 3H, rotamers, 1:1), 3.53-3.59 (m, 1H), 2.35-2.46 (m, 1H), 2.21-2.29 (m, 2H), 2.06-2.17 (m, 3H), 1.84-2.01 (m, 4H), 1.66-1.76 and 1.41-1.47 (m, 1H, rotamers, 1:1); LCMS: Anal. Calcd. for $C_{41}H_{42}ClN_7O_5$: 747; found: 748 $(M+H)^+$.
Example 107-40	methyl ((1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{47}ClN_8O_4$: 810; found: 811 $(M+H)^+$.
Example 107-41	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(2-chlorophenyl)-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-		LCMS: Anal. Calcd. for $C_{46}H_{45}ClN_8O_6$: 840; found: 841 $(M+H)^+$.

	phenylethyl)carbamate		
Example 107-42	methyl ((1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(4-hydroxy-4-methyl-1-piperidinyl)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{50}H_{53}ClN_8O_5$: 880; found: 881 $(M+H)^+$.
Example 107-43	methyl ((1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-methoxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{44}ClN_7O_5$: 797; found: 798 $(M+H)^+$.
Example 107-44	methyl ((1R)-1-(2-chlorophenyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(2-chlorophenyl)-2-(dimethylamino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{46}Cl_2N_8O_4$: 844; found: 845 $(M+H)^+$.

Example 108

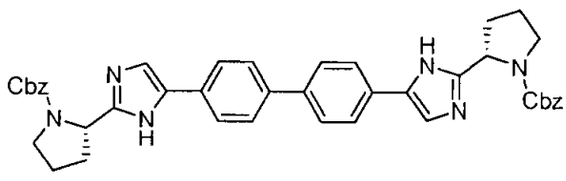
methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(ethylcarbamoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate



Ethyl isocyanate (5 μL, 0.063 mmol) was added to a methanol (1.0 mL) solution of 28f (30 mg, 0.049 mmol) and stirred at ambient condition for 1.8 hours. The residue was treated with 2.0 M NH_3/methanol (2 mL) and stirred for an additional 30 minutes, and all the volatile components were removed *in vacuo*. The resulting material was purified by a reverse phase HPLC (H_2O/methanol/TFA) to provide the TFA salt of Example 108 as a light yellow foam (16.7 mg) LC: 1.95 minutes (Cond. 2); >98% homogeneity index; LC/MS: Anal. Calcd. for [M+H]+ $C_{39}H_{43}N_8O_4$: 687.34; found 687.53; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{43}N_8O_4$: 687.3407; found 687.3417.

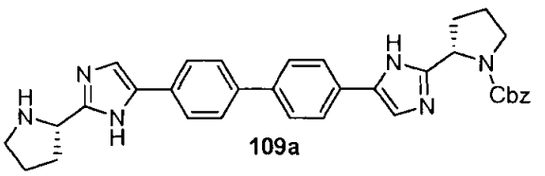
Example 109

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



Example 109, Step a

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

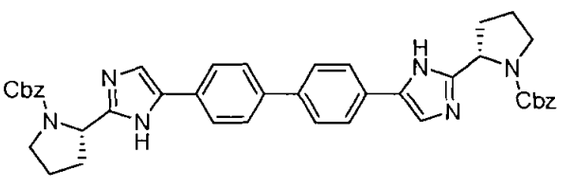


109a

The Boc-deprotection of 28c using the procedure described for the synthesis of pyrrolidine 1e from carbamate 1d provided 109a. RT = 1.92 minutes (Cond 2); > 98% homogeneity index; LC/MS: Anal. Calcd. $C_{34}H_{35}N_6O_2$: 559.28; found 559.44

Example 109

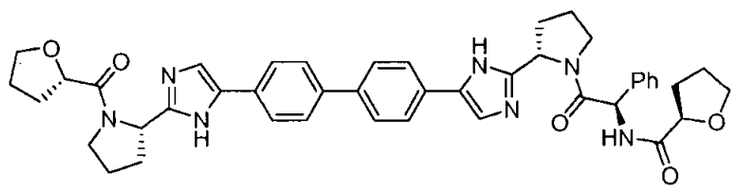
dibenzyl (2S,2'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))di(1-pyrrolidinecarboxylate)



Benzyl chloroformate (10.5 µL, 0.0736 mmol) was added to a THF (2.0 mL) solution of 109a (37.1 mg, 0.664 mmol) and triethylamine (15 µl, 0.107 mmol), and stirred under ambient conditions for 6 hours. The volatile component was removed *in vacuo*, and the residue was treated with 2N NH_3/methanol (2 mL) and stirred for 15 minutes. The volatile component was removed *in vacuo*, and the residue purified by a reverse phase HPLC (H_2O/methanol/TFA) to provide the TFA salt of Example 109 as an off-white foam (37.9 mg). LC (Cond. 2): RT = 2.25 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_6O_4$: 693.32; found 693.59; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_6O_4$: 693.3189; found 693.3220.

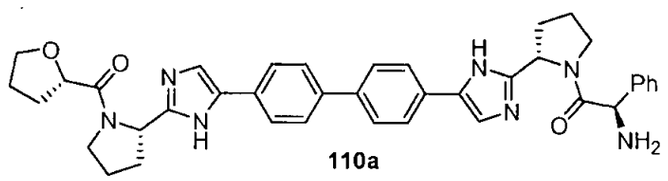
Example 110

(2R)-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)tetrahydro-2-furancarboxamide



Example 110, Step a

(1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine

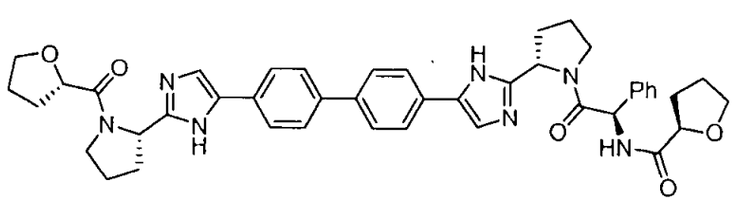


110a

Amine 110a was synthesized starting from 28d and (*S*)-tetrahydrofuran-2-carboxylic by sequentially employing procedures described in the preparation of 28f (from 28d) and 25b (from 1e). LC (Cond. 1): RT = 1.13 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_3$: 656.34; found 656.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{42}N_7O_3$: 656.3349; found 656.3377.

Example 110

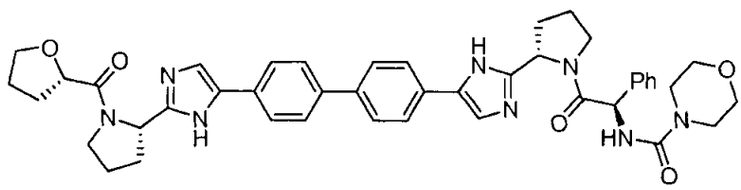
(2R)-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)tetrahydro-2-furancarboxamide



Example 110 (TFA salt) was prepared from Example 110a and (*S*)-tetrahydrofuran-2-carboxylic acid using the conditions described for the synthesis Example 1 from amine 1c. LC (Cond. 1): RT = 1.28 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.37; found 754.60; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.3717; found 754.3690.

Example 111

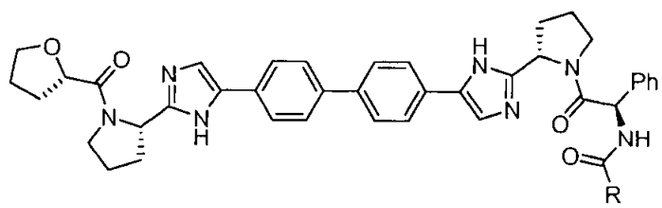
N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-morpholinecarboxamide

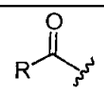
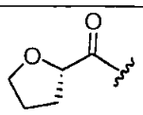
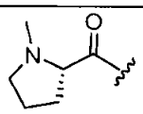
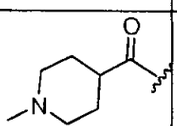


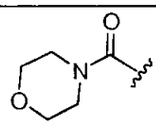
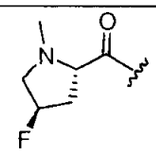
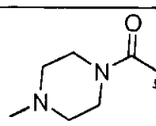
Example 111 (TFA salt) was prepared from amine 110a and morpholine 4-carbonyl chloride using the procedure described for the synthesis of Example 29 from amine 28f. LC (Cond. 1): RT = 1.28 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{49}N_8O_5$: 769.38; found 769.60.

Using similar methods described for the preparation of Example 111, the following compounds (Example 112-120) were synthesized as TFA salts.

Example 112-117

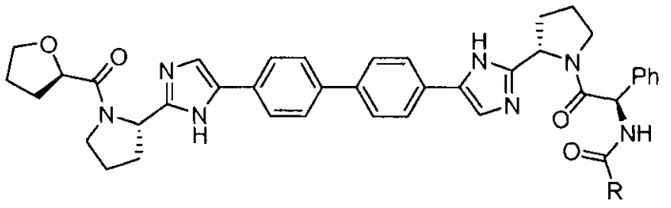


Example	*Compound Name*		*Retention time (LC-Condition); homogeneity index MS data*
112	(2S)-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)tetrahydro-2-furancarboxamide		1.28 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.37; found 754.59; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.3717; found 754.3731
113	1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-L-prolinamide		1.14 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{51}N_8O_4$: 767.40; found 767.68; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{51}N_8O_4$: 767.4033; found 767.4035
114	1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-piperidinecarboxamide		1.12 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{53}N_8O_4$: 781.42; found 781.67; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{53}N_8O_4$: 781.4190; found 781.4195

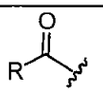
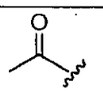
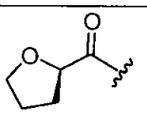
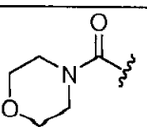
115	N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)tetrahydro-2H-pyran-4-carboxamide		1.24 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}N_7O_5$: 768.39; found 768.66; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}N_7O_5$: 768.3873; found 768.3897
116	(4R)-4-fluoro-1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-L-prolinamide	 *Cap*-11	1.16 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}FN_8O_4$: 785.39; found 785.63; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}FN_8O_4$: 785.3939; found: 785.3940
117	4-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-1-piperazinecarboxamide		1.15 minutes (Cond. 1); 97.6%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{52}N_9O_4$: 782.41; found 782.64; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{52}N_9O_4$: 782.4142; found 782.4161

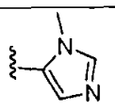
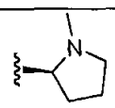
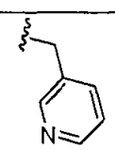
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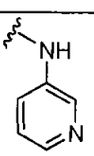
Examples 118 to 120-9



Examples 118 to 120-9 were prepared as described in the preparation of Example 110a substituting (R)-tetrahydrofuryl carboxylic acid and the appropriate carboxylic acid, carboxylic acid chloride, carbamoyl chloride, or isocyanate.

Example	*Compound Name*		*Retention time (LC-Condition); homogeneity index; MS data*
118	N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)acetamide		1.89 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}N_7O_4$: 698.35; found 698.25; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{44}N_7O_4$: 698.3455; found 698.3474
119	(2R)-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)tetrahydro-2-furancarboxamide		1.99 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.37; found 754.28; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.3717; found 754.3705
120	N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-		2.00 minutes (Cond. 2); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{49}N_8O_5$:

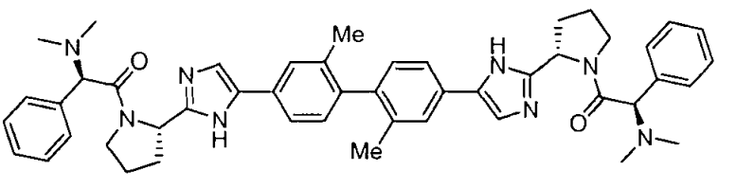
	furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-4-morpholinecarboxamide		769.38; found 769.32
120-5	1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-1H-imidazole-5-carboxamide		RT = 4.02 (97%); HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.87 minutes, 97% homogeneity index; LCMS: Anal. Calcd. for: $C_{44}H_{45}N_9O_4$ 763.91; Found: 764.52 $(M+H)^+$
120-6	1-methyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-L-prolinamide		RT = 3.68 (99%); HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.87 minutes, 97% homogeneity index; LCMS: Anal. Calcd. for: $C_{45}H_{50}N_8O_4$ 766.95; Found: 767.47 $(M+H)^+$
120-7	N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-		RT = 3.81 (99%); HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2%

	4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-2-(3-pyridinyl)acetamide		H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.87 minutes, 97% homogeneity index; LCMS: Anal. Calcd. for: $C_{46}H_{46}N_8O_4$ 774.93; Found: 775.47 $(M+H)^+$
120-8	N^2,N^2-dimethyl-N-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)glycinamide		^1H NMR (500 MHz, DMSO-d_6) δ ppm 1.71-2.44 (m, 12H), 2.65-2.89 (m, 6H), 3.04-3.21 (m, *J*=8.55 Hz, 1H), 3.46-3.68 (m, 1H), 3.64-4.07 (m, 6H), 4.64 (dd, *J*=8.09, 5.34 Hz, 1H), 5.09-5.30 (m, 2H), 5.66-5.86 (m, 1H), 7.32-7.49 (m, 4H), 7.82-8.22 (m, 10H), 9.15-9.38 (m, 1H), 9.68 (s, 1H), 14.60 (s, 2H); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid, RT = 3.61 min; LCMS: Anal. Calcd. for: $C_{52}H_{56}N_{10}O_6$ 740.91; Found: 741.48 $(M+H)^+$.
120-9	1-((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-		^1H NMR (500 MHz, DMSO-d_6) δ ppm 1.64-2.40 (m, 12H), 3.11-3.27 (m, 1H), 3.51-3.65 (m, 1H), 3.80 (dd, *J*=18.46, 6.87 Hz, 3H), 3.96-4.11 (m, 1H), 4.64 (dd,

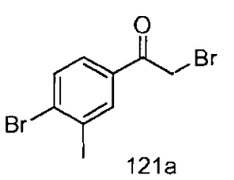
	imidazol-2-yl)-1-pyrrolidinyl)ethyl)-3-(3-pyridinyl)urea		*J*=7.78, 5.34 Hz, 1H), 5.13-5.23 (m, 1H), 5.21-5.35 (m, 1H), 5.66 (d, *J*=7.02 Hz, 1H), 7.29-7.57 (m, 7H), 7.82-8.07 (m, 10H), 8.14 (s, 1H), 8.22 (d, *J*=4.58 Hz, 1H), 8.68 (s, 1H), 9.32 (s, 1H), 14.46 (s, 2H); HPLC Xterra 4.6 X 50 mm, 0 to 100% B over 10 minutes, one minute hold time, A = 90% water, 10% methanol, 0.2% phosphoric acid, B = 10% water, 90% methanol, 0.2% phosphoric acid, RT = 3.83 min; LCMS: Anal. Calcd. for: $C_{45}H_{45}N_9O_4$ 775.92; Found: 776.53 $(M+H)^+$.

Example 121

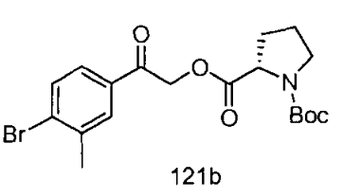
(1R,1'R)-2,2'-((2,2'-dimethyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)



Example 121, Step a-b



121a



121b

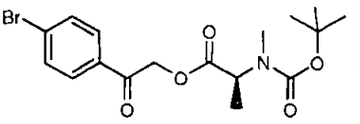
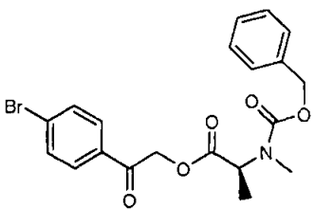
$PdCl_2(Ph_3P)_2$ (257 mg, 0.367 mmol) was added to a dioxane (45 mL) solution of 1-bromo-4-iodo-2-methylbenzene (3.01 g, 10.13 mmol) and tri-*n*-butyl(1-

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).

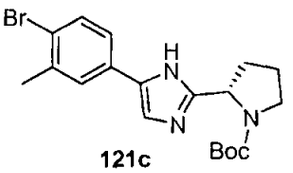
A CH_3CN (15 mL) solution of 121a (2.69 g, < 9.21 mmol) was added dropwise over 3 minutes to a CH_3CN (30 mL) solution of (*S*)-Boc-proline (2.215 g, 10.3 mmol) and triethylamine (1.40 mL, 10.04 mmol), and stirred for 90 minutes. The volatile component was removed *in vacuo*, and the residue was partitioned 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 $(M+Na)^+$.

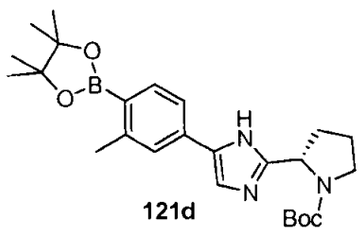
Example 121, Step c



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



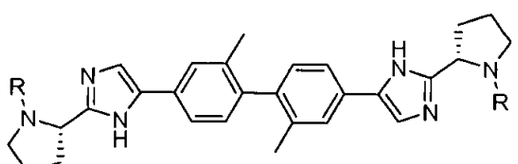
121d

$PdCl_2dppf{\cdot}CH_2Cl_2$ (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, 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: Anal. Calcd. for $[M+H]^+$ $C_{25}H_{37}BN_3O_4$ 454.29; found 454.15

Example 121, Step e

and

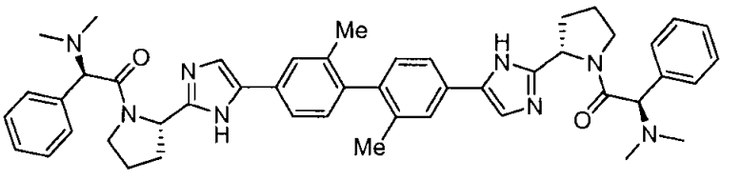
Example 121, Step f



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. ^{1}H 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



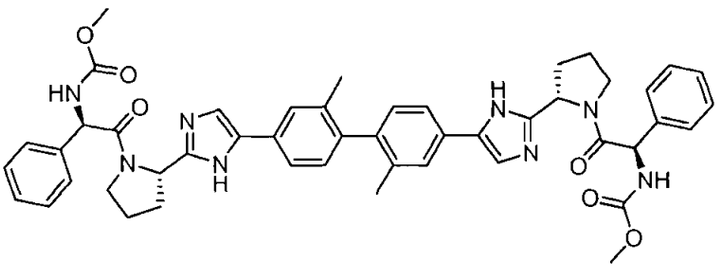
Example 121

(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

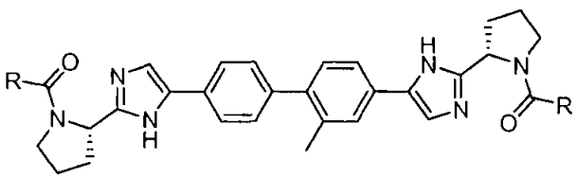
Example 122

dimethyl ((2,2'-dimethyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate

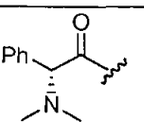


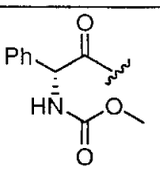
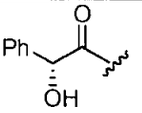
Example 122 (TFA salt) was prepared from pyrrolidine 121f and *Cap*-4 by using the procedure described for the preparation of Example 1 from pyrrolidine 1e. LC (Cond. 1): RT = 1.35 min; >98% homogeneity index; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{51}N_8O_6$ 835.3932; found 835.3954

Example 123-125

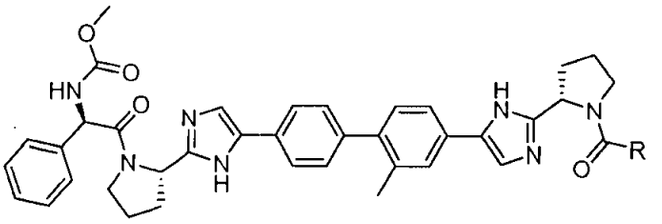


Example 123-125 were prepared starting from boronate 1c and bromide 121c by using the methods described in Example 1, step d, Example 1, step e, and in the step describing the final preparation of Example 1.

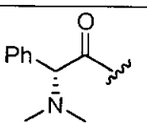
Example	*Compound Name*		*RT (LC-Cond.); % homogeneity index; MS data*
123	(1R,1'R)-2,2'-((2-methyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)	 *Cap-1*	1.12 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{53}N_8O_2$: 761.43; found 761.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{53}N_8O_2$: 761.4291; found 761.4311

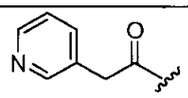
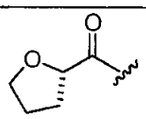
124	dimethyl ((2-methyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 *Cap-4*	1.34 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{49}N_8O_6$: 821.38; found 821.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{49}N_8O_6$: 821.3775; found 821.3785
125	(1R,1'R)-2,2'-((2-methyl-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(2-oxo-1-phenylethanol)		1.23 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{43}N_6O_4$: 707.34; found 707.38; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{43}N_6O_4$: 707.3346; found 707.3356

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.

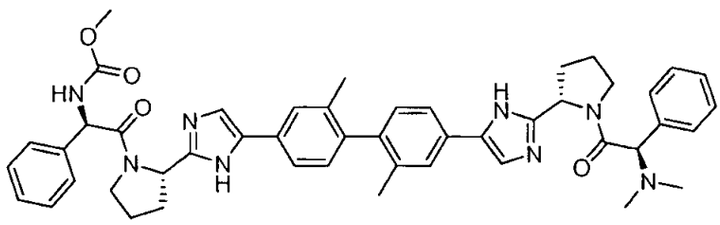
Example	*Compound Name*		*RT (LC-Cond.); % homogeneity index; MS data*
126	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-	 *Cap-1*	1.22min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{51}N_8O_4$: 791.40; found 791.70; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{51}N_8O_4$: 791.4033; found 791.4061

	imidazol-5-yl)-2'-methyl-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		
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-phenylethyl)carbamate		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

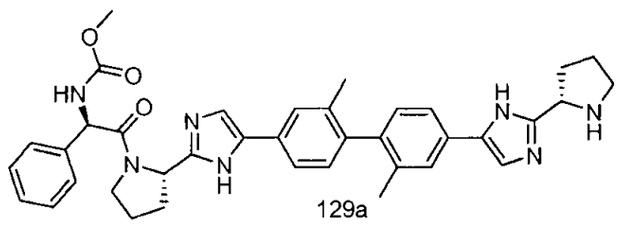
5

Example 129

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



Example 129, Step a

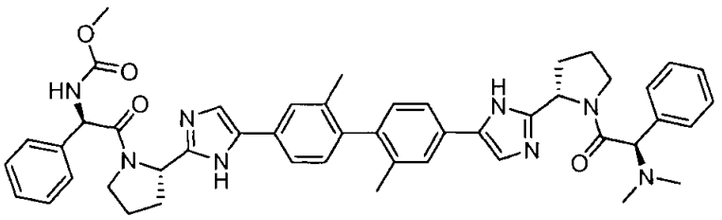


129a

HATU (104.3 mg, 0.274 mmol) was added to a mixture of 121f, *Cap*-4 (58.8 mg, 0.281 mmol) and diisopropylethylamine (110 µL, 0.631 mmol) in DMF (6.0 mL), and stirred for 90 minutes. The volatile component was removed *in vacuo* and the resulting crude material was purified by reverse phase HPLC (H_2O/methanol/TFA), and free-based by MCX column (methanol wash; 2.0 M NH_3/methanol) to provide 129a (89.9 mg). LC (Cond. 1): RT = 1.22 min; 95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{42}N_7O_3$ 644.34; found 644.55.

Example 129

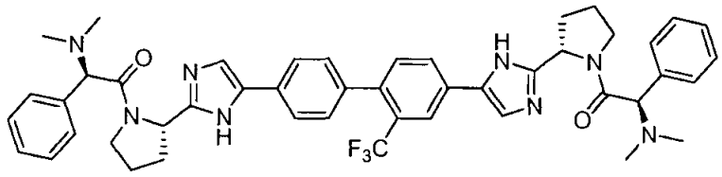
methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2,2'-dimethyl-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate



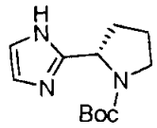
Example 129 (TFA salt) was prepared from 129a by the method used to convert Example 1e to Example 1. LC (Cond. 1): RT = 1.27 min; 97% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{53}N_8O_4$ 805.42; found 805.61.

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). ^1H 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

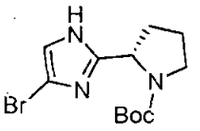
Solvent: 1.7% ethanol/heptane (isocratic)

Flow rate: 1 mL/min

Wavelength: either 220 or 256 nm

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

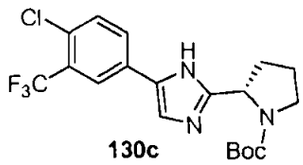
Example 130, Step b



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.

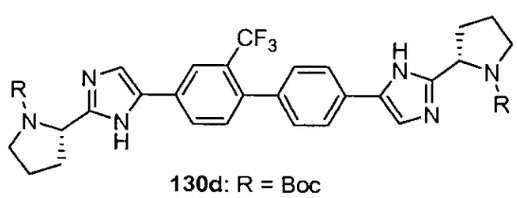
Example 130, Step c



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

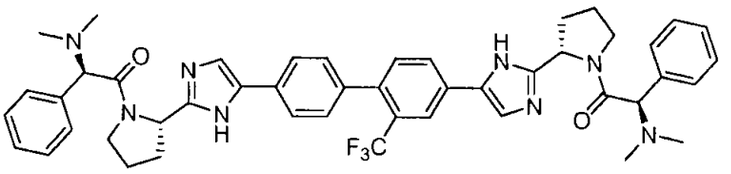
$Pd[P(t\text{-}Bu)_3]_2$ (48 mg, 0.094 mmol) was added to a mixture of chloride 130c (245 mg, 0.589 mmol), boronate 1c (277.1 mg, 0.631 mmol), KF (106.7 mg, 1.836 mmol) in DMF (6 mL), and heated at 110 °C for ~30 hours. The volatile component

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 aqueous 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

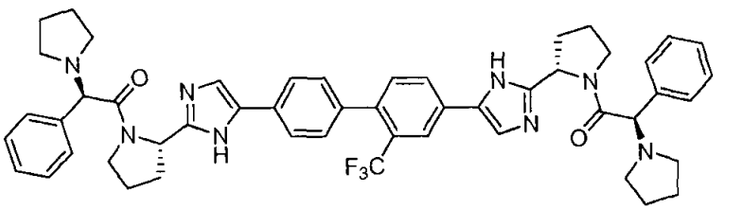
(1R,1'R)-2,2'-((2-(trifluoromethyl)-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)



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

5,5'-(2-(trifluoromethyl)-4,4'-biphenyldiyl)bis(2-((2S)-1-((2R)-2-phenyl-2-(1-pyrrolidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazole)



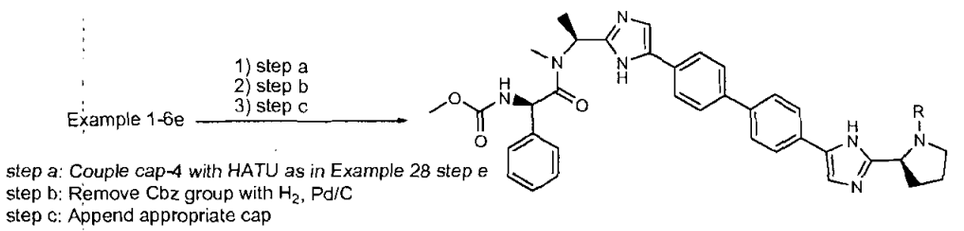
Example 131 (TFA salt) was synthesized from 130e and *Cap*-5 according to the preparation of Example 130.

LC (Cond. 1): RT = 1.19 min; >98% homogeneity index

LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{54}F_3N_8O_2$ 867.43; found 867.51

HRMS: Anal. Calcd. for $[M+H]^+$ $C_{51}H_{54}F_3N_8O_2$ 867.4322; found 867.4315

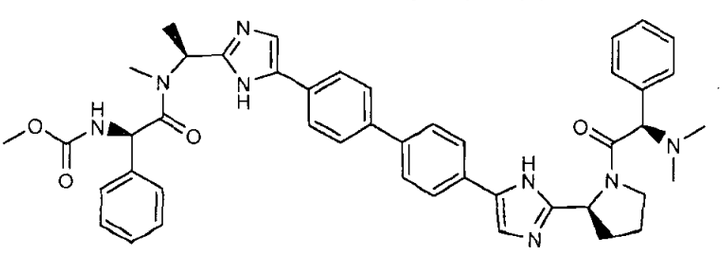
Example 131.1-1 to 131.1-2



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 $Pd/C/H_2$.

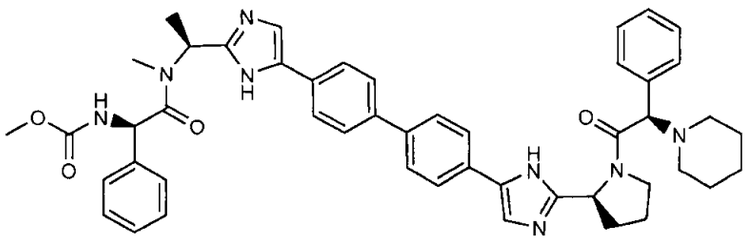
LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume. t_R = 1.42 min

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 $Pd/C/H_2$.

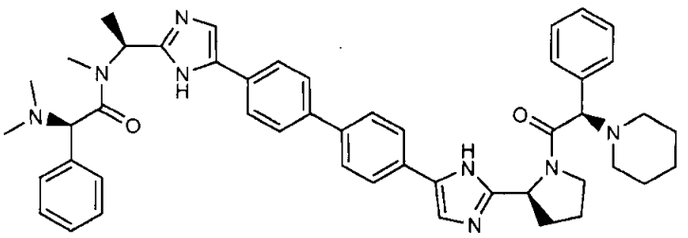
LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume. t_R = 1.45 min (>95 %)

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 $Pd/C/H_2$.

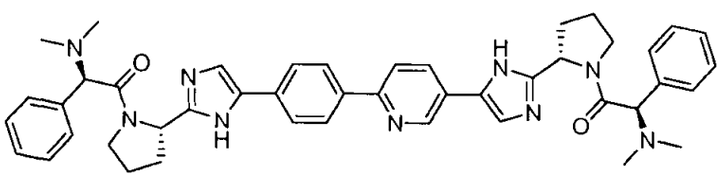
LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume. t_R = 1.28 min

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

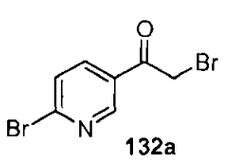
HRMS: Anal. Calcd. $C_{48}H_{54}N_8O_2$ Calcd 775.4448 found: 775.4460 $(M+H)^+$.

Example 132

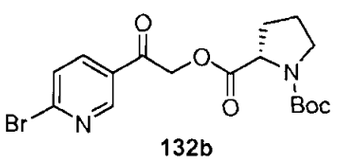
(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine



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).

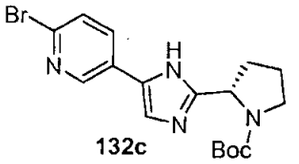
Boc-L-proline (9.70 g, 45.06 mmol) was added in one batch to a heterogeneous mixture of crude 132a (15.4 g) and CH_3CN (150 mL), and immediately afterward Et_3N (13.0 mL, 93.2 mmol) was added drop-wise over 6 min. The reaction mixture was stirred for 50 min, the volatile component was removed *in vacuo* 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% homogenicity 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%

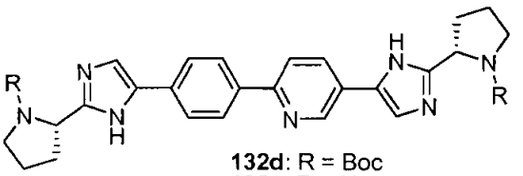
EtOAc/hexanes) to afford imidzaole 132c as an off-white foam (1.025 g). ^{1}H NMR (DMSO, δ = 2.5 ppm, 400 MHz): 12.33/12.09/12.02 (br m, 1H), 8.74 (d, J = 2.3, 0.93H), 8.70 (app br s, 0.07H), 8.03/7.98 (dd for the first peak, J = 8.3, 1H), 7.69/7.67 (br m, 1H), 7.58/7.43 (d for the first peak, J = 8.3, 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]

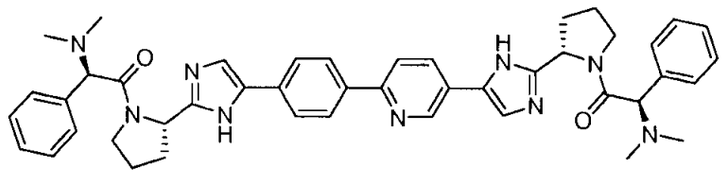
LC (Cond. 1): RT = 1.21min; >98% homogeneity index

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).

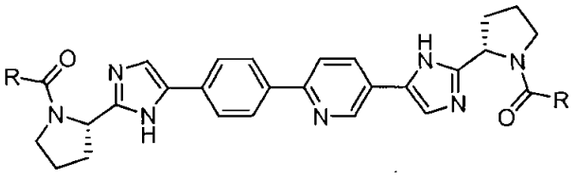
LC (Cond. 1): RT = 1.37min; >98% homogeneity index

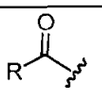
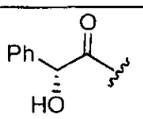
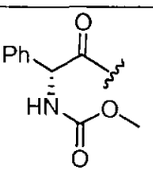
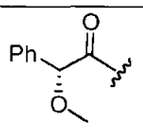
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{50}N_9O_2$: 748.41; found 748.53

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.

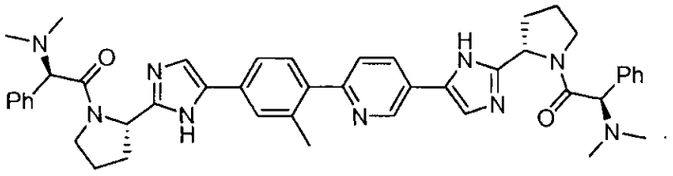
Example 133-135



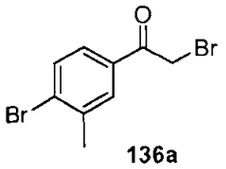
Example	*Compound Name*		*RT (LC-Cond.); % homogeneity index; MS data*
133	(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanol		1.49 min (Cond. 1); >98% LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{40}N_7O_4$: 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-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)pyridine		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 $[M+H]^+$ $C_{43}H_{44}N_7O_4$: 722.3455; found 722.3464

Example 136

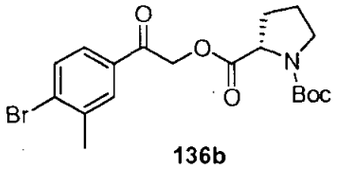
(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-methylphenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine



Example 136, Step 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).

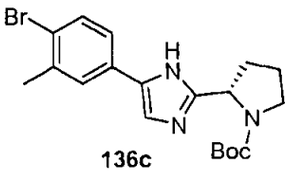
An CH_3CN (15 mL) solution of 136a (2.69 g, < 9.21 mmol) was added drop wise over 3 min to a CH_3CN (30 mL) solution of (*S*)-Boc-proline (2.215 g, 10.3 mmol) and Et_3N (1.40 mL, 10.04 mmol), and stirred for 90 min. The volatile component was removed *in vacuo*, and the residue was partitioned between 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). ^{1}H 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



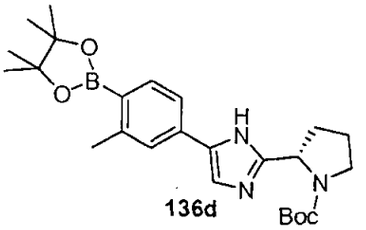
136c

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). ^{1}H 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

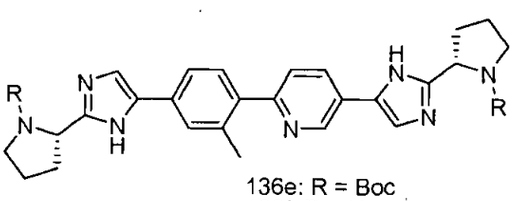
$PdCl_2dppf.CH_2Cl_2$ (50.1 mg, 0.061 mmol) was added to a pressure tube containing a mixture of bromide 136c (538.3 mg, 1.325 mmol),

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 ^{1}H NMR the sample contains residual pinacol in a product/pinacol ratio of ~3. ^{1}H 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 132c to afford 136f as a light yellow foam. ^{1}H 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

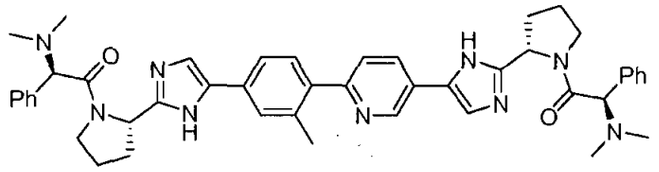
appears in the region 3.22-2.80 and is too broad to make a chemical shift assignment.]

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.

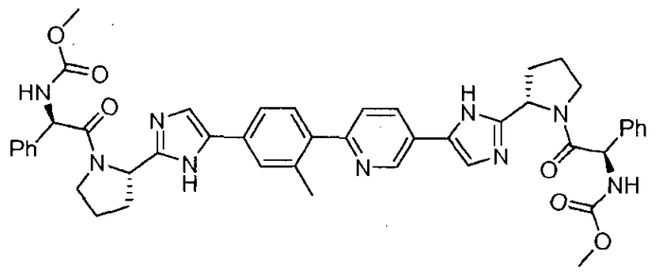
1.05 min (Cond.1); >98%

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.

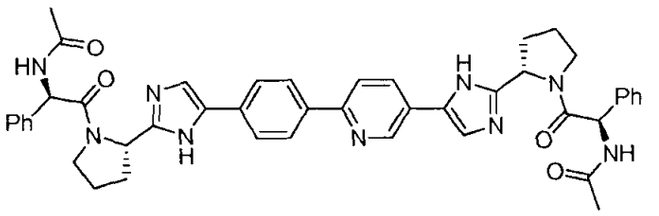
1.60 min (Cond. 1); >98%

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

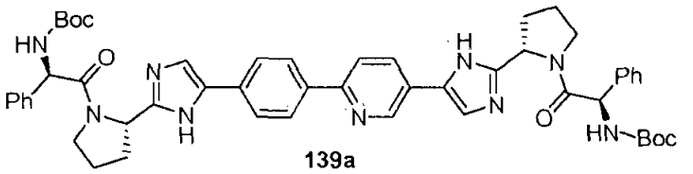
HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{48}N_9O_6$: 822.3728; found 822.3760

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



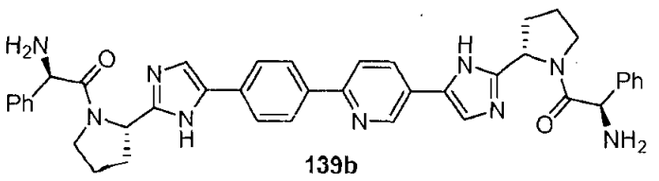
139a

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

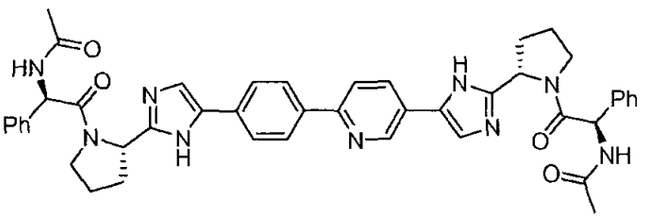
Carbamate 139a was deprotected to amine 139b by using the procedure described for the preparation of pyrrolidine 132e from 132d.

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).

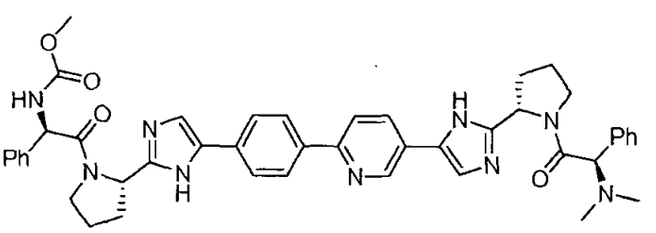
LC (Cond. 1): RT = 1.53 min; >98% homogeneity index

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

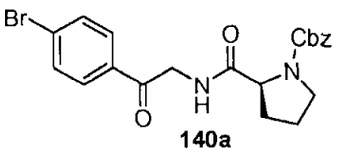
HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{46}N_9O_4$: 776.3673; found 776.3680

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



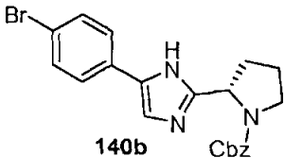
140a

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). ^{1}H 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

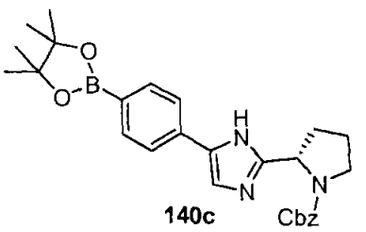
Solvent: 20% ethanol/heptane (isocratic)

Flow rate: 1 ml/min

Wavelength: 254 nm

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

Example 140, Step c



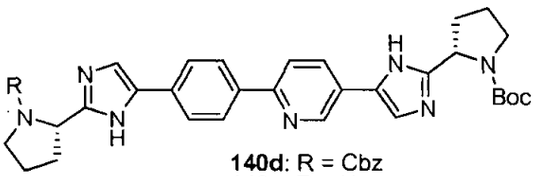
140c

$Pd(Ph_3P)_4$ (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, Step 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

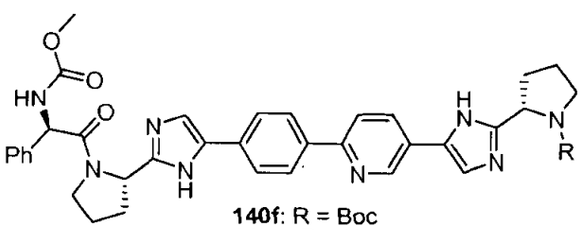
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{42}N_7O_4$: 660.33; found 660.30

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, Step f-g



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

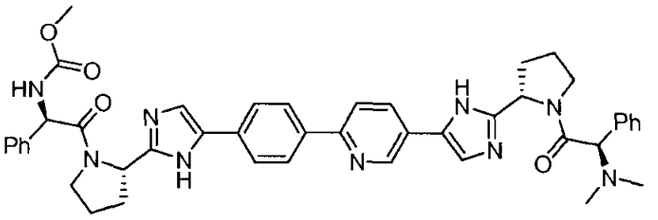
Pyrrolidine 140g was prepared from 140e and *Cap*-4, *via* the intermediacy of carbamate 140f, by sequentially employing the amide forming and Boc-deprotection protocols used in the synthesis of Example 132.

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.

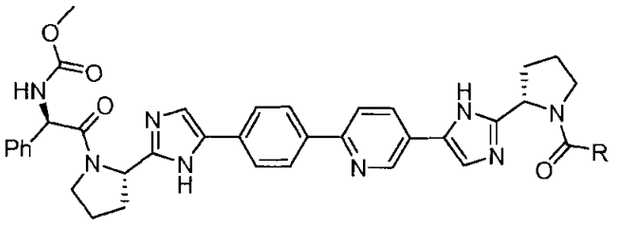
1.15 min (Cond. 1); >98% homogeneity index

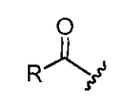
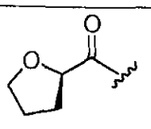
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{40}N_7O_4$: 778.38; found 778.48

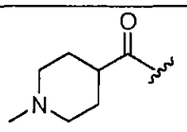
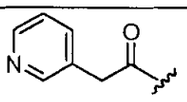
HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{40}N_7O_4$: 778.3829; found 778.3849

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

Example 141-143

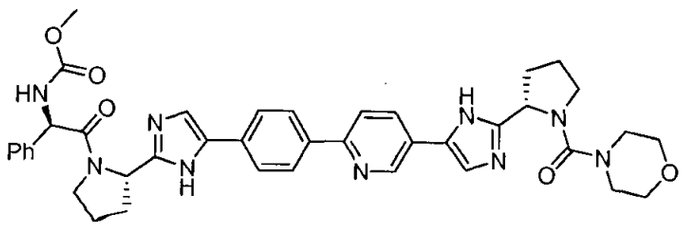


Example	*Compound Name*		*RT (LC-Cond.); % homogeneity index; MS data*
141	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-tetrahydro-		1.15 min (Cond. 1); >98% LC/MS: Anal. Calcd. for

	2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		$[M+H]^+$ $C_{40}H_{43}N_8O_5$: 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-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		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 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).

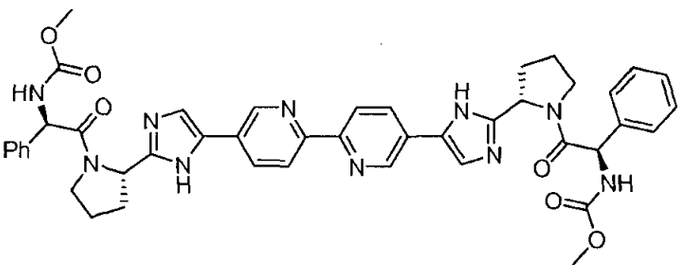
1.17 min (Cond. 1); >98%

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

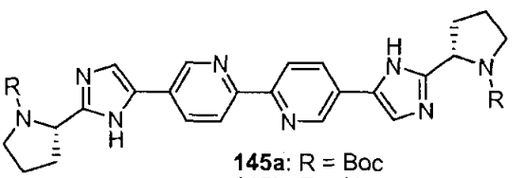
HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{44}N_9O_5$: 730.3465; found 730.3477

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

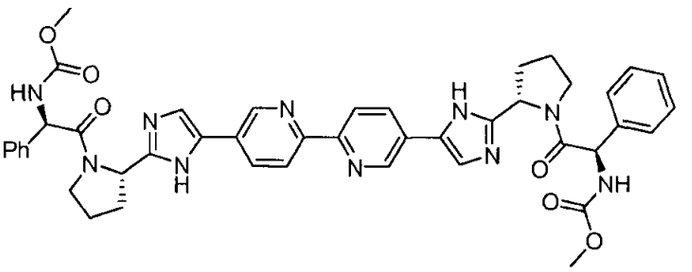
Carbamate 145a was elaborated to pyrrolidine 145b according to the preparation of 132c from 132d. ^1H NMR (DMSO, δ = 2.5 ppm; 400 MHz): 12.02 (br signal, 2H), 9.04 (d, J = 1.6, 2H), 8.34 (d, J = 8.3, 2H), 8.20 (dd, J = 8.3, 2.3, 2H), 7.67 (br s, 1H), 4.21 (m, 2H), 3.00-2.85 (m, 4H), 2.12-2.04 (m, 2H), 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



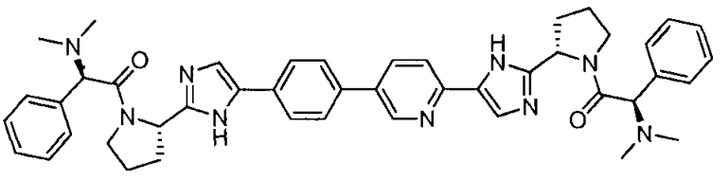
Example 145 (TFA salt) was synthesized from 145b according to the preparation of Example 132 from 132e.

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

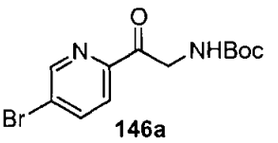
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{45}N_{10}O_6$: 809.35; found 809.40

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



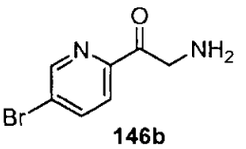
146a

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



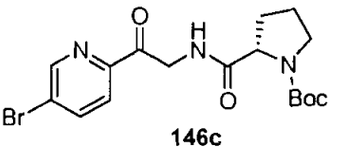
146b

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



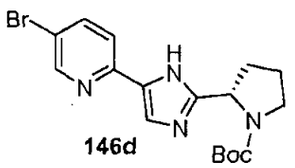
146c

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). ^{1}H 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



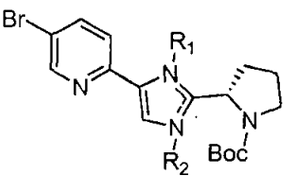
146d

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)

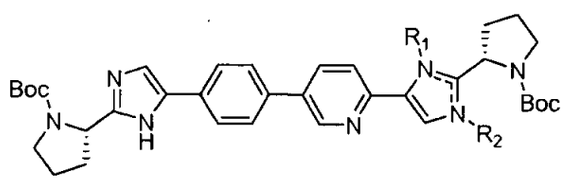
NaH (60%; 11.6 mg, 0.29 mmol) was added in one batch to a heterogeneous mixture of imidazole 146d (80 mg, 0.203 mmol) and DMF (1.5 mL), and stirred at ambient condition for 30 min. SEM-Cl (40 μL, 0.226 mmol) was added drop-wise over 2 min to the above reaction mixture, and stirring was continued for 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. ^1H 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



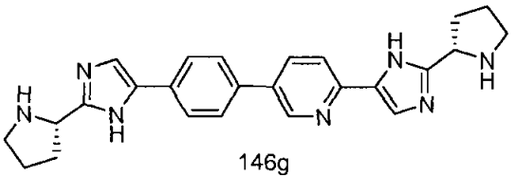
146f: (R_1 = H, R_2 = SEM) or (R_1 = SEM, R_2 = H)

$Pd(Ph_3P)_4$ (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

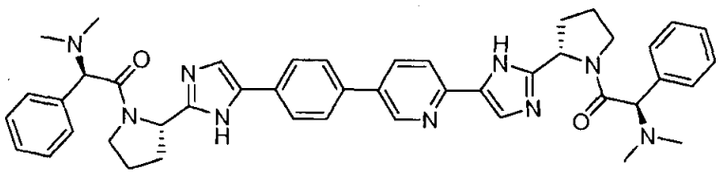
Carbamate 146f (208 mg, 0.275 mmol) was treated with 25% TFA/CH_2Cl_2 (4.0 mL) and stirred at ambient temperature for 10 hr. The volatile component was removed *in vacuo* and the residue was first free-based by MCX (MeOH wash; 2.0 M NH_3/MeOH elution) and then purified by a reverse phase HPLC (H_2O/MeOH/TFA), 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.

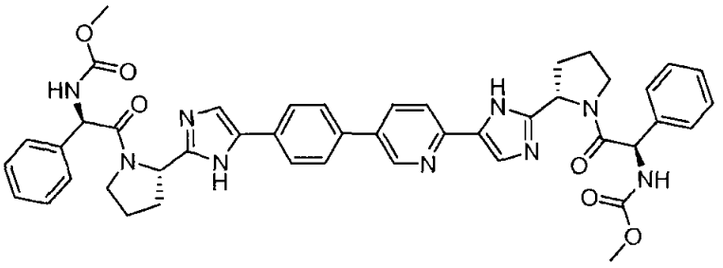
LC (Cond. 1): RT = 1.42 min; 96.5% homogenity index

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



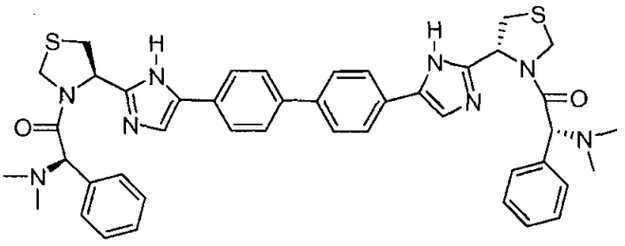
The TFA salt of Example 147 was prepared similarly from intermediate 146g by using *Cap*-4.

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

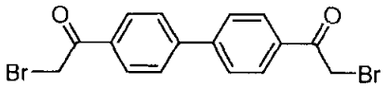
LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{46}N_9O_6$: 808.36; found 808.55

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



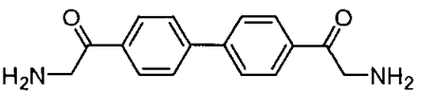
A solution of bromine (1.3mL, 25.0mmol) in 15mL glacial acetic acid was added drop-wise to a solution of 4-4'-diacetylbiphenyl (3.0g, 12.5mmol) in 40mL acetic acid at 50°C. Upon completion of addition the mixture was stirred at room temperature overnight. The precipitated product was filtered off and 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



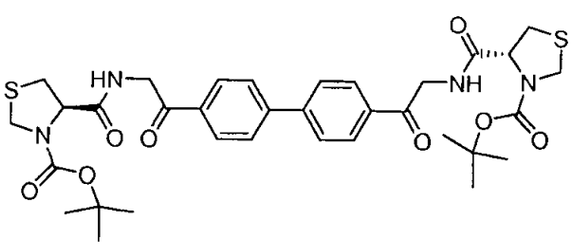
.2HCl

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

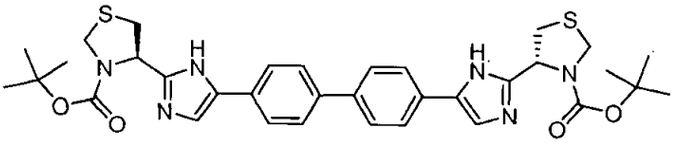


To a stirred solution of 1,1'-(biphenyl-4,4'-diyl)bis(2-aminoethanone) dihydrochloride (0.7g, 2.1mmol), N-(tert-butoxy carbonyl) –L-thioproline (0.96g, 4.2mmol), and HATU(1.68g, 4.4mmol) in 14mL DMF was added diisopropylethyl amine (1.5mL, 8.4mmol) drop-wise over 5 minutes. The resulting clear yellow 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



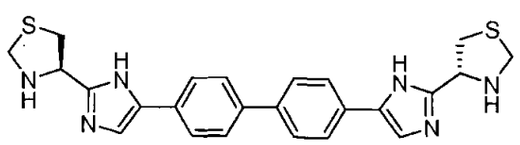
(4S,4'S)-tert-butyl 4,4'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))dithiazolidine-3-carboxylate (0.39g, 0.56mmol) and ammonium acetate (0.43g, 5.6mmol) were suspended in 8mL o-xylene in a microwave reaction vessel. The mixture was heated under standard microwave conditions at 140°C for 70 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

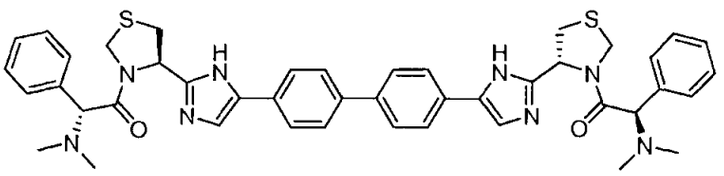
To a solution of (4S,4'S)-tert-butyl 4,4'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2- diyl))dithiazolidine-3-carboxylate in 1mL dioxane was added 0.3mL of a 4.0M solution of HCl in dioxane. The reaction was stirred for 3 hours at room temperature and concentrated under reduced pressure. The resulting 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%)

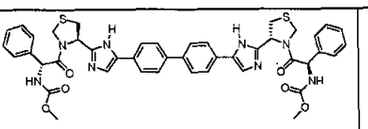
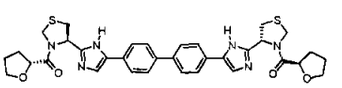
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.59 - 7.91 (20 H, m) 5.62 (2 H, dd, *J*=6.56, 2.59 Hz) 4.99 (2 H, d, *J*=8.85 Hz) 4.82/4.35 (2 H, s) 4.22 (2 H, s) 3.42 (2 H, s) 3.25 (2 H, s) 2.35-2.61 (12H, m)

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 $(M+H)^+$

Examples 149 and 150 were prepared in similar fashion as described for the preparation of example 148.

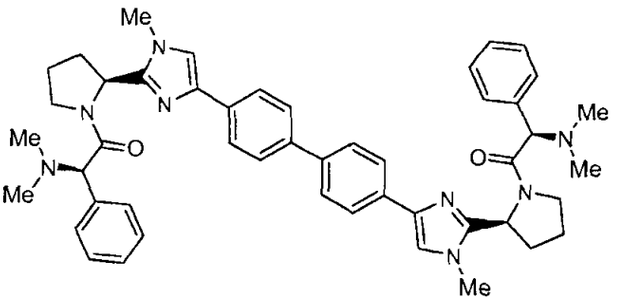
Example	*Compound Name*	*Structure*	*Data*
Example 149	dimethyl (4,4'-biphenyldiylbis(1H-		t_R = 3.36 min (LCMS - Luna C-

	imidazole-5,2-diyl(4R)-1,3-thiazolidine-4,3-diyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 from 148e and *Cap*-4	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) LRMS: Anal. Calcd. for $C_{44}H_{42}N_8O_6S_2$ 842.99 found: 843.25 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{44}H_{43}N_8O_6S_2$ 843.2747 found: 843.2724 $(M+H)^+$
Example 150	(4R,4'R)-4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))bis(3-((2R)-tetrahydro-2-furanylcarbonyl)-1,3-thiazolidine)	 from 148e and tetrahydrofuroic acid	t_R = 4.32 min (HPLC – X-Terra C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold

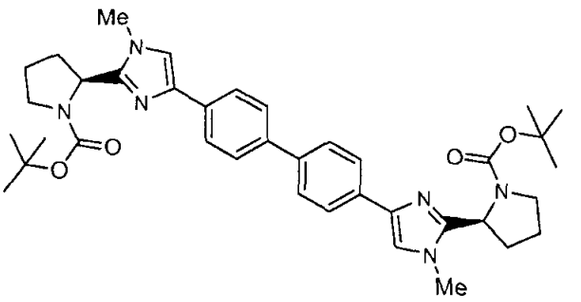
			time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA) LRMS: Anal. Calcd. for $C_{34}H_{36}N_6O_4S_2$ 656.83 found: 657.32 $(M+H)^+$

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)



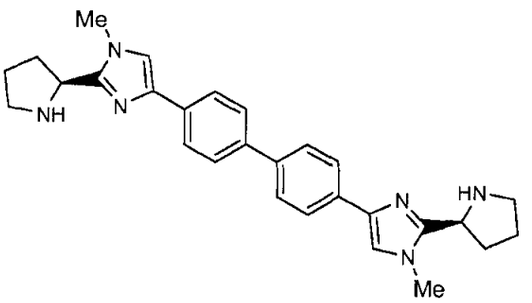
Example 151, Step a



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)*

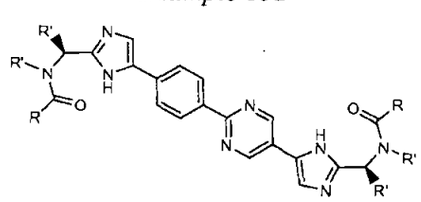
(10.2 mg, 11%) as a colorless wax.

^{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%.

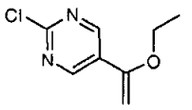
LCMS: Anal. Calcd. for: $C_{48}H_{54}N_8O_2$ 775.02; Found: 775.52 $(M+H)^+$.

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.

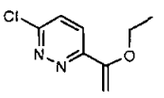
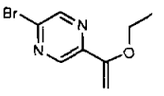
LCMS: Anal. Calcd. for $C_8H_{10}ClN_2O$ 185.05; found: 185.04 $(M+H)^+$.

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.

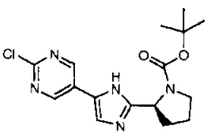
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

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 152d-1 to 152d-6

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 $(M+H)^+$.

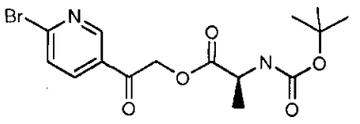
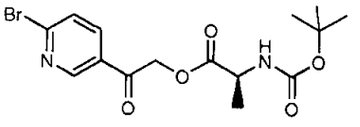
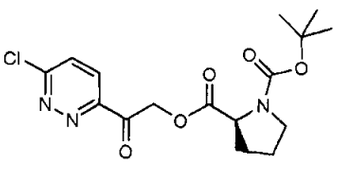
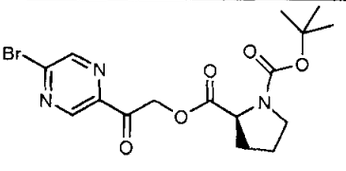
Example 152c-1, step c.

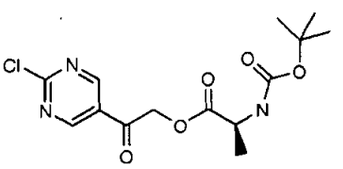
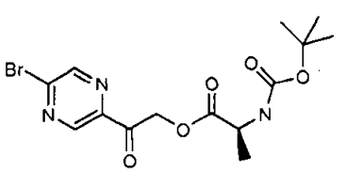
Half of the crude residue (2-bromo-1-(2-chloropyrimidin-5-yl)ethanone, ~14.5g) was dissolved into anhydrous acetonitrile (150 mL) and treated directly with N-Boc-L-proline (9.76 g, 45.35 mmol) and diisopropylethylamine (7.9 mL, 45.35 mmol). After being stirred for 3h, the solvent was removed *in vacuo* 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 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.

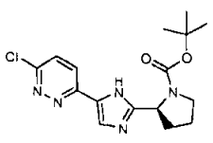
LRMS: Anal. Calcd. for $C_{16}H_{21}ClN_5O_2$ 350.14; found: 350.23 $(M+H)^+$.

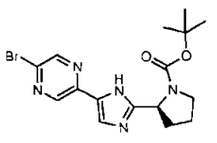
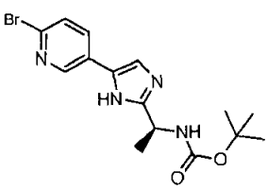
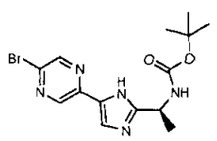
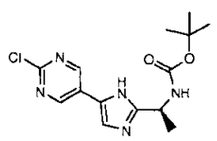
HRMS: Anal. Calcd. for $C_{16}H_{21}ClN_5O_2$ 350.1384; found: 350.1398 $(M+H)^+$.

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.

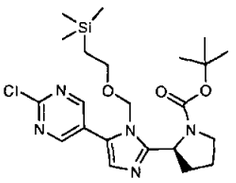
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

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.

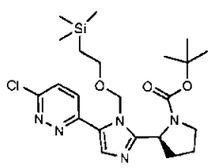
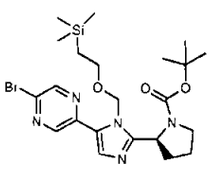
LRMS: Anal. Calcd. for $C_{22}H_{35}ClN_5O_3Si$ 480.22; found: 480.23 $(M+H)^+$.

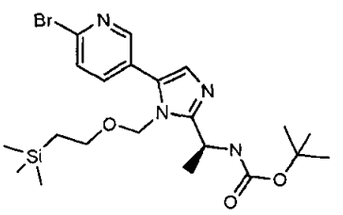
HRMS: Anal. Calcd. for $C_{22}H_{35}ClN_5O_3Si$ 480.2198; found: 480.2194 $(M+H)^+$.

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.

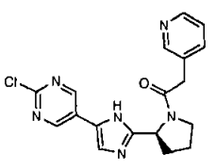
Example 152e-2	 from 152d-2	t_R = 2.34 min (85.7%); condition 1 LCMS: Anal. Calcd. for $C_{22}H_{35}ClN_5O_3Si$ 480.22; found: 480.22 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{35}ClN_5O_3Si$ 480.2198 found: 480.2198 $(M+H)^+$.
Example 152e-3	 from 152d-3	t_R = 3.18 min (>95%); condition 1 LCMS: Anal.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

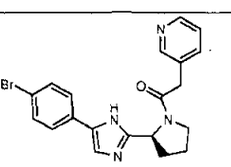
^{1}H NMR (500 MHz, DMSO-d_6) δ 9.10-9.08 (2s, 2H), 8.72-8.55 (series of m, 2H), 8.21-8.20 and 8.11-8.10 (2m, 1H), 8.00 and 7.93 (2s, 1H), 7.84-7.77 (series of m, 1H), 5.43-5.41 and 5.17-5.15 (2m, 1H), 4.02-3.94 (3m, 2H), 3.90-3.58 (3m, 2H), 2.37-2.26 (m, 1H), 2.16-1.85 (2m, 3H).

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 $(M+H)^+$.

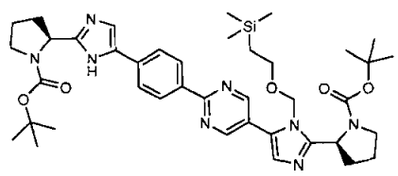
HRMS: Anal. Calcd. for $C_{18}H_{18}ClN_6O$ 369.1231; found: 369.1246 $(M+H)^+$.

Example 152f-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.

Example 152f-2	 prepared from 1b with same procedure describing the preparation of 152f-1 from 152d-1	t_R = 1.56min (>95%) LRMS: Anal. Calcd. for $C_{20}H_{20}BrN_4O$ 413.08; found: 412.99 $(M+H)^+$.

Examples 152g-1 to 152g-16

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.

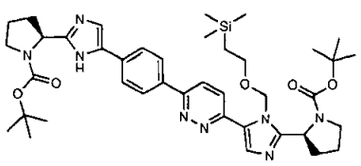
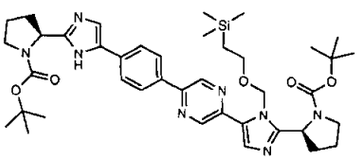
LRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.42; found: 757.42 $(M+H)^+$.

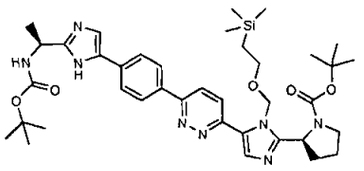
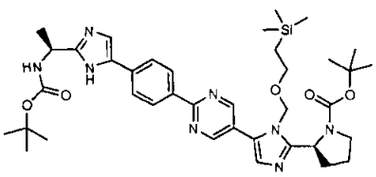
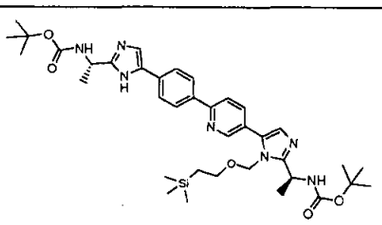
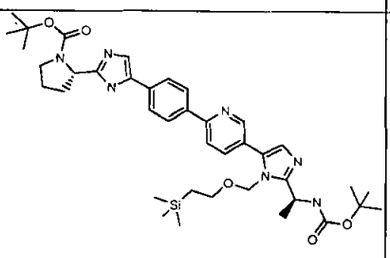
HRMS: Anal. Calcd. for $C_{40}H_{57}N_8O_5Si$ 757.4221; found: 757.4191 $(M+H)^+$.

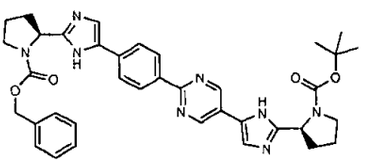
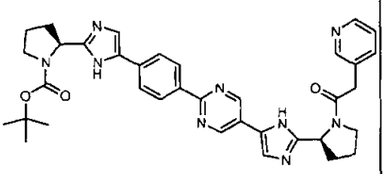
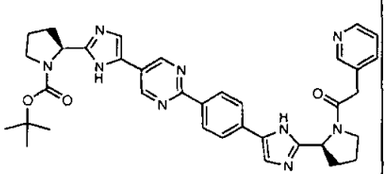
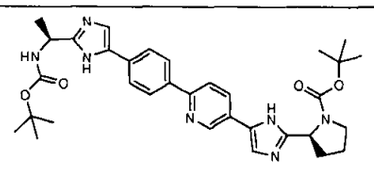
The same procedure was used to prepare Examples 152g-2 through 152g-17:

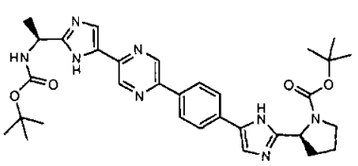
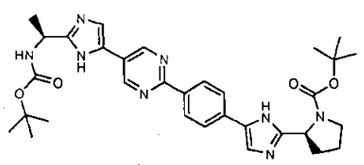
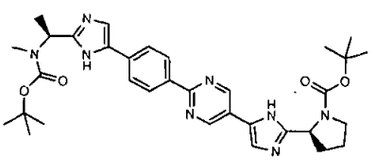
LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

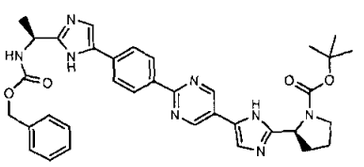
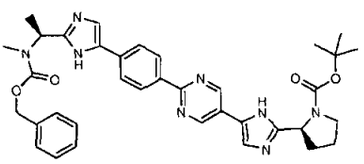
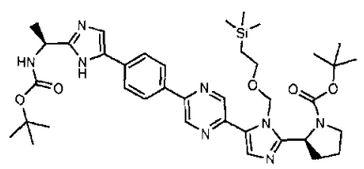
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

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 $C_{38}H_{55}N_8O_5S_i$ 731.41; found: 731.26 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{55}N_8O_5S_i$ 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 $(M+H)^+$.

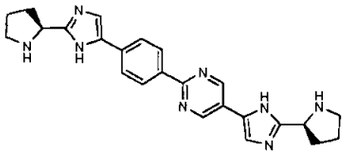
Example 152g-8	 Prepared from 1-5c and 152d-1	t_R = 2.15 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{37}H_{41}N_8O_4$ 661.33; found: 661.39 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{37}H_{41}N_8O_4$ 661.3251; found: 661.3268 $(M+H)^+$.
Example 152g-9	 Prepared from 1c and 152f-1	t_R = 1.71 min (>95%); 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	 Prepared from 1c and 152d-6	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 $(M+H)^+$. 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.

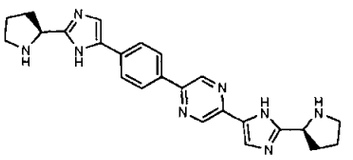
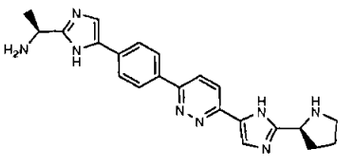
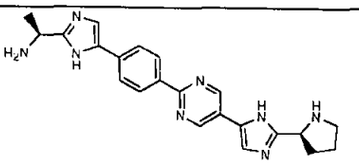
LRMS: Anal. Calcd. for $C_{24}H_{27}N_8$ 427.24; found: 427.01 $(M+H)^+$.

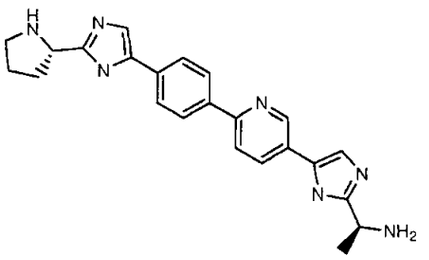
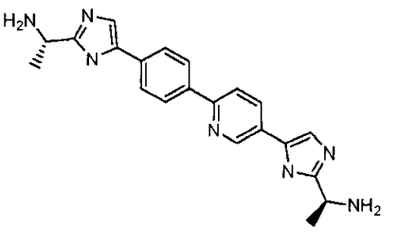
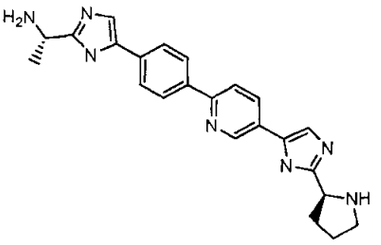
HRMS: Anal. Calcd. for $C_{24}H_{27}N_8$ 427.2359; found: 427.2363 $(M+H)^+$.

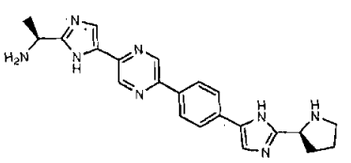
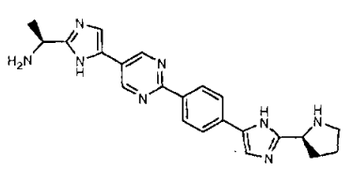
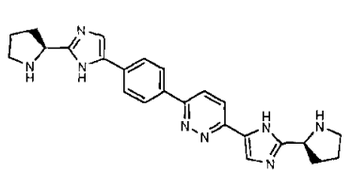
The same conditions were used to prepare Examples 152h-2 through 152h-14.

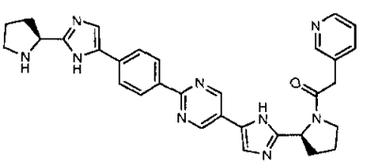
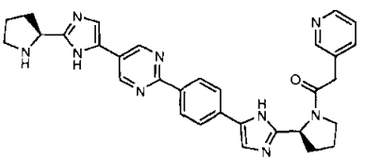
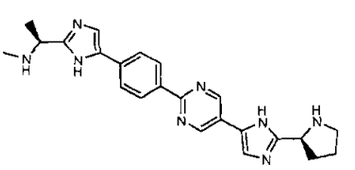
LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

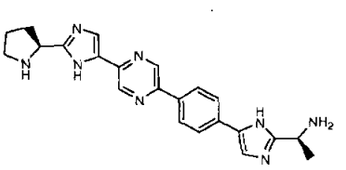
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

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		t_R = 1.28 min (89.3%); Condition 1

	Prepared from 152g-5	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

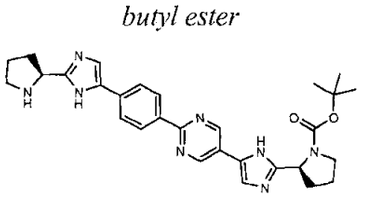
		$(M+H)^+$.
Example 152h-8	 Prepared from 152g-12	t_R = 1.29 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.22; found: 401.21 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{25}N_8$ 401.2202; found: 401.2204 $(M+H)^+$.
Example 152h-9	 Prepared from 152g-13	t_R = 1.29 min (97.6%); Condition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

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).

^1H 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.

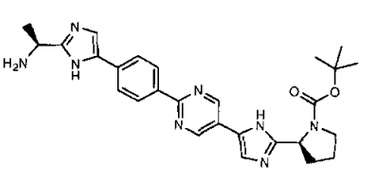
LRMS: Anal. Calcd. for $C_{29}H_{35}N_8O_2$ 527.29; found: 527.34 $(M+H)^+$.

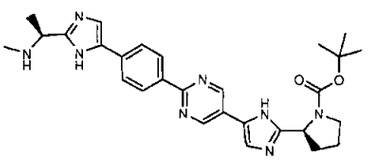
HRMS: Anal. Calcd. for $C_{29}H_{35}N_8O_2$ 527.2883; found: 527.2874 $(M+H)^+$.

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 $(M+H)^+$.

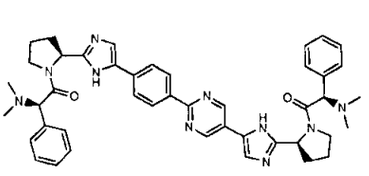
		HRMS: Anal. Calcd. for $C_{27}H_{33}N_8O_2$ 501.2726 found: 501.2709 $(M+H)^+$.
Example 152i-3	 Prepared from 152g-16	t_R = 1.77 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{28}H_{35}N_8O_2$ 515.29; found: 515.37 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{28}H_{35}N_8O_2$ 515.2883 found: 515.2869 $(M+H)^+$.

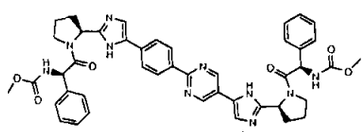
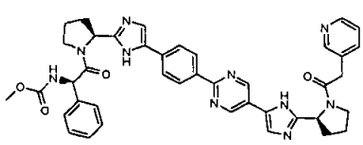
Examples 152j-1 to 152j-28

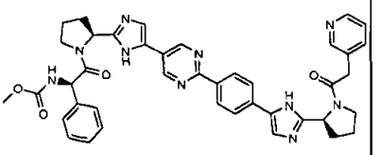
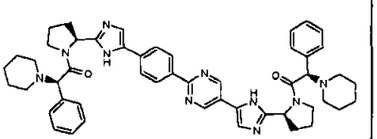
Examples 152j were isolated as TFA or AcOH salts prepared using the procedure to convert Example 148e to 148.

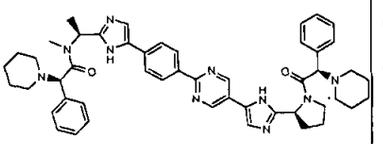
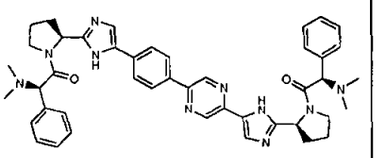
LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

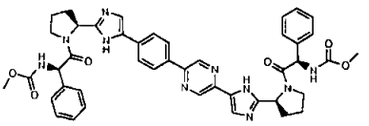
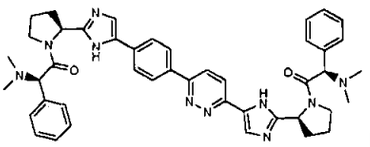
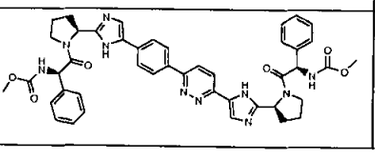
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

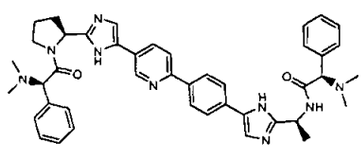
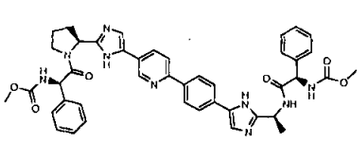
Example	*Compound Name*	*Structure*	*Data*
Example 152j-1	(1R)-2-((2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-	 Prepared from 152h-1 and *Cap*-1.	t_R = 1.61 min; (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{44}H_{49}N_{10}O_2$

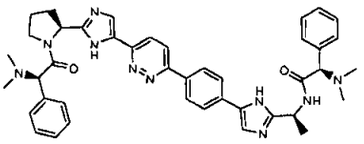
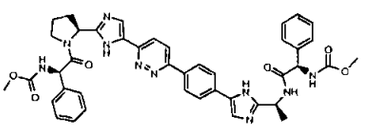
	pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine		749.40 found: 749.32 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{44}H_{49}N_{10}O_2$ 749.4040 found: 749.4042 $(M+H)^+$
Example 152j-2	methyl ((1R)-2-((2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 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 $(M+H)^+$ 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 $(M+H)^+$

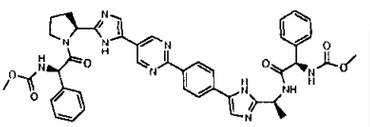
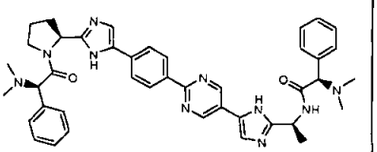
			HRMS: Anal. Calcd. for $C_{41}H_{41}N_{10}O_4$ 737.3312 found: 737.3342 $(M+H)^+$
Example 152j-4	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(2-(4-(2-((2S)-1-(3-pyridinylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate	 Prepared from 152h-12 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 $C_{50}H_{57}N_{10}O_2$

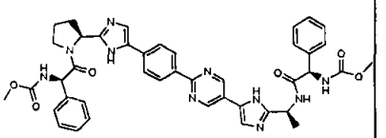
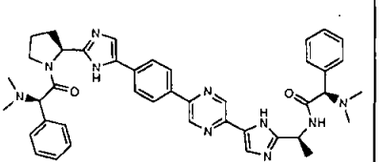
			829.4666 found: 829.4658 $(M+H)^+$
Example 152j-6	(2R)-N-methyl-2-phenyl-N-((1S)-1-(4-(4-(5-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)ethyl)-2-(1-piperidinyl)acetamide	 Prepared from 152h-13 and *Cap*-14	t_R = 1.66 min (>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 $(M+H)^+$

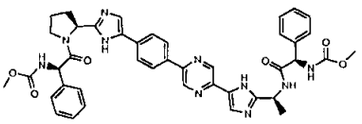
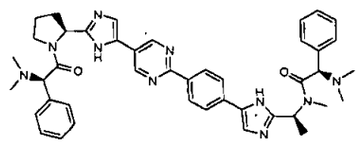
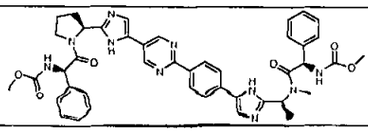
Example 152j-8	methyl ((1R)-2-((2S)-2-(5-(5-(4-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-2-pyrazinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from 152h-2 and *Cap*-4	t_R = 2.01 min (>95%); Condition 1 LRMS: Anal. 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-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	t_R = 1.76 min (>95%); Condition 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-		t_R = 2.17 min (>95%); Condition 1

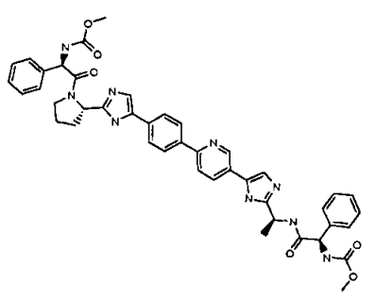
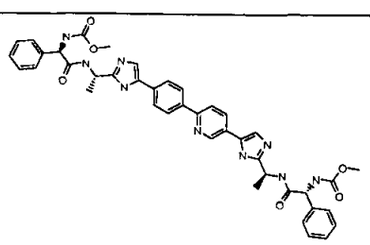
	((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-3-pyridazinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	Prepared from 152h-10 and *Cap*-4	LRMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 809.35 found: 809.59 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{44}H_{45}N_{10}O_6$ 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-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyridinyl)phenyl)-1H-imidazol-2-yl)ethyl)-2-phenylacetamide	 Prepared from 152h-7 and *Cap*-1	t_R = 1.56 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{43}H_{48}N_9O_2$ 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)e	 Prepared from 152h-7 and *Cap*-4	t_R = 1.95 min (>95%); Condition 1 LRMS: Anal. Calcd. for

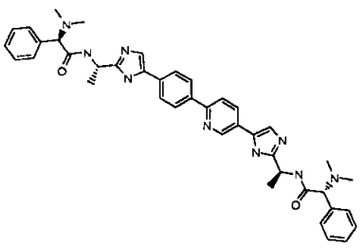
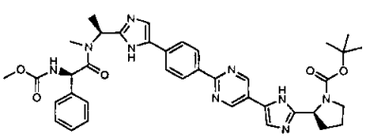
	thyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		$C_{43}H_{44}N_9O_6$ 782.34 found: 782.93 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{43}H_{44}N_9O_6$ 782.3415 found: 782.3398 $(M+H)^+$
Example 152j-13	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(4-(6-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-pyridazinyl)phenyl)-1H-imidazol-2-yl)ethyl)-2-phenylacetamide	 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 $(M+H)^+$ 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-	 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 $(M+H)^+$

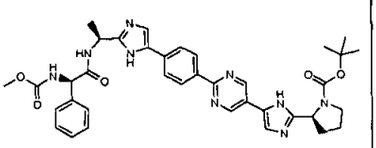
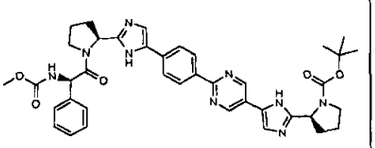
	imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		HRMS: Anal. Calcd. for $C_{42}H_{43}N_{10}O_6$ 783.3367 found: 783.3337 $(M+H)^+$
Example 152j-15	methyl ((1R)-2-((2S)-2-(5-(2-(4-(2-((1S)-1-(((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)amino)ethyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 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 $C_{42}H_{43}N_{10}O_6$ 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

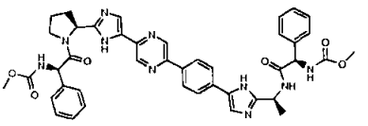
			$C_{42}H_{47}N_{10}O_2$ 723.3883 found: 723.3893 $(M+H)^+$
Example 152j-17	methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((1S)-1-(((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)amino)ethyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from 152h-9 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-		t_R = 2.00 min (>95%); Condition

	(((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	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)e	 Prepared from 152h-6 and *Cap*-4	t_R = 1.44 min condition 2, 90%) LRMS: Anal. Calcd. for $C_{41}H_{41}N_9O_6$

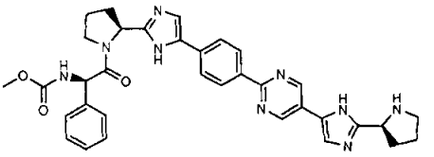
	thyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)ethyl)amino)-2-oxo-1-phenylethyl)carbamate		755.32; found: 756.35 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{42}N_9O_6$ 756.3258 found: 756.3239 $(M+H)^+$.
Example 152j-24	(2R)-2-(dimethylamino)-N-((1S)-1-(5-(6-(4-(2-((1S)-1-(((2R)-2-(dimethylamino)-2-phenylacetyl)amino)ethyl)-1H-imidazol-5-yl)phenyl)-3-pyridinyl)-1H-imidazol-2-yl)ethyl)-2-phenylacetamide	 Prepared from 152h-6 and Cap1	t_R = 1.18 min (condition 2, 91%) LRMS: Anal. Calcd. for $C_{41}H_{45}N_9O_2$ 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.

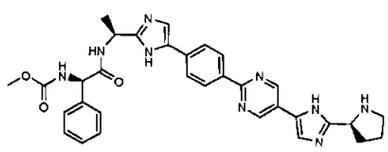
LRMS: Anal. Calcd. for $C_{34}H_{36}N_9O_3$ 618.29; found: 618.42 $(M+H)^+$.

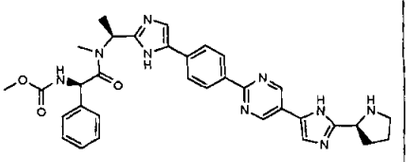
HRMS: Anal. Calcd. for $C_{34}H_{36}N_9O_3$ 618.2921; found: 618.2958 $(M+H)^+$.

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.

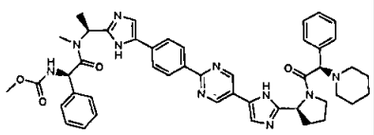
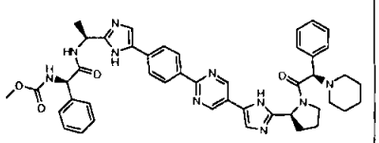
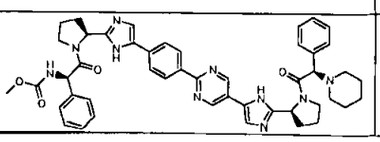
			Calcd. for $C_{32}H_{34}N_9O_3$ 592.2785; found: 592.2775 $(M+H)^+$.
Example 152k-3		 Prepared from 152j-25	t_R = 1.79 min (>95 %); Condition 1 LRMS: Anal. Calcd. for $C_{33}H_{36}N_9O_3$ 606.29; found: 606.43 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{33}H_{36}N_9O_3$ 606.2941; found: 606.2925 $(M+H)^+$.

Examples 152l-1 to 152l-

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.

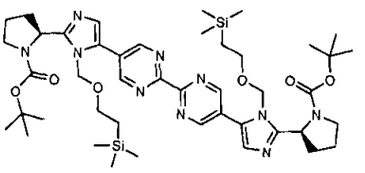
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

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-		t_R = 1.87 min (>95%); Condition

	(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*	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 $(M+H)^+$

Example 153a-1 from 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.

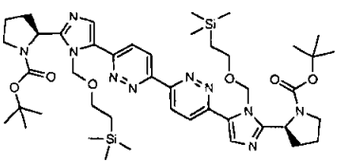
LRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.49; found: 889.57 $(M+H)^+$.

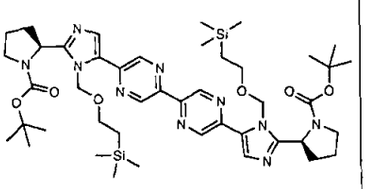
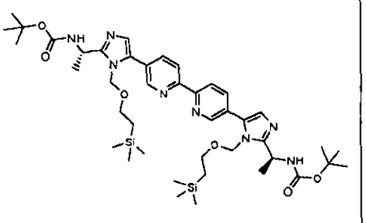
HRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.4940; found: 889.4920 $(M+H)^+$.

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.

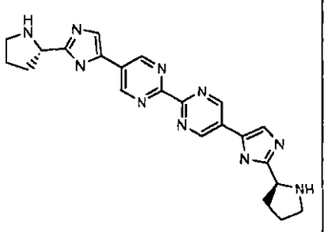
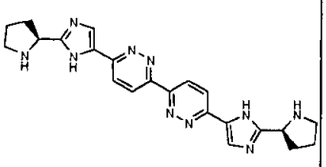
			Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.494; found: 889.4951 $(M+H)^+$.
Example 153a-3		 Prepared from 152e-3	t_R = 3.37 min (95%); Condition 1 LRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.49; found: 889.51 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{44}H_{69}N_{10}O_6Si_2$ 889.4940; found: 889.4915 $(M+H)^+$.
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 $(M+H)^+$.

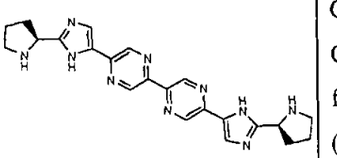
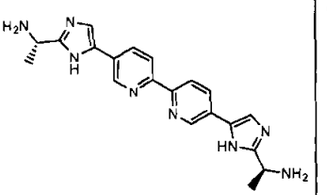
Example 153b-1-153b-3

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 $(M+H)^+$

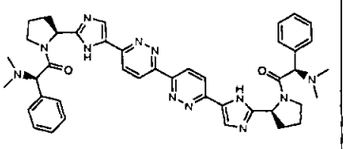
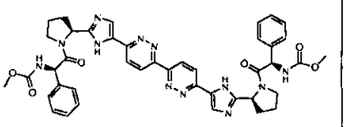
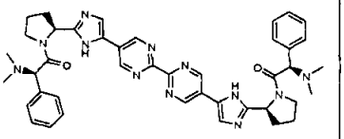
Example 153b-3		 Prepared from 153a-3	t_R = 1.40 min (>95%); Condition 1 LRMS: Anal. Calcd. for $C_{22}H_{25}N_{10}$ 429.23; found: 429.20 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{22}H_{25}N_{10}$: 429.2264; Found: 429.2254 $(M+H)^+$
Example 153b-4		 Prepared from 153a-4	t_R = 0.85 min (condition 1) LCMS: Anal. Calcd. for $C_{20}H_{22}N_8$ 374; found: 375 $(M+H)^+$.

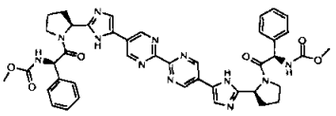
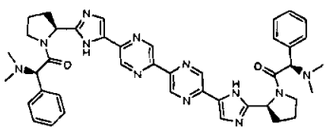
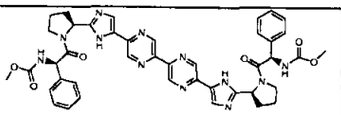
Examples 153c-1 to 153c-7

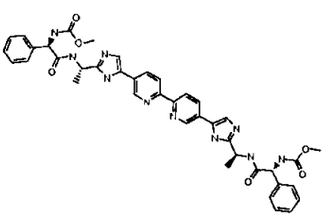
Examples 153c-1 through 153c-7 were isolated as TFA or AcOH salts using the procedure used to convert Example 148e to 148.

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)))biscarbamate	 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 $(M+H)^+$ 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-	 Prepared from 153b-3 and *Cap*-4	t_R = 2.00 min (>95%); Condition 1 LRMS: Anal. Calcd.

	pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate		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 LS LC Conditions:

Condition 1: Solvent A: 10%methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Phenomenex-Luna 3.0 x 5.0mm S10; Wavelength: 220nM; Flow rate: 4mL/min; 0%B to 100% B over 4min with a 1min hold time

Condition 2: Solvent A: 10%methanol/90% water/0.1% TFA; Solvent B: 90% methanol/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 4min with a 1min hold time

Condition 3: Solvent A: 5% acetonitrile/95% water/10mmol ammonium acetate; Solvent B: 95% acetonitrile/5% water/10mmol ammonium acetate; Column: Phenomenex 10u C18 4.6 x 5.0mm; Wavelength: 220nM; Flow rate: 4mL/min; 0%B to 100% B over 4min with a 1min hold time

Condition 4: Solvent A: 5% acetonitrile/95% water/10mmol ammonium acetate; Solvent B: 95% acetonitrile/5% water/10mmol ammonium acetate; Column: Luna 4.6 x 50mm S10; Wavelength: 220nM; Flow rate: 4mL/min; 0%B to 100% B over 3min with a 1min hold time

Condition 5: Solvent A: 10%methanol/90% water/0.1% TFA; Solvent B: 90% methanol/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 3min with a 1min hold time

Condition 6: Solvent A: 5% acetonitrile/95% water/10mmol ammonium acetate; Solvent B: 95% acetonitrile/5% water/10mmol ammonium acetate; Column: Phenomenex-Luna 3.0 x 50mm S10; Wavelength: 220nM; Flow rate: 4mL/min; 0%B to 100% B over 8min with a 2min hold time

Condition 7: Solvent A: 10%methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Phenomenex-Luna 3.0 x 5.0mm S10; Wavelength: 220nM; Flow rate: 4mL/min; 0%B to 100% B over 3min with a 1min hold time

Condition 8: Solvent A: 10%methanol/90% water/0.2% H_3PO_4; Solvent B: 90% methanol/10% water/0.2% H_3PO_4; Column: YMC ODS-A 4.6 x 50mm S5; Wavelength: 220nM; Flow rate: 4mL/min; 0%B to 100% B over 4min with a 1min hold time

Condition 9: Solvent A: 10%methanol/90% water/0.2% H_3PO_4; Solvent B: 90% methanol/10% water/0.2% H_3PO_4; Column: YMC ODS-A 4.6 x 50mm S5;

Wavelength: 220nM; Flow rate: 2.5mL/min; 0%B to 50% B over 8min with a 3min hold time

Condition 10: Xbridge C18, 150 x4.6 mm I.D. S-3.5um; Mobile Phase A: 95%Water-5% Acetonitrile with 10 mM ammonium acetate (pH=5); Mobile phase B: 95% Acetonitrile-5% Water with 10 mM ammonium acetate (pH=5); Isocratic 30% B for 20 min; Flow rate: 1 mL/min; UV detection: 220 nm

Condition 11: Solvent A: 10%methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Phenomenex 10u C18 3.0 x 5.0mm; Wavelength: 220nM; Flow rate: 4mL/min; 30%B to 100% B over 4min with a 1min hold time

Condition 12: Solvent A: 10%methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Phenomenex 10u C18 3.0 x 5.0mm; Wavelength: 220nM; Flow rate: 4mL/min; 20%B to 100% B over 4min with a 1min hold time

Condition 13: Solvent A: 10%methanol/90% water/0.2% H_3PO_4; Solvent B: 90% methanol/10% water/0.2% H_3PO_4; Column: YMC ODS-A 4.6 x 50mm S5; Wavelength: 220nM; Flow rate: 2.5mL/min; 0%B to 100% B over 8min with a 3min hold time

Section LS Preparative HPLC Conditions:

Condition 1: Solvent A: 10%methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Phenomenex-Luna 30 x 100mm S10; Wavelength: 220nM; Flow rate: 30mL/min; 0%B to 100% B over 10min with a 2min hold time

Condition 2: Solvent A: 10%methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Xterra Prep MS C18 30 x 50mm 5u;

Wavelength: 220nM; Flow rate: 30mL/min; 0%B to 100% B over 8min with a 3min hold time

Condition 3: Solvent A: 10%methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Xterra Prep MS C18 30 x 50mm 5u; Wavelength: 220nM; Flow rate: 25mL/min; 10%B to 100% B over 8min with a 2min hold time

Condition 4: Solvent A: 10%methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Xterra 19 x 100mm S5; Wavelength: 220nM; Flow rate: 20mL/min; 30%B to 100% B over 5min with a 3min hold time

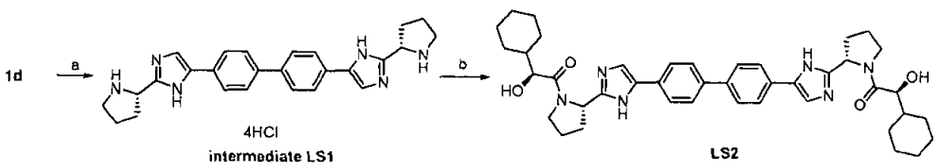
Condition 5: Solvent A: 10%methanol/90% water/0.1% TFA; Solvent B: 90% methanol/10% water/0.1% TFA; Column: Phenomenex-Luna 30 x 100mm S10; Wavelength: 220nM; Flow rate: 30mL/min; 10%B to 100% B over 8min with a 2min hold time

Condition 6: Solvent A: 10% Acetonitrile/90% water/0.1% TFA; Solvent B: 90% Acetonitrile/10% water/0.1% TFA; Column: Phenomenex-Luna 21 x 100mm S10; Wavelength: 220nM; Flow rate: 25mL/min; 0%B to 60% B over 10min with a 5min hold time

Experimentals:

Compound LS2

(1S,1'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(1-cyclohexyl-2-oxoethanol)

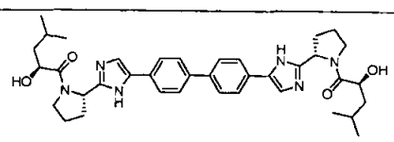


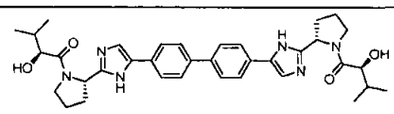
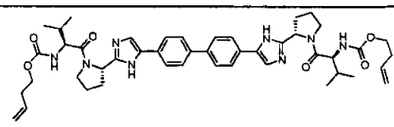
Step a: To 1d (1.4g; 2.24mmol) was added 30mL 4N HCl in dioxane. After 3h, 60mL ether was added and the precipitate was filtered and dried under high vacuum providing 1.02g (80%) intermediate LS1 as a pale yellow powder. ^{1}H NMR (DMSO-

d_6, δ = 2.5 ppm, 500 MHz): δ 10.41 (s, 2H), 9.98 (s, 2H), 8.22 (s, 2H), 8.06 (d, *J* = 8.54Hz, 4H), 7.92 (d, *J* = 8.55Hz, 4H), 5.07 (s, 2H), 3.43-3.54 (m, 2H), 3.33-3.43 (m, 2H), 2.43-2.59 (m, 4H), 2.16-2.28 (m, 2H), 1.94-2.09 (m, 2H). LC (Cond. 1): RT = 1.28 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{28}N_6$: 425.24; found 425.56.

Step b: To intermediate LS1 (200mg; 0.35mmol) in 2mL DMF was added DIPEA (0.30mL; 1.75mmol), (S)-2-cyclohexyl-2-hydroxyacetic acid (61mg; 0.39mmol), followed by HATU (147mg; 0.38mmol). After stirring at ambient temperature for 18h, the reaction mixture was split into two portions and purified *via* preparative HPLC (Cond'n 1). Fractions containing desired product were pooled and passed through an MCX cartridge (Oasis; 6g; preconditioned with two column lengths of methanol). The cartridge was washed with two column lengths of methanol and product was eluted with ammonia/methanol. Concentration provided 65mg of LS2 (26%) as a colorless powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.87-1.30 (m, 12H) 1.38-1.53 (m, *J*=24.72, 11.90 Hz, 4H) 1.54-1.75 (m, 8H) 1.95-2.21 (m, 6H) 3.72-3.86 (m, 6H) 5.13 (t, *J*=6.56 Hz, 2H) 7.87 (d, *J*=7.93 Hz, 4H) 7.96 (d, *J*=6.41 Hz, 4H) 8.13 (s, 2H) (imidazole NH and hydroxyl protons unaccounted for). LC (Cond'n 2): RT = 3.07 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{52}N_6O_4$: 705.9; found 705.6.

The following analogs were prepared in similar fashion to the preparation of LS2 from intermediate LS1 employing the appropriate carboxylic acid:

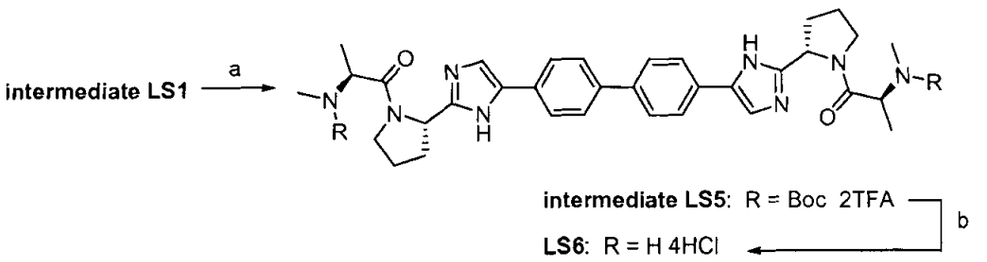
Example Number	*Compound Name*	*Structure*	*Analytical Data*
LS3	(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(4-methyl-1-oxo-2-pentanol)		LC/MS: 2.02 min (Cond'n 1); Anal. Calcd. for $[M+H]^+$ $C_{38}H_{48}N_6O_4$: 653.4; found 653.2.

LS4	(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(3-methyl-1-oxo-2-butanol)		LC/MS: 1.99 min (Cond'n 3); Anal. Calcd. for $[M+H]^+$ $C_{36}H_{44}N_6O_4$: 625.3; found 625.3.
LS16	3-buten-1-yl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(((3-buten-1-yloxy)carbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 from intermediate LS1 and (S)-2-((but-3-enyloxy)carbonylamino)-3-methylbutanoic which was prepared from L-valine and butenylchloroformate in similar fashion to the preparation of *Cap-51*	^{1}H NMR (500 MHz, CH_3OD) δ ppm 0.81-1.10 (m, 12H) 1.90-2.15 (m, 4H) 2.15-2.51 (m, 8H) 3.82-3.96 (m, 2H) 3.97-4.05 (m, 2H) 4.05-4.19 (m, 4H) 4.25 (d, *J*=7.02 Hz, 2H) 4.62 (s, 2H) 5.00-5.17 (m, 4H) 5.20 (t, *J*=5.65 Hz, 2H) 5.79-5.93 (m, 2H) 7.20-7.47 (m, 2H) 7.59-7.90 (m, 8H)

5

Example LS6

(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N-methyl-1-oxo-2-propanamine)

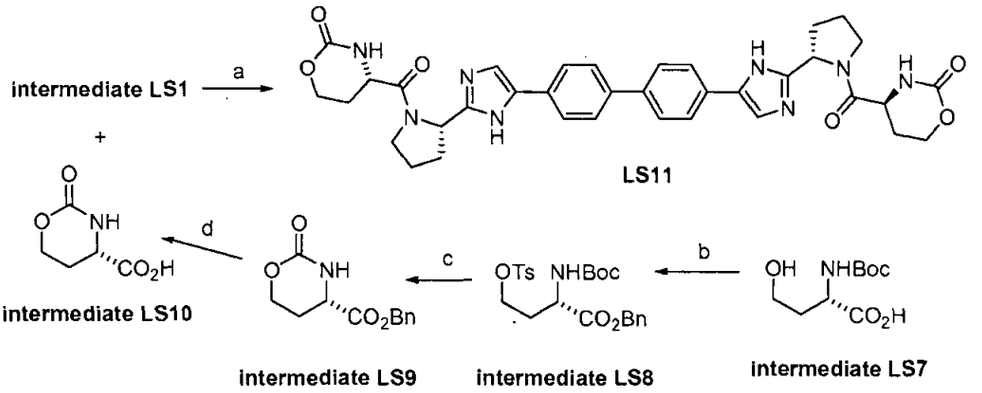


Step a: To intermediate LS1 (64mg; 0.11mmol) in 1 mL DMF was added (S)-2-(tert-butoxycarbonyl(methyl)amino)propanoic acid (48mg; 0.24mmol), Hunig's base (0.12mL; 0.67mmol) and HATU (90mg; 0.24mmol). After 3h, the reaction was purified *via* preparative HPLC (Cond'n 2). Fractions containing intermediate LS5 were pooled and concentrated providing intermediate LS5 as a colorless powder (43mg; 48%) after drying under high vacuum. LC (Cond'n 4): RT = 2.12 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{58}N_8O_6$: 795.4; found 795.5.

Step b: Intermediate LS5 was allowed to stir in 2mL HCl/Dioxane (4N) for 18h at which time 10mL ether was added and the resultant precipitate was filtered and dried under high vacuum providing LS6 (45mg; 155%) as a colorless solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.00-2.11 (m, 2H) 2.12-2.27 (m, 4H) 2.38-2.47 (m, 2H) 2.39-2.48 (m, 2H) 2.58 (t, *J*=5.19 Hz, 2H) 3.78-3.85 (m, 2H) 3.91-4.02 (m, 2H) 4.21-4.32 (m, 2H) 5.26 (t, *J*=7.17 Hz, 2H) 7.93 (d, *J*=7.32 Hz, 4H) 8.02 (d, *J*=7.94 Hz, 4H) 8.12-8.21 (m, 2H) 8.69-8.81 (m, 2H) 9.09-9.17 (m, 2H); N-Me protons obscured by DMSO peak with 2 other protons unaccounted for. LC (Cond'n 5): RT = 1.71 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{42}N_8O_2$: 595.3; found 595.6.

Example LS11

(4S,4'S)-4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl))bis(1,3-oxazinan-2-one)



Step a: To intermediate LS1 (65mg; 0.11mmol) in 1mL DMF was added HATU (91mg; 0.24mmol), (S)-2-oxo-1,3-oxazinane-4-carboxylic acid (intermediate LS10; 35mg; 0.24mmol), followed by DIPEA (0.12mL; 0.68mmol. After 3h, the reaction mixture was twice purified *via* preparative HPLC (Cond'n 3). Appropriate fractions were pooled and concentrated under high vacuum providing 8mg (10%) bis TFA LS11 as a colorless oil. ^{1}H NMR (500 MHz, CH_3OD) δ ppm ^{1}H NMR (500 MHz, CH_3OD) δ ppm 1.99-2.43 (m, 10H) 2.48-2.66 (m, 1.98 Hz, 2H) 3.82-3.95 (m, 4H) 4.17-4.40 (m, 4H) 4.57 (t, *J*=5.80 Hz, 2H) 5.23-5.41 (m, 2H) 7.73-7.97 (m, 10H); imidazole and carbamate NH protons are unaccounted for. LC (Cond'n 6): RT = 2.28 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{42}N_8O_2$: 679.3; found 679.4.

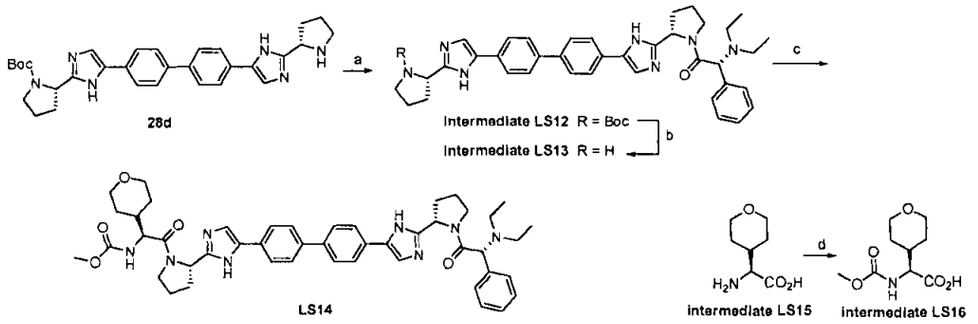
Step b: Performed as in Baldwin et al, *Tetrahedron* 1988, *44*, 637

Step c: Performed as in Sakaitani and Ohfune, *J. Am. Chem. Soc.* 1990, *112*, 1150 for the conversion of compound 1 to 5. Purification *via* Biotage (40M cartridge; 1:1 ether/ethyl acetate) then preparative HPLC (Cond'n 4) provided 77mg (8%) intermediate LS9 as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.02-2.21 (m, 1H) 2.23-2.41 (m, 1H) 4.11-4.38 (m, 3H) 5.11-5.31 (m, 2H) 6.15 (s, 1H) 7.27-7.46 (m, 5H). LC (Cond'n 7): RT = 1.24 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{34}H_{42}N_8O_2$: 236.1; found 236.4.

Step d: Intermediate LS9 was hydrogenated under 1 atm H_2 in 3mL methanol with 10mg Pd/C (10%) for 18h. The reaction mixture was filtered through a pad of diatomaceous earth (Celite®) and concentrated to provide intermediate LS10 (40mg; 83%) as a colorless powder. ^{1}H NMR (500 MHz, CH_3OD) δ ppm 2.08-2.18 (m, 1H) 2.26-2.38 (m, 1H) 4.19 (t, *J*=5.95 Hz, 1H) 4.25-4.40 (m, 2H).

Example LS14

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



Step a: To 28 (1.5g; 2.86mmol) in 25mL DMF was added sequentially *Cap*-2 (697mg; 2.86mmol), HATU (1.2g; 3.14mmol), and Hunig's base (1.5mL; 8.57mmol). After 3h, the solution was concentrated to 10mL and partitioned between chloroform and water. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to an amber oil which was subjected to silica gel chromatography (Biotage; loaded on 40 samplet with dichloromethane; eluted on 40M cartridge with 0 to 12% dichloromethane/methanol over 1200mL). Fractions containing intermediate LS12 were pooled and concentrated to provide material which contained residual DMF. This material was redissolved in dichloromethane and washed with water (3 x 50mL) and then brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated to 761mg powder which was repurified *via* silica gel chromatography (Biotage; loaded on 40 samplet with dichloromethane; eluted on 40M cartridge with 0 to 80% 4:1 chloroform : methanol/ethyl acetate over 1500mL) to provide intermediate LS12 (501mg; 25%) as a colorless powder. LC (Cond'n 8): RT = 1.24 min.

Step b: To intermediate LS12 (490mg; 0.69mmol) was added 6mL HCl/Dioxane followed by 25mL dichloromethane. After 24h, 75mL ether was added, the reaction mixture was filtered and the precipitate was dried under vacuum providing intermediate LS13 · 4HCl (434mg; quant) as a tan solid. ^{1}H NMR (300 MHz, CH_3OD) δ ppm 1.16-1.29 (m, 3H) 1.37 (t, *J*=6.95 Hz, 3H) 1.89-2.06 (m, 6.95 Hz, 1H) 2.12-2.51 (m, 5H) 2.52-2.85 (m, 4H) 3.02-3.24 (m, 2H) 3.42-3.55 (m, 7.32 Hz, 1H) 3.58-3.71 (m, 2H) 4.26-4.41 (m, 1H) 5.18-5.37 (m, 2H) 5.65 (s, 1H) 7.57-7.66 (m, 3H) 7.67-7.75 (m, 1H) 7.86-8.04 (m, 10H) 8.14 (s, 1H). LC (Cond'n 8): RT = 1.92 min.

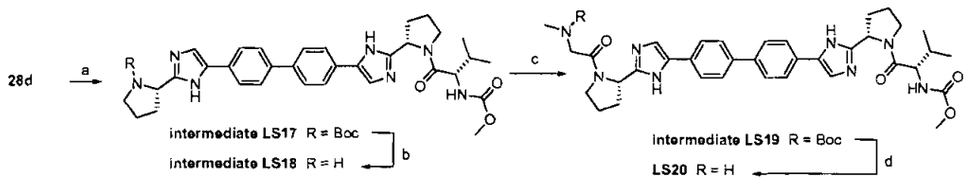
Step c: To intermediate LS13 · 4HCl (75mg; 0.099mmol) in 0.7mL DMF was added sequentially intermediate LS16 (26mg; 0.118mmol), HATU (45mg; 0.118mmol), and Hunig's base (0.10mL; 0.591mmol). After 2h, the reaction mixture was filtered through diatomaceous earth (Celite®), the pad washed with 0.3mL methanol and the resultant filtrate was purified *via* preparative HPLC (Cond'n 5) in two separate injections. The fractions containing desired product were passed through an MCX cartridge (Oasis; 1g; preconditioned with two column lengths of methanol). The cartridge was washed with two column lengths of methanol and product was eluted with ammonia/methanol. Concentration provided 36mg of LS14 as a colorless powder which was assayed to be of 82% diastereomeric purity (most likely epimeric at the stereogenic carbon in intermediate 16). Resubjected to preparative HPLC purification (2x) providing LS14 (13mg; 16%) as a colorless solid. ^{1}H NMR (500 MHz, CH_3OD) δ ppm 0.99 (q, *J*=6.92 Hz, 6H) 1.25-1.72 (m, 5H) 1.80-2.42 (m, 10H) 2.47-2.61 (m, 3H) 2.66-2.78 (m, 2H) 3.35-3.43 (m, 2H) 3.65-3.71 (m, 3H) 3.89-4.01 (m, 4H) 4.01-4.10 (m, 1H) 4.32 (d, *J*=8.24 Hz, 1H) 5.11-5.22 (m, 1H) 6.95-7.17 (m, 3H) 7.30-7.44 (m, 3H) 7.53 (d, *J*=7.02 Hz, 1H) 7.62-7.89 (m, 8H). LC (Cond'n 9): RT = 5.31 min.

Step d: Intermediate LS16 was prepared in analogous fashion to the procedure describing the synthesis of *Cap*-51 substituting (S)-2-amino-2-(tetrahydro-2H-pyran-4-yl)acetic acid (available from Astatech) for L-Valine. ^{1}H NMR (300 MHz, DMSO-

d_6) δ ppm 1.15-1.63 (m, 5H) 1.75-2.03 (m, 1H) 3.54 (s, 3H) 3.76-3.98 (m, 4H) 7.45 (d, *J*=8.42 Hz, 1H); one proton obscured by water peak.

Example LS20

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-methylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate

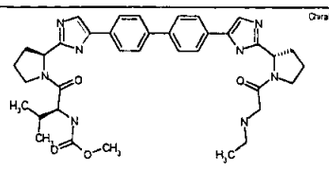
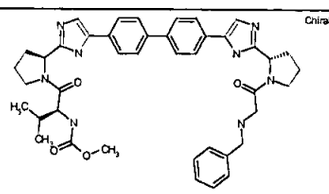
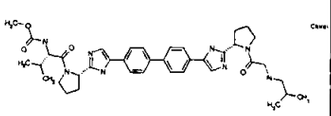


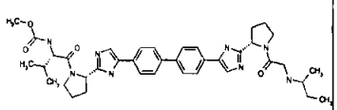
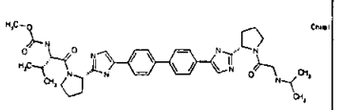
Step a & b: Intermediate LS18 was prepared in analogous fashion to the procedure describing the synthesis of intermediate LS13 substituting *Cap*-51 for *Cap*-2.

Step c: To intermediate LS18 (100mg; 0.14mmol) in 1.4mL DMF was added sequentially N-Boc Sarcosine (30mg; 0.16mmol), Hunig's base (0.13mL; 0.72mmol) and HATU (60mg; 0.16mmol). After 2h the reaction mixture was partitioned into dichloromethane, washed with $NaHCO_3$ (aq), brine, dried over magnesium sulfate, filtered and concentrated to crude intermediate LS19 which was used directly in the next step. LC (Cond'n 5): RT = 2.42 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{52}N_8O_6$: 753.4; found 753.9.

Step d: Crude intermediate LS19 was dissolved in 0.5mL methanol and 5mL 4N HCl/Dioxane. After stirring for 1h, the reaction was concentrated and purified *via* preparative HPLC (Cond'n 6) and the fractions containing desired product were passed through an MCX cartridge (Oasis; 1g; preconditioned with two column lengths of methanol). The cartridge was washed with two column lengths of methanol and product was eluted with ammonia/methanol. Concentration provided LS20 (32mg; 34%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.74-0.98 (m, 6H) 1.79-2.24 (m, 9H) 2.29-2.38 (m, 2H) 3.19-3.51 (m, 8H) 3.50-3.56 (m, 3H) 3.59-3.71 (m, 1H) 3.81 (s, 1H) 3.97-4.17 (m, 1H) 5.01-5.16 (m, 2H) 7.30 (d, *J*=7.93 Hz, 1H) 7.51 (s, 1H) 7.59-7.74 (m, 4H) 7.79 (d, *J*=7.63 Hz, 4H) 11.78 (s, 1H). LC (Cond'n 5): RT = 2.00 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{44}N_8O_4$: 653.4; found 653.7.

The following analogs were prepared in similar fashion to the preparation of LS20 from LS18 substituting the appropriate carboxylic acid for N-Boc Sarcosine :

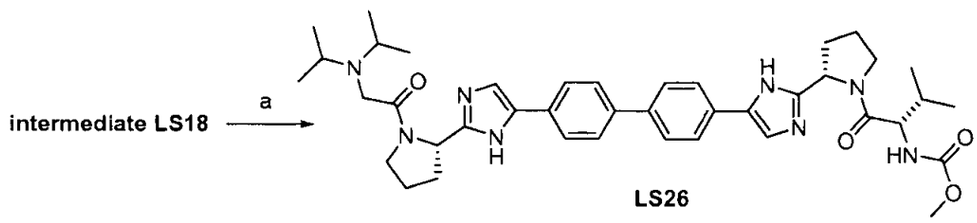
Example Number	*Compound Name*	*Structure*	*Analytical Data*
LS21	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-ethylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LC/MS: 2.34 min (Cond'n 2); Anal. Calcd. for $[M+H]^+$ $C_{37}H_{46}N_8O_4$: 667.4; found 667.7.
LS22	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-benzylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LC/MS: 2.34 min (Cond'n 5); Anal. Calcd. for $[M+H]^+$ $C_{42}H_{48}N_8O_4$: 729.4; found 729.8.
LS23	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-isobutylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-		LC/MS: 2.07 min (Cond'n 5); Anal. Calcd. for $[M+H]^+$ $C_{39}H_{50}N_8O_4$: 695.4; found 695.8.

	biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		
LS24	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-sec-butylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LC/MS: 2.03 min (Cond'n 5); Anal. Calcd. for $[M+H]^+$ $C_{39}H_{50}N_8O_4$: 695.4; found 695.9.
LS25	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-isopropylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LC/MS: 1.97 min (Cond'n 5); Anal. Calcd. for $[M+H]^+$ $C_{38}H_{48}N_8O_4$: 681.4; found 681.7.

5

Example LS26

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diisopropylglycyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate



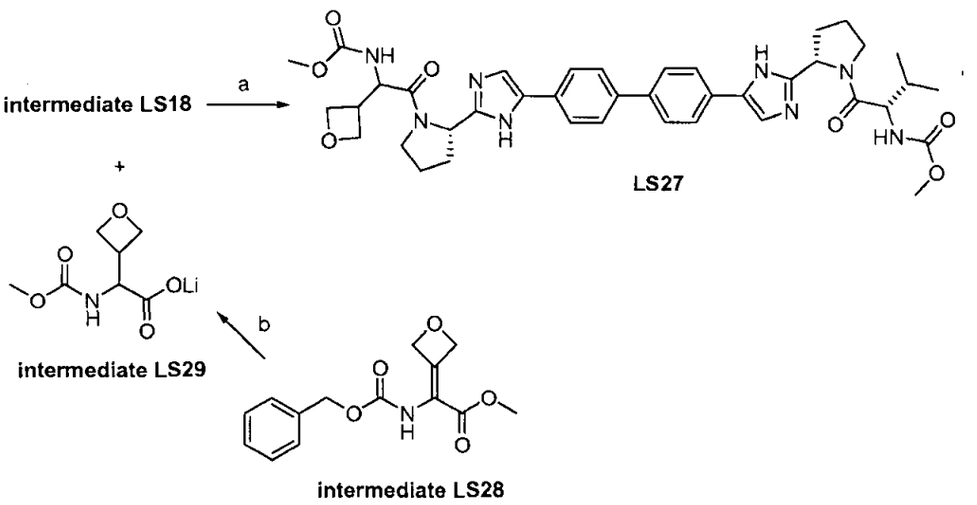
Step a: Compound LS26 was prepared in a similar fashion to the preparation of intermediate LS19 employing 2-(diisopropylamino)acetic acid as the carboxylic acid coupling partner. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.74-1.04 (m, 18H) 1.74-2.21 (m, 13H) 2.86-3.09 (m, 3H) 3.54 (s, 3H) 3.71-3.89 (m, 3H) 4.06 (t, *J*=8.55 Hz, 1H) 4.98-5.13 (m, 2H) 5.56 (d, *J*=8.55 Hz, 1H) 7.21-7.34 (m, 1H) 7.42-7.54 (m, 1H) 7.61-7.87 (m, 8H). LC (Cond'n 5): RT = 1.98 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{54}N_8O_4$: 723.4; found 723.4.

Example LS27 Diastereomer 1

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-(3-oxetanyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

Example LS27 Diastereomer 2

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(3-oxetanyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

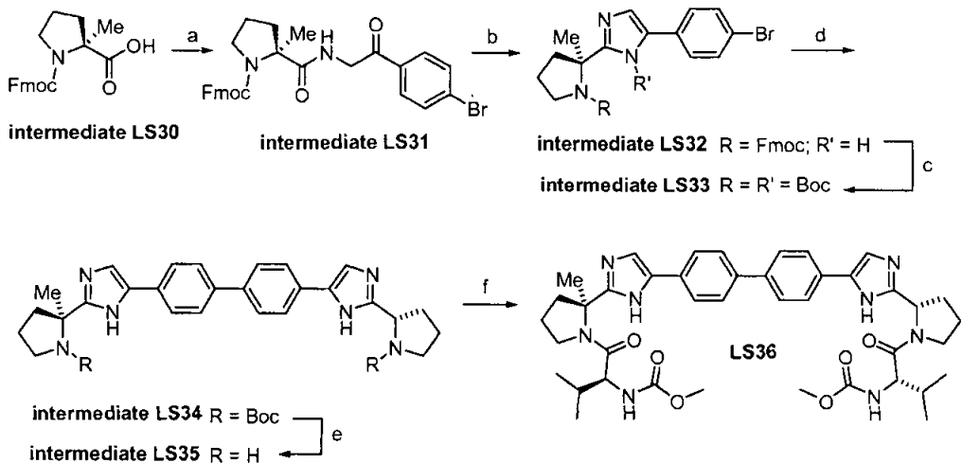


Step a: Compound LS27 was prepared in a similar fashion to the preparation of intermediate LS19 employing 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetic acid (intermediate LS29) as the carboxylic acid coupling partner. The two diastereomers of LS27 were separated *via* preparative HPLC (Xbridge C18, 100 x 19 mm I.D. S-5μm; Mobile Phase A: 95%Water-5% Acetonitrile with 10 mM ammonium acetate (pH=5); Mobile phase B: 95%Acetonitrile-5% Water with 10 mM ammonium acetate (pH=5); Isocratic 30% B for 7 min; Flow rate: 25 mL/min; UV detection: 220 nm; Sample amount: ~5 mg/each injection, 300 μl sample solution in methanol (~17 mg/mL)). Diastereomer 1: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.80-0.96 (m, 6H) 1.91-2.06 (m, 6H) 2.09-2.21 (m, 3H) 3.54 (s, 3H) 3.59 (s, 3H) 3.77-3.83 (m, 2H) 3.87 (t, *J*=7.63 Hz, 1H) 4.06 (t, *J*=8.24 Hz, 1H) 4.31 (t, *J*=6.41 Hz, 1H) 4.43 (t, *J*=6.10 Hz, 1H) 4.49 (t, *J*=7.17 Hz, 1H) 4.51-4.57 (m, 1H) 4.80 (t, *J*=8.55 Hz, 1H) 5.00-5.05 (m, 1H) 5.06-5.11 (m, 1H) 7.30 (d, *J*=8.55 Hz, 1H) 7.50 (s, 1H) 7.58-7.89 (m, 8H) 11.77 (s, 2H). LC (Cond'n 10): RT = 7.14 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{48}N_8O_7$: 753.4; found 753.9. Diastereomer 2: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.79-0.98 (m, 6H) 1.91-2.06 (m, 4H) 2.07-2.23 (m, 4H) 3.51-3.69 (m, 8H) 3.74-3.90 (m, 2H) 4.06 (t, *J*=7.48 Hz, 1H) 4.20-4.33 (m, 1H) 4.36-4.49 (m, 2H) 4.55 (s, 2H) 4.71 (s, 1H) 4.97-5.05 (m, 1H) 5.08 (s, 1H) 5.53 (s, 1H) 7.30 (d, *J*=7.93 Hz, 1H) 7.51 (s, 1H) 7.58-7.91 (m, 8H) 11.53 (s, 1H) 11.78 (s, 1H). LC (Cond'n 10): RT = 8.79 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{48}N_8O_7$: 753.4; found 753.9.

Step b: A solution of methyl 2-(benzyloxycarbonylamino)-2-(oxetan-3-ylidene)acetate (intermediate LS28; Source: Moldes et al, *Il Farmaco*, 2001, *56*, 609 and Wuitschik et al, *Ang. Chem. Int. Ed. Engl*, 2006, *45*, 7736; 200 mg, 0.721 mmol) in ethyl acetate (7 mL) and CH_2Cl_2 (4.00 mL) was degassed by bubbling nitrogen for 10min. Dimethyl dicarbonate (0.116 mL, 1.082 mmol) and Pd/C (20 mg, 0.019 mmol) were then added, the reaction mixture was fitted with a hydrogen balloon and allowed to stir at ambient temperature overnight. The reaction mixture was filtered through diatomaceous earth (Celite®) and concentrated. The residue was purified *via* Biotage (load with dichloromethane on 25 samplet; elute on 25S column with dichloromethane for 3CV then 0 to 5% methanol/dichloromethane over 250mL then hold at 5% methanol/dichloromethane for 250mL; 9mL fractions). Fractions containing the desired product were concentrated to provide 167mg methyl 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetate as a colorless oil which solidified on standing. ^{1}H NMR (500 MHz, CHLOROFORM-D) δ ppm 3.29-3.40 (m, 1H) 3.70 (s, 3H) 3.74 (s, 3H) 4.55 (t, *J*=6.41 Hz, 1H) 4.58-4.68 (m, 2H) 4.67-4.78 (m, 2H) 5.31 (br s, 1H). MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{13}NO_5$: 204.1; found 204.0. To methyl 2-(methoxycarbonylamino)-2-(oxetan-3-yl)acetate (50 mg, 0.246 mmol) in THF (2mL) and Water (0.5mL) was added lithium hydroxide monohydrate (10.33 mg, 0.246 mmol). The resultant solution was allowed to stir overnite at ambient temperature then concentrated to dryness to provide intermediate LS29 as a colorless powder. ^{1}H NMR (500 MHz, CH_3OD) δ ppm 3.38-3.50 (m, 1H) 3.67 (s, 3H) 4.28 (d, *J*=7.63 Hz, 1H) 4.57-4.79 (m, 4H).

Example LS36

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate



Step a: To (S)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)-2-methylpyrrolidine-2-carboxylic acid (intermediate LS30; 1.5g; 4.3mmol) in 50mL DMF was added sequentially 2-amino-1-(4-bromophenyl)ethanone hydrochloride (1.2g; 4.7mmol), HOAT (290mg; 2.1mmol), Hunig's base (0.7mL; 4.3mmol) and EDCI (1.2g; 6.4mmol). After 1h, the reaction mixture was poured into 150mL water and allowed to stir for 15min before filtering the resultant precipitate which was dissolved in dichloromethane and dried over magnesium sulfate. The dichloromethane mixture was filtered and applied to a Biotage 40 samplet. Chromatography on a 40M column (25 to 60% ethyl acetate/hexane over 1200mL) provided (S)-(9H-fluoren-9-yl)methyl 2-(2-(4-bromophenyl)-2-oxoethylcarbamoyl)-2-methylpyrrolidine-1-carboxylate (intermediate LS31; 2.4g; quant) as a yellow foam. LC (Cond'n 11): RT = 3.75 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{29}H_{27}BrN_2O_4$: 547.1; found 547.0.

Step b: A mixture of ammonium acetate (844mg; 10.97mmol) and (S)-(9H-fluoren-9-yl)methyl 2-(2-(4-bromophenyl)-2-oxoethylcarbamoyl)-2-methylpyrrolidine-1-carboxylate (intermediate LS31; 1.00g; 1.83mmol) was heated to 140°C in 25mL xylene for 2.5h at which time the reaction mixture was concentrated and loaded with dichloromethane onto a Biotage 40 samplet. Purification *via* Biotage (5 to 60% ethyl acetate /hexane over 1000mL with 400mL hold time) provided (S)-(9H-fluoren-9-

yl)methyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)-2-methylpyrrolidine-1-carboxylate (intermediate LS32; 469mg; 49%) as an amber liquid. LC (Cond'n 12): RT = 3.09 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{29}H_{26}BrN_3O_2$: 528.1; found 528.5.

Step c: To (S)-(9H-fluoren-9-yl)methyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)-2-methylpyrrolidine-1-carboxylate (intermediate LS32; 329mg; 0.62mmol) in 3mL DMF was added 1.5mL piperidine. The reaction mixture was concentrated *via* a nitrogen stream overnite. The resultant residue was washed with hexane and passed through an MCX cartridge (Oasis; 6g; preconditioned with two column lengths of methanol). The cartridge was washed with two column lengths of methanol and product was eluted with ammonia/methanol. Concentration provided 193mg of (S)-5-(4-bromophenyl)-2-(2-methylpyrrolidin-2-yl)-1H-imidazole which was dissolved in 6mL dichloromethane and combined with di-t-butyldicarbonate (413mg; 1.89mmol), DMAP (15mg; 0.13mmol) and TEA (0.17mL; 1.30mmol). After 48h, the reaction mixture was concentrated and purified *via* chromatography on a Biotage system providing (S)-tert-butyl 5-(4-bromophenyl)-2-(1-(tert-butoxycarbonyl)-2-methylpyrrolidin-2-yl)-1H-imidazole-1-carboxylate (intermediate LS33; 150mg; 48%) as an off white solid. LC (Cond'n 5): RT = 3.75 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{32}BrN_3O_4$: 506.2; found 506.4

Step d: (S)-tert-butyl 2-(5-(4'-(2-((S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-yl)-2-methylpyrrolidine-1-carboxylate (intermediate LS34) was prepared in a similar fashion to the preparation of 1d employing intermediate LS33 in place of 1b. ^{1}H NMR (300 MHz, DMSO-d_6; 100°C) δ ppm 1.18-1.29 (m, 9H) 1.29-1.40 (m, 9H) 1.75-1.82 (m, 3H) 1.81-2.39 (m, 8H) 3.35-3.75 (m, 4H) 4.81-4.92 (m, 1H) 7.36-7.45 (m, 1H) 7.57-7.74 (m, 5H) 7.76-7.89 (m, 4H) 11.29-11.63 (m, 2H). LC (Cond'n 5): RT = 2.49 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{46}N_6O_4$: 639.4; found 639.9.

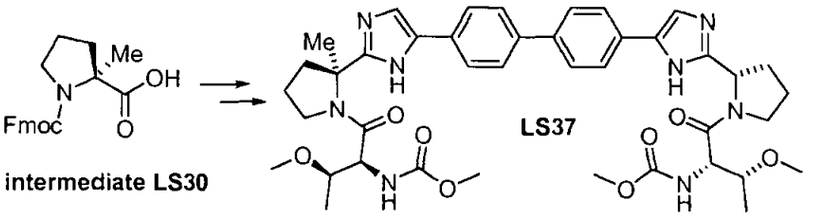
Step e: 2-((S)-2-methylpyrrolidin-2-yl)-5-(4'-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazole (intermediate LS35) was prepared in a similar fashion to the preparation of 1e employing intermediate LS34 in place of 1d. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.76-1.83 (m, 3H) 1.92-2.23 (m, 6H) 3.31-3.49

(m, 4H) 4.88-4.97 (m, 1H) 7.76-7.88 (m, 5H) 7.90-8.04 (m, 5H) 9.72-9.82 (m, 1H) 10.04-10.16 (m, 1H); imidazole and pyrrolidine NH protons unaccounted for. LC (Cond'n 5): RT = 1.79 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{30}N_6$: 439.2; found 439.5.

Step f: Compound LS36 was prepared in a similar fashion to the preparation of example 1 employing intermediate LS35 in place of 1e and *Cap*-51 in place of *Cap*-1. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.72-0.97 (m, 12H) 1.77 (s, 3H) 1.86-2.08 (m, 8H) 2.09-2.19 (m, 2H) 2.25-2.39 (m, 2H) 3.49-3.59 (m, 6H) 3.81 (d, *J*=6.71 Hz, 4H) 4.06 (q, *J*=7.83 Hz, 2H) 5.08 (dd, *J*=7.02, 3.05 Hz, 1H) 7.12 (d, *J*=8.85 Hz, 1H) 7.27-7.34 (m, 1H) 7.46-7.55 (m, 1H) 7.59-7.73 (m, 4H) 7.75-7.86 (m, 3H) 11.66 (s, 1H) 11.77 (s, 1H). LC (Cond'n 5): RT = 2.25 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{52}N_8O_6$: 753.4; found 754.0.

Example LS37

methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-methyl-1-pyrrolidinyl)carbonyl)propyl)carbamate



Compound LS37 was prepared in a similar fashion to the preparation of LS36 from intermediate LS30 using *Cap-86* in place of *Cap*-51. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.99-1.17 (m, 6H) 1.76 (s, 3H) 1.87-2.09 (m, 4H) 2.10-2.23 (m, 2H) 2.34-2.38 (m, 2H) 2.56-2.60 (m, 1H) 2.63 (d, *J*=1.83 Hz, 1H) 3.17 (s, 3H) 3.19 (s, 3H) 3.37-3.51 (m, 2H) 3.54 (s, 6H) 3.75-3.96 (m, 4H) 4.13-4.36 (m, 2H) 5.07 (dd, *J*=7.48, 3.20 Hz, 1H) 7.20 (d, *J*=8.54 Hz, 1H) 7.24-7.34 (m, 1H) 7.50 (dd, *J*=7.17, 1.98 Hz, 1H) 7.59-7.73 (m, 4H) 7.76-7.86 (m, 3H) 11.65 (s, 1H) 11.77 (s, 1H). LC (Cond'n 13): RT = 4.30 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{52}N_8O_8$: 785.4; found 785.4.

Section F LC Conditions for determining retention time

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 10u 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

Condition 4

Column: Phenomenex-Luna 3.0 X 50 mm S10

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

Condition 5

Column: Phenomenex-Luna 4.6 X 50 mm S10

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

Condition 6

Column: Xbridge C18 4.6 X 50 mm S5

Start % B = 0

Final % B = 100

Gradient Time = 3 min

Flow Rate = 4 mL/Min

Wavelength = 220

Solvent A = H_2O : ACN 95% : 5% 10 mm Ammonium Acetate

Solvent B = H_2O : ACN 5% : 95% 10 mm Ammonium Acetate

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

Condition 8

Column: Phenomenex LunaC18 10u 4.6 X 30 mm

Start % B = 0

Final % B = 100

Gradient Time = 2 min

Flow Rate = 5 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 9

Column: Phenomenex C18 10u 4.6 X 30 mm

Start % B = 0

Final % B = 100

Gradient Time = 10min

Flow Rate = 4 mL/Min

Wavelength = 220

Solvent A = H_2O : ACN 95% : 5% 10 mm Ammonium Acetate

Solvent B = H_2O : ACN 5% : 95% 10 mm Ammonium Acetate

Condition 10

Column: Phenomenex 10u 3.0 X 50 mm

Start % B = 0

Final % B = 100

Gradient Time = 3min

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 11

Column: Xterra 4.6 X 30 mm S5

Start % B = 0

Final % B = 100

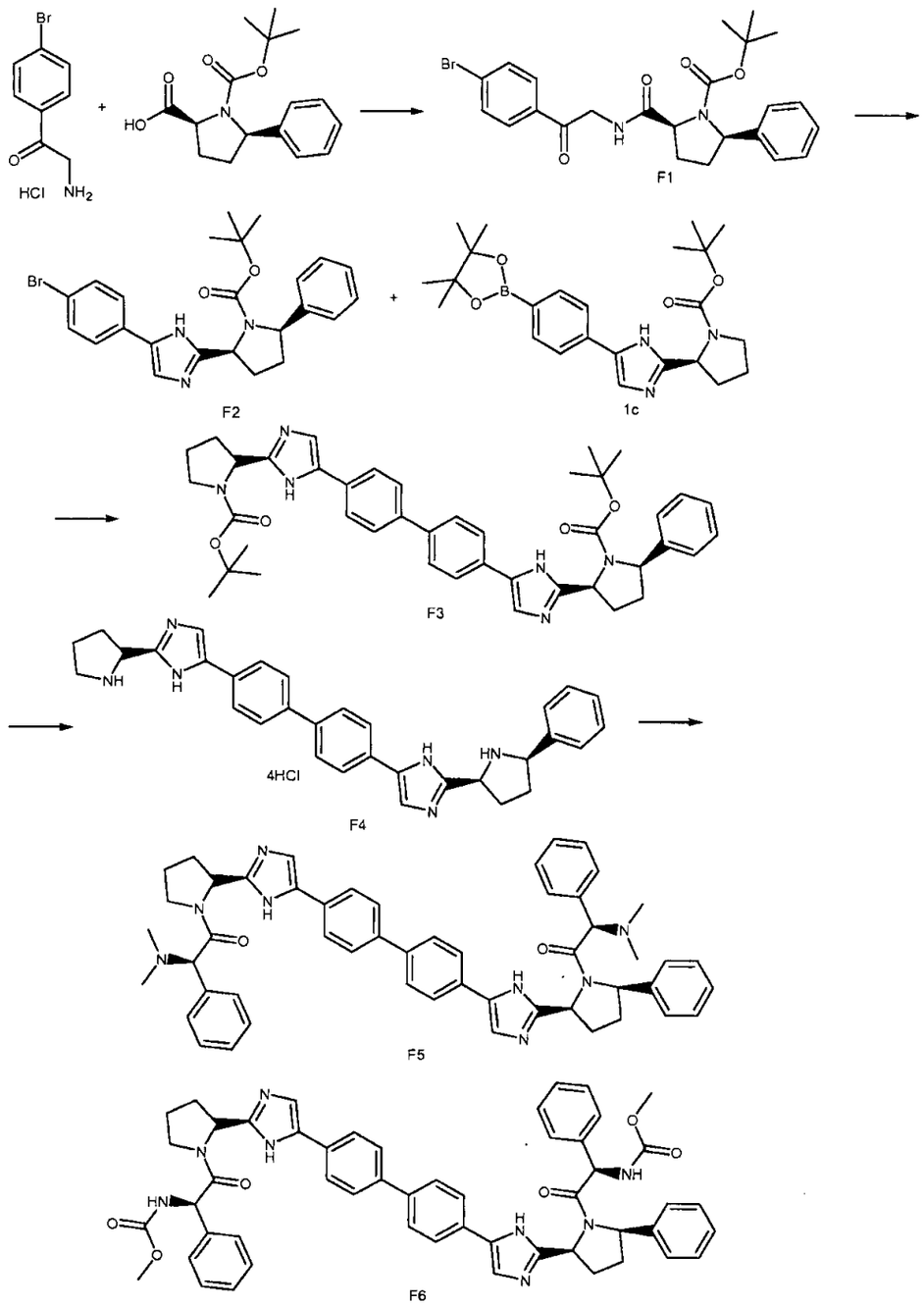
Gradient Time = 2min

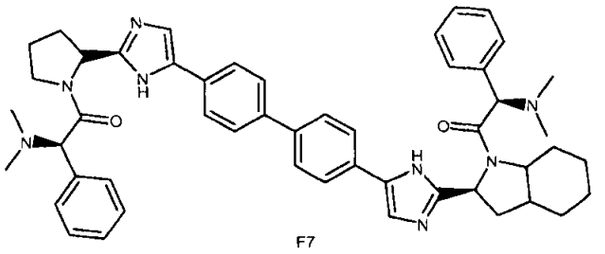
Flow Rate = 5 mL/Min

Wavelength = 220

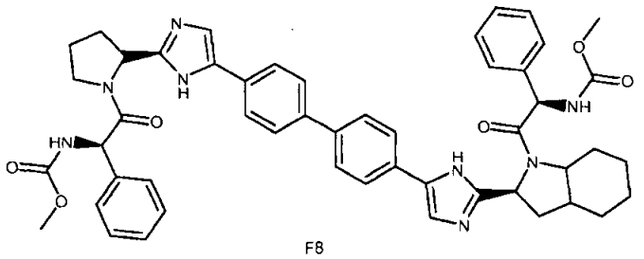
Solvent A = H_2O : ACN 95% : 5% 10 mm Ammonium Acetate

Solvent B = H_2O : ACN 5% : 95% 10 mm Ammonium Acetate


Br
HCl NH2
HO
F1
F2
1c
F3
4HCl
F4
F5
F6



F7



F8

Compound F1 was prepared in analogous fashion to the procedure used to synthesize 1a with following modification: (2S,5R)-1-(tert-butoxycarbonyl)-5-phenylpyrrolidine-2-carboxylic acid was used in place of N-Boc-L-proline.

Compound F2 was prepared in analogous fashion to the procedure used to sythesize 1b.

Compound F3 was prepared in analogous fashion to the procedure used to sythesize 1d.

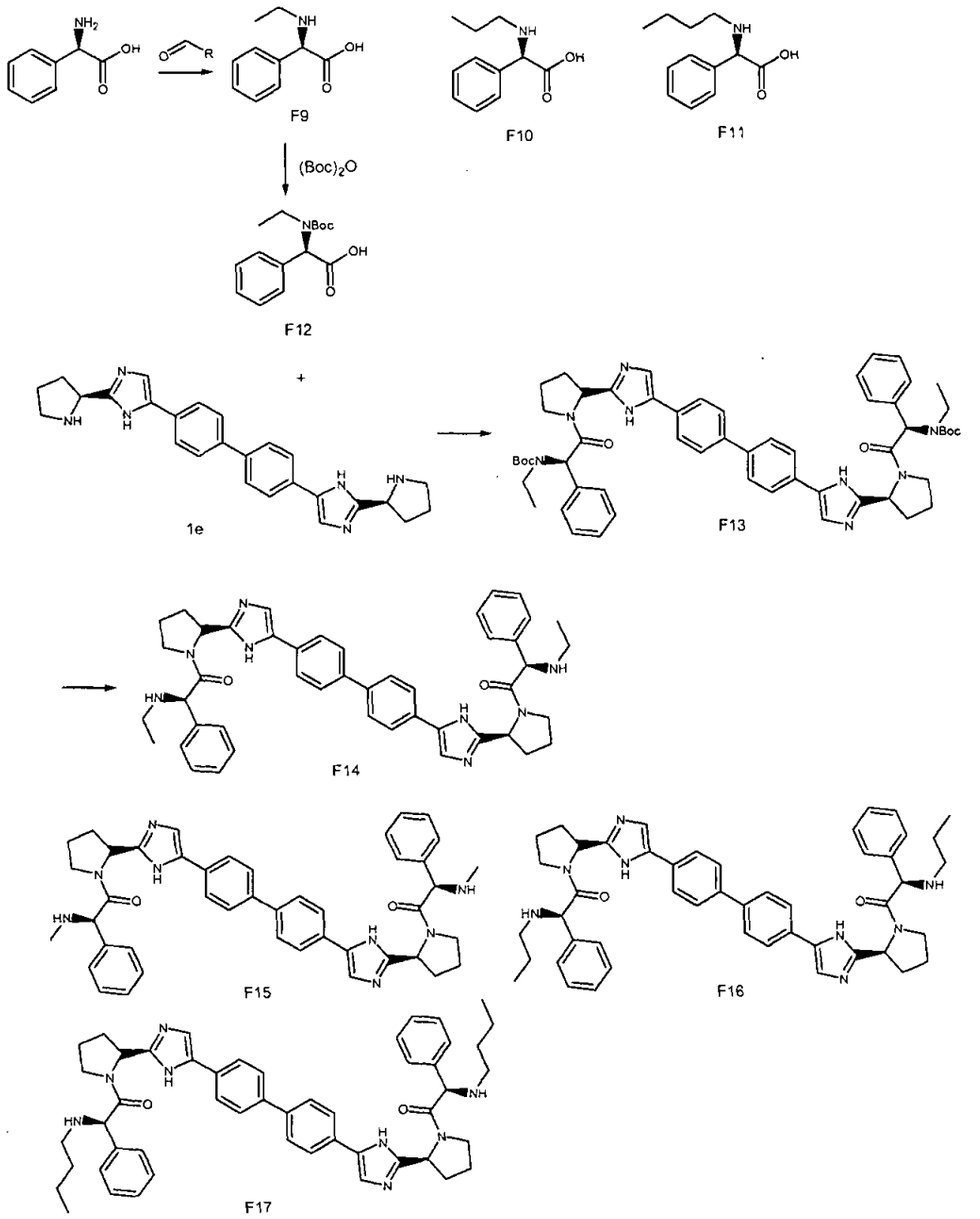
Compound F4 was prepared in analogous fashion to the procedure used to sythesize 1c.

Compound F5, F6 was prepared in analogous fashion to the procedure used to sythesize example 1from Compound F4.

Compound F7, F8 was prepared in analogous fashsion to the procedure used to sythesize F5 with following modification: (2S)-1-(tert-butoxycarbonyl)octahydro-1H-indole-2-carboxylic acid was used in place of (2S,5R)-1-(tert-butoxycarbonyl)-5-phenylpyrrolidine-2-carboxylic acid.

Entry	*Compound Name*	*Retention time (LC-Condition); homogeneity index MS data*
F1		RT = 3.838 minutes (condition 1, 94%); LRMS: Anal. Calcd. for C24H27BrN2O4 486.12; found: 487.26 $(M+H)^+$.
F2		RT = 3.175 minutes (condition 1, 83%); LRMS: Anal. Calcd. for C24H27BrN2O4 467.12; found: 468.26 $(M+H)^+$.
F3		RT = 2.965 minutes (condition 1, 93%); LRMS: Anal. Calcd. for C42H48N6O4 700.37; found: 701.49 $(M+H)^+$.
F4		RT = 2.083 minutes (condition 1, 98%); LRMS: Anal. Calcd. for C32H32N6 500.27; found: 501.40 $(M+H)^+$.
F5		RT = 1.222 minutes (condition 3, 98%); LRMS: Anal. Calcd. for C52H54N8O2 822.44; found: 823.5 $(M+H)^+$.
F6	methyl ((1*R*)-2-((2*R*)-2-(5-(4'-(2-((2*S*,5*R*)-1-((2*R*)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-5-phenyl-2-pyrrolidinyl)-1*H*-imidazol-5-yl)-4-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	RT = 1.512 minutes (condition 3, 98%); LRMS: Anal. Calcd. for C52H50N8O6 882.39; found: 883.45 $(M+H)^+$.
F7	*rel*-(1*R*)-2-((2*S*)-2-(4-(4'-(2-((2*S*)-1-((2*R*)-2-	RT = 1.223 minutes (condition 3, 98%); LRMS: Anal. Calcd.

	(dimethylamino)-2-phenylacetyl)octahydro-1*H*-indol-2-yl)-1*H*-imidazol-5-yl)-4-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)-*N*,*N*-dimethyl-2-oxo-1-phenylethanamine	for C50H56N8O2 800.45; found: 801.51 $(M+H)^+$.
F8	methyl *rel*-((1*R*)-2-((2*S*)-2-(4-(4'-(2-((2*S*)-1-((2*R*)-2-((methoxycarbonyl)amino)-2-phenylacetyl)octahydro-1*H*-indol-2-yl)-1*H*-imidazol-5-yl)-4-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	RT = 1.513 minutes (condition 3, 98%); LRMS: Anal. Calcd. for C50H56N8O2 860.40; found: 861.42 $(M+H)^+$.



Compound F9, F10, and F11 was prepared in analogous fashion to the procedure used to sythesize *Cap*-3 first half procedure using acetaldehyde, propionaldehyde, and butyraldehyde respectively.

Compound F12

$(Boc)_2O$ (2.295 g, 10.20 mmol) was added to a mixture of compound F9 (1.0 g, 4.636 mmol), hunig's base (1.78 mL, 10.20 mmol) in CH_2Cl_2 (12 mL), and the

resulting mixture was stirred over night. The volatile component was removed *in vacuo*, and the residue was purified by a reverse phase HPLC system (H_2O/methanol/TFA) to provide compound F12 as a clear wax (0.993 g). LC (Cond.3): RT = 1.663 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ C15H21NO4: 279.33; found $[M+Na]^+$ 302.30

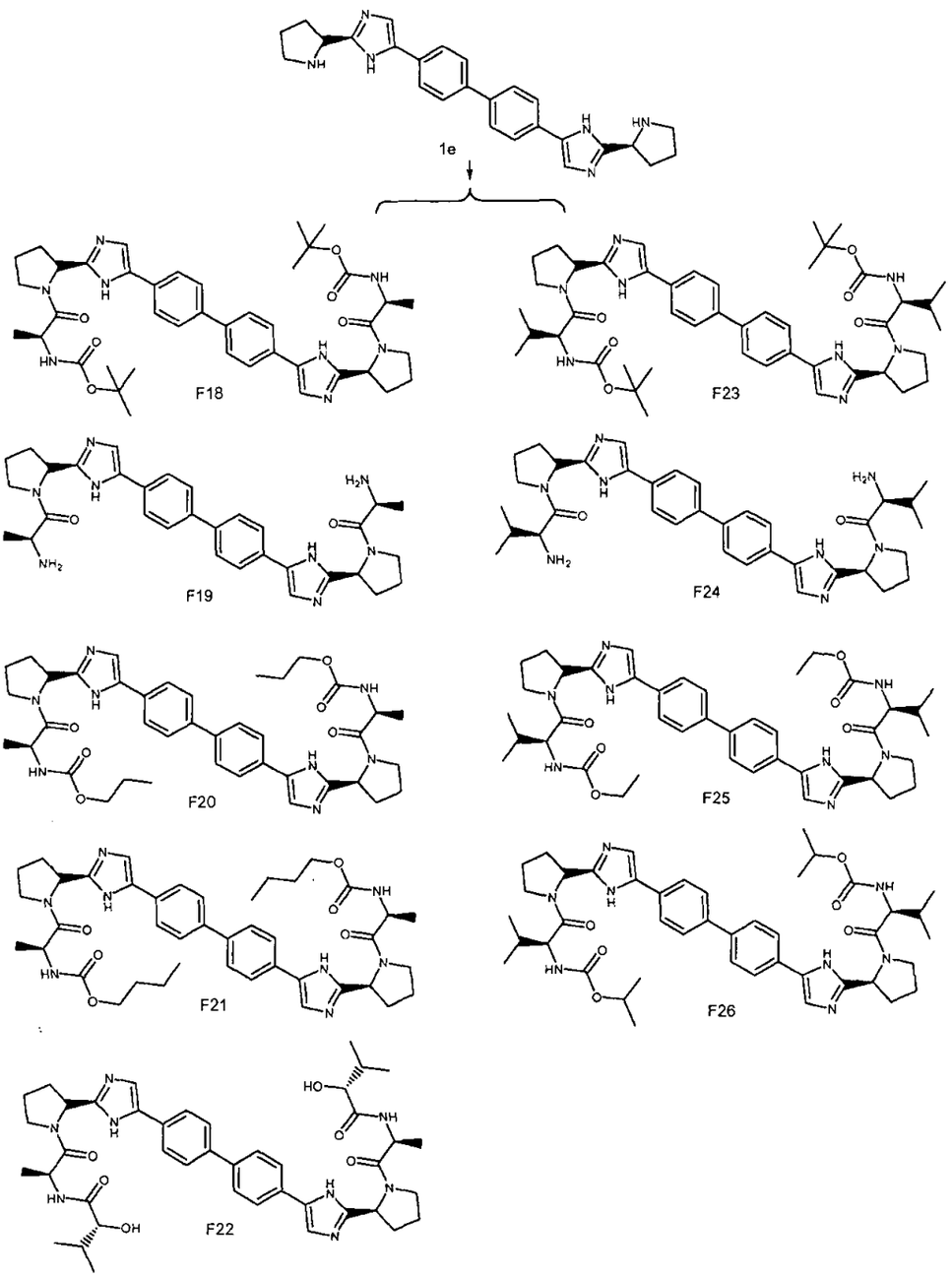
Compound F13 was prepared in analogous fashion to the procedure used to sythesized example 1 from Compound 1e and F12.

Compound F14 was prepared in analogous fashion to the procedure used to sythesized 132e.

Compound F15, F16, and F17 was prepared in analogous fashion to the procedure used to sythesize F14.

Entry	*Compound Name*	*Retention time (LC-Condition); homogeneity index MS data*
F9		RT = 0.580 minutes (condition 1, 94%); LRMS: Anal. Calcd. for C10H13NO2 179.09; found: 180.26 $(M+H)^+$.
F10		RT = 0.563 minutes (condition 3, 94%); LRMS: Anal. Calcd. for C11H15NO2 193.11; found: 194.26 $(M+H)^+$.
F11		RT = 1.023 minutes (condition 3, 94%); LRMS: Anal. Calcd. for C12H17NO2 207.13; found: 208.31 $(M+H)^+$.
F12		RT = 1.663 minutes (condition 3, 95%); LRMS: Anal. Calcd. for C15H21NO4 279.15; found: 302.30 $(Na+H)^+$.
F13		RT = 2.595 minutes (condition 4,

		94%); LRMS: Anal. Calcd. for C56H66N8O6 946.51; found: 947.64 $(M+H)^+$.
F14	(1*R*)-*N*-ethyl-2-((2*S*)-2-(4-(4'-(2-((2*S*)-1-((2*R*)-2-(ethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1*H*-imidazol-5-yl)-4-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine	RT = 1.55 minutes (condition 5, 90%); LRMS: Anal. Calcd. for C46H50N8O2 746.41; found: 747.72 $(M+H)^+$.
F15	(1*R*)-*N*-methyl-2-((2*S*)-2-(4-(4'-(2-((2*S*)-1-((2*R*)-2-(methylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1*H*-imidazol-5-yl)-4-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine	RT = 1.50 minutes (condition 5, 94%); LRMS: Anal. Calcd. for C44H46N8O2 718.37; found: 719.69 $(M+H)^+$.
F16	*N*-((1*R*)-2-oxo-1-phenyl-2-((2*S*)-2-(4-(4'-(2-((2*S*)-1-((2*R*)-2-phenyl-2-(propylamino)acetyl)-2-pyrrolidinyl)-1*H*-imidazol-5-yl)-4-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)ethyl)-1-propanamine	RT = 1.63 minutes (condition 5, 90%); LRMS: Anal. Calcd. for C48H54N8O2 774.43; found: 775.76$(M+H)^+$.
F17	*N*-((1*R*)-2-((2*S*)-2-(4-(4'-(2-((2*S*)-1-((2*R*)-2-(butylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1*H*-imidazol-5-yl)-4-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)-1-butanamine	RT = 1.81 minutes (condition 5, 85%); LRMS: Anal. Calcd. for C50H58N8O2 802.47; found: 803.79 $(M+H)^+$.



Compound F18 and F23 was prepared in analogous fashion to the procedure used to sythesize example1 with following modification: N-Boc-L-alanine and N-Boc-L-valine was used in place of N-Boc-L-proline respectively.

Compound F22 was prepared in analogous fashion to the procedure used to sythesize example 1from Compound F19.

Compound F19, F24 was prepared in analogous fashion to the procedure used to sythesize 132e.

Compound F25

ethyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((ethoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

To a solution of F24 (0.06 g, 0.074 mmol) in DMF (1 mL) was added Hunig's base (0.105 mL, 0.593 mmol) and ethyl carbonochloridate (0.016 mL, 0.163 mmol) then stirred it at room temperature. Two hours later, checked it by LCMS. There were three major peaks which indicated desired compound, tri-coupled, and tetra-coupled compound. Stopped reaction and concentrated it by reduced pressure to get light brown oil which was treated with 10 mL of 2 M NH_3 in methanol for 20 minutes then concentrated it again to a yellow solid which was purified by preparative LC to provide compound F25 as a white TFA salt (57.6 mg).

LC (Cond.6): RT = 1.932 min, LC/MS: Anal. Calcd. for $[M+H]^+$ C42H54N8O6: 766.42; found 767.55.

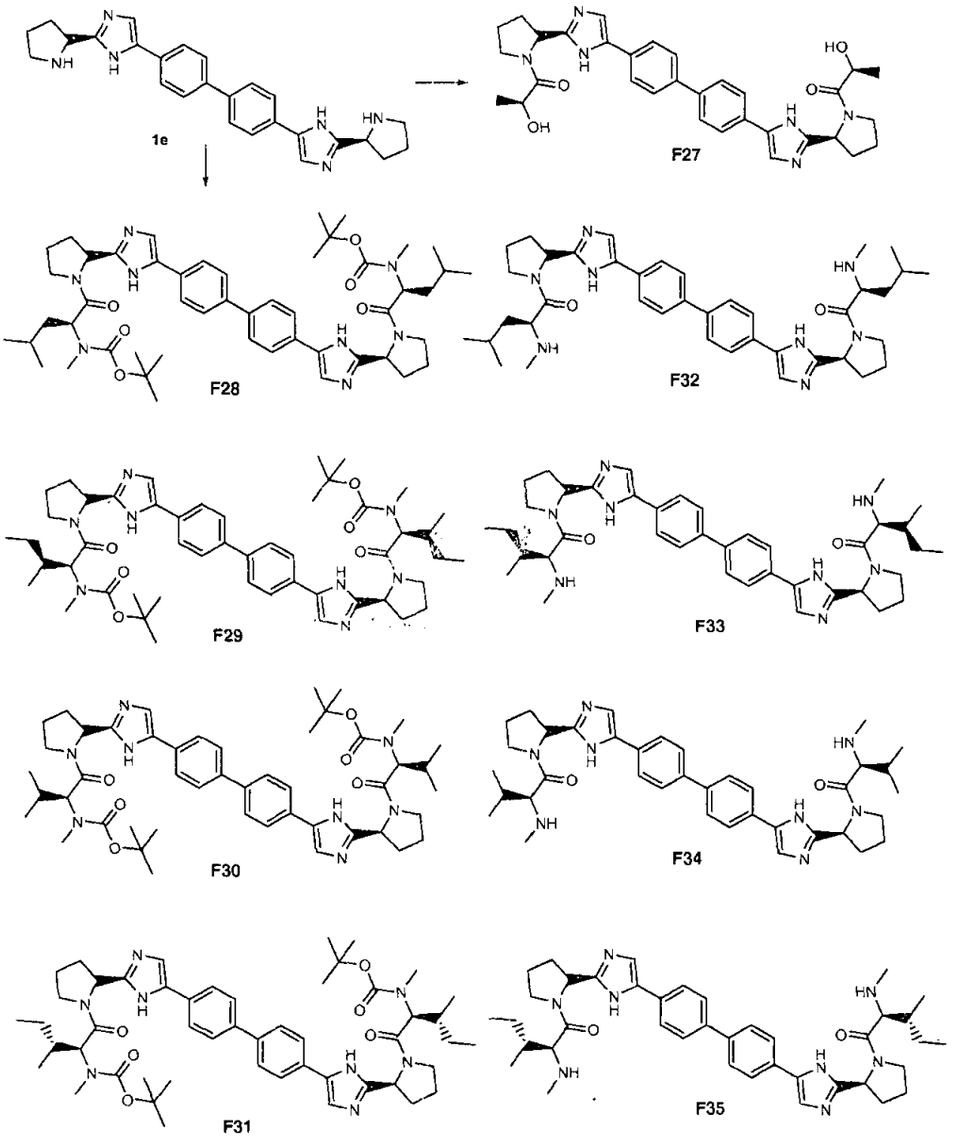
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.69-0.94 (m, 12H) 1.16 (t, *J*=7.02 Hz, 6H) 1.90-2.26 (m, 8H) 2.40 (d, *J*=4.88 Hz, 2H) 3.73-3.92 (m, 4H) 3.94-4.08 (m, 4H) 4.12 (t, *J*=7.78 Hz, 2H) 5.15 (t, *J*=7.02 Hz, 2H) 7.26 (d, *J*=8.54 Hz, 2H) 7.85-7.93 (m, 4H) 7.93-8.01 (m, 4H) 8.13 (s, 2H) 14.68 (s, 2H)

Compound F20, F21, and F26 was prepared in analogous fashion to the procedure used to sythesize example1.

Entry	*Compound Name*	*Retention time (LC-Condition): homogeneity index MS data*
F18		RT = 2.257 minutes (condition 5, 96%); LRMS: Anal. Calcd. for C42H54N8O6 766.42; found: 767.88 $(M+H)^+$.

F19		RT = 1.462 minutes (condition 5, 95%); LRMS: Anal. Calcd. for C32H38N8O2 566.31; found: 567.79 $(M+H)^+$.
F20	propyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(propoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate	RT = 1.338 minutes (condition 3, 89%); LRMS: Anal. Calcd. for C40H50N8O6 738.39; found: 739.95 $(M+H)^+$.
F21	butyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(butoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	RT = 1.447 minutes (condition 3, 96%); LRMS: Anal. Calcd. for C42H54N8O6 766.93; found: 768.02 $(M+H)^+$.
F22	(2S)-2-hydroxy-N-((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-((2S)-2-hydroxy-3-methylbutanoyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)-3-methylbutanamide	RT = 1.703 minutes (condition 4, 98%); LRMS: Anal. Calcd. for C42H54N8O 766.93; found: 768.02 $(M+H)^+$.
F23		RT = 2.881 minutes (condition 7, 93%); LRMS: Anal. Calcd. for C46H62N8O6 822.48; found: 823.95 $(M+H)^+$.
F24		RT = 1.743 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C36H46N8O2 622.37; found: 624.07 $(M+H)^+$.
F25	ethyl ((1S)-1-(((2S)-2-(4-(4'-(2-	RT = 1.932 minutes (condition 6,

	((2S)-1-((2S)-2-((ethoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	97%); LRMS: Anal. Calcd. for C42H54N8O6 766.42; found: 767.55 $(M+H)^+$.
F26	isopropyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((isopropoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	RT = 2.122 minutes (condition 6, 98%); LRMS: Anal. Calcd. for C44H58N8O6 794.45; found: 795.58 $(M+H)^+$.



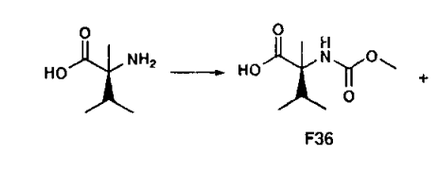
Entry	*Compound Name*	*Retention time (LC-Condition); homogeneity index MS data*
F27	(2S)-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-hydroxypropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-propanol	RT = 1.03 minutes (condition 3, 98%); LRMS: Anal. Calcd. for C32H36N6O4 568.28; found: 569.76 $(M+H)^+$.
F28	tert-butyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((tert-	RT = 1.847 minutes (condition 3, 95%); LRMS: Anal. Calcd. for

	butoxycarbonyl)(methyl)amino)-4-methylpentanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-methylbutyl)methylcarbamate	C50H70N8O6 878.54; found: 879.53 $(M+H)^+$.
F29	tert-butyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-methylpentanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylbutyl)methylcarbamate	RT = 2.202 minutes (condition 8, 98%); LRMS: Anal. Calcd. for C50H70N8O6 878.54; found: 879.57 $(M+H)^+$.
F30	tert-butyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)methylcarbamate	RT = 1.743 minutes (condition 8, 96%); LRMS: Anal. Calcd. for C48H66N8O6 850.51; found: 851.52 $(M+H)^+$.
F31	tert-butyl ((1S,2R)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tert-butoxycarbonyl)-N-methyl-L-alloisoleucyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylbutyl)methylcarbamate	RT = 1.82 minutes (condition 8, 98%); LRMS: Anal. Calcd. for C50H70N8O6 878.54; found: 879.54 $(M+H)^+$.
F32	(2S)-N,4-dimethyl-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-4-methyl-2-(methylamino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-	RT = 3.715 minutes (condition 9, 98%); LRMS: Anal. Calcd. for C40H54N8O2 678.44; found: 679.46 $(M+H)^+$.

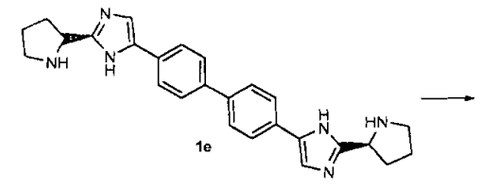
	1-pyrrolidinyl)-1-oxo-2-pentanamine	
F33	(2S)-N,3-dimethyl-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-methyl-2-(methylamino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-pentanamine	RT = 3.058 minutes (condition 9, 99%); LRMS: Anal. Calcd. for C36H46N8O2 678.44; found: 679.61 $(M+H)^+$.
F34	(2S)-N,3-dimethyl-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-methyl-2-(methylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-butanamine	RT = 3.206 minutes (condition 9, 99%); LRMS: Anal. Calcd. for C38H50N8O2 650.41; found: 651.41 $(M+H)^+$.
F35	(2S,3R)-N,3-dimethyl-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S,3R)-3-methyl-2-(methylamino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-pentanamine	RT = 3.43 minutes (condition 9, 98%); LRMS: Anal. Calcd. for C40H54N8O2 678.44; found: 679.44 $(M+H)^+$.

Compound F27 to F31 was prepared in analogous fashion to the procedure used to sythesize example 1.

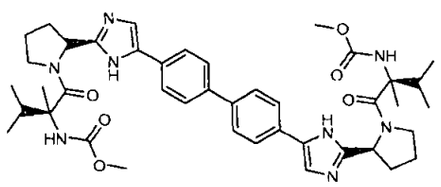
Compound F32 to F35 was prepared in analogous fashsion to the procedure used to synthesize 1e.



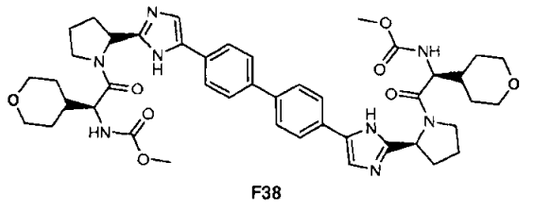
F36



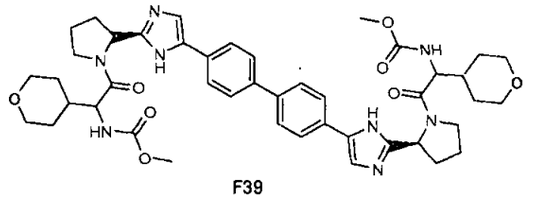
1e



F37



F38



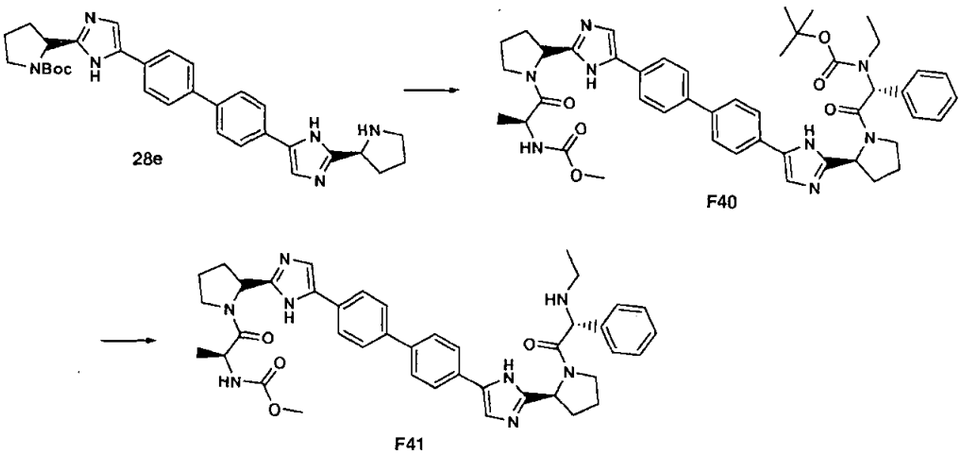
F39

Compound F36 was prepared in analogous fashion to the procedure used to sythesize *Cap*-52.

Compound F37, F38, and F39 was prepared in analogous fashion to the procedure used to synthesize example 1 from Compound F36 and LS16 respectively.

Entry	*Compound*	*Retention time (LC-Condition); homogeneity index MS data*
F36		RT = 1.55 minutes (condition 10); LRMS: Anal. Calcd. for C10H13NO2 189.1; found: 190.13 $(M+H)^+$. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.71-1.00 (m, 6H) 1.16-1.41 (m, 3H) 1.75-2.09 (m, 1H) 3.39-3.64 (m, 3H) 7.13 (s, 1H) 12.27 (s, 1H)
F37	methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2,3-dimethylbutanoyl)-2-pyrrolidinyl)-	RT = 2.572 minutes (condition 4, 98%); LRMS: Anal. Calcd. for C42H54N8O6 766.42;

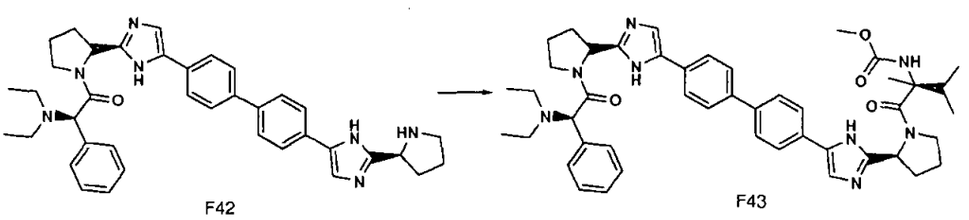
	1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1,2-dimethylpropyl)carbamate	found: 767.48 $(M+H)^+$.
F38	methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate	RT = 2.128 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C44H54N8O8 822.41; found: 823.45 $(M+H)^+$.
F39	methyl (2-((2S)-2-(4-(4'-(2-((2S)-1-(((methoxycarbonyl)amino)(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)carbamate	RT = 2.162 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C44H54N8O8 822.42; found: 823.49 $(M+H)^+$.



Compound F41 was prepared in analogous fashion to the procedure used to sythesize example 1.

Compound F42 was prepared in analogous fashsion to the procedure used to sythesize 1e.

Entry	*Compound Name*	*Retention time (LC-Condition); homogeneity index MS data*
F40		RT = 2.72 minutes (condition 10); LRMS: Anal. Calcd. for C46H54N8O6 814.42; found: 815.98 $(M+H)^+$.
F41	methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(ethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	RT = 2.048 minutes (condition 10, 95%); LRMS: Anal. Calcd. for C41H46N8O4 714.36; found: 715.84 $(M+H)^+$.

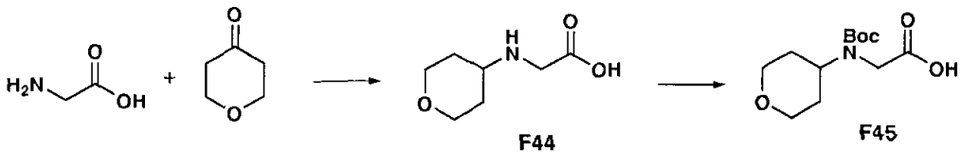


Compound F42 was prepared in analogous fashion to the procedure used to sythesize example 28f employing *Cap*-2 in place of *Cap*-4.

Compound F43 was prepared in analogous fashion to the procedure used to sythesize 2 from Compound F42.

Entry	*Compound Name*	*Retention time (LC-Condition); homogeneity index MS data*
F42		RT = 2.0 minutes (condition 10, 95%); LRMS: Anal. Calcd. for C38H43N7O 613.35; found: 614.40 $(M+H)^+$.
F43	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-	RT = 2.308 minutes (condition 10, 98%); LRMS: Anal. Calcd. for C50H70N8O6 784.44; found: 785.49 $(M+H)^+$.

	2-yl)-1-pyrrolidinyl)carbonyl)-1,2-dimethylpropyl)carbamate	



F44 F45

Compound F44 was prepared following below paper with following modification: glycine was used in place of leucine.

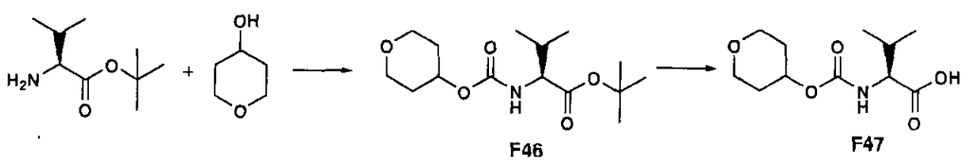
A simple method for preparation of *N*-mono- and *N,N*-di-alkylated α-amino acids Yuntao Song et al., *Tetrahedron Lett.* 41, October 2000, Pages 8225-8230.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.37-1.62 (m, 2H) 1.86 (dd, *J*=12.36, 1.98 Hz, 2H) 3.01-3.12 (m, 1H) 3.15 (s, 2H) 3.25 (t, *J*=11.75 Hz, 2H) 3.86 (dd, *J*=11.44, 4.12 Hz, 2H) 7.67-8.48 (m, 1H).

Compound F45

2-(tetrahydro-2H-pyran-4-ylamino)acetic acid (0.2 g, 1.256 mmol) F44 was dissolved in DMF (22.5 mL) and Et_3N (2.5 mL, 17.94 mmol) .After 5 minutes BOC_2O (0.583 mL, 2.51 mmol) was added and the reaction solution was heated to 60 °C for 1 h. The reaction was concentrated by reduced pressure providing a light yellow oil to which was added 20 mL HCl/H2O which was adjusted to PH3 at 0 °C and stirred for 10 minutes. The reaction mixture was extracted by ethyl acetate 3 X 20 mL, dried ($MgSO_4$), filtered, and concentrated to dryness. Ether was added and the mixture was sonicated and filtered providing a white solid F45 2-(tert-butoxycarbonyl(tetrahydro-2H-pyran-4-yl)amino)acetic acid (0.14 g, 0.540 mmol, 43.0 % yield).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.27-1.44 (m, 9H) 1.43-1.69 (m, 4H) 3.19-3.39 (m, 2H) 3.74 (s, 2H) 3.79-3.92 (m, 2H) 3.97-4.16 (m, 1H) 12.46 (s, 1H).



F46 F47

Compound F46 was prepared following the below referenced procedure with following modification: (S)-tert-butyl 2-amino-3-methylbutanoate was used in place of (S)-methyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-methylbutanoate.

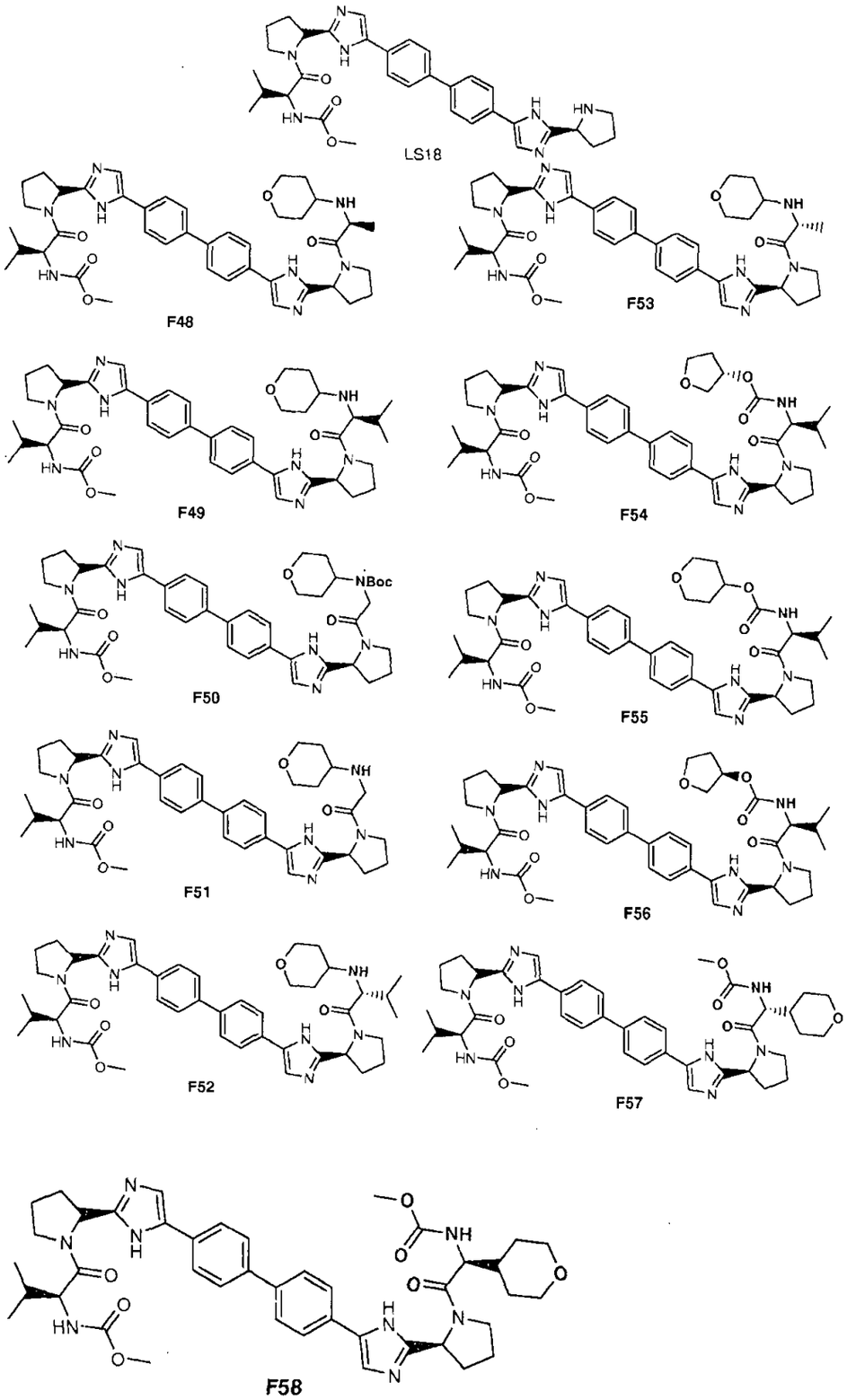
Hans-Joachim Knölker, et al. *Synlett* 1997; 925-928

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.77-0.97 (m, 6H) 1.32-1.45 (m, 9H) 1.45-1.56 (m, 2H) 1.74-1.91 (m, 2H) 1.94-2.11 (m, 1H) 3.36-3.53 (m, 2H) 3.76 (dd, *J*=8.09, 6.26 Hz, 1H) 3.77-3.90 (m, 2H) 4.69 (dd, *J*=9.00, 4.73 Hz, 1H) 7.35 (d, *J*=8.24 Hz, 1H)

Compound F47

To a Compound 46 (S)-tert-butyl 3-methyl-2-((tetrahydro-2H-pyran-4-yloxy)carbonylamino)butanoate (0.21 g, 0.697 mmol) was added HCl in dioxane (15 mL, 60.0 mmol) and the mixture was stirred at room temperature under nitrogen for three hours. The reaction was done and concentrated under reduced pressure to provide F47(S)-3-methyl-2-((tetrahydro-2H-pyran-4-yloxy)carbonylamino)butanoic acid (0.1694g, 0.691 mmol, 100 % yield) as a clear wax.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.88 (t, *J*=6.71 Hz, 6H) 1.41-1.60 (m, 2H) 1.85 (d, *J*=12.21 Hz, 2H) 1.97-2.08 (m, 1H) 3.41 (t, *J*=10.68 Hz, 1H) 3.45-3.52 (m, 1H) 3.64-3.74 (m, 1H) 3.77-3.89 (m, 2H) 4.63-4.72 (m, 1H) 7.32 (d, *J*=8.55 Hz, 1H) 12.52 (s, 1H)


LS18
F48
F53
F49
F54
F50
F55
F51
F56
F52
F57
F58

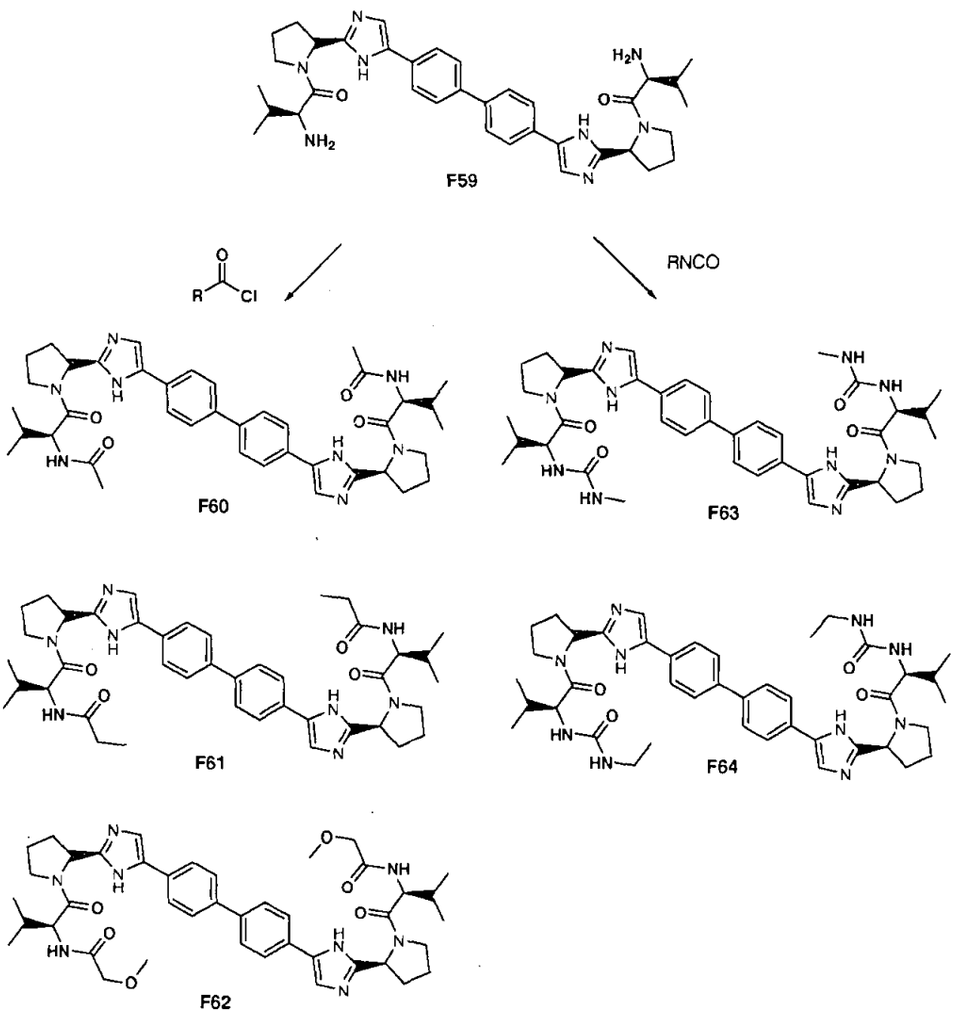
Compound F48 to F58 except F51 was prepared in analogous fashion to the procedure used to sythesize example 1 from LS18.

Compound F51 was prepared in analogous fashion to the procedure used to sythesize 1e from F50.

Entry	*Compound Name*	*Retention time (LC-Condition); homogeneity index MS data*
F48	methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	RT = 2.103 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C41H52N8O5 736.41; found: 737.07 $(M+H)^+$.
F49	methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	RT = 2.117 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C43H56N8O5 764.44; found: 765.75 $(M+H)^+$.
F50		RT = 2.547 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C45H58N8O7 822.44; found: 823.17 $(M+H)^+$.
F51	methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)glycyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	RT = 2.138 minutes (condition 7, 96%); LRMS: Anal. Calcd. for C40H50N8O5 722.39; found: 723.63 $(M+H)^+$.
F52	methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)-D-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	RT = 2.083 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C43H56N8O5 764.44; found: 765.78 $(M+H)^+$.

F53	methyl ((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahydro-2H-pyran-4-yl)-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	RT = 0.963 minutes (condition 11, 95%); LRMS: Anal. Calcd. for C43H54N8O7 736.41; found: 737.54 $(M+H)^+$.
F54	(3S)-tetrahydro-3-furanyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	RT = 2.378 minutes (condition 7, 95%); LRMS: Anal. Calcd. for C43H54N8O7 794.41; found: 795.94 $(M+H)^+$.
F55	tetrahydro-2H-pyran-4-yl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	RT = 2.447 minutes (condition 7, 99%); LRMS: Anal. Calcd. for C44H56N8O7 808.43; found: 809.42 $(M+H)^+$.
F56	(3R)-tetrahydro-3-furanyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	RT = 2.398 minutes (condition 7, 96%); LRMS: Anal. Calcd. for C43H54N8O7 794.41; found: 795.36 $(M+H)^+$.
F57	methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	RT = 2.272 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C42H52N8O7 780.40; found: 781.34 $(M+H)^+$.
F58	methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-	RT = 2.225 minutes (condition

	1-((2S)-2-((methoxycarbonyl)amino)-2-(tetrahydro-2H-pyran-4-yl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	7, 98%); LRMS: Anal. Calcd. for C42H52N8O7 780.40; found: 781.27 $(M+H)^+$.



Compound F59

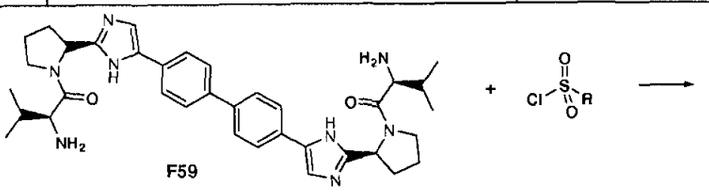
Compound F59 was prepared in analogous fashion to the procedure used to sythesize 26a with following modification: Boc-L-val-OH was used in place of Boc-D-val-OH.

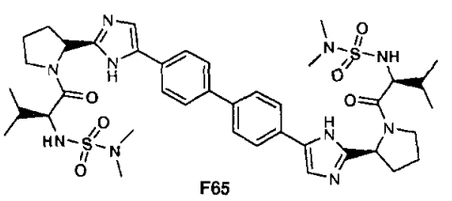
Compound F60 to F62 were prepared in analogous fashion to the procedure used to sythesize example 29 from F59.

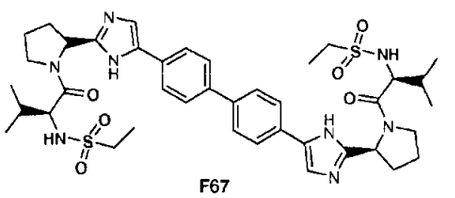
Compound F63 and F64 were prepared in analogous fashion to the procedure used to sythesized Cap45.

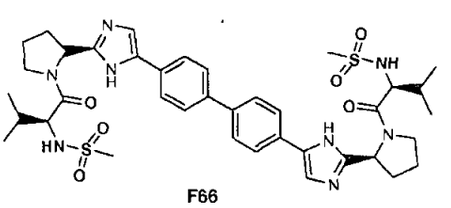
Entry	*Compound Name*	*Retention time (LC-Condition); homogeneity index MS data*
F59		RT = 1.743 minutes (condition 7, 98%); LRMS: Anal. Calcd. for C36H46N8O2 622.37; found: 624.07 $(M+H)^+$.
F60	N-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-acetamido-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)acetamide	RT = 2.047 minutes (condition 10, 98%); LRMS: Anal. Calcd. for C40H50N8O4 706.44; found: 707.77 $(M+H)^+$.
F61	N-((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-methyl-2-(propionylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)propanamide	RT = 2.215 minutes (condition 10 98%); LRMS: Anal. Calcd. for C42H54N8O4 734.43; found: 735.87$(M+H)^+$.
F62	2-methoxy-N-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxyacetyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)acetamide	RT = 2.232 minutes (condition 10, 99%); LRMS: Anal. Calcd. for C42H54N8O6 766.93; found: 768.05 $(M+H)^+$.
F63	1-methyl-3-((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methylcarbamoyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-	RT = 2.082 minutes (condition 10, 95%); LRMS: Anal. Calcd. for C40H52N10O4 736.42; found: 737.86

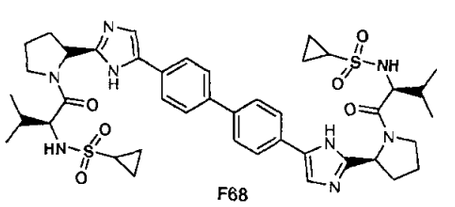
	pyrrolidinyl)carbonyl)propyl)urea	$(M+H)^+$.
F64	1-ethyl-3-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((ethylcarbamoyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)urea	RT = 1.617 minutes (condition 12, 93%); LRMS: Anal. Calcd. for C42H56N10O4 764.45; found: 765.57 $(M+H)^+$.

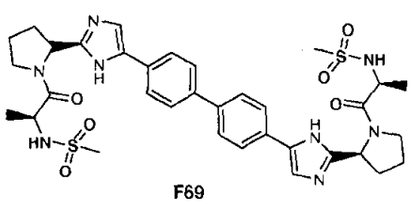












Compound F65

To a solution of F59 (0.06 g, 0.074 mmol in DMF (1 mL) was added dimethylsulfamoyl chloride (0.016 mL, 0.148 mmol) and Hunig'sBase (0.078 mL, 0.445 mmol) then stirred it at room temperature for 3 h. Solvent was removed by reduced pressure to get light brown oil which was purified by PreHPLC providing F65 N-((S)-1-((S)-2-(5-(4'-(2-((S)-1-((S)-2-(N,N-dimethylsulfamoylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl-4-yl)-1H-imidazol-2-

yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)propane-2-sulfonamide (19.0 mg, 0.018 mmol, 24.08 % yield)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.65-1.03 (m, 12H) 1.87-2.08 (m, 4H) 2.06-2.27 (m, 4H) 2.37-2.46 (m, 2H) 2.56-2.69 (m, 12H) 3.66-3.92 (m, 6H) 5.14 (t, *J*=7.63 Hz, 2H) 7.49 (d, *J*=9.16 Hz, 2H) 7.89 (d, *J*=8.24 Hz, 4H) 7.96 (s, 4H) 8.14 (s, 2H) 14.72 (s, 2H)

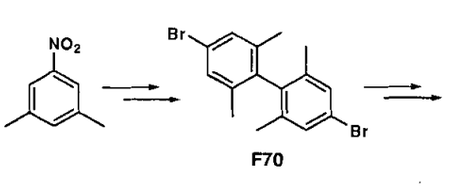
RT = 2.047 minutes (condition 10, 98%); LRMS: Anal. Calcd. for C40H50N8O4 706.38; found: 707.77 $(M+H)^+$.

1b Fret (EC50,uM) = 0.21

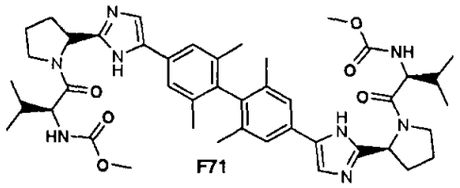
Compound F66 to F69 was prepared in analogous fashion to the procedure used to sythesize F65 from Compound F59.

Entry	*Compound Name*	*Retention time (LC-Condition); homogeneity index MS data*
F66	N-((1S)-2-methyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-methyl-2-((methylsulfonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)methanesulfonamide	RT = 2.02 minutes (condition 10, 98%); LRMS: Anal. Calcd. for C38H50N8O6S2 778.38; found: 779.60 $(M+H)^+$.
F67	N-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((ethylsulfonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)ethanesulfonamide	RT = 2.172 minutes (condition 10 98%); LRMS: Anal. Calcd. for C40H54N8O6S2 807.04; found: 808.42 $(M+H)^+$.
F68	N-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((cyclopropylsulfonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-	RT = 2.217 minutes (condition 10, 93%); LRMS: Anal. Calcd. for C42H54N8O6S2 831.06; found: 832.49 $(M+H)^+$.

	methylpropyl)cyclopropanesulfonamide	
F69	N-((1S)-1-methyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methylsulfonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)methanesulfonamide	RT = 1.983 minutes (condition 10, 95%); LRMS: Anal. Calcd. for C34H42N8O6S2 722.27; found: 723.68 $(M+H)^+$.



F70



F71

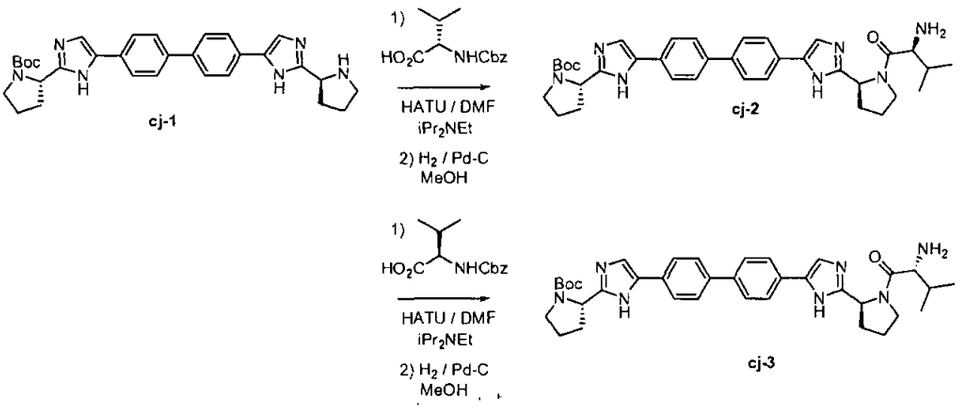
Compound F70 was prepared following the procedure described in Anna Helms et al., *J. Am. Chem. Soc.* 1992 114(15) pp 6227-6238.

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

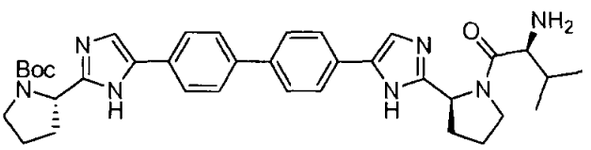
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.69-0.95 (m, 12H) 1.92 (s, 12H) 1.97-2.27 (m, 8H) 2.40 (s, 2H) 3.55 (s, 6H) 3.73-3.97 (m, 4H) 4.12 (t, *J*=7.78 Hz, 2H) 5.14 (t, *J*=7.02 Hz, 2H) 7.34 (d, *J*=8.24 Hz, 2H) 7.49-7.70 (m, 4H) 8.04 (s, 2H) 14.59 (s, 2H) RT = 2.523 minutes (condition 7, 96%); LRMS: Anal.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

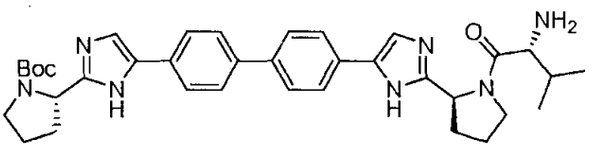


To a solution of (*S*)-*tert*-butyl 2-(5-(4'-(2-((*S*)-pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-1) (1.00 g, 1.91 mmol), iPr_2NEt (1.60 mL, 9.19 mmol) and *N*-Z-valine (0.62 g, 2.47 mmol) in DMF (10 mL) was added HATU (0.92 g, 2.42 mmol). The 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%).

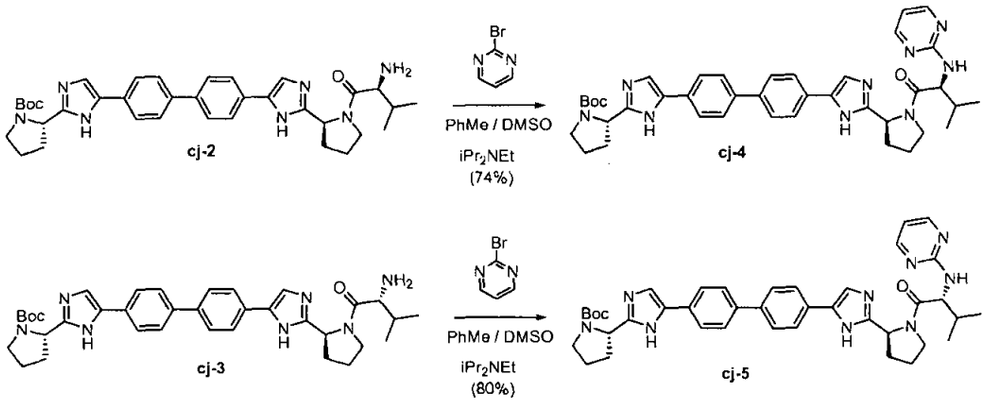
^{1}HNMR (400 MHz, DMSO-d_6) δ 12.18 (s, 0.35H), 11.73 (s, 0.65H), 11.89 (s, 0.65H), 11.82 (s, 0.35H), 7.77–7.81 (m, 3H), 7.57–7.71 (m, 5H), 7.50–7.52 (m, 2H), 5.17 (dd, *J* = 3.6, 6.5 Hz, 0.3H), 5.08 (dd, *J* = 3.6, 6.5 Hz, 0.7H), 4.84 (m, 0.3H), 4.76 (m, 0.7H), 3.67–3.69 (m, 1H), 3.50-3.62 (m, 1H), 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)

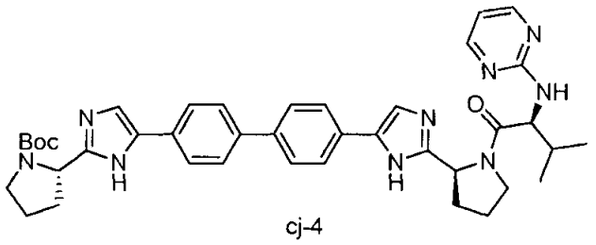


(*S*)-*tert*-Butyl 2-(5-(4'-(2-((*S*)-1-((*R*)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-3) was prepared using the same method used to prepare cj-2 to give a colorless foam (1.15 g, 76%). ^{1}HNMR (400 MHz, DMSO-d_6) δ 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)



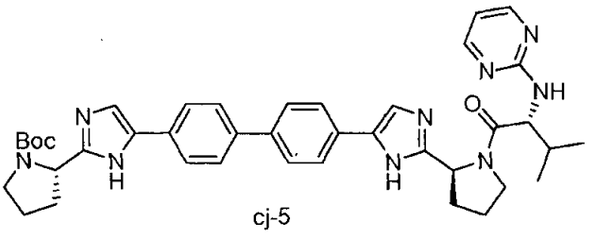
A mixture of (*S*)-*tert*-butyl 2-(5-(4'-(2-((*S*)-1-((*S*)-2-amino-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-2) (0.45 g, 0.72 mmol), 2-bromopyrimidine (0.37 g, 2.34 mmol) and iPr_2NEt (0.20 mL, 1.18 mmol) in toluene-DMSO (4:1, 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)



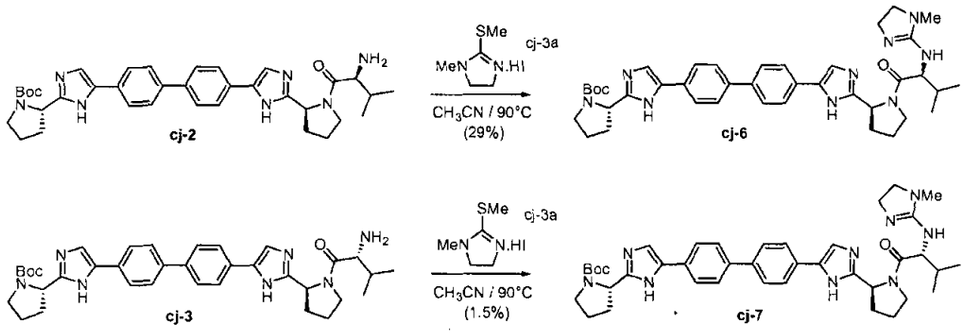
cj-5

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

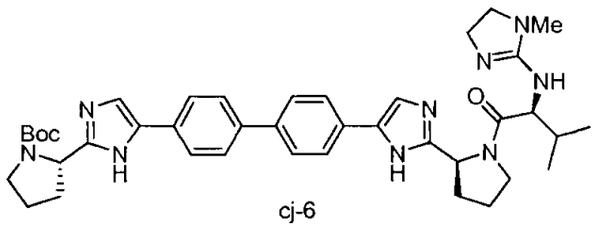
The title compound was prepared according to : Kister, J.; Assef, G.; Dou, H. J.-M.; Metzger, J. *Tetrahedron* 1976, *32*, 1395. Thus, a solution of *N*-methylethylenediamine (10.8 g, 146 mmol) in EtOH-H_2O (1:1, 90 mL) was preheated to 60°C and CS_2 (9.0 mL, 150 mmol) was added dropwise. The resulting 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).

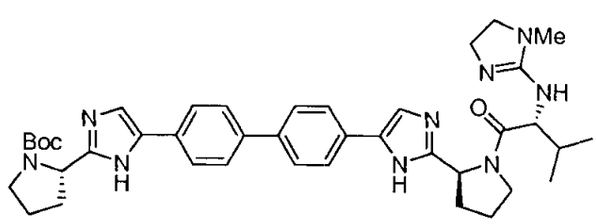
Preparation of (*S*)-*tert*-Butyl 2-(5-(4'-(2-((*S*)-1-((*S*)-3-methyl-2-(1-methyl-4-5-dihydroimidazol-2-ylamino)butanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-6)



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 $(M+H)^+$.

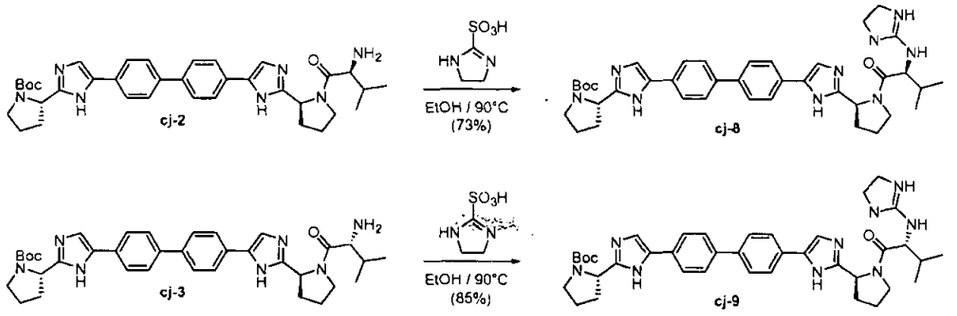
Preparation of (S)-*tert*-Butyl 2-(5-(4'-(2-((*S*)-1-((*R*)-3-methyl-2-(1-methyl-4-5-dihydroimidazol-2-ylamino)butanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-7)



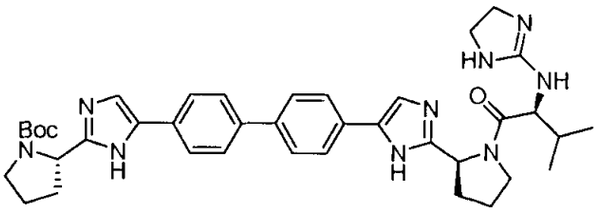
cj-7

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)

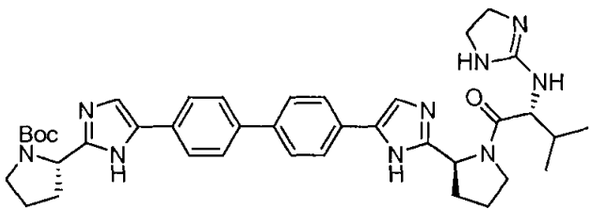


cj-8

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 $(M+H)^+$.

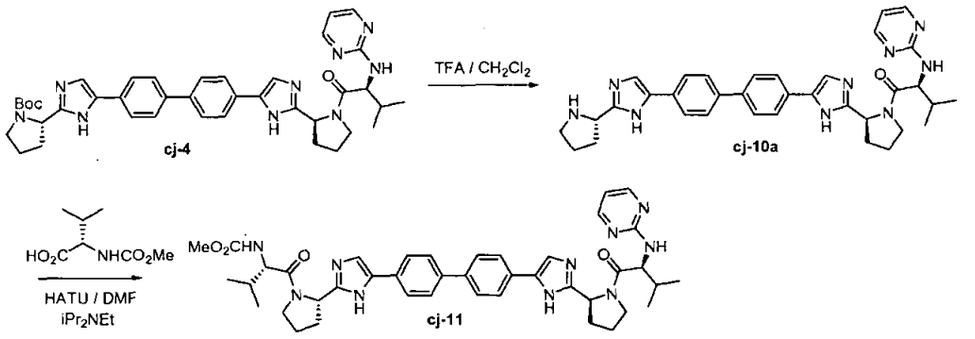
Preparation of (*S*)-*tert*-Butyl 2-(5-(4'-(2-((*S*)-1-((*R*)-3-methyl-2-(3,4-dihydroimidazol-2-ylamino)butanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-9)



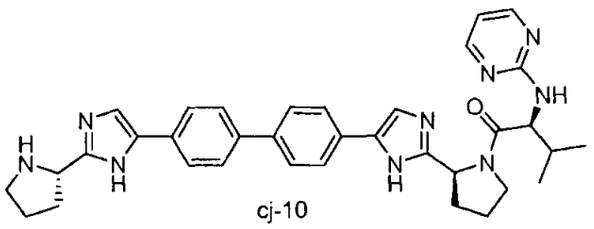
cj-9

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).

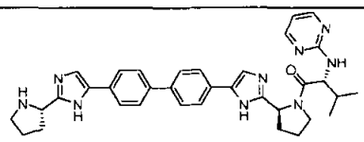
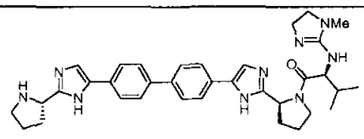
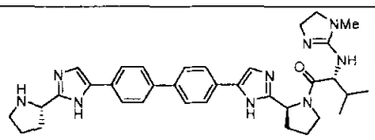
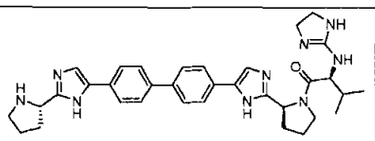
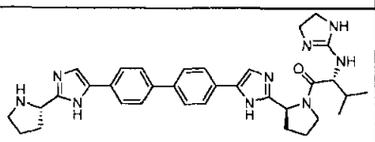


Step 1: A solution of the TFA salt of (*S*)-*tert*-butyl 2-(5-(4'-(2-((*S*)-1-((*S*)-3-methyl-2-(pyrimidin-2-ylamino)butanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (cj-4) (0.208 g, 0.199 mmol) in a mixture CH_2Cl_2 (4 mL) and TFA (3 mL) was stirred 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.

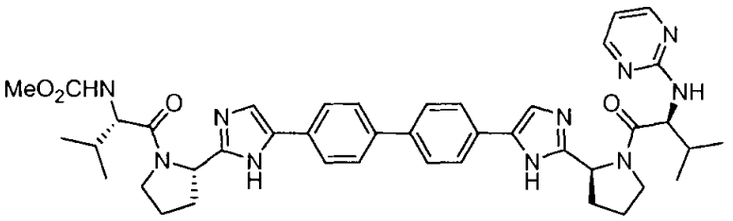
^{1}HNMR (400 MHz, DMSO-d_6) δ 14.53 (br s, 3H), 9.52 – 9.57 (m, 2H), 8.98 – 9.04 (m, 2H), 8.28 (d, J = 4.6 Hz, 2H), 8.13 (br s, 1H), 7.79 – 7.91 (m, 7H), 7.07 (d, J = 8.1 Hz, 1H), 6.62 (app t, J = 4.8 Hz, 1H), 5.07 (t, J = 7.1 Hz, 1H), 4.72 – 4.78 (m, 2H), 4.48 – 4.51 (m, 1H), 4.08-4.12 (m, 2H), 3.28 – 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 examples were 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 $(M+H)^+$.
cj-10b (from cj-2)		LCMS: Anal. Calcd. for $C_{35}H_{43}N_9O$: 605; found: 606 $(M+H)^+$.
cj-10c (from cj-3)		LCMS: Anal. Calcd. for $C_{35}H_{43}N_9O$: 605; found: 606 $(M+H)^+$.
cj-10d (from cj-2)		LCMS: Anal. Calcd. for $C_{34}H_{41}N_9O$: 591; found: 592 $(M+H)^+$.
cj-10e (from cj-3)		LCMS: Anal. Calcd. for $C_{34}H_{41}N_9O$: 591; found: 592 $(M+H)^+$.

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

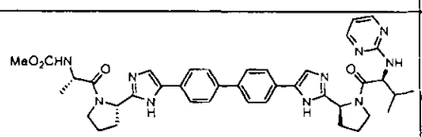
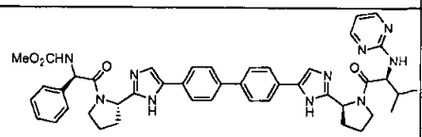
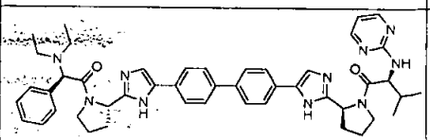
methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate

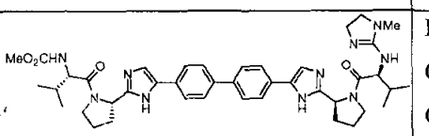
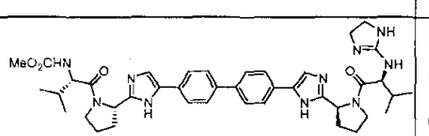
Step 2: To a solution of the TFA salt of (*S*)-3-methyl-2-(pyrimidin-2-ylamino)-1-((*S*)-2-(5-(4'-(2-((*S*)-pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)butan-1-one (cj-10) (0.208 g, 0.197 mmol) in DMF (4 mL) was added iPr_2NEt (0.20 mL, 1.15 mmol), (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic 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.

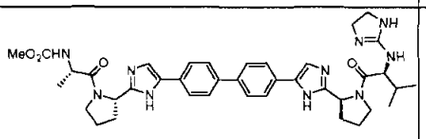
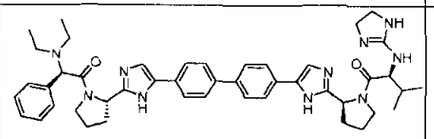
^{1}HNMR (400 MHz, DMSO-d_6) δ 11.78 (br s, 1H), 8.28 (d, *J* = 4.5 Hz, 1H), 7.76 – 7.79 (m, 4H), 7.66 – 7.69 (m, 4H), 7.48-7.51 (m, 2H), 7.29 (d, *J* = 8.6 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.60 (app t, *J* = 4.5 Hz, 1H), 5.03 – 5.09 (m, 2H), 4.48 (t. *J* = 8.1 Hz, 1H), 3.99 – 4.08 (m, 2H), 3.78 – 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).

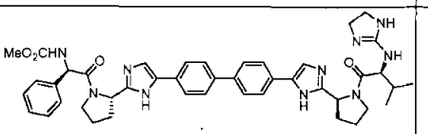
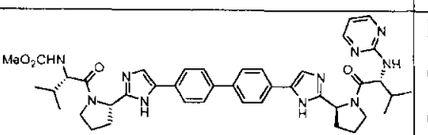
LCMS: Anal. Calcd. for $C_{42}H_{50}N_{10}O_4$:758; found: 759 $(M+H)^+$.

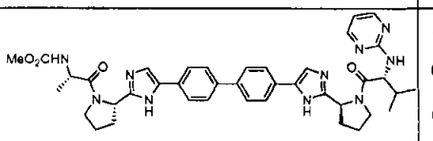
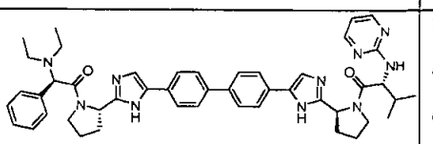
Similarly, the following examples were prepared according to the representative method above;

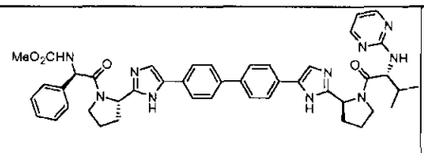
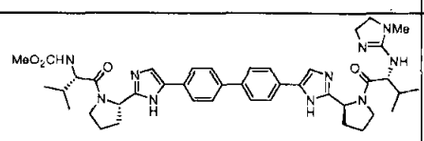
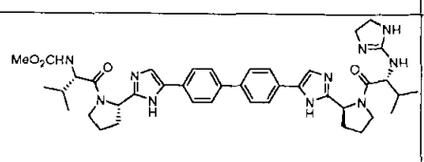
Example	*Compound Name*	*Structure*	*LCMS*
cj-11a (from cj-10 and *Cap*-52)	methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{40}H_{46}N_{10}O_4$: 730; found: 731 $(M+H)^+$.
cj-11b (from cj-10 and *Cap*-4)	methyl ((1R)-2-oxo-1-phenyl-2-((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)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{48}N_{10}O_4$: 792; found: 793 $(M+H)^+$.
cj-11c (from cj-10 and *Cap*-2)	N-((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-		LCMS: Anal. Calcd. for $C_{47}H_{54}N_{10}O_2$: 790; found: 791 $(M+H)^+$.

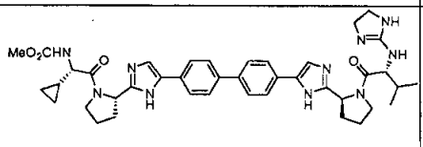
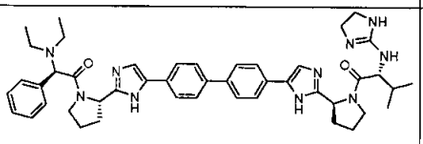
	2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-2-pyrimidinamine		
cj-11d (from cj-10b and *Cap*-51)	methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{54}N_{10}O_4$: 762; found: 763 $(M+H)^+$.
cj-11e (from cj-10d and *Cap*-51)	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1H-imidazol-2-yl)-L-valyl)-2-		LCMS: Anal. Calcd. for $C_{41}H_{52}N_{10}O_4$: 748; found: 749 $(M+H)^+$.

	pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		
cj-11f (from cj-10d and *Cap*-52)	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1H-imidazol-2-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{39}H_{48}N_{10}O_4$: 720; found: 721 $(M+H)^+$.
cj-11g (from cj-10d and *Cap*-2)	N-((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-		LCMS: Anal. Calcd. for $C_{46}H_{56}N_{10}O_2$: 780; found: 781 $(M+H)^+$.

	imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-4,5-dihydro-1H-imidazol-2-amine		
cj11h (from cj-10d and *Cap*-4)	methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{50}N_{10}O_4$: 782; found: 783 $(M+H)^+$.
cj-11i (from cj-10a and *Cap*-51)	methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carb		LCMS: Anal. Calcd. for $C_{42}H_{50}N_{10}O_4$: 758; found: 759 $(M+H)^+$.

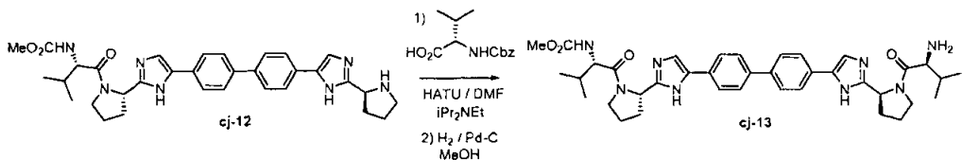
	onyl)propyl)carbamate		
cj-11j (from cj-10a and *Cap*-52)	methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{40}H_{46}N_{10}O_4$: 730; found: 731 $(M+H)^+$.
cj-11k (from cj-10a and *Cap*-2)	N-((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-2-pyrimidinamine		LCMS: Anal. Calcd. for $C_{47}H_{54}N_{10}O_2$: 790; found: 791 $(M+H)^+$.

cj-11l (from cj-10a and *Cap*-4)			LCMS: Anal. Calcd. for $C_{45}H_{48}N_{10}O_4$: 792; found: 793 $(M+H)^+$.
cj-11m (from cj-10c and *Cap*-51)	methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{54}N_{10}O_4$: 762; found: 763 $(M+H)^+$.
cj-11n (from cj-10e and *Cap*-51)	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1H-imidazol-2-yl)-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carb		LCMS: Anal. Calcd. for $C_{41}H_{52}N_{10}O_4$: 748; found: 749 $(M+H)^+$.

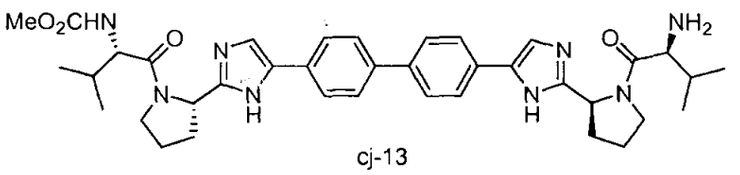
	onyl)-2-methylpropyl)carbamate		
cj-11o (from cj-10e and *Cap*-54b)	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1H-imidazol-2-yl)-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{50}N_{10}O_4$: 746; found: 747 $(M+H)^+$.
cj-11p (from cj-10e and *Cap*-2)	N-((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-4,5-dihydro-1H-		LCMS: Anal. Calcd. for $C_{46}H_{56}N_{10}O_2$: 780; found: 781 $(M+H)^+$.

	imidazol-2-amine		

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)



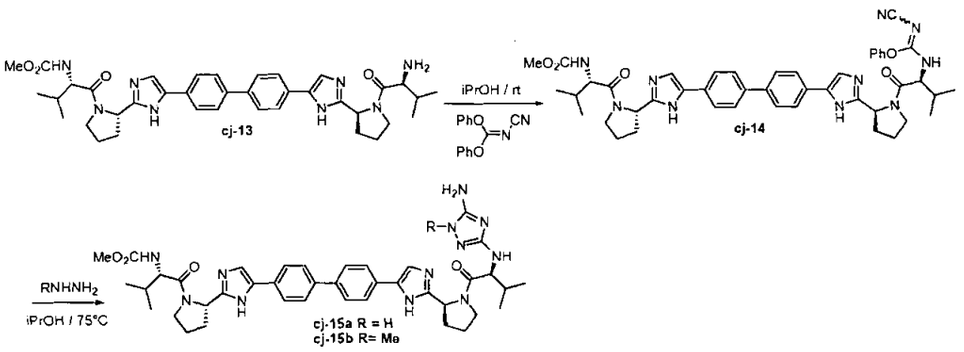
cj-13

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 $(M+H)^+$.

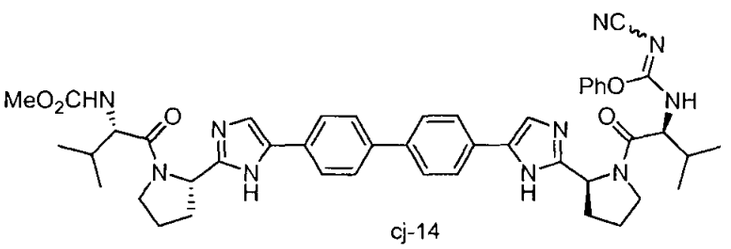
The obtained solid was dissolved in MeOH (80 mL), 10% Pd-C (1.0 g) was added and the mixture was hydrogenated at room temperature and atmospheric pressure for 3 h. The mixture was then filtered and the filtrate concentrated *in vacuo*. The resulting residue was purified by flash chromatography (SiO_2/ 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

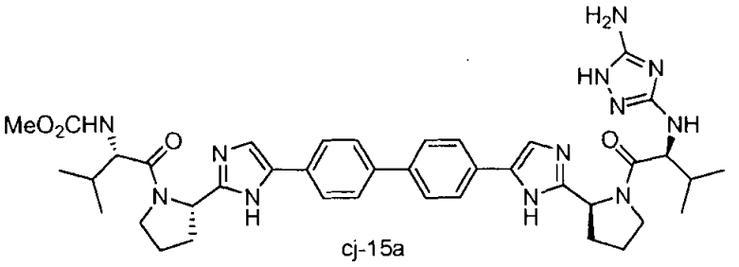


Preparation of Methyl (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-((*Z*/*E*)-(cyanoimino)(phenoxy)methylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-14)



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)



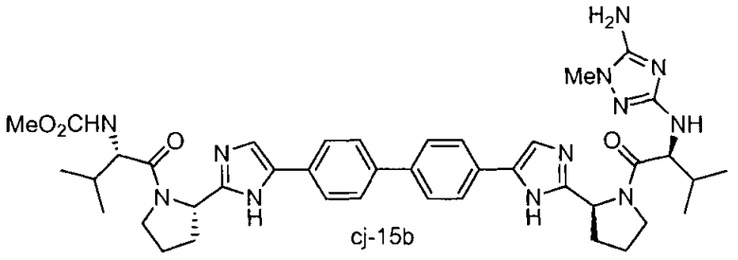
cj-15a

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.

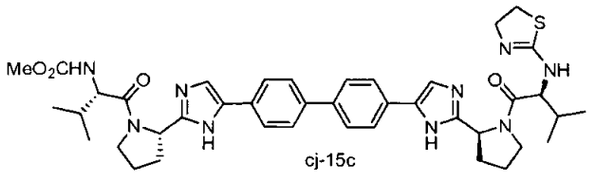
^{1}HNMR (400 MHz, DMSO-d_6) δ 13.79 (s, 0.4H), 12.19 (s, 1H), 11.76 (m, 1.6H), 7.77 – 7.85 (m, 4H), 7.62 – 7.71 (m, 4H), 7.49 – 7.51 (m, 1H), 7.24 – 7.29 (m, 1H), 6.31 (d, *J* = 9.1 Hz, 0.5H), 6.09 (d, *J* = 9.1 Hz, 1.5H), 5.87 (s, 1H), 5.34 – 5.36 (m, 1H), 5.04 – 5.08 (m, 2H), 4.89 (s, 1H), 4.75 (s, 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-15c

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihydro-1,3-thiazol-2-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

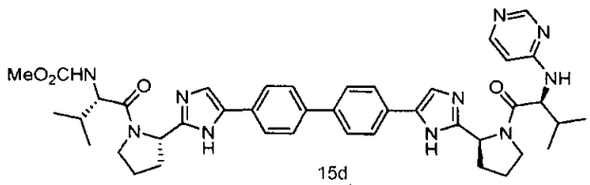


cj-15c

Example cj-15c was prepared by the condensation of Intermediate cj-13 with 2-(methylthio)-4,5-dihydrothiazole (Aldrich) using conditions analgous to those in the preparation of Intermediate cj-4. LCMS: Anal. Calcd. for $C_{41}H_{51}N_9O_4S$: 765; found: 766 $(M+H)^+$.

Example 15-d

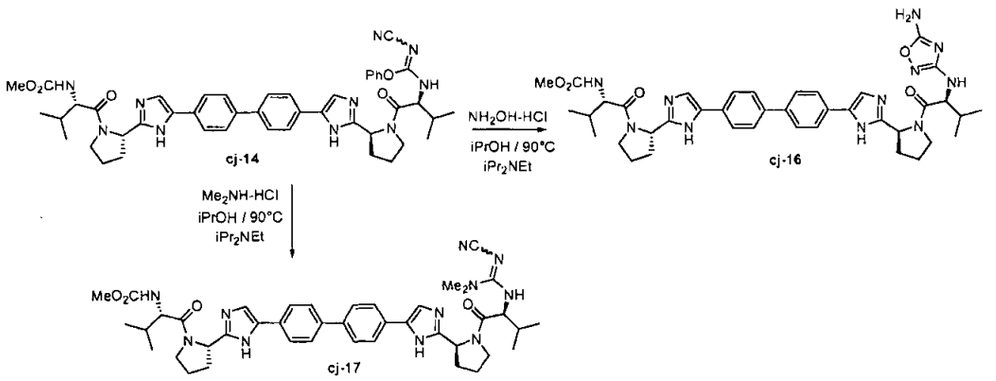
methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-4-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate



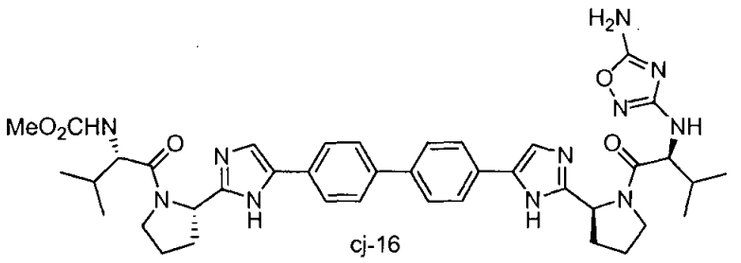
15d

Example cj-15d was prepared by the condensation of Intermediate cj-13 with 4,6-dichloropyrimidine (Aldrich) using conditions analgous to those in the preparation of Intermediate cj-4, followed by hydrogenation with 10% Pd-C. LCMS: Anal. Calcd. for $C_{42}H_{50}N_{10}O_4$: 758; found: 759 $(M+H)^+$.

Example cj-16 and cj-17



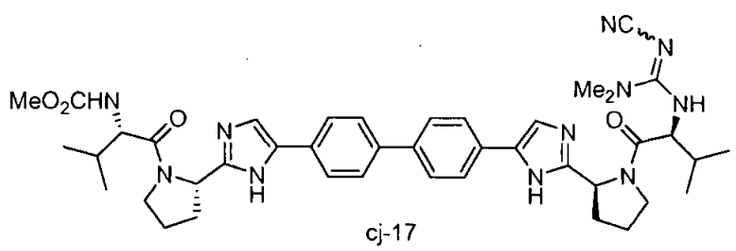
Preparation of methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(5-amino-1,2,4-oxadiazol-3-yl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (cj-16)



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

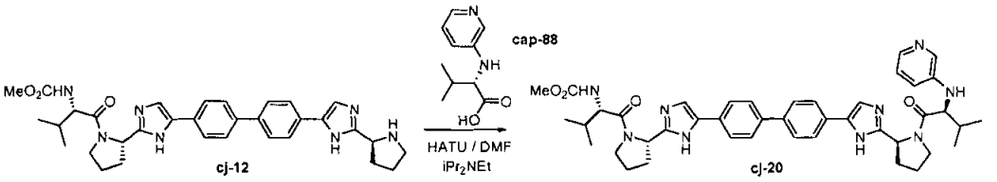
A solution of methyl (*S*)-1-((*S*)-2-(5-(4'-(2-((*S*)-1-((*S*)-2-((*Z/E*)-(cyanoimino)(phenoxy)methylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (cj-14) (0.115 g, 0.198 mmol) and dimethylamine hydrochloride (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 =

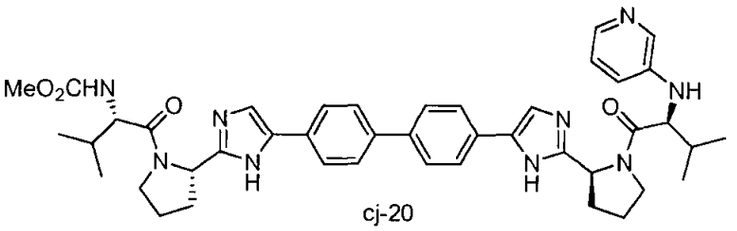
8.1 Hz, 1H), 5.06 – 5.08 (m, 2H), 4.47 (t, J = 8.1 Hz, 2H), 4.06 (unresolved dd, J = 8.0, 8.6 Hz, 1H), 3.84 – 3.90 (m, 2H), 3.76 – 3.82 (m, 3H), 3.53 (s, 3H), 3.00 (s, 6H), 2.11 – 2.20 (m, 3H), 1.90 – 2.04 (m, 5H), 0.97 (d, J = 6.5 Hz, 3H), 0.89 – 0.91 (m, 6H), 0.84 (d, J = 6.5 Hz, 3H).

LCMS: Anal. Calcd. for $C_{42}H_{53}N_{11}O_4$: 775; found: 776 $(M+H)^+$

Example cj-20



Preparation of methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-3-pyridinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate (cj-20)

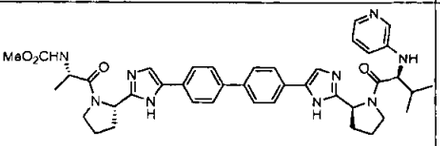
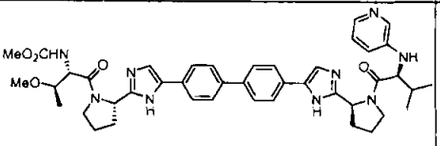


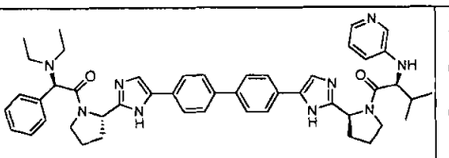
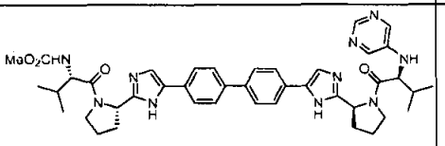
To a solution of methyl (*S*)-3-methyl-1-oxo-1-((*S*)-2-(5-(4'-(2-((*S*)-pyrrolidin-2-yl)-1*H*-imidazol-5-yl)biphenyl-4-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)butan-2-ylcarbamate (cj-13) (0.060 g, 0.103 mmol) in DMF (2 mL) was added iPr_2NEt (0.18 mL, 1.02 mmol), (*S*)-3-methyl-2-(pyridin-3-ylamino)butanoic acid (*Cap*-88) (0.040 g, 0.206 mmol) and HATU (0.078 g, 0.205 mmol). The reaction mixture was stirred for 1.5 h at room temperature and then it was directly purified by prep HPLC (Luna 5u C18/MeCN-H_2O-NH_4OAc). The resulting solid was repurified by flash chromatography (SiO_2/0-10% MeOH-CH_2Cl_2) and the obtained product was lyophilized from CH_3CN-H_2O to give the title compound (0.044 g, 56%) as a solid. ^{1}HNMR (400 MHz, DMSO-d_6) δ 12.19 (s, 1H), 11.76 (s, 1H), 8.07 (d, J = 2.6 Hz, 1H), 7.62 – 7.85 (m, 8H), 7.49 – 7.51 (m, 2H), 7.24 – 7.29 (m, 1H), 6.99 – 7.06 (m,

2H), 6.46 – 6.49 (m, 0.5H), 5.97 – 5.99 (m, 0.5H), 5.71 (d, J = 9.0 Hz, 1H), 5.55 (d, J = 10.6 Hz, 1H), 5.22 – 5.44 (m, 1H), 5.03 – 5.09 (m, 2H), 4.04 – 4.13 (m, 2H), 3.78 – 3.90 (m, 3H), 3.66 – 3.71 (m, 1H), 3.53 (s, 3H), 2.03 – 2.19 (m, 2H), 1.84 – 2.01 (m, 4H), 0.81 – 1.01 (m, 12H).

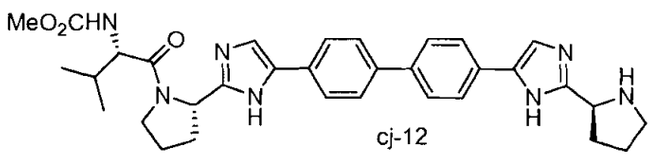
LCMS: Anal. Calcd. for $C_{43}H_{51}N_9O_4$: 757; found: 758 $(M+H)^+$.

Similarly, the following examples were prepared according to the representative method above;

Example	*Compound Name*	*Structure*	*LCMS*
cj-20a (from cj-22 and *Cap*-88)	methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-3-pyridinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{47}N_9O_4$: 729; found: 730 $(M+H)^+$.
cj-20b (from cj-23 and *Cap*-88)	methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-3-pyridinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		LCMS: Anal. Calcd. for $C_{43}H_{51}N_9O_5$: 773; found: 774 $(M+H)^+$.

cj-20c (from cj-24 and *Cap*-88)	N-((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-3-pyridinamine		LCMS: Anal. Calcd. for $C_{48}H_{55}N_9O_2$: 789; found: 790 $(M+H)^+$.
cj-20d (from cj-12 and *Cap*-88)	methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-5-pyrimidinyl-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{50}N_{10}O_4$: 758; found: 759 $(M+H)^+$.

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)

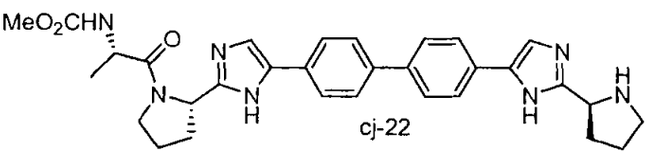


Synthesized from Intermediate-28d and *Cap*-51 as in Example 28e, followed by Boc removal with TFA/CH_2Cl_2 and free base formation with MCX resin.

^{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 $(M+H)^+$.

Preparation of Methyl (*S*)-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)propan-2-ylcarbamate (cj-22).



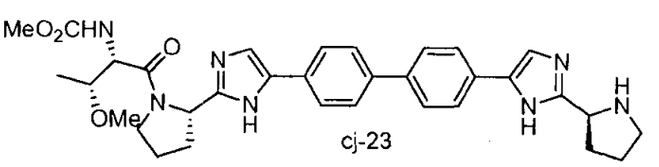
cj-22

Synthesized from Intermediate-28d and *Cap*-52 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 7.68 – 7.79 (m, 4H), 7.59-7.65 (m, 4H), 7.44 (d, J = 6.6 Hz, 1H), 7.37 (s, 0.3H), 7.27 (s, 0.7H), 5.18 (dd, J = 4.0, 7.6 Hz, 1H), 4.74 (t, J = 8.0 Hz, 1H), 4.46 (dd, J = 6.8, 13.9 Hz, 1H), 3.84 (unresolved dd, J = 6.1, 6.5 Hz, 1H), 3.62 (s, 3H), 3.54 (s, 1H), 3.32 – 3.46 (m, 3H), 2.40 – 2.46 (m, 1H), 2.26 – 2.39 (m, 2H), 2.14 – 2.24 (m, 2H), 2.01 – 2.12 (m, 2H), 0.32 (d, J = 7.1 Hz, 3H).

LCMS: Anal. Calcd. for $C_{31}H_{35}N_7O_3$: 553; found: 554 $(M+H)^+$.

Preparation of Methyl (2*S*,3*R*)-3-methoxy-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-23).



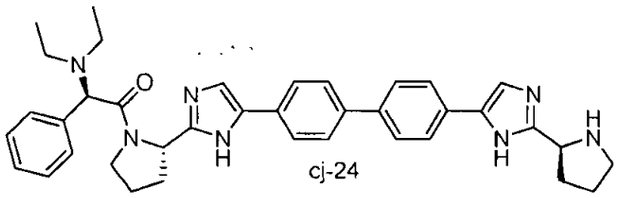
cj-23

Synthesized from Intermediate-28d and *Cap*-86 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 7.72 (m, 4H), 7.64 -7.69 (m, 4H), 7.48 (d, J = 4.1 Hz, 1H), 7.38 (s, 0.3H), 7.33 (s, 0.7H), 5.51 – 5.54 (m, 0.2H), 5.22 (dd, J = 4.9, 7.6 Hz, 0.8H), 4.76 (t, J = 8.0 Hz, 1H), 4.48 (d, J = 5.1 Hz, 0.8H), 4.35 – 4.36 (m, 0.2H), 3.90 – 3.99 (m, 1H), 3.68 (s, 3H), 3.54 (s, 1H), 3.35 – 3.48 (m, 4H), 3.29 (s, 3H), 2.42 – 2.50 (m, 1H), 2.30 – 2.37 (m, 2H), 2.19 – 2.26 (m, 2H), 2.05 – 2.15 (m, 2H), 1.19 (d, J = 6.1 Hz, 3H).

LCMS: Anal. Calcd. for $C_{33}H_{39}N_7O_4$: 597; found: 598 $(M+H)^+$.

Preparation of (*R*)-2-(Diethylamino)-2-phenyl-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)ethanone (cj-24).



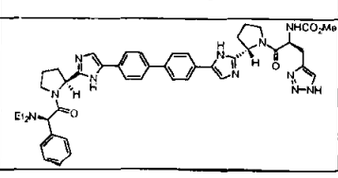
cj-24

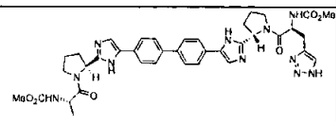
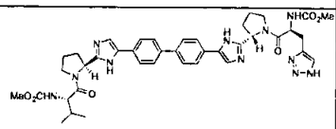
Synthesized from Intermediate-28d and *Cap*-2 as in Example 28e, followed by Boc removal with TFA/CH_2Cl_2 and free base formation with MCX resin.

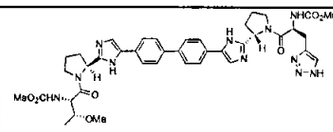
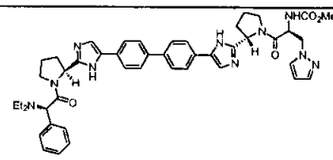
^{1}HNMR (400 MHz, MeOH-d_4) δ 7.59 – 7.82 (m, 10H), 7.36 – 7.51 (m, 4H), 7.01 – 7.15 (m, 1H), 5.09 – 5.13 (m, 2H), 4.77 (t, J = 8.5 Hz, 1H), 4.03 – 4.05 (m, 1H), 3.67 – 3.93 (m, 1H), 3.35 – 3.47 (m, 2H), 3.18 – 3.23 (m, 1H), 2.91-3.07 (m, 2H), 2.70 – 2.84 (m, 2H), 2.34 – 2.60 (m, 2H), 1.97 – 2.24 (m, 5H), 1.07 – 1.17 (m, 6H).

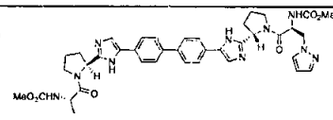
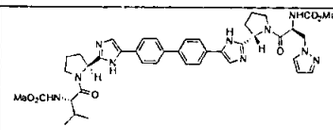
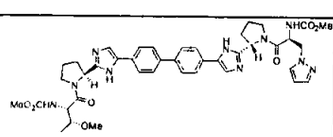
LCMS: Anal. Calcd. for $C_{38}H_{43}N_7O$: 613; found: 614 $(M+H)^+$.

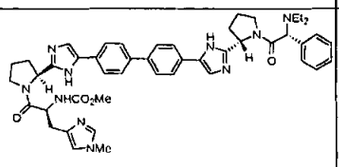
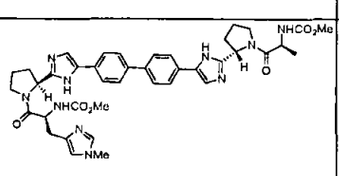
The following were prepared according to the procedure in example 28 starting with 28d. The caps are given in the table in the order they were appended to 28d. Where a cap number is not given the corresponding carboxylic acid is commercially available.

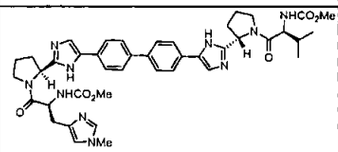
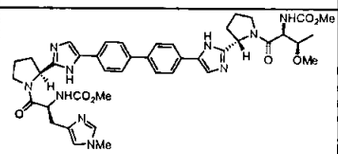
Example	*Compound Name*	*Structure*	*LCMS*	*Cap*
cj-32	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-		LCMS: Anal. Calcd. for $C_{45}H_{51}N_{11}O_4$:	2/128

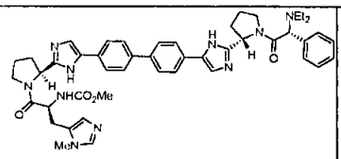
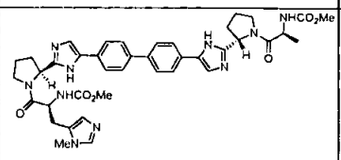
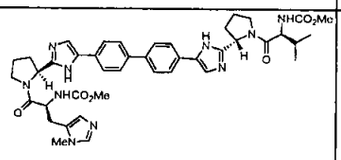
	(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-1,2,3-triazol-4-ylmethyl)ethyl)carbamate		809; found: 810 $(M+H)^+$.	
cj-33	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-1,2,3-triazol-4-ylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{38}H_{43}N_{11}O_6$: 749; found: 750 $(M+H)^+$.	52/128
cj-34	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1H-1,2,3-triazol-4-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-		LCMS: Anal. Calcd. for $C_{40}H_{47}N_{11}O_6$: 777; found: 777 $(M+H)^+$.	51/128

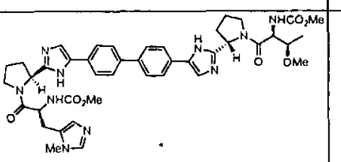
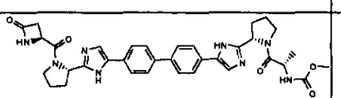
	imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate			
cj-35	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-1,2,3-triazol-4-ylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{40}H_{47}N_{11}O_7$: 793; found: 794 $(M+H)^+$.	86/128
cj-36	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-pyrazol-1-ylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{52}N_{10}O_4$: 808; found: 809 $(M+H)^+$.	2/129

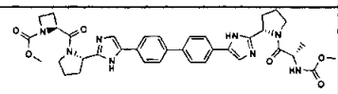
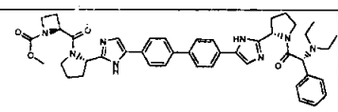
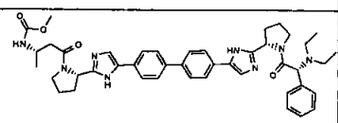
cj-37	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-pyrazol-1-ylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for C39H44N10O6: 748; found: 749 $(M+H)^+$.	52/129
cj-38	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1H-pyrazol-1-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{40}H_{47}N_{11}O_7$: 776; found: 777 $(M+H)^+$.	51/129
cj-39	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-		LCMS: Anal. Calcd. for $C_{41}H_{48}N_{10}O_7$: 792; found: 793 $(M+H)^+$.	86/129

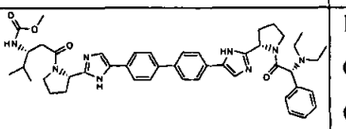
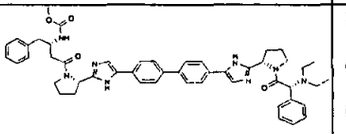
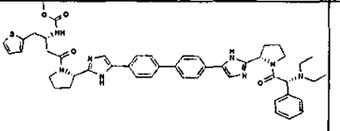
	pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-pyrazol-1-ylmethyl)ethyl)carbamate			
cj-40	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-4-yl)methyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{47}H_{54}N_{10}O_4$: 822; found: 823 $(M+H)^+$.	2/127
cj-41	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-4-		LCMS: Anal. Calcd. for $C_{40}H_{46}N_{10}O_6$: 762; found: 763 $(M+H)^+$.	52/127

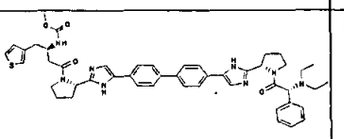
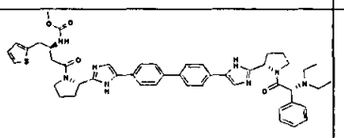
	yl)methyl)-2-oxoethyl)carbamate			
cj-42	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1-methyl-1H-imidazol-4-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{50}N_{10}O_6$ 790; found: 791 $(M+H)^+$.	51/127
cj-43	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-4-yl)methyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{50}N_{10}O_7$ 806; found: 806 $(M+H)^+$.	86/127

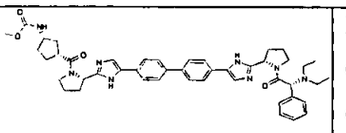
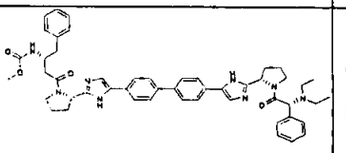
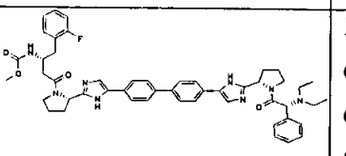
cj-44	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-5-yl)methyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{47}H_{54}N_{10}O_4$ 822; found: 823 $(M+H)^+$.	2/126
cj-45	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-5-yl)methyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{40}H_{46}N_{10}O_6$: 762; found: 763 $(M+H)^+$.	52/126
cj-46	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1-methyl-1H-imidazol-5-		LCMS: Anal. Calcd. for $C_{42}H_{50}N_{10}O_6$ 790; found: 791	51/126

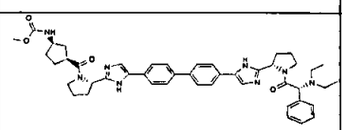
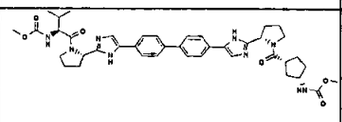
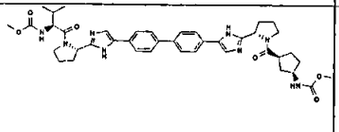
	yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate			
cj-47	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-methyl-1H-imidazol-5-yl)methyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{50}N_{10}O_7$ 806; found: 807 $(M+H)^+$.	86/126
cj-48	methyl ((1S)-1-methyl-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(((2S)-4-oxo-2-azetidinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)c		LCMS: Anal. Calcd. for $C_{35}H_{38}N_8O_5$ 650; found: 651 $(M+H)^+$.	52/-

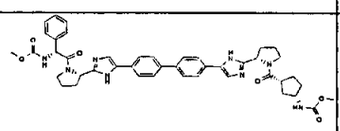
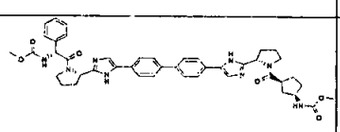
	arbamate			
cj-49	methyl (2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate		LCMS: Anal. Calcd. for $C_{37}H_{42}N_8O_6$ 694; found: 695 $(M+H)^+$.	52/114
cj-50	methyl (2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1-azetidinecarboxylate		LCMS: Anal. Calcd. for $C_{44}H_{50}N_8O_4$ 754; found: 755 $(M+H)^+$.	2/114
cj-51	methyl ((1S)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-		LCMS: Anal. Calcd. for $C_{44}H_{52}N_8O_4$ 756; found: 757 $(M+H)^+$.	2/115

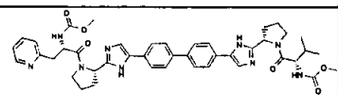
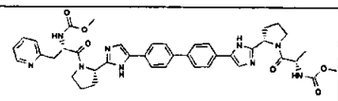
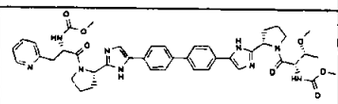
	imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-3-oxopropyl)carbamate			
cj-52	methyl ((1R)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-isopropyl-3-oxopropyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{56}N_8O_4$ 784; found: 785 $(M+H)^+$.	2/116
cj-53	methyl ((1S)-1-benzyl-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxopropyl)carbamate		LCMS: Anal. Calcd. for $C_{50}H_{56}N_8O_4$ 833; found: 834 $(M+H)^+$.	2/96
cj-54	methyl ((1R)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-		LCMS: Anal. Calcd. for $C_{48}H_{54}N_8O_4S$ 838; found:	2/119

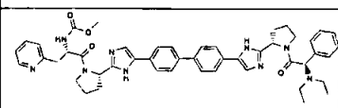
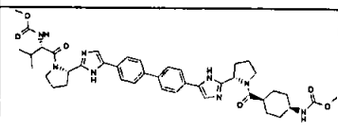
	phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-(2-thienylmethyl)propyl)carbamate		839 $(M+H)^+$.	
cj-55	methyl ((1R)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-(3-thienylmethyl)propyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{54}N_8O_4S$ 838; found: 839 $(M+H)^+$.	2/120
cj-56	methyl ((1S)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-(2-thienylmethyl)propyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{54}N_8O_4S$ 838; found: 839 $(M+H)^+$.	2/118

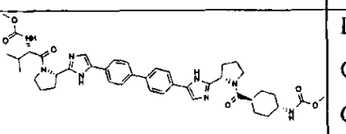
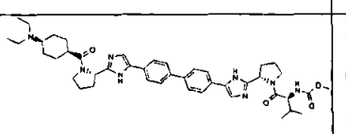
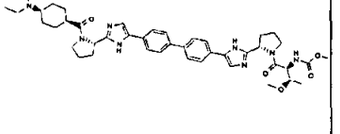
cj-57	methyl ((1S,3R)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{54}N_8O_4$ 782; found: 783 $(M+H)^+$.	2/99a
cj-58	methyl ((1R)-1-benzyl-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxopropyl)carbamate		LCMS: Anal. Calcd. for $C_{50}H_{56}N_8O_4$ 832; found: 833 $(M+H)^+$.	2/117
cj-59	methyl ((1R)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(2-		LCMS: Anal. Calcd. for $C_{50}H_{55}N_8O_4F$ 850; found: 851 $(M+H)^+$.	2/100

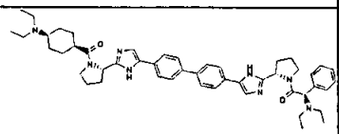
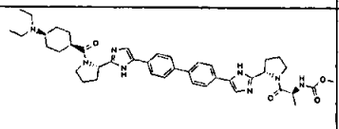
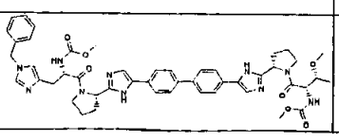
	fluorobenzyl)-3-oxopropyl)carbamate			
cj-60	methyl ((1R,3S)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{54}N_8O_4$ 782; found: 783 $(M+H)^+$.	2/99
cj-61	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(((1R,3S)-3-((methoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{50}N_8O_6$ 750; found: 751 $(M+H)^+$.	52/99a
cj-62	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(((1S,3R)-3-((methoxycarbonyl)		LCMS: Anal. Calcd. for $C_{41}H_{50}N_8O_6$ 750; found: 751 $(M+H)^+$.	52/99

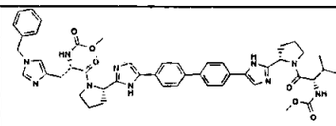
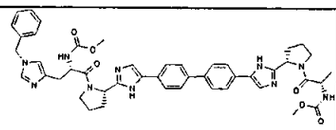
	amino)cyclopentyl) carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate			
cj-63	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1R,3S)-3-((methoxycarbonyl) amino)cyclopentyl) carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{48}N_8O_6$ 784; found: 785 $(M+H)^+$.	4/99a
cj-64	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1S,3R)-3-((methoxycarbonyl) amino)cyclopentyl) carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-		LCMS: Anal. Calcd. for $C_{44}H_{48}N_8O_6$ 784; found: 785 $(M+H)^+$.	4/99

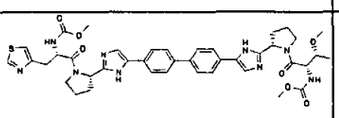
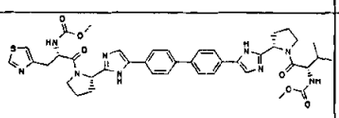
	imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate			
cj-65	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(2-pyridinyl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{43}H_{49}N_9O_6$ 787; found: 788 $(M+H)^+$.	51/93
cj-66	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(2-pyridinylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{45}N_9O_6$ 759; found: 760 $(M+H)^+$.	52/93
cj-67	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-		LCMS: Anal. Calcd. for $C_{43}H_{49}N_9O_7$	86/93

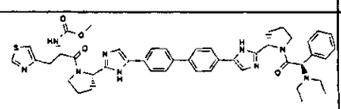
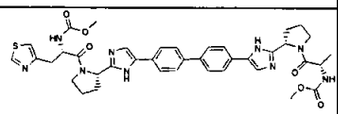
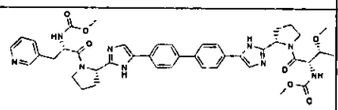
	methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(2-pyridinylmethyl)ethyl)carbamate		803; found: 804 $(M+H)^+$.	
cj-68	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(2-pyridinylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{53}N_9O_4$ 819; found: 820 $(M+H)^+$.	2/93
cj-69	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-((methoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbon		LCMS: Anal. Calcd. for $C_{42}H_{52}N_8O_6$ 764; found: 765 $(M+H)^+$.	51/104

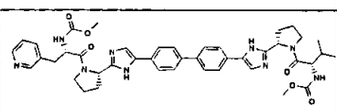
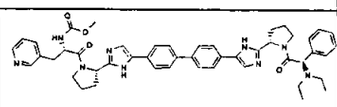
	yl)-2-methylpropyl)carbamate			
cj-70	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((trans-4-((methoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{52}N_8O_6$ 764; found: 765 $(M+H)^+$.	51/105
cj-71	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-(diethylamino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{58}N_8O_4$ 762; found: 763 $(M+H)^+$.	51/106
cj-72	methyl ((1S,2R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-(diethylamino)cyclohexyl)carbonyl)-		LCMS: Anal. Calcd. for $C_{44}H_{58}N_8O_5$ 778; found: 779 $(M+H)^+$.	86/106

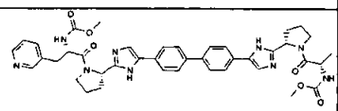
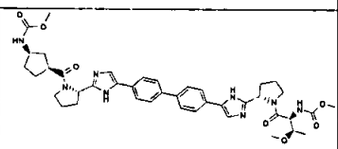
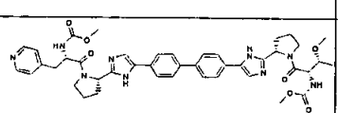
	2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate			
cj-73	cis-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-N,N-diethylcyclohexanamine		LCMS: Anal. Calcd. for $C_{49}H_{62}N_8O_2$ 794; found: 795 $(M+H)^+$.	2/106
cj-74	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-(diethylamino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{54}N_8O_4$ 734; found: 735 $(M+H)^+$.	52/106
cj-75	methyl ((1S)-1-((1-benzyl-1H-		LCMS: Anal. Calcd. for	86/108

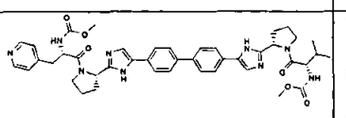
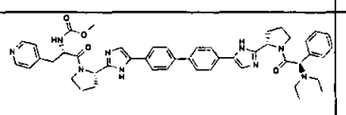
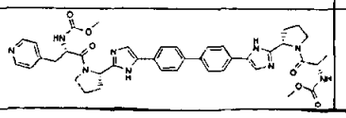
	imidazol-4-yl)methyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		$C_{48}H_{54}N_{10}O_7$ 882; found: 883 $(M+H)^+$.	
cj-76	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1-benzyl-1H-imidazol-4-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{54}N_{10}O_6$ 866; found: 867 $(M+H)^+$.	51/108
cj-77	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1-benzyl-1H-imidazol-4-yl)-2-((methoxycarbonyl)amino)propanoyl)-		LCMS: Anal. Calcd. for $C_{46}H_{50}N_{10}O_6$ 838; found: 839 $(M+H)^+$.	52/108

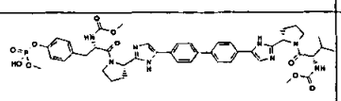
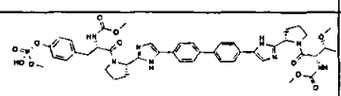
	2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate			
cj-78	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1,3-thiazol-4-ylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{47}N_9O_7S$ 809; found: 810 $(M+H)^+$.	86/107
cj-79	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1,3-thiazol-4-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-		LCMS: Anal. Calcd. for $C_{41}H_{47}N_9O_6S$ 793; found: 794 $(M+H)^+$.	51/107

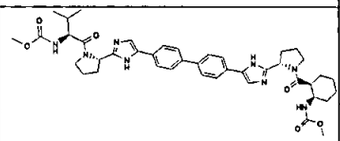
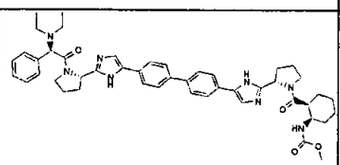
	methylpropyl)carbamate			
cj-80	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1,3-thiazol-4-ylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{51}N_9O_4S$ 825; found: 826 $(M+H)^+$.	2/107
cj-81	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1,3-thiazol-4-ylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{39}H_{43}N_9O_6S$ 765; found: 766 $(M+H)^+$.	51/107
cj-82	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)		LCMS: Anal. Calcd. for $C_{43}H_{49}N_9O_7$ 803; found: 804$(M+H)^+$.	86/109

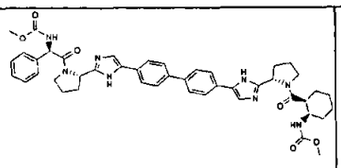
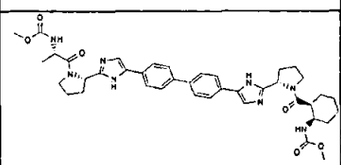
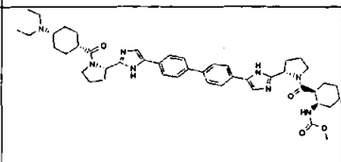
	amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(3-pyridinylmethyl)ethyl)carbamate			
cj-83	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(3-pyridinylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{43}H_{49}N_9O_6$ 787; found: 788 $(M+H)^+$.	51/109
cj-84	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(3-pyridinylmethyl)eth		LCMS: Anal. Calcd. for $C_{48}H_{53}N_9O_4$ 819; found: 820 $(M+H)^+$.	2/109

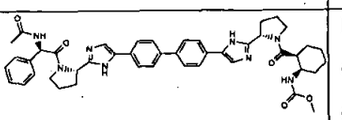
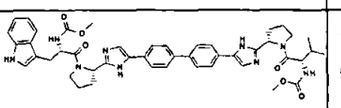
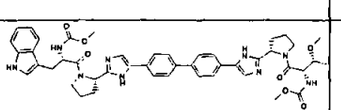
	yl)carbamate			
cj-85	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(3-pyridinylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{45}N_9O_6$ 759; found: 760 $(M+H)^+$.	52/109
cj-86	methyl ((1R,3S)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{50}N_8O_7$ 766; found: 767 $(M+H)^+$.	86/99
cj-87	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-		LCMS: Anal. Calcd. for $C_{43}H_{49}N_9O_7$ 803; found: 804 $(M+H)^+$.	86/110

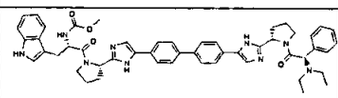
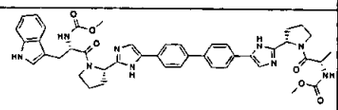
	biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(4-pyridinylmethyl)ethyl)carbamate			
cj-88	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(4-pyridinylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{43}H_{49}N_9O_6$ 787; found: 788 $(M+H)^+$.	51/110
cj-89	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(4-pyridinylmethyl)ethyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{53}N_9O_4$ 819; found: 820 $(M+H)^+$.	2/110
cj-90	methyl ((1S)-2-((2S)-2-(5-(4'-(2-		LCMS: Anal. Calcd. for	52/110

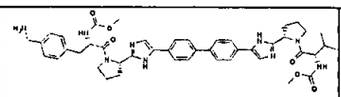
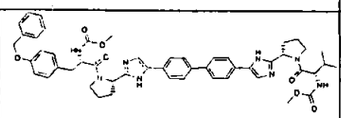
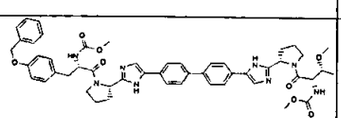
	((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(4-pyridinylmethyl)ethyl)carbamate		$C_{41}H_{45}N_9O_6$ 759; found: 760 $(M+H)^+$.	
cj-91	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(O-(hydroxy(methoxy)phosphoryl)-N-(methoxycarbonyl)-L-tyrosyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{53}N_8O_{10}P$ 896; found: 897 $(M+H)^+$.	51/111
cj-92	methyl ((1S,2R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(O-(hydroxy(methoxy)phosphoryl)-N-(methoxycarbonyl)-L-tyrosyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-		LCMS: Anal. Calcd. for $C_{45}H_{53}N_8O_{11}P$ 912; found: 913 $(M+H)^+$.	86/111

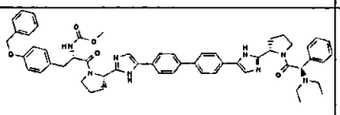
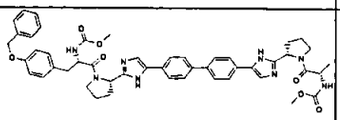
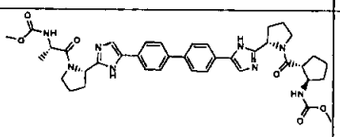
	biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate			
cj-93	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(((1S,2R)-2-((methoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{42}H_{52}N_8O_6$ 764; found: 765 $(M+H)^+$.	98/51
cj-94	methyl ((1R,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate		LCMS: Anal. Calcd. for $C_{47}H_{56}N_8O_4$ 796; found: 797 $(M+H)^+$.	98/2

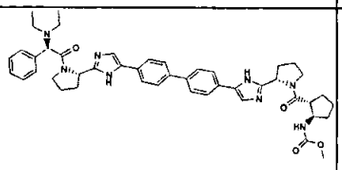
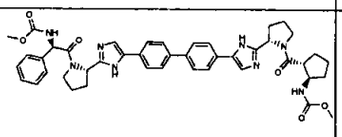
cj-95	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1S,2R)-2-((methoxycarbonyl)amino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{50}N_8O_6$ 798; found: 799 $(M+H)^+$.	98/4
cj-96	methyl ((1R,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate		LCMS: Anal. Calcd. for $C_{40}H_{48}N_8O_6$ 736; found: 737 $(M+H)^+$.	98/51
cj-97	methyl ((1R,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-(diethylamino)cyclohexyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-		LCMS: Anal. Calcd. for $C_{46}H_{60}N_8O_4$ 788; found: 789 $(M+H)^+$.	98/106

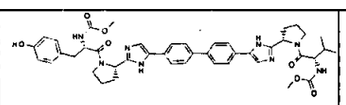
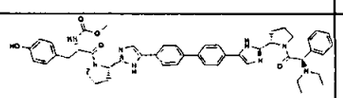
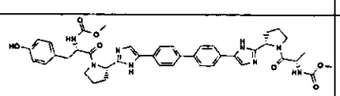
	imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate			
cj-98	methyl ((1R,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-acetamido-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclohexyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{50}N_8O_5$ 782; found: 783 $(M+H)^+$.	98/130
cj-99	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1H-indol-3-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{56}H_{51}N_9O_6$ 825; found: 826 $(M+H)^+$.	51/112
cj-100	methyl ((1S)-1-(1H-indol-3-ylmethyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-		LCMS: Anal. Calcd. for $C_{46}H_{51}N_9O_7$ 841; found: 842 $(M+H)^+$.	86/112

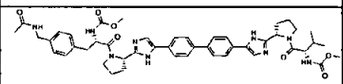
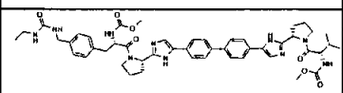
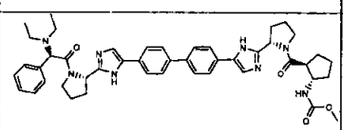
	methoxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate			
cj-101	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(1H-indol-3-ylmethyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{51}H_{55}N_9O_4$ 857; found: 858 $(M+H)^+$.	2/112
cj-102	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1H-indol-3-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{47}N_9O_6$ 797; found: 798 $(M+H)^+$.	52/112

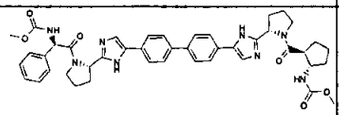
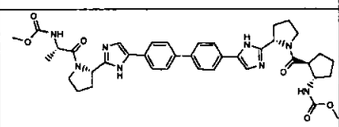
cj-103	methyl ((1S)-1-(4-(aminomethyl)benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{45}H_{53}N_9O_6$ 815; found: 816 $(M+H)^+$.	see text
cj-104	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(O-benzyl-N-(methoxycarbonyl)-L-tyrosyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{51}H_{56}N_8O_7$ 892; found: 893 $(M+H)^+$.	51/113
cj-105	methyl ((1S,2R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(O-benzyl-N-(methoxycarbonyl)-L-tyrosyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-		LCMS: Anal. Calcd. for $C_{51}H_{56}N_8O_8$ 908; found: 909 $(M+H)^+$.	86/113

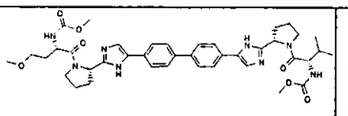
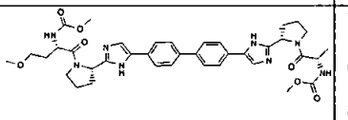
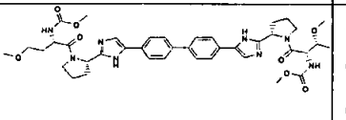
	biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate			
cj-106	methyl ((1S)-1-(4-(benzyloxy)benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{56}H_{60}N_8O_5$ 924; found: 925 $(M+H)^+$.	2/113
cj-107	methyl ((1S)-1-(4-(benzyloxy)benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{49}H_{52}N_8O_7$ 864; found: 865 $(M+H)^+$.	52/113
cj-108	methyl ((1R,2R)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-		LCMS: Anal. Calcd. for $C_{39}H_{46}N_8O_6$ 722; found: 723 $(M+H)^+$.	122/52

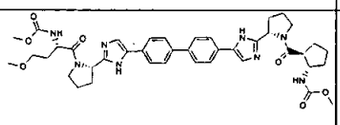
	pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate			
cj-109	methyl ((1R,2R)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate		LCMS: Anal. Calcd. for $C_{46}H_{54}N_8O_4$ 782; found: 783 $(M+H)^+$.	122/2
cj-110	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1R,2R)-2-((methoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{48}N_8O_6$ 784; found: 785 $(M+H)^+$.	122/4

cj-111	methyl ((1S)-1-(4-hydroxybenzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{50}N_8O_7$ 802; found: 803 $(M+H)^+$.	see text
cj-112	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(4-hydroxybenzyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{49}H_{54}N_8O_5$ 834; found: 835 $(M+H)^+$.	see text
cj-113	methyl ((1S)-1-(4-hydroxybenzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-		LCMS: Anal. Calcd. for $C_{42}H_{46}N_8O_7$ 774; found: 775 $(M+H)^+$.	see text

	pyrrolidinyl)-2-oxoethyl)carbamate			
cj-114	methyl ((1S)-1-(4-(acetamidomethyl) benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl) amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{47}H_{55}N_9O_7$ 857; found: 585 $(M+H)^+$.	see text
cj-115	methyl ((1S)-1-(4-(((ethylcarbamoyl)amino)methyl)benzyl)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl) amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{48}H_{58}N_{10}O_7$ 886; found: 887 $(M+H)^+$.	see text
cj-116	methyl ((1S,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-		LCMS: Anal. Calcd. for $C_{46}H_{54}N_8O_4$ 782; found: 783 $(M+H)^+$.	121/2

	pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate			
cj-117	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1S,2S)-2-((methoxycarbonyl)amino)cyclopentyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{44}H_{48}N_8O_6$ 784; found: 785 $(M+H)^+$.	121/4
cj-118	methyl ((1S,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate		LCMS: Anal. Calcd. for $C_{39}H_{46}N_8O_6$ 722; found: 723 $(M+H)^+$.	121/52

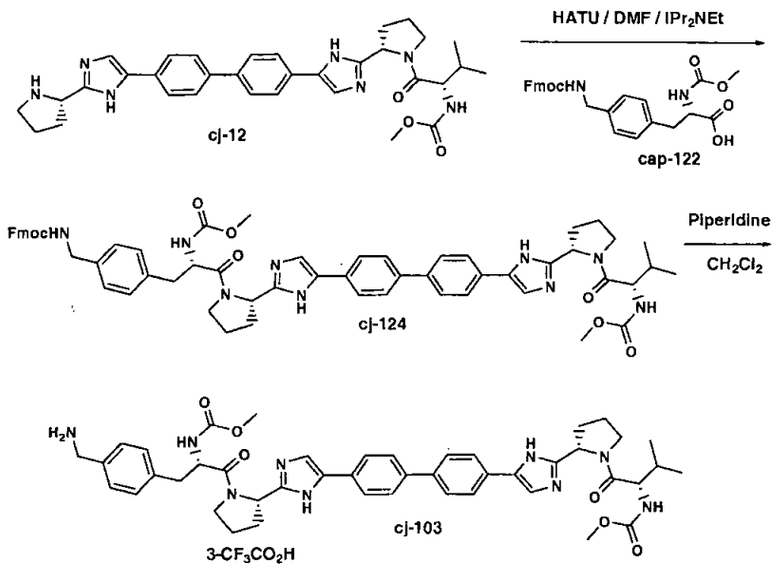
cj-119	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{40}H_{50}N_8O_7$ 754; found: 755 $(M+H)^+$.	51/87
cj-120	methyl ((1S)-3-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		LCMS: Anal. Calcd. for $C_{38}H_{46}N_8O_7$ 726; found: 727 $(M+H)^+$.	52/87
cj-121	methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-		LCMS: Anal. Calcd. for $C_{40}H_{50}N_8O_8$ 770; found: 771 $(M+H)^+$.	86/87

	imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate			
cj-122	methyl ((1S,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{50}N_8O_7$ 766; found: 767 $(M+H)^+$.	121/87

Examples cj-111 to cj-113.

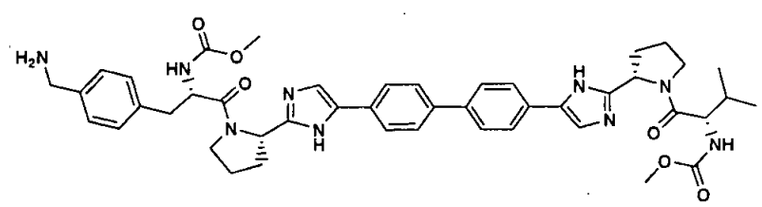
For Examples cj-111 to cj-113 the compounds of Examples cj-105 to cj-107 were hydrogenated under conditions analogous to those used in Example 28, step d (with the exception that K_2CO_3 was not employed).

Preparation of examples cj-103, cj-114 and cj-115.



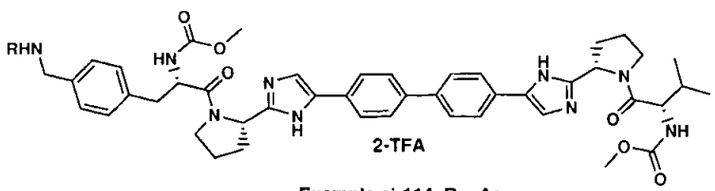
Intermediate cj-124 was prepared by coupling of intermediate cj-12 and *Cap*-122, as described in Example 28, step e. LCMS: Anal. Calcd. for $C_{60}H_{63}N_9O_8$ 1037; found: 520 $(1/2M+H)^+$. This corresponds to the doubly charged molecular ion.

Example cj-103.



Intermediate cj-124 (83.0 mg, 0.08 mmol) was dissolved in DMF (5 mL) and piperidine (1 mL) was added at room temperature. After 2h the volatiles were removed *in vacuo* and the residue was purified by preparative HPLC (YMC-Pack C-18, 30X100mm, CH_3CN-H_2O-TFA) to give the TFA salt of the amine (87.0 mg, 94%). LCMS: Anal. Calcd. for $C_{45}H_{53}N_9O_6$ 815; found: 816 $(M+H)^+$.

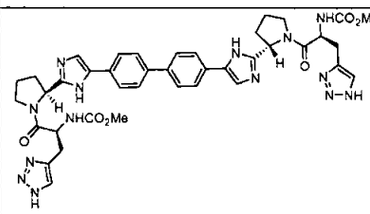
Examples cj-114 to cj-115.

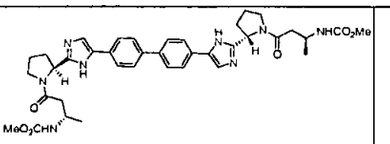
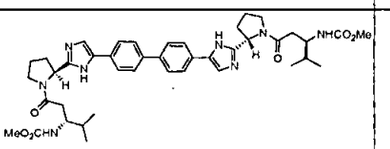
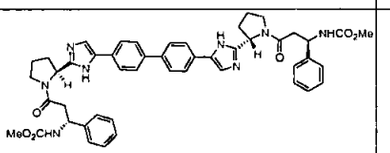
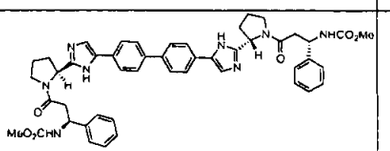


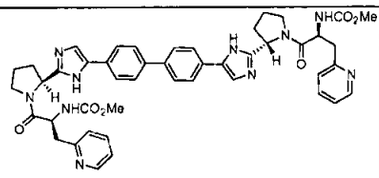
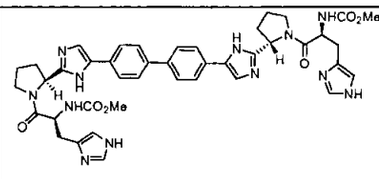
Example cj-114, R = Ac
Example cj-115, R = CONHEt

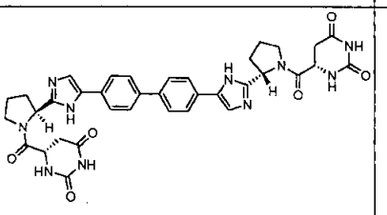
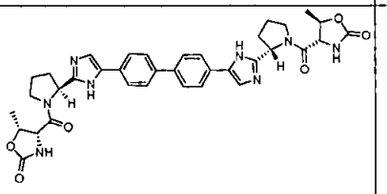
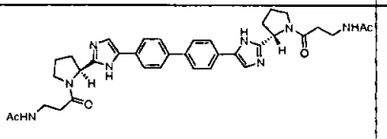
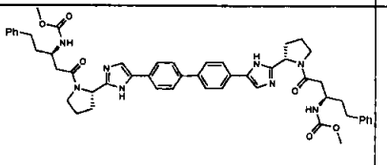
The product from Example cj-103 was acylated with either acetic anhydride or ethyl isocyanate as shown in scheme under conditions analogous to those in Example 25. Example cj-114, LCMS: Anal. Calcd. for $C_{47}H_{55}N_9O_7$ 857; found: 858 $(M+H)^+$. Example cj-115, LCMS: Anal. Calcd. for $C_{48}H_{58}N_{10}O_7$ 886; found: 887 $(M+H)^+$.

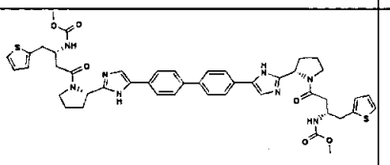
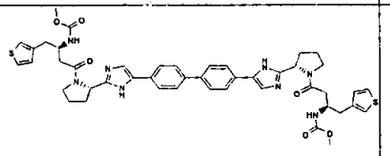
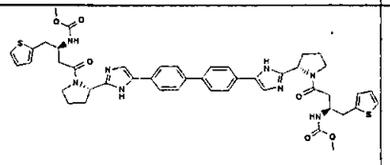
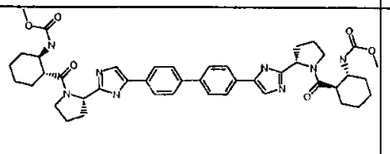
The following examples were prepared from intermediate 1e using a procedure analogous to Example 1. The appended cap is indicated in the Table and where no cap number is give the carboxylic acid was commercially available.

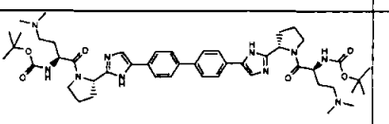
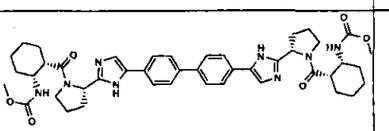
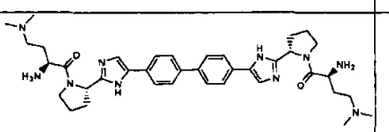
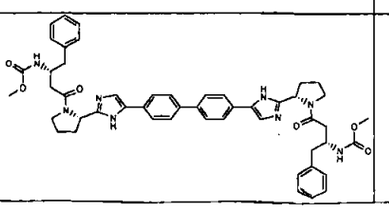
Example	*Compound Name*	*Structure*	*Cap*	*LCMS*
cj-125	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(1H-1,2,3-triazol-4-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1H-1,2,3-triazol-4-ylmethyl)ethyl)carbamate		128	LCMS: Anal. Calcd. for $C_{40}H_{44}N_{14}O_6$: 816; found: 817 $(M+H)^+$.

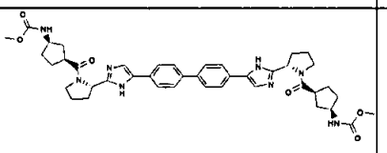
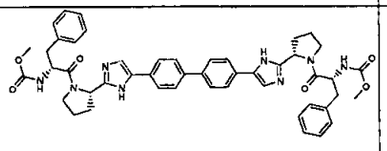
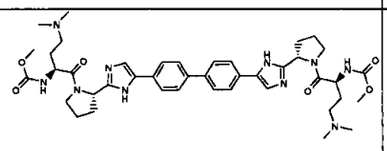
cj-126	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-4-oxo-4,2-butanediyl)))biscarbamate		115	LCMS: Anal. Calcd. for $C_{38}H_{46}N_8O_6$ 710; found: 711 $(M+H)^+$.
cj-127	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((3R)-4-methyl-1-oxo-1,3-pentanediyl)))biscarbamate		116	LCMS: Anal. Calcd. for $C_{42}H_{54}N_8O_6$ 766; found: 777 $(M+H)^+$.
cj-128	methyl ((1R)-3-((2S)-2-(5-(4'-(2-(1-((3R)-3-((methoxycarbonyl)amino)-3-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-phenylpropyl)carbamate		92	LCMS: Anal. Calcd. for $C_{48}H_{50}N_8O_6$ 834; found: 835 $(M+H)^+$.
cj-129	methyl ((1S)-3-((2S)-2-(5-(4'-(2-(1-((3S)-3-((methoxycarbonyl)		91	LCMS: Anal. Calcd. for $C_{48}H_{50}N_8O_6$ 834; found:

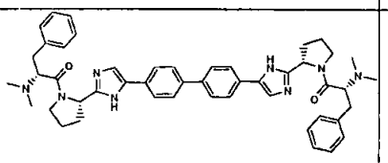
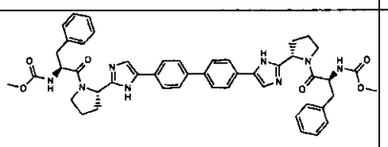
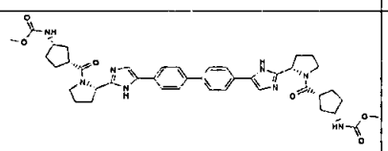
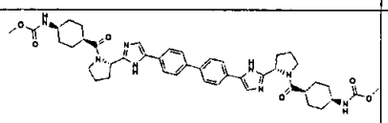
	amino)-3-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxo-1-phenylpropyl)carbamate			835 $(M+H)^+$.
cj-130	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-(2-pyridinyl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(2-pyridinylmethyl)ethyl)carbamate		93	LCMS: Anal. Calcd. for $C_{46}H_{48}N_{10}O_6$ 836; found: 837 $(M+H)^+$.
cj-131	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1H-imidazol-4-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-		94	LCMS: Anal. Calcd. for $C_{42}H_{46}N_{12}O_6$ 814; found: 815 $(M+H)^+$.

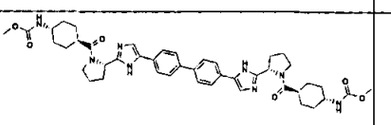
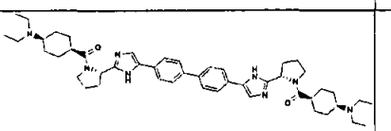
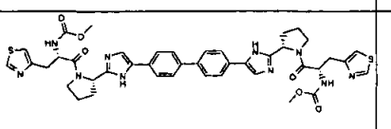
	pyrrolidinyl)-1-(1H-imidazol-4-ylmethyl)-2-oxoethyl)carbamate			
cj-132	(6S,6'S)-6,6'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl))didihydro-2,4(1H,3H)-pyrimidinedione		-	LCMS: Anal. Calcd. for $C_{36}H_{36}N_{10}O_6$ 704; found: 705 $(M+H)^+$.
cj-133	(4S,5R,4'S,5'R)-4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl))bis(5-methyl-1,3-oxazolidin-2-one)		124	LCMS: Anal. Calcd. for $C_{37}H_{40}N_8O_5$ 676; found: 677 $(M+H)^+$.
cj-134	N-(3-((2S)-2-(5-(4'-(2-((2S)-1-(3-acetamidopropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-3-oxopropyl)acetamide		-	LCMS: Anal. Calcd. for $C_{36}H_{42}N_8O_4$ 650; found: 651 $(M+H)^+$.
cj-135	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-		95	LCMS: Anal. Calcd. for $C_{52}H_{58}N_8O_6$ 890; found:

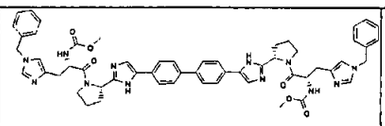
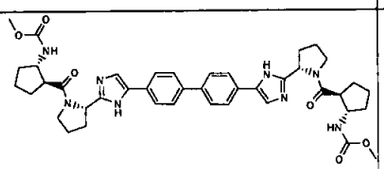
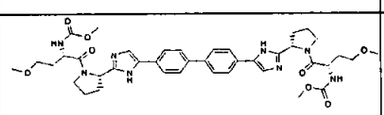
	pyrrolidinediyl((3R)-1-oxo-5-phenyl-1,3-pentanediyl)))biscarbamate			890 $(M+H)^+$.
cj-136	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2R)-4-oxo-1-(2-thienyl)-4,2-butanediyl)))biscarbamate		119	LCMS: Anal. Calcd. for $C_{46}H_{50}N_8O_6S_2$ 874; found: 875 $(M+H)^+$.
cj-137	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2R)-4-oxo-1-(3-thienyl)-4,2-butanediyl)))biscarbamate		120	LCMS: Anal. Calcd. for $C_{46}H_{50}N_8O_6S_2$ 874; found: 875 $(M+H)^+$.
cj-138	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-4-oxo-1-(2-thienyl)-4,2-butanediyl)))biscarbamate		118	LCMS: Anal. Calcd. for $C_{46}H_{50}N_8O_6S_2$ 874; found: 875 $(M+H)^+$.
cj-139	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-		97	LCMS: Anal. Calcd. for $C_{44}H_{54}N_8O_6$

	diyl(2S)-2,1-pyrrolidinediylcarbonyl(1R,2R)-2,1-cyclohexanediyl))biscarbamate			790; found: 791 $(M+H)^+$.
cj-140	di-tert-butyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-4-(dimethylamino)-1-oxo-1,2-butanediyl)))biscarbamate		125	LCMS: Anal. Calcd. for $C_{48}H_{68}N_{10}O_6$ 880; found: 881 $(M+H)^+$.
cj-141	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl(1R,2S)-2,1-cyclohexanediyl))biscarbamate		98	LCMS: Anal. Calcd. for $C_{44}H_{54}N_8O_6$ 790; found: 791 $(M+H)^+$.
cj-142	(3S,3'S)-4,4'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N~1~,N~1~-dimethyl-4-oxo-1,3-butanediamine)		see text	LCMS: Anal. Calcd. for $C_{38}H_{52}N_{10}O_2$ 680; found: 681 $(M+H)^+$.
cj-143	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-		117	LCMS: Anal. Calcd. for $C_{50}H_{54}N_8O_6$ 862; found:

	pyrrolidinediyl((2R)-4-oxo-1-phenyl-4,2-butanediyl)))biscarbamate			863 $(M+H)^+$.
cj-144	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl(1R,3S)-3,1-cyclopentanediyl))biscarbamate		99	LCMS: Anal. Calcd. for $C_{42}H_{50}N_8O_6$ 762; found: 763 $(M+H)^+$.
cj-145	methyl ((1R)-1-benzyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-3-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		101	LCMS: Anal. Calcd. for $C_{48}H_{50}N_8O_6$ 834; found: 835 $(M+H)^+$.
cj-146	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-4-(dimethylamino)-1-oxo-1,2-butanediyl)))biscar		see text	LCMS: Anal. Calcd. for $C_{42}H_{56}N_{10}O_6$ 796; found: 797 $(M+H)^+$.

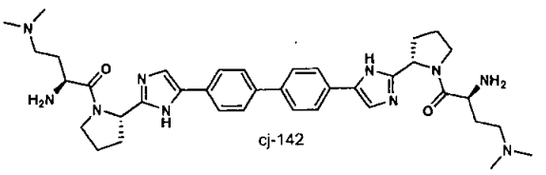
	bamate			
cj-147	(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-1-oxo-3-phenyl-2-propanamine)		90	LCMS: Anal. Calcd. for $C_{48}H_{54}N_8O_2$ 774; found: 775 $(M+H)^+$.
cj-148	methyl ((1S)-1-benzyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-phenylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		102	LCMS: Anal. Calcd. for $C_{48}H_{50}N_8O_6$ 834; found: 835 $(M+H)^+$.
cj-149	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl(1R,3S)-3,1-cyclopentanediyl))biscarbamate		99a	LCMS: Anal. Calcd. for $C_{42}H_{50}N_8O_6$ 806; found: 807 $(M+H)^+$.
cj-150	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarb		104	LCMS: Anal. Calcd. for $C_{44}H_{54}N_8O_6$ 790; found: 791 $(M+H)^+$.

	onylcis-4,1-cyclohexanediyl))bi scarbamate			
cj-151	dimethyl (4,4'-biphenyldiylbis(1H -imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarb onyltrans-4,1-cyclohexanediyl))bi scarbamate		105	LCMS: Anal. Calcd. for $C_{44}H_{54}N_8O_6$ 790; found: 791 $(M+H)^+$.
cj-152	({cis)-4,4'-(4,4'-biphenyldiylbis(1H -imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarb onyl))bis(N,N-diethylcyclohexana mine)		106	LCMS: Anal. Calcd. for $C_{48}H_{66}N_8O_2$ 766; found: 777 $(M+H)^+$.
cj-153	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl) amino)-3-(1,3-thiazol-4-yl)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-(1,3-thiazol-4-ylmethyl)ethyl)carb amate		107	LCMS: Anal. Calcd. for $C_{42}H_{44}N_{10}O_6S_2$ 848; found: 849 $(M+H)^+$.

cj-154	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1-benzyl-1H-imidazol-4-yl)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-((1-benzyl-1H-imidazol-4-yl)methyl)-2-oxoethyl)carbamate		108	LCMS: Anal. Calcd. for $C_{56}H_{58}N_{12}O_6$ 994; found: 995 $(M+H)^+$.
cj-155	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl(1S,2S)-2,1-cyclopentanediyl))biscarbamate		121	LCMS: Anal. Calcd. for $C_{42}H_{50}N_8O_6$ 762; found: 763 $(M+H)^+$.
cj-156	methyl ((1S)-3-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-homoseryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-		87	LCMS: Anal. Calcd. for $C_{40}H_{50}N_8O_8$ 770; found: 771 $(M+H)^+$.

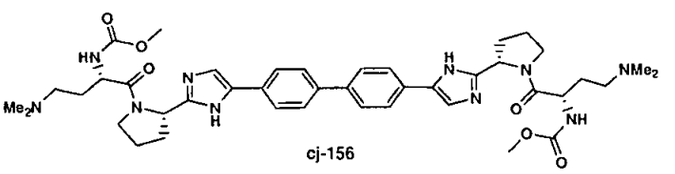
	pyrrolidinyl)carbonyl)propyl)carbamate			

Example cj-142.



Example cj-142 was prepared from the product obtained in Example cj-140 by treatment with 40% TFA in CH_2Cl_2. The mixture was allowed to stir for 3 h at room temperature and then concentrated *in vacuo*. The residue was purified by prep HPLC (YMC-Pack, C18 30X100mm, CH_3CN-H_2O-TFA).

Example cj-156.



The compound of Example-cj-156 was prepared by carbamoylation of the compound prepared in Example-cj-142 according to the method shown for *Cap*-51.

Section JG

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

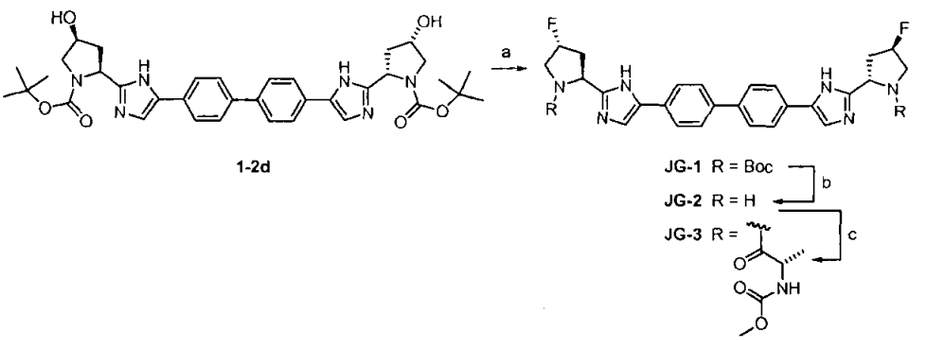
Method E: LCMS – Gemini C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate.

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.

Method G: HPLC – Phenomenex Gemini C-18 4.6 x 150mm, 10 to 80% B over 35 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate

Method H: HPLC – Phenomenex Gemini C-18 4.6 x 150mm, 10 to 80% B over 25 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate

Method I: HPLC –Waters-X-Bridge C-18 4.6 x 150mm, 10 to 70% B over 30 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate



Step a:

(3S,3'S,5S,5'S)-tert-butyl 5,5'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(3-hydroxypyrrolidine-1-carboxylate) (1.40g, 2.13mmol) was added as a solid to a solution of bis(2-methoxyethyl) aminosulfur trifluoride (0.87mL, 4.69mmol) in 14.0mL CH_2Cl_2 cooled to -78°C. Reaction was stirred at -78°C for two hours and then warmed to room temperature and stirred for 2 hours. Reaction was poured into saturated sodium bicarbonate solution and stirred until bubbling ceased. Layers were separated and aqueous layer washed one time with CH_2Cl_2. Combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a yellow oil. The oil was triturated with CH_2Cl_2 and pentane to yield (3R,3'R,5S,5'S)-tert-butyl 5,5'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(3-fluoropyrrolidine-1-carboxylate) JG-1 as a tan solid (0.98g, 71%).

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.10 (2H, m) 7.60-7.82 (8H, m) 7.35 (2H, m) 5.45 (1H, s) 5.35 (1H, s) 4.85-4.90 (2H, m) 3.69-3.79 (4H, m) 2.53-2.61 (2H, m) 2.28-2.37 (2H, m) 1.40 (8H, s) 1.12 (10H, 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, (t_R= 3.04 min) Anal Calcd. for $C_{36}H_{42}F_2N_6O_4$ 660.70; found 661.68 $(M+H)^+$

Step b:

To a solution of (3R,3'R,5S,5'S)-tert-butyl 5,5'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(3-hydroxypyrrolidine-1-carboxylate) (0.098g, 1.48mmol) in 4mL dioxane was added 2.0mL of a 4.0M solution of HCl in dioxane. The reaction was stirred for 2 hours at room temperature and concentrated under reduced pressure.

The resulting tan solid was dried under vacuum to give 4,4'-bis(2-((2S,4S)-4-fluoropyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl tetrahydrochloride JG-2 (0.89g, 100%yield). No further purification.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.05 (2H, s), 8.18 (2H, s), 8.00-8.09 (4H, m) 7.89 (4H, d, *J*=7.63 Hz) 5.71 (1H, s) 5.61 (1H, s) 5.24-5.33 (2H, m) 3.92 (2H, d, *J*=10.68Hz) 3.63-3.71 (2H, m) 2.79-2.89 (2H, 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= 2.12 min) Anal Calcd. for $C_{26}H_{26}F_2N_6$ 460.53; found 461.37 $(M+H)^+$

Step c:

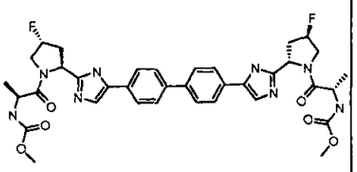
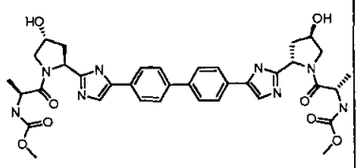
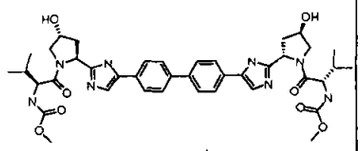
To a stirred solution of 4,4'-bis(2-((2S,4R)-4-fluoropyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyltetrahydrochloride (0.060g, 0.10mmol), (S)-2-(methoxycarbonylamino)propanoic acid (0.031g, 0.21mmol), and HATU (0.081g, 0.21mmol) in 3mL DMF was added diisopropylethyl amine (0.11mL, 0..61mmol).The reaction was stirred at room temperature overnight (16 hours) and concentrated under reduced pressure. The crude product was purified by reverse-phase preparative HPLC and secondly by passing it through a Waters MCX extraction cartridge to provide Dimethyl (2S,2'S)-1,1'-((3R,3'R,5S,5'S)-5,5'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(3-fluoropyrrolidine-5,1-diyl))bis(1-oxopropane-2,1-diyl)dicarbamate JG-3 , free base (0.0097g, 7.5%).

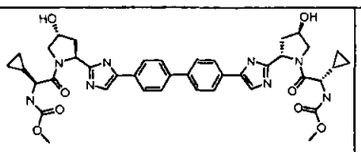
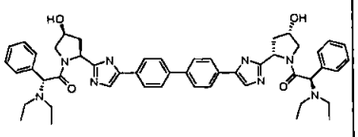
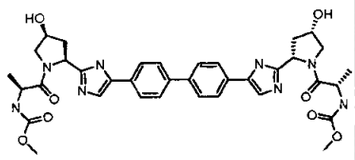
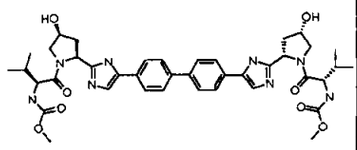
^{1}H NMR (500MHz, DMSO-d_6) δ ppm 11.91 (2H, m), 7.76-7.84 (3H, m), 7.64-7.84 (5H, m), 7.48-7.58 (2H, m), 5.55 (1H, s), 5.11 (1H, s), 4.29-4.38 (2H, m), 4.13 (2H, d, *J*=12.51 Hz), 3.89-3.98 (2H, m), 3.53 (6H, s), 2.54-2.64 4H, m), 1.21 (6H, s)

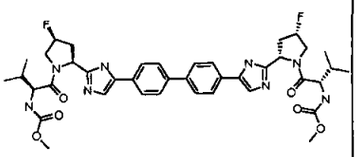
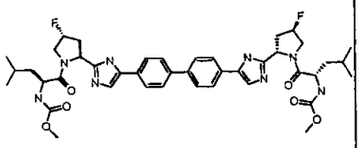
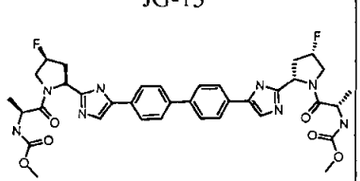
LCMS – Luna C-18 3.0 x 50mm, 0 to 100% B over 7.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate, (t_R=2.40 min)

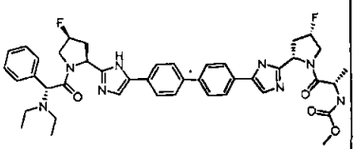
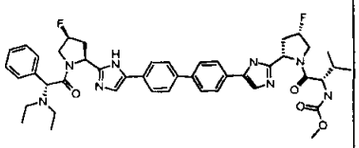
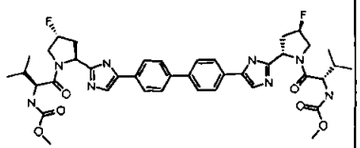
Nominal/LRMS – Calcd. for $C_{36}H_{40}F_2N_8O_6$ 718.30; found 719.24$(M+H)^+$

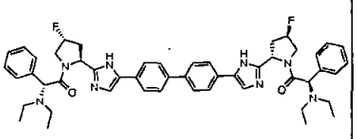
Accurate/HRMS – Calcd. for $C_{36}H_{41}F_2N_8O_6$ 719.3117; found 719.3114$(M+H)^+$

Structure	*Compound Name*	*Data*
JG-3 	methyl ((1S)-2-((2S,4R)-4-fluoro-2-(5-(4'-(2-((2S,4R)-4-fluoro-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	RT = 13.60 min, method I LRMS: Anal. Calcd. for $C_{36}H_{40}F_2N_8O_6$ 718.30 found: 719.24 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{36}H_{41}F_2N_8O_6$ 719.3117 found 719.3114 $(M+H)^+$
JG-4  From 1-1e and *Cap*-12	methyl ((1S)-2-((2S,4R)-4-hydroxy-2-(5-(4'-(2-((2S,4R)-4-hydroxy-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	RT = 9.27 min, method H LRMS: Anal. Calcd. for $C_{36}H_{42}N_8O_8$ 714.77 found: 715.33 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{36}H_{43}N_8O_8$ 715.3204 found: 715.3186 $(M+H)^+$
JG-5  From 1-1e and *Cap*-51	methyl ((1S)-1-(((2S,4R)-4-hydroxy-2-(5-(4'-(2-((2S,4R)-4-hydroxy-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	RT = 15.08 min, method G LRMS: Anal. Calcd. for $C_{40}H_{50}N_8O_8$ 770.88 found: 771.76 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{40}H_{51}N_8O_8$ 771.3830 found: 771.3798 $(M+H)^+$
JG-6	dimethyl (4,4'-biphenyldiylbis(1H-	RT = 13.67 min, method G

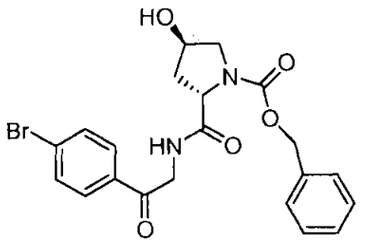
 From 1-1e and *Cap*-54b	imidazole-5,2-diyl((2S,4R)-4-hydroxy-2,1-pyrrolidinediyl)((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate	LRMS: Anal. Calcd. for $C_{40}H_{46}N_8O_8$ 766.85 found: 767.65 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{40}H_{47}N_8O_8$ 767.3517 found: 767.3483 $(M+H)^+$
JG-7  From 1-2e and *Cap*-2	(3S,5S,3'S,5'S)-5,5'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))bis(1-((2R)-2-(diethylamino)-2-phenylacetyl)-3-pyrrolidinol)	RT = 15.88min, method H LRMS: Anal. Calcd. for $C_{50}H_{58}N_8O_4$ 834.45 found: 835.38$(M+H)^+$ HRMS: Anal. Calcd. for $C_{50}H_{59}N_8O_4$ 835.4659 found: 835.4627$(M+H)^+$
JG-8  From 1-2e and *Cap*-52	methyl ((1S)-2-((2S,4S)-4-hydroxy-2-(5-(4'-(2-((2S,4S)-4-hydroxy-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	RT = 9.99 min, method H LRMS: Anal. Calcd. for $C_{36}H_{42}N_8O_8$ 714.77 found: 715.71 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{36}H_{43}N_8O_8$ 715.3204 found: 715.3188 $(M+H)^+$
JG-9  From 1-2e and *Cap*-51	methyl ((1S)-1-(((2S,4S)-4-hydroxy-2-(5-(4'-(2-((2S,4S)-4-hydroxy-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-	RT = 14.12 min, method H LRMS: Anal. Calcd. for $C_{40}H_{50}N_8O_8$ 770.88 found: 771.74 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{40}H_{51}N_8O_8$ 771.3830

	biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	found: 771.3799 $(M+H)^+$
JG-10  From 1-2e2 and *Cap*-51	methyl ((1S)-1-(((2S,4S)-4-fluoro-2-(5-(4'-(2-((2S,4S)-4-fluoro-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	RT = 17.66 min, method I LRMS: Anal. Calcd. for $C_{40}H_{48}F_2N_8O_6$ 774.86 found: 775.49 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{40}H_{49}F_2N_8O_6$ 775.3743 found: 775.3717 $(M+H)^+$
JG-12  From (S)-2-(methoxycarbonylamino)-4-methylpentanoic acid and JG-2	methyl ((1S)-1-(((2S,4R)-4-fluoro-2-(5-(4'-(2-((2S,4R)-4-fluoro-1-((2S)-2-((methoxycarbonyl)amino)-4-methylpentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-methylbutyl)carbamate	RT = 9.69 min, method I LRMS: Anal. Calcd. for $C_{42}H_{52}F_2N_8O_6$ 802.92 found: 803.42 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{42}H_{53}F_2N_8O_6$ 803.4056 found: 803.4018 $(M+H)^+$
JG-13  From 1-2e2 and *Cap*-52	methyl ((1S)-2-((2S,4S)-4-fluoro-2-(5-(4'-(2-((2S,4S)-4-fluoro-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-	RT = 13.60 min, method I LRMS: Anal. Calcd. for $C_{36}H_{40}F_2N_8O_6$ 718.30 found: 719.45 $(M+H)^+$ HRMS: Anal. Calcd. for

	2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	$C_{36}H_{41}F_2N_8O_6$ 719.3117 found 719.3090 $(M+H)^+$
JG-14  From JG-25 and *Cap*-52	methyl ((1S)-2-((2S,4S)-2-(5-(4'-(2-((2S,4S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-4-fluoro-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4-fluoro-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	RT = 15.13 min, method I LCMS: Anal. Calcd. for $C_{43}H_{48}F_2N_8O_4$ 778.91 found: 779.79 $(M+H)^+$
JG-15  From JG-25 and *Cap*-51	methyl ((1S)-1-(((2S,4S)-2-(5-(4'-(2-((2S,4S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-4-fluoro-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4-fluoro-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	RT = 17.51 min, method I LCMS: Anal. Calcd. for $C_{45}H_{52}F_2N_8O_4$ 806.96 found: 807.50 $(M+H)^+$
JG-16  From JG-2 and *Cap*-51	methyl ((1S)-1-(((2S,4R)-4-fluoro-2-(5-(4'-(2-((2S,4R)-4-fluoro-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	RT =16.51 min, method I LRMS: Anal. Calcd. for $C_{40}H_{48}F_2N_8O_6$ 774.86 found: 775.39 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{40}H_{49}F_2N_8O_6$ 775.3743 found: 775.3740 $(M+H)^+$

JG-17  From JG-2 and *Cap*-2	(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl((2S,4R)-4-fluoro-2,1-pyrrolidinediyl)))bis(N,N-diethyl-2-oxo-1-phenylethanamine)	RT = 8.13 min, method I LCMS: Anal. Calcd. for $C_{50}H_{56}F_2N_8O_2$ 839.04 found: 839.46 $(M+H)^+$ HRMS: Anal. Calcd. for $C_{50}H_{57}F_2N_8O_2$ 839.4572 found: 839.4543 $(M+H)^+$

Synthesis of JG-18 as in Example 28 step a using hydroxyproline in place of proline.

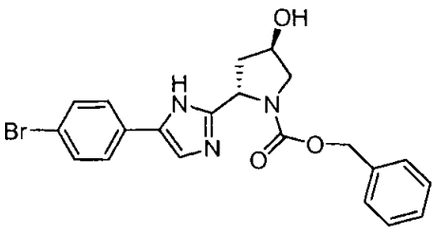


JG-18

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.89(2H, t, *J*=8.39 Hz) 7.74 (2H, t, *J*=8.24 Hz) 7.28-7.37 (5H, m) 5.01-5.08 (3H, m) 4.27-4.57 (4H, m) 3.44-3.53 (1H, m) 3.37(1H, d, *J*=10.99 Hz) 2.12 (1H, d, *J*=11.60 Hz) 1.93 (1H, dd, *J*=12.05 Hz, 6.56 Hz)

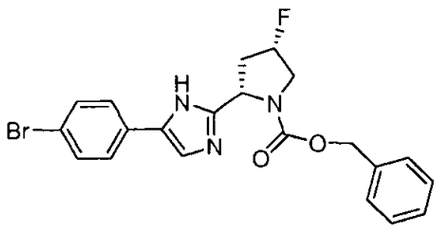
LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA mobile phase, t_R= 3.62 min, Anal Calcd. for $C_{21}H_{21}BrN_2O_5$ 461.32; found 462.64 $(M+H)^+$.

Synthesis of JG-19 from JG-18 as in Example 28 step b.



JG-19

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= 1.88 min, Anal. Calcd. for $C_{21}H_{20}BN_3O_3$ 441.07; found 442.22 $(M+H)^+$

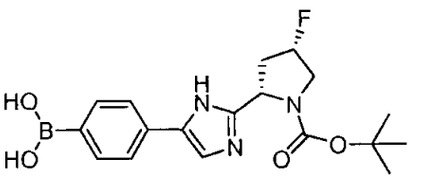


JG-20

(2S,4R)-benzyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)-4-hydroxypyrrolidine-1-carboxylate (1.5g, 3.4mmol) was added as a solid to a solution of bis(2-methoxyethyl) aminosulfur trifluoride (0.98mL, 5.1mmol) in 15mL CH_2Cl_2 cooled to -78°C. Reaction was stirred at -78°C for two hours and then warmed to room temperature and stirred for 2 hours. Reaction was poured into saturated sodium bicarbonate solution and stirred until bubbling ceased. Layers were separated and aqueous layer washed one time with CH_2Cl_2. Combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a yellow oil. The oil was triturated with CH_2Cl_2 and pentane to yield (2S,4S)-benzyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)-4-fluoropyrrolidine-1-carboxylate JG-20 as a yellow solid (0.96g, 62%).

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.70 (2H, d, J=7.02 Hz) 7.48-7.55 (3H, m) 7.41 -7.35 (3H, m) 7.19-7.11 (2H, m) 5.15 -5.02 (3H, m) 3.84 -3.78 (2H, m) 3.33 (2H, s) 2.53-2.61 (1H, m) 2.33-2.42 (1H, 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= 2.10 min, Anal. Calcd. for $C_{21}H_{19}Br_1F_1N_3O_2$ 443.06; found 444.05 $(M+H)^+$

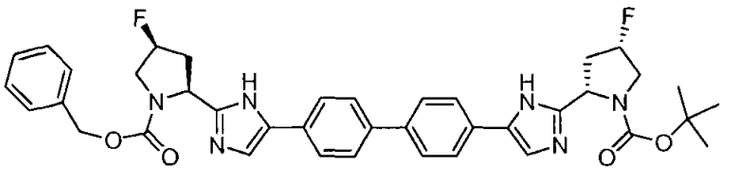


JG-21

(2S,4R)-tert-butyl 4-hydroxy-2-(5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate, 1-2c (1.5g, 3.3mmol) was added as a solid to a solution of bis(2-methoxyethyl) aminosulfur trifluoride (0.91mL, 5.0mmol) in 15mL CH_2Cl_2 cooled to -78°C. Reaction was stirred at -78°C for two hours and then warmed to room temperature and stirred for 2 hours. Reaction was poured into saturated sodium bicarbonate solution and stirred until bubbling ceased. Layers were separated and aqueous layer washed one time with CH_2Cl_2. Combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a brown oil. The oil was chromatographed on silica gel with with 5% MeOH/CH_2Cl_2 to yield 4-(2-((2S,4S)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidin-2-yl)-1H-imidazol-5-yl)phenylboronic acid as a tan solid (0.46g, 37%).

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= 1.46 min, Anal. Calcd. for $C_{18}H_{23}B_1F_1N_3O_4$ 375.18; found 376.12 $(M+H)^+$

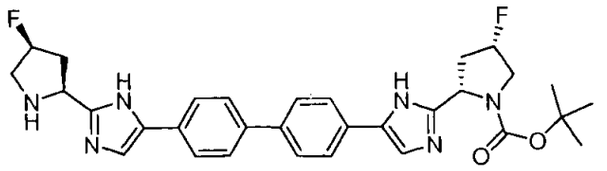
JG-22 is synthesized from JG-20 and JG-21 as described in Example 28 step c.



JG-22

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= 2.27 min, Anal. Calcd. for $C_{39}H_{40}F_2N_6O_4$ 694.31; found 695.35 $(M+H)^+$

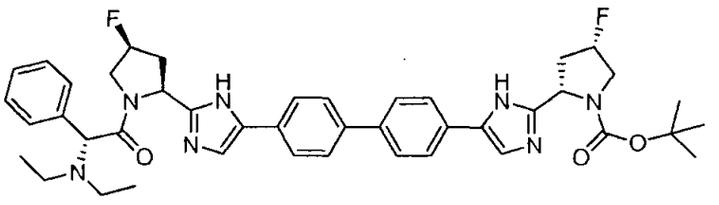
JG-23 is synthesized from JG-22 as described in Example 28 step d.



JG-23

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, t_R= 2.62 min, Anal Calcd. for $C_{31}H_{34}F_2N_6O_2$ 560.27; found 561.52 $(M+H)^+$.

JG-24 is synthesized from JG-22 and *Cap*-2 as in Example 28 step e.

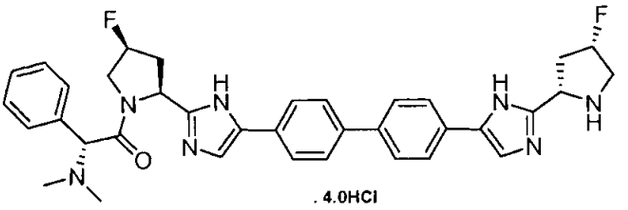


JG-24

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= 2.30 min, Anal. Calcd. for $C_{41}H_{45}F_2N_7O_3$ 721.36; found 722.42 $(M+H)^+$

JG-25 is synthesized from JG-24 *via* reaction with methanolic HCl as described in Example LS14 step b.



JG-25

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= 1.98 min, Anal. Calcd. for $C_{36}H_{37}F_2N_7O_1$ 621.30; found 622.48 $(M+H)^+$

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

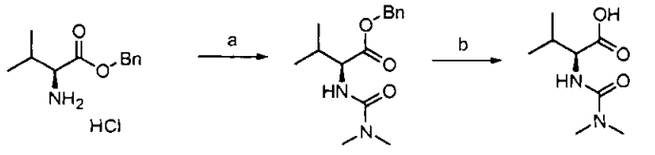
Condition 5: Solvent A: 5% acetonitrile / 95% water / 10mmol ammonium acetate; Solvent B: 95% acetonitrile / 5% water / 10mmol ammonium acetate; Column: Phenomenex GEMINI 5u C18 4.6 x 5.0mm; Wavelength: 220nM; Flow rate: 4 ml / min; 0%B to 100% B over 9 min with a 1 min hold time

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

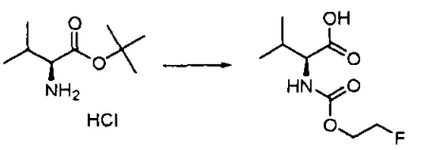
Step a: Dimethylcarbamoyl chloride (0.92 mL, 10 mmol) was added slowly to a solution of (S)-benzyl 2-amino-3-methylbutanoate hydrochloride (2.44 g; 10 mmol) and Hunig's base (3.67 mL, 21 mmol) in THF (50 mL). The resulting white suspension was stirred at room temperature overnight (16 hours) and concentrated 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.



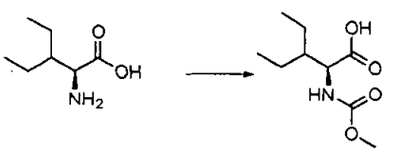
Cap OL-3

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)

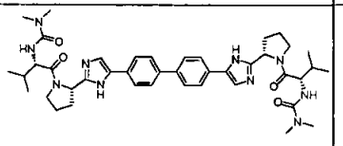
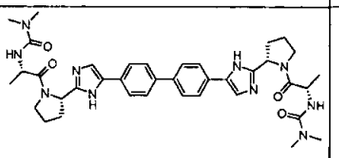
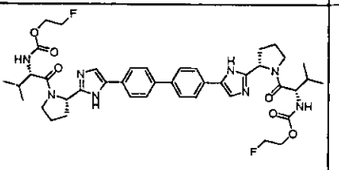


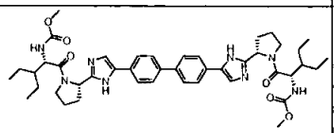
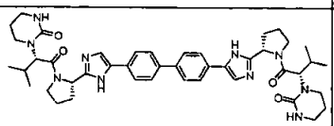
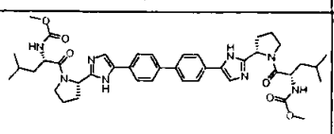
Cap OL-5

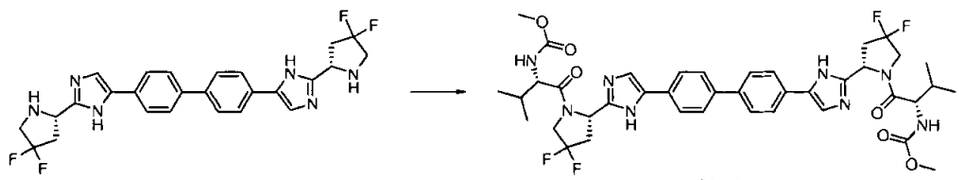
Cap OL-5 was prepared from (S)-diethyl alanine and methyl chloroformate according to the method described for *Cap*-51. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.72-0.89 (m, 6H) 1.15-1.38 (m, 4H) 1.54-1.66 (m, 1H) 3.46-3.63 (m, 3H) 4.09 (dd, J=8.85, 5.19 Hz, 1H) 7.24 (d, J=8.85 Hz, 1H) 12.55 (s, 1H). LC (Cond. 2): RT = 0.66 min; MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{18}NO_4$:204.12; found 204.02.

New Examples:

The following analogs were prepared from 1e in similar fashion to the preparation of Example 1 and employing the appropriate Cap.

Example Number	*Compound Name*	*Structure*	*Analytical Data*
OL-1	3-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((dimethylcarbamoyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)-1,1-dimethylurea	 From 1e and Cap OL-2	LC/MS: 2.16 min (Cond'n 3); Anal. Calcd. for $[M+H]^+$ $C_{42}H_{57}N_{10}O_4$: 765.45; found 765.47.
OL-2	3-((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(dimethylcarbamoyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)-1,1-dimethylurea	 From 1e and Cap OL-3	LC/MS: 1.86 min (Cond'n 3); Anal. Calcd. for $[M+H]^+$ $C_{38}H_{49}N_{10}O_4$: 709.39; found 709.43.
OL-3	2-fluoroethyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-(((2-fluoroethoxy)carbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-	 From 1e and Cap OL-4	LC/MS: 2.83 min (Cond'n 4); Anal. Calcd. for $[M+H]^+$ $C_{42}H_{53}F_2N_8O_6$: 803.40; found 803.47.

	2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		
OL-4	methyl ((1S)-2-ethyl-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-ethyl-2-((methoxycarbonyl)amino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl)carbamate	 From 1e and Cap OL-5	LC/MS: 2.64 min (Cond'n 3); Anal. Calcd. for $[M+H]^+$ $C_{44}H_{59}N_8O_6$: 795.45; found 795.48.
OL-5	1,1'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-3-methyl-1-oxo-1,2-butanediyl)))ditetrahydro-2(1H)-pyrimidinone	 From 1e and (S)-3-methyl-2-(2-oxotetrahydropyrimidin-1(2H)-yl)butanoic acid	LC/MS: 2.95 min (Cond'n 4); Anal. Calcd. for $[M+H]^+$ $C_{44}H_{57}N_{10}O_6$: 789.46; found 789.52.
OL-6	methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-4-methylpentanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-methylbutyl)carbamate	 From 1e and (S)-2-(methoxycarbonylamino)-4-methylpentanoic acid which was prepared from L-Isoleucine and methylchloroformate in similar fashion to the preparation of *Cap*-51	LC/MS: 2.95 min (Cond'n 3); Anal. Calcd. for $[M+H]^+$ $C_{42}H_{53}N_8O_6$: 767.42; found 767.43.



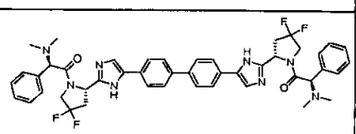
1-2e-3 OL-7

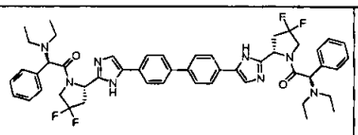
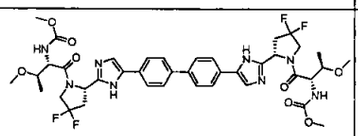
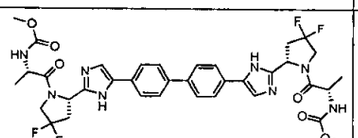
Example OL-7

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

Example OL-7 was prepared from 1-2e-3 in similar fashion to the preparation of Example 1, using *Cap*-51 as the coupling partner. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.80 (dd, *J*=6.41, 2.44 Hz, 12H) 1.87-1.98 (m, 2H) 2.79-2.91 (m, 2H) 3.01-3.13 (m, 2H) 3.54 (s, 6H) 3.98 (t, *J*=7.93 Hz, 2H) 4.22-4.37 (m, 2H) 4.52 (t, *J*=14.19 Hz, 2H) 5.31 (t, *J*=8.39 Hz, 2H) 7.50 (d, *J*=7.93 Hz, 2H) 7.82-7.87 (m, 4H) 7.88-7.97 (m, 6H) 8.08 (s, 2H). LC (Cond'n 6): 7.64 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}F_4N_8O_6$: 811.35; found 811.46. HRMS: Anal. Calcd. for $(M+H)^+$ $C_{40}H_{47}F_4N_8O_6$ 811.3549 found 811.3553.

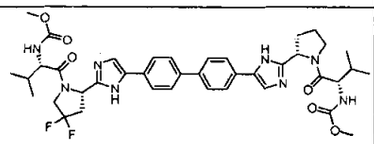
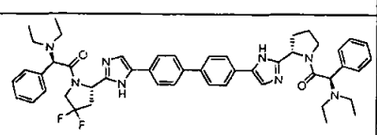
The following analogs were prepared from 1-2e-3 in similar fashion to the preparation of Example 1 and employing the appropriate Cap.

Example Number	*Compound Name*	*Structure*	*Analytical Data*
OL-8	(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S)-4,4-difluoro-2,1-pyrrolidinediyl)))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)	 From 1-2e-3 and *Cap*-1	LC/MS: 3.98 min (Cond'n 5); Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}F_4N_8O_2$: 819.37; found 819.78.

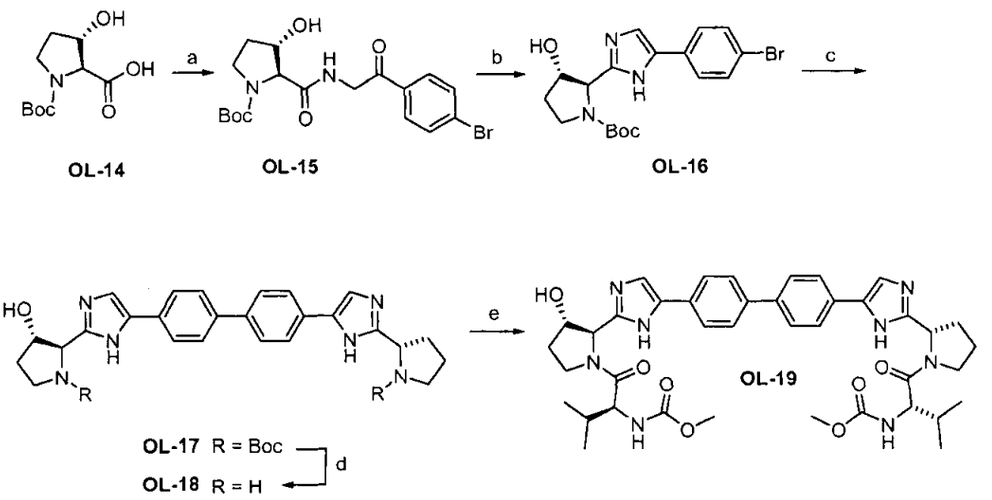
OL-9	(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S)-4,4-difluoro-2,1-pyrrolidinediyl)))bis(N,N-diethyl-2-oxo-1-phenylethanamine)	 From 1-2e-3 and *Cap*-2	LC/MS: 4.58 min (Cond'n 5); Anal. Calcd. for $[M+H]^+$ $C_{50}H_{55}F_4N_8O_2$: 875.449; found 875.90.
OL-10	methyl ((1S,2R)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate	 From 1-2e-3 and *Cap*-86	LC/MS: 2.18 min (Cond'n 7); Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}F_4N_8O_8$: 843.84; found 844.04.
OL-11	methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4,4-	 From 1-2e-3 and *Cap*-52	LC/MS: 2.04 min (Cond'n 7); Anal. Calcd. for $[M+H]^+$ $C_{36}H_{39}F_4N_8O_6$: 755.29; found 755.78.

	difluoro-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate		

The following analogs were prepared from 1-3e in similar fashion to the preparation of Example 1 and employing the appropriate Cap.

Example Number	*Compound Name*	*Structure*	*Analytical Data*
OL-12	methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 From 1-3e and *Cap*-51	LC/MS: 2.33 min (Cond'n 3); Anal. Calcd. for $[M+H]^+$ $C_{40}H_{49}F_2N_8O_2$: 775.37; found 775.37.
OL-13	rac-(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-4,4-difluoro-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-	 From 1-3e and *Cap*-2	LC/MS: 3.93 min (Cond'n 5); Anal. Calcd. for $[M+H]^+$ $C_{50}H_{57}F_2N_8O_2$: 839.40; found 839.93.

	imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine		



Example OL-19

methyl ((1S)-1-(((2R,3S)-3-hydroxy-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

Step a: Intermediate OL-15 was prepared in similar fashion as intermediate 1a, where *N*-Boc-L-proline was substituted for *N*-Boc-*trans*-3-hydroxy-L-proline. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.34/1.4) (2 br. s., 9H) 1.65-1.77 (m, 1H) 1.83-1.95 (m, 1H) 3.33-3.42 (m, 1H) 3.43-3.51 (m, 1H) 3.96-4.07 (m, 1H) 4.16 (s, 1H) 4.44-4.65 (m, 2H) 5.22-5.28 (m, 1H) 7.74 (d, *J*=8.54 Hz, 2H) 7.86-7.94 (m, 2H) 8.15-8.32 (m, 1H). LC (Cond. 4): RT = 3.33 min; MS: Anal. Calcd. for $[2M+Na]^+$ $C_{36}H_{46}Br_2N_4NaO_{10}$: 877.57; found 877.11.

Step b: Intermediate OL-16 was prepared from intermediate OL-15 in similar fashion as intermediate 1b. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.16/1.39 (2 br. s., 9H) 1.71-1.81 (m, *J*=6.10 Hz, 1H) 2.01-2.17 (m, 1H) 3.37-3.50 (m, 1H) 3.50-3.62 (m, 1H) 4.15 (s, 1H) 4.49-4.70 (m, 1H) 5.36 (dd, *J*=6.71, 3.66 Hz, 1H) 7.44-7.62 (m, 3H)

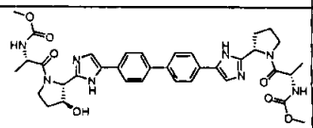
7.68 (d, *J*=7.02 Hz, 2H) 11.96/11.99/12.26/12.30 (m, 1H). LC (Cond. 8): RT = 1.87 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{23}BrN_3O_3$: 408.08; found 408.09.

Step c: Intermediate OL-17 was prepared by coupling intermediate OL-16 with 1c in similar fashion to the preparation of 1d. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.09-1.49 (m, 18H) 1.71-2.04 (m, 4H) 2.06-2.28 (m, 2H) 3.33-3.40 (m, 1H) 3.41-3.65 (m, 3H) 4.18 (s, 1H) 4.52-4.69 (m, 1H) 4.70-4.88 (m, 1H) 5.38 (s, 1H) 6.64-7.35 (m, 1H) 7.39-7.96 (m, 9H) 11.71 – 12.0/12.10 – 12.36 (m, 2H). LC (Cond. 2): RT = 1.36 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{45}N_6O_5$: 641.77; found 641.39.

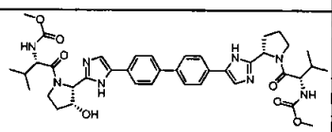
Step d: Intermediate OL-18 was prepared by deprotection of intermediate OL-17 with HCl in similar fashion to the preparation of 1-1e. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.92-2.07 (m, 2H) 2.14-2.25 (m, 1H) 2.35-2.44 (m, 1H) 3.15 (s, 4H) 3.32-3.41 (m, *J*=7.02, 7.02, 7.02 Hz, 1H) 3.41-3.51 (m, *J*=7.32 Hz, 2H) 3.54-3.66 (m, 1H) 4.68 (d, *J*=4.27 Hz, 1H) 4.78-4.89 (m, *J*=4.88 Hz, 1H) 5.04 (s, 1H) 6.89/7.73 (2d, *J*= 8.70 Hz, 1H) 7.89 (dd, *J*=8.24, 4.58 Hz, 4H) 7.96-8.07 (m, 4H) 8.15 (d, *J*=23.19 Hz, 2H) 9.62-10.12 (m, 2H) 10.21-10.74 (m, 2H).). LC (Cond. 8): RT = 1.30 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{29}N_6O$: 441.24; found 441.18.

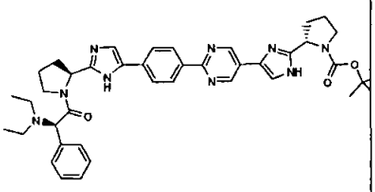
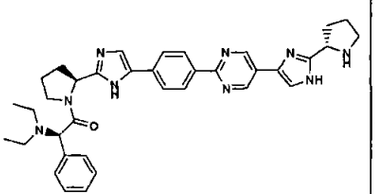
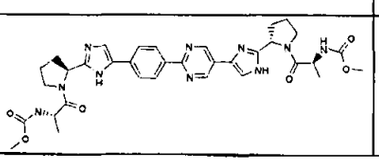
Step e: Example OL-19 was prepared by coupling of intermediate OL-18 with *Cap*-51 in similar fashion to the preparation of Example 1. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.78 (d, *J*=6.41 Hz, 6H) 0.83 (d, *J*=6.71 Hz, 6H) 1.92-2.12 (m, 5H) 2.12-2.21 (m, 1H) 2.31 (dd, *J*=12.21, 5.80 Hz, 1H) 2.35-2.43 (m, 1H) 3.54 (d, *J*=4.27 Hz, 6H) 3.78-3.89 (m, 3H) 3.91-4.02 (m, 1H) 4.07-4.19 (m, 2H) 4.36-4.50 (m, 1H) 4.81 (d, *J*=3.66 Hz, 1H) 5.13 (t, *J*=7.17 Hz, 1H) 5.79 (s, 1H) 7.34 (dd, *J*=11.29, 8.85 Hz, 2H) 7.83-7.90 (m, 4H) 7.90-8.01 (m, 4H) 8.12 (s, 2H) [Note: the signal for the imidazole NH was too broad to assign a chemical shift].). LC (Cond. 4): RT = 2.76 min; MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_7$: 755.39; found 755.38. HRMS: Anal. Calcd. for $(M+H)^+$ $C_{40}H_{51}N_8O_7$ 755.3881 found 755.3873.

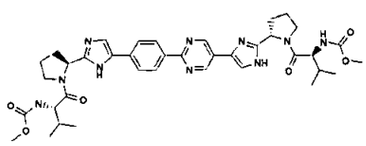
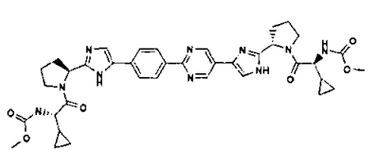
The following analog was prepared from intermediate OL-18 in similar fashion to the preparation of Example 1 and employing *Cap*-52.

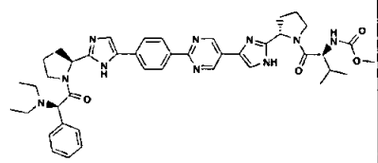
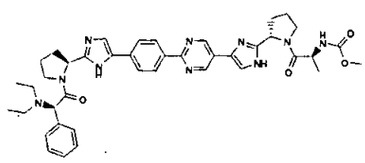
Example Number	*Compound Name*	*Structure*	*Analytical Data*
OL-20	methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2R,3S)-3-hydroxy-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 From OL-18 and *Cap*-52	LC/MS: 2.32 min (Cond'n 4); Anal. Calcd. for $[M+H]^+$ $C_{36}H_{43}N_8O_7$: 699.78; found 699.32.

The following analog was prepared in similar fashion to the preparation of OL-19 but using *N*-Boc-*cis*-3-hydroxy-L-proline as starting material.

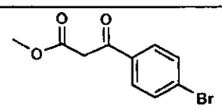
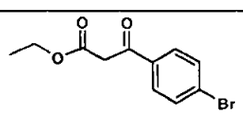
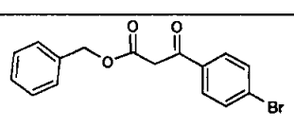
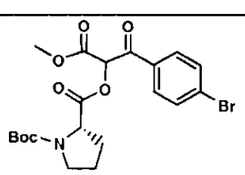
Example Number	*Compound Name*	*Structure*	*Analytical Data*
OL-21	methyl ((1S)-1-(((2R)-3-hydroxy-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 From *N*-Boc-*cis*-3-hydroxy-L-proline and *Cap*-51	LC/MS: 2.74 min (Cond'n 4); Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_7$: 755.39; found 755.34.

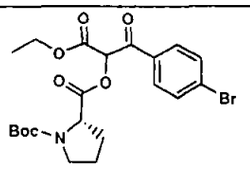
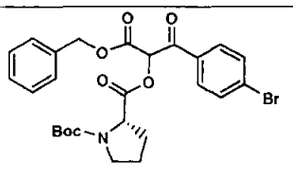
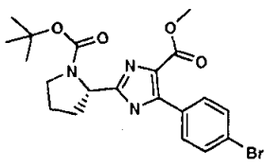
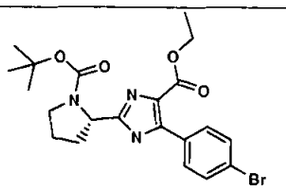
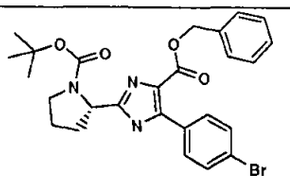
Example Number	*Compound Name*	*Heterocycles with New Caps*	*Analytical Data (Cond 1: 3 min gradient, 4 min run; Cond 2: 2 min gradient, 3 min run)*
D71	tert-butyl (2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 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-1.	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)

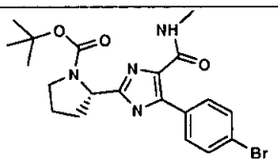
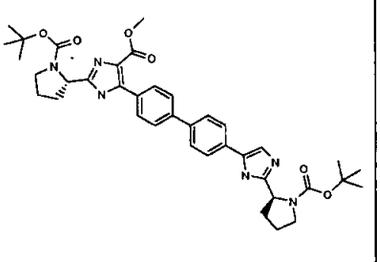
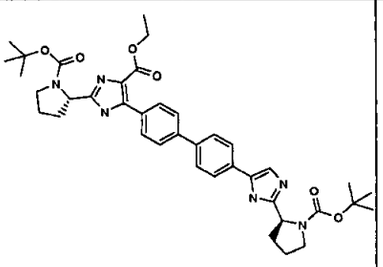
	(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	Prepared from 152h-1 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148	LRMS: Anal. Calcd. for $C_{34}H_{41}N_{10}O_6$ 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:

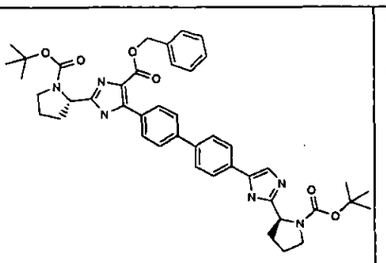
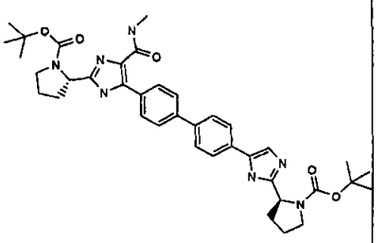
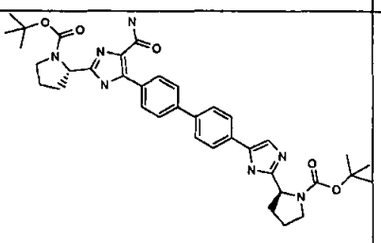
	imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		737.3555 $(M+H)^+$.
D76	methyl ((1S)-1-(((2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)phenyl)-5-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry 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 $(M+H)^+$.

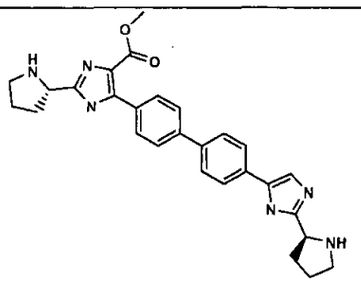
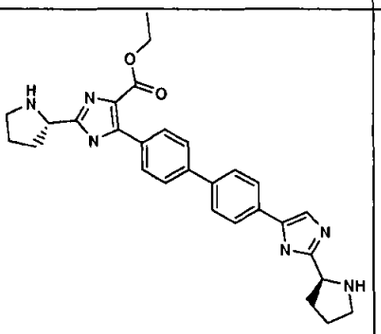
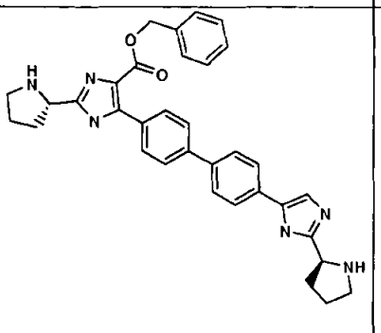
Section J

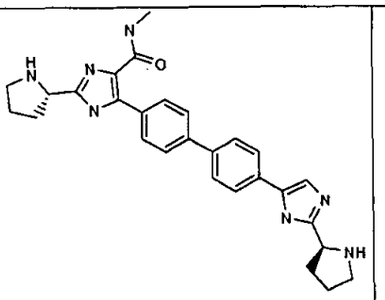
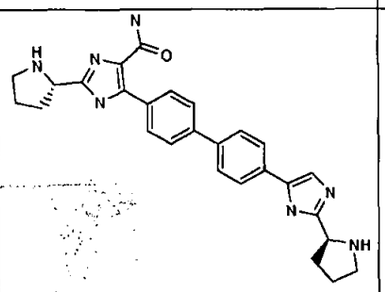
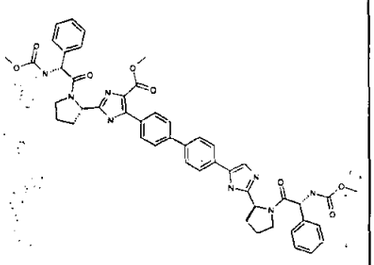
Example Number	*Compound Name*	*Structure*	*Analytical Data*
J.1a		 Prepared from 4-bromoacetophenone and dimethylcarbonate from Bioorg.Med.Chem.Lett (2001)11, 641	t_R = 1.7 min, (Cond 2); LCMS: $C_{10}H_9BrO_3$ found: 257 $(M+H)^+$.
J.1b		 Prepared from 4-bromoacetophenone and diethylcarbonate from 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 $(M+H)^+$.

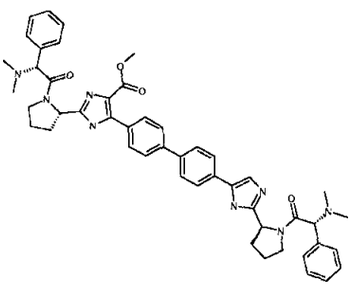
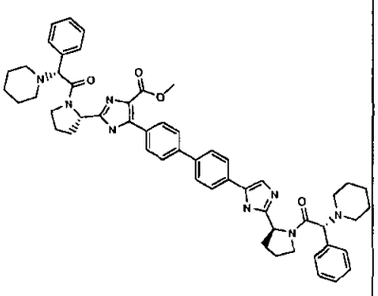
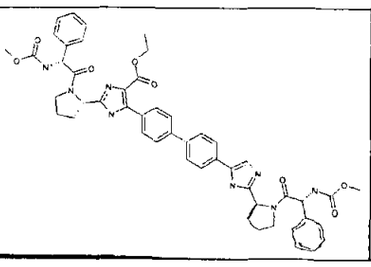
J2		 Prepared from entry J.1b and proline using experimental conditions in Example J2.	t_R = 2.2min, (Cond 2); LCMS: $C_{21}H_{26}BrNO_7$ found: 484 $(M+H)^+$.
J3		 Prepared from entry J.1c (in lieu of J.1b) and proline using experimental conditions in Example J2.	t_R = 2.3min, (Cond 2); LCMS: $C_{26}H_{28}BrNO_7$ 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 $C_{26}H_{29}BrN_3O_4$

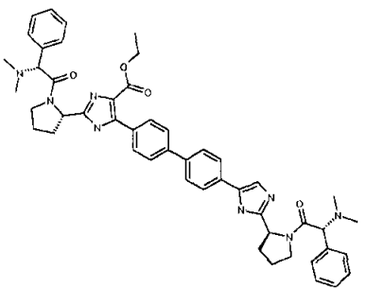
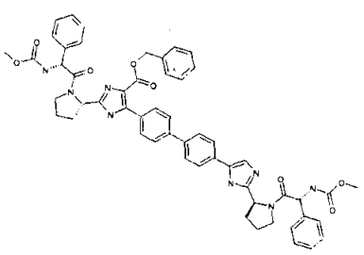
		entry J1) using experimental conditions in J5.	526.13; found: 526.16 and 528.16 $(M+H)^+$.
J7		 Prepared from entry J5 using experimental in J7.	t_R = 1.7 min, (100%) (Cond 2); Reported in J7.
J8	methyl 2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate	 Prepared from entry J4 (in lieu of 152e-1) and 1c using experimental conditions outlined in Example 152g-1.	t_R = 1.70 min, (95%) (Cond 2); LRMS: Anal. Calcd. for $C_{38}H_{47}N_6O_6$ 683.36; found: 683.42 $(M+H)^+$.
J9	ethyl 2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate	 Prepared from entry J5 (in lieu of 152e-1) and 1c using experimental conditions outlined in Example 152g-1.	t_R = 1.78 min, (97.5%) (Cond 2); LRMS: Anal. Calcd. for $C_{39}H_{49}N_6O_6$ 697.37; found: 697.38 $(M+H)^+$.

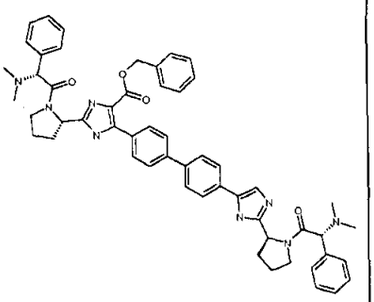
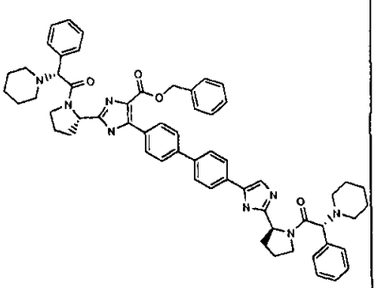
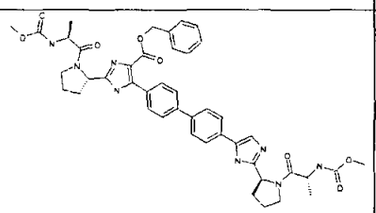
J10	benzyl 2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate	 Prepared from entry J6 (in lieu of 152e-1) and 1c using experimental conditions outlined in Example 152g-1.	t_R = 1.88 min, (85%) (Cond 2); LRMS: Anal. Calcd. for $C_{44}H_{51}N_6O_6$ 759.39; found: 759.48 $(M+H)^+$.
J11	tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(methylcarbamoyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry J7 (in lieu of 152e-1) and 1c using experimental conditions outlined in Example 152g-1.	t_R = 1.65 min, (90%) (Cond 2); LRMS: Anal. Calcd. for $C_{38}H_{48}N_7O_5$ 682.37; found: 682.42 $(M+H)^+$.
J11.a		 Prepared from entry J9 as described in J11.a.	t_R = 1.60 min, (Cond 2); LCMS: $C_{37}H_{46}N_7O_5$ found: 668 $(M+H)^+$.

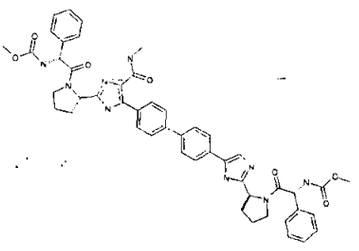
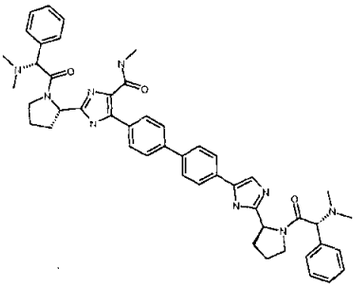
J12		 Prepared from entry J8 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.25min, (97%) (Cond 2); LCMS: $C_{28}H_{31}N_6O_2$ found: 483 $(M+H)^+$.
J13		 Prepared from entry J9 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.34 min, (Cond 2); LCMS: $C_{29}H_{33}N_6O_2$ found: 497 $(M+H)^+$.
J14		 Prepared from entry J10 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.51 min, (90%) (Cond 2); LCMS: $C_{34}H_{35}N_6O_2$ found: 559$(M+H)^+$.

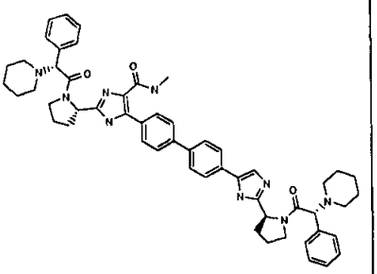
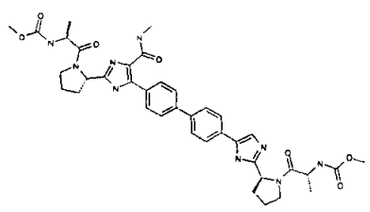
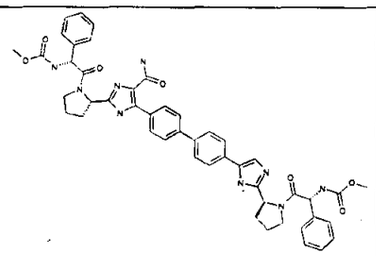
J15		 Prepared from entry J11 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.32 min, (99%) (Cond 2); LCMS: $C_{28}H_{32}N_7O$ found: 482 $(M+H)^+$.
J15.a		 Prepared from entry J11.a (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.07 min, (98%) (Cond 2); LCMS: $C_{27}H_{30}N_7O$ found: 468 $(M+H)^+$.
J16	methyl 2-((2S)-1-((2R)-2-((methoxycarbonyl) amino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl) amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-	 Prepared from entry J12 (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	t_R = 1.62 min, (99.5%) (Cond 2); LRMS: Anal. Calcd. for C48H49N8O8 865.37; found: 865.34 $(M+H)^+$. HRMS: Anal. Calcd. for C48H49N8O8 865.3673; found: 865.3715 $(M+H)^+$.

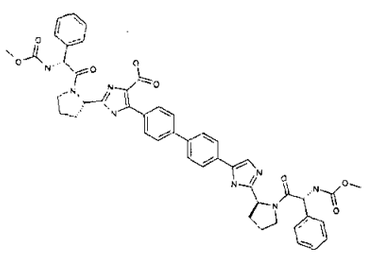
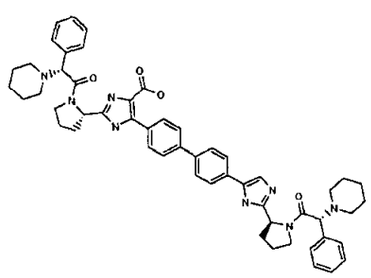
	biphenylyl)-1H-imidazole-4-carboxylate		
J17	methyl 2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate	 Prepared from entry J12 (in lieu of 148e) and *Cap*-1 using experimental conditions outlined in Example 148.	t_R = 1.37 min, (92%) (Cond 2); LRMS: Anal. Calcd. for C48H53N8O4 804.42; found: 805.51 $(M+H)^+$. HRMS: Anal. Calcd. for C48H53N8O4 805.4190; found: 805.4211 $(M+H)^+$.
J18	methyl 2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate	 Prepared from entry J12 (in lieu of 148e) and *Cap*-14 using experimental conditions outlined in Example 148.	t_R = 1.46 min, (94%) (Cond 2); LRMS: Anal. Calcd. for C54H61N8O6 885.48; found: 885.48 $(M+H)^+$. HRMS: Anal. Calcd. for C54H61N8O6 885.4816; found: 885.4852 $(M+H)^+$.
J19	ethyl 2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-		t_R = 1.68 min, (99%) (Cond 2); LRMS: Anal. Calcd. for C49H51N8O8

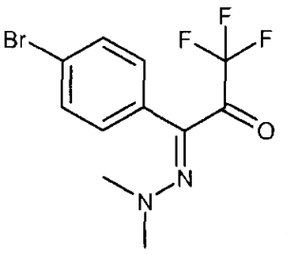
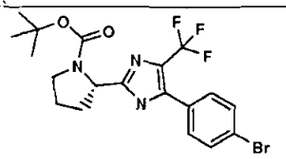
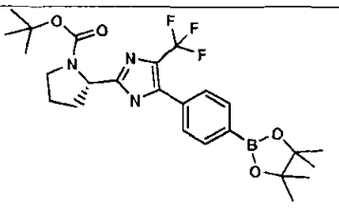
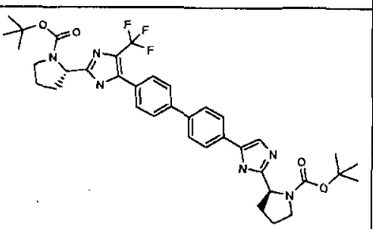
	pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl) amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate	Prepared from entry J13 (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	879.38; found: 879.37 $(M+H)^+$. HRMS: Anal. Calcd. for C49H51N8O8 879.3830; found: 879.3814 $(M+H)^+$.
J20	ethyl 2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate	 Prepared from entry J13 (in lieu of 148e) and *Cap*-1 using experimental conditions outlined in Example 148.	t_R = 1.45 min, (89%) (Cond 2); LRMS: Anal. Calcd. for C49H55N8O4 818.44; found: 818.40 $(M+H)^+$. HRMS: Anal. Calcd. for C49H55N8O4 819.4346; found: 819.4340 $(M+H)^+$.
J21	benzyl 2-((2S)-1-((2R)-2-((methoxycarbonyl) amino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl) amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-	 Prepared from entry J14 (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	t_R = 1.80 min, (92%) (Cond 2); LRMS: Anal. Calcd. for C54H53N8O8 941.40; found: 941.39 $(M+H)^+$. HRMS: Anal. Calcd. for C54H53N8O8 941.3986; found: 941.4033 $(M+H)^+$.

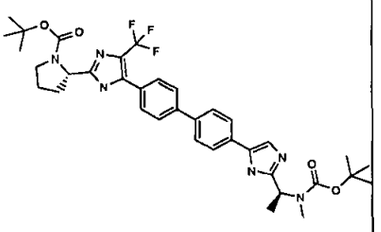
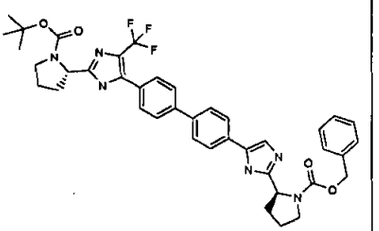
	biphenylyl)-1H-imidazole-4-carboxylate		
J22	benzyl 2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate	 Prepared from entry J14 (in lieu of 148e) and *Cap*-1 using experimental conditions outlined in Example 148.	t_R = 1.56 min, (96%) (Cond 2); LRMS: Anal. Calcd. for C54H57N8O4 881.45; found: 881.46 $(M+H)^+$. HRMS: Anal. Calcd. for C54H57N8O4 881.4503; found: 881.4536 $(M+H)^+$.
J23	benzyl 2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate	 Prepared from entry J14 (in lieu of 148e) and *Cap*-14 using experimental conditions outlined in Example 148.	t_R = 1.63 min, (96%) (Cond 2); LRMS: Anal. Calcd. for C60H65N8O4 961.51; found: 961.54 $(M+H)^+$. HRMS: Anal. Calcd. for C60H65N8O4 961.5129; found: 961.5164 $(M+H)^+$.
J24	benzyl 2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-5-(4'-		t_R = 1.64 min, (94%) (Cond 2); LRMS: Anal. Calcd. for C44H49N8O8

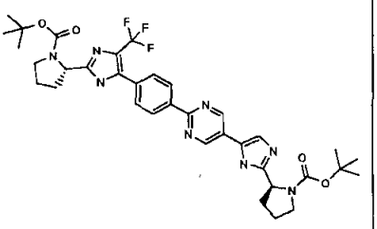
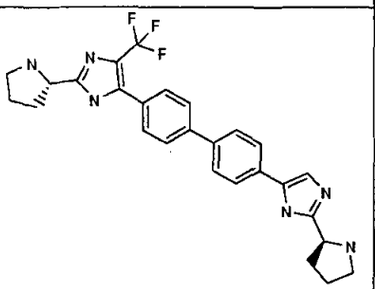
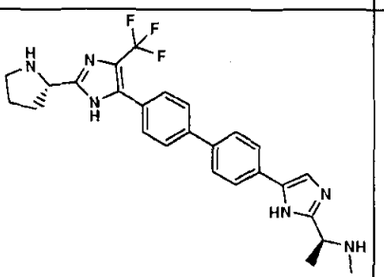
	(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate	Prepared from entry J14 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148.	817.37; found: 817.38 $(M+H)^+$. HRMS: Anal. Calcd. for C44H49N8O8 817.3673; found: 817.3675 $(M+H)^+$.
J25	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(methylcarbamoyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from entry J15 (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	t_R = 1.58 min, (99.6%) (Cond 2); LRMS: Anal. Calcd. for C48H50N9O7 864.38; found: 864.47 $(M+H)^+$. HRMS: Anal. Calcd. for C48H50N9O7 864.3833; found: 864.3849 $(M+H)^+$.
J26	2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-N-methyl-1H-imidazole-4-	 Prepared from entry J15 (in lieu of 148e) and *Cap*-1 using experimental conditions outlined in Example 148.	t_R = 1.31 min, (93.2%) (Cond 2); LRMS: Anal. Calcd. for C48H54N9O3 804.44; found: 804.51 $(M+H)^+$. HRMS: Anal. Calcd. for C48H54N9O3 804.4350; found: 804.4369 $(M+H)^+$.

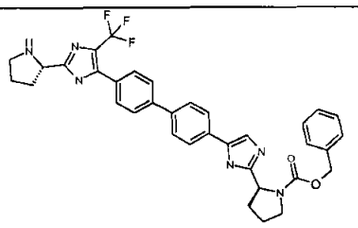
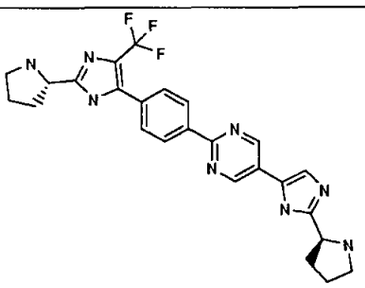
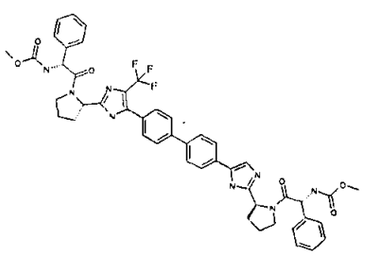
	carboxamide		
J27	N-methyl-2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxamide	 Prepared from entry J15 (in lieu of 148e) and *Cap*-14 using experimental conditions outlined in Example 148.	t_R = 1.39 min, (95.4%) (Cond 2); LRMS: Anal. Calcd. for C54H62N9O3 884.50; found: 884.52 $(M+H)^+$. HRMS: Anal. Calcd. for C54H62N9O3 884.4976; found: 884.4973 $(M+H)^+$.
J28	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-4-(methylcarbamoyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 Prepared from entry J15 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148.	t_R = 1.34 min, (89.3%) (Cond 2); LRMS: Anal. Calcd. for C38H46N9O7 740.35; found: 740.31 $(M+H)^+$. HRMS: Anal. Calcd. for C38H46N9O7 740.3520; found: 740.3497 $(M+H)^+$.
J29	methyl ((1R)-2-((2S)-2-(4-carbamoyl-5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-	 Prepared from entry J15.a (in	t_R = 1.55 min, (96.4%) (Cond 2); LRMS: Anal. Calcd. for C47H48N9O7 740.35; found: 740.31 $(M+H)^+$.

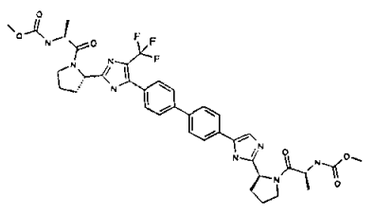
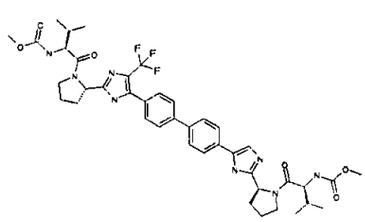
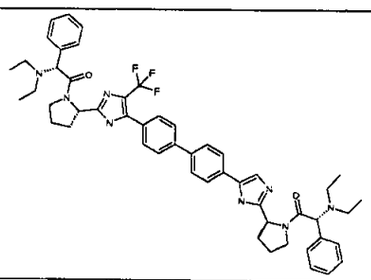
	pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	HRMS: Anal. Calcd. for C47H48N9O7 740.3520; found: 740.3497 $(M+H)^+$.
J30	2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylic acid	 Prepared from entry 21 (in lieu of 28c) using experimental conditions outlined in Example 28 step d.	t_R = 1.52 min, (92.8%) (Cond 2); LRMS: Anal. Calcd. for C47H47N8O8 851.35; found: 851.37 $(M+H)^+$. HRMS: Anal. Calcd. for C47H47N8O8 851.3517; found: 851.3553 $(M+H)^+$.
J31	2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylic acid	 Prepared from entry 23 (in lieu of 28c) using experimental conditions outlined in Example 28 step d.	t_R = 1.36 min, (96.5%) (Cond 2); LRMS: Anal. Calcd. for C53H59N8O4 871.47; found: 871.47 $(M+H)^+$. HRMS: Anal. Calcd. for C53H59N8O4 871.4659; found: 871.4692 $(M+H)^+$.

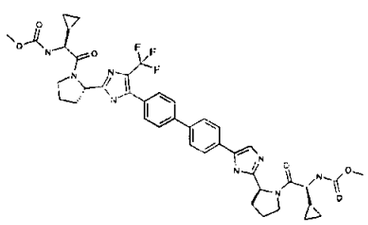
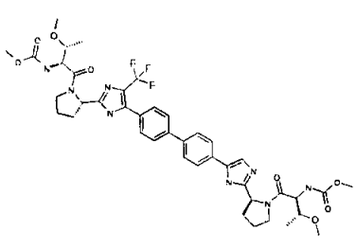
J32		 Prepared from 4-bromobenzaldehyde according to procedure described in J.Org.Chem. (1988), 53, 129.	t_R = 1.96 min, (96%) (Cond 2); LRMS: Anal. Calcd. for $C_{11}H_{11}BrF_3N_2O$ 323.00; found: 323.05 and 325.05 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 7.58 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 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 of 1b) using experimental conditions outlined in Example 1 step c.	t_R = 2.3 min, (73%) (Cond 2); LCMS: $C_{25}H_{34}BF_3N_3O_4$ found: 508 $(M+H)^+$.
J33	tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-	 Prepared from entry J32.a (in	t_R = 2.7 min, (95%) (Cond 2); LRMS: Anal. Calcd. for $C_{37}H_{44}F_3N_6O_4$ 693.34; found: 693.33 $(M+H)^+$.

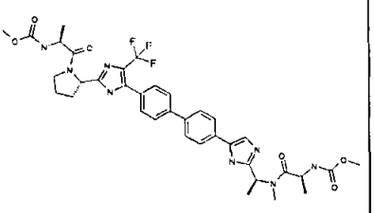
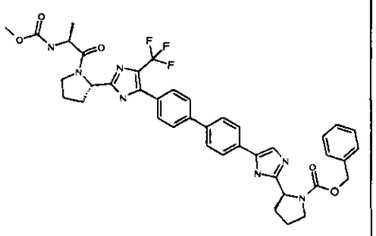
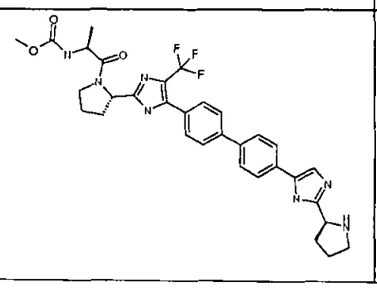
	(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	lieu of 152e-1) and 1c using experimental conditions outlined in Example 152g-1.	HRMS: Anal. Calcd. for $C_{37}H_{44}F_3N_6O_4$ 693.3376; found: 693.3370 $(M+H)^+$.
J33.a	tert-butyl (2S)-2-(5-(4'-(2-((1S)-1-((tert-butoxycarbonyl)(methyl)amino)ethyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-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	tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-((benzyloxy)carbonyl)-2-pyrrolidinyl)-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 1-5c using experimental conditions outlined in Example 152g-1.	t_R = 2.0 min, (95%) (Cond 2); LRMS: Anal. Calcd. for $C_{40}H_{42}F_3N_6O_4$ 727.32; found: 727.19 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{42}F_3N_6O_4$ 727.3220; found: 727.3251 $(M+H)^+$.

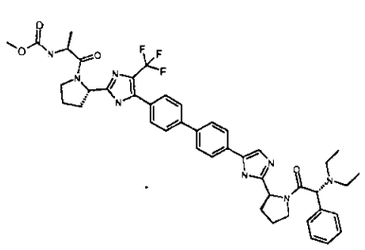
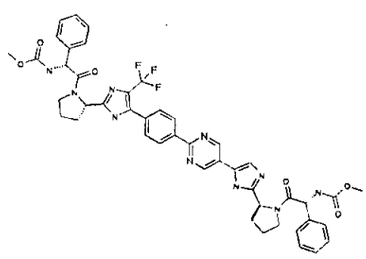
J34.a	tert-butyl (2S)-2-(5-(4-(5-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry J32.b (in lieu of 152e-1) and 152d-1 using experimental conditions outlined in Example 152g-1.	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		 Prepared from entry J33 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.46 min, (92%) (Cond 2); LCMS: $C_{27}H_{28}F_3N_6O$ found: 493 $(M+H)^+$.
J35.a		 Prepared from entry J33.a (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	LCMS: $C_{26}H_{28}F_3N_6$ found: 481 $(M+H)^+$.

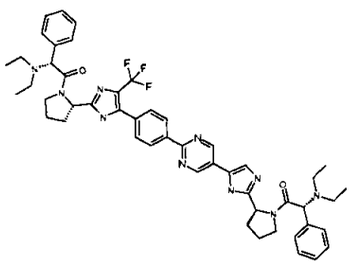
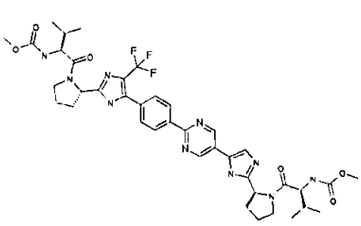
J36		 Prepared from entry J34 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	LCMS: $C_{35}H_{34}F_3N_6O_2$ found: 626 $(M+H)^+$.
J36.a		 Prepared from entry J34.a (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.45 min, (Cond 2); LCMS: $C_{25}H_{26}F_3N_8$ found: 495 $(M+H)^+$.
J37	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl) amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbam ate	 Prepared from entry J35 (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	t_R = 1.9 min, (95%) (Cond 2); LRMS: Anal. Calcd. for $C_{47}H_{46}F_3N_8O_4$ 875.35; found: 875.35 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{47}H_{46}F_3N_8O_4$ 875.3492; found: 875.3504 $(M+H)^+$.

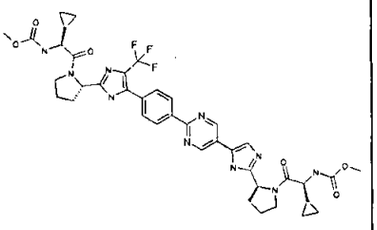
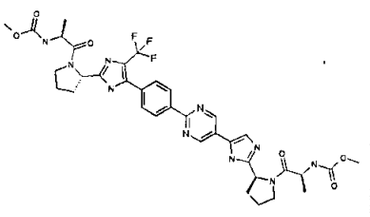
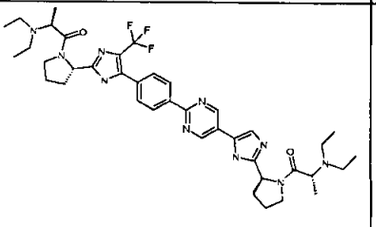
J38	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-4-(trifluoromethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 Prepared from entry J35 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148.	t_R = 1.7 min, (95.5%) (Cond 2); LRMS: Anal. Calcd. for $C_{37}H_{42}F_3N_8O_6$ 751.32; found: 751.32 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{37}H_{42}F_3N_8O_6$ 751.3179; found: 751.3163 $(M+H)^+$.
J39	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry J35 (in lieu of 148e) and *Cap*-51 using experimental conditions outlined in Example 148.	t_R = 1.9 min, (96%) (Cond 2); LRMS: Anal. Calcd. for $C_{41}H_{50}F_3N_8O_6$ 807.38; found: 807.33 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{50}F_3N_8O_6$ 807.3805; found: 807.3773 $(M+H)^+$.
J40	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-		t_R = 1.6 min, (95%) (Cond 2); LRMS: Anal. Calcd. for $C_{51}H_{58}F_3N_8O_2$ 871.46; found:

	imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine	Prepared from entry J35 (in lieu of 148e) and *Cap*-2 using experimental conditions outlined in Example 148.	871.48 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{51}H_{58}F_3N_8O_2$ 871.4635; found: 871.4647 $(M+H)^+$.
J41	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 Prepared from entry J35 (in lieu of 148e) and *Cap*-54b using experimental conditions outlined in Example 148.	t_R = 1.8 min, (96.9%) (Cond 2); LRMS: Anal. Calcd. for $C_{41}H_{46}F_3N_8O_6$ 803.35; found: 803.35 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{46}F_3N_8O_6$ 803.3492; found: 803.3507 $(M+H)^+$.
J42	methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-4-(trifluoromethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbon	 Prepared from entry J35 (in lieu of 148e) and *Cap*-86 using experimental conditions outlined in Example 148.	t_R = 1.8 min, (92%) (Cond 2); LRMS: Anal. Calcd. for $C_{41}H_{50}F_3N_8O_8$ 839.37; found: 839.30 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{50}F_3N_8O_8$ 839.3704; found: 839.3677 $(M+H)^+$.

	yl)propyl)carbamat e		
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 $(M+H)^+$.
J43	benzyl (2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-4-(trifluoromethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry J36 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148.	t_R = 1.9 min, (95%) (Cond 2); LRMS: Anal. Calcd. for $C_{40}H_{41}F_3N_7O_5$ 756.31; found: 756.19 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{41}F_3N_7O_5$ 756.3121; found: 756.3127 $(M+H)^+$.
J44			LCMS: $C_{32}H_{35}F_3N_7O_3$ found: 622 $(M+H)^+$.

		Prepared from entry J43 (in lieu of 152g-8) using experimental conditions outlined in Example 152i-1.	
J45	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 Prepared from entry J44 (in lieu of 148e) and *Cap*-2 using experimental conditions outlined in Example 148.	t_R = 1.7 min, (93%) (Cond 2); LRMS: Anal. Calcd. for $C_{44}H_{50}F_3N_8O_4$ 811.39; found: 811.34 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{44}H_{50}F_3N_8O_4$ 811.3907; found: 811.3913 $(M+H)^+$.
J46	methyl ((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-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	t_R = 1.82 min, (98%) (Cond 2); LRMS: Anal. Calcd. for $C_{45}H_{44}F_3N_{10}O_6$ 877.34; found: 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-pyrimidinyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 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 $C_{39}H_{48}F_3N_{10}O_6$ 809.3710; found: 809.3683 $(M+H)^+$.

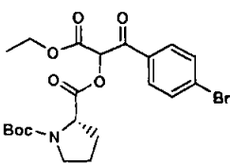
J49	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2S)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 Prepared from entry J34.a (in lieu of 148e) and *Cap*-54b 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-	 Prepared from entry J34.a (in	t_R = 1.41 min, (92%) (Cond 2); LRMS: Anal. Calcd. for $C_{39}H_{52}F_3N_{10}O_2$ 749.42; found:

	imidazol-5-yl)-2-pyrimidinyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-1-oxo-2-propanamine	lieu of 148e) and *Cap*-70b using experimental conditions outlined in Example 148	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

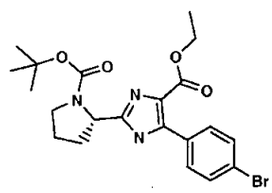
The ethyl 3-(4-bromophenyl)-3-oxopropanoate (15 g, 55 mmol) was dissolved in CH_2Cl_2 (600 mL) and freshly recrystallized NBS (9.8 g, 55 mmol) was added and the solution stirred 18 hr. The reaction mixture was washed with $NaHCO_3$ solution, brine, and dried ($MgSO_4$), filtered, and concentrated to 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. ^1H 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

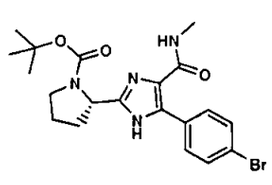


J5

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%). ^1H 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

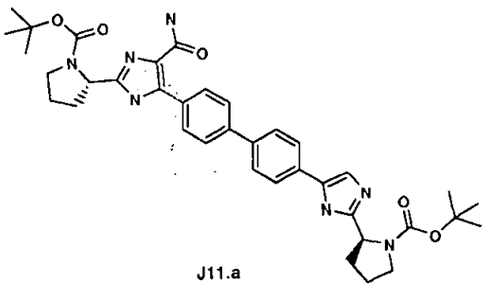


J7

(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 J11.a.

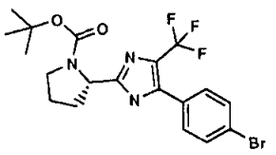


J11.a

Entry J9 (1.1g, 1.58 mmol) was taken up in ethanol (60 mL), 28% concentrated ammonium hydroxide soln (10 mL) was added, and the reaction heated in a pressure vessel at 75°C for 48 h. The solvent was removed by rotary evaporation and the residue taken up in ethyl acetate and washed with water, brine. Concentration and application to a 25 M Biotage cartridge, gradient elution with 10% - 100% ethyl acetate/CH_2Cl_2, gave J11.a 90 mg (8.5%) and recovered starting material J9 696 mg (63%).

Example J32.a.

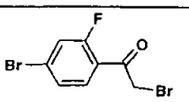
(S)-tert-butyl 2-(5-(4-bromophenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

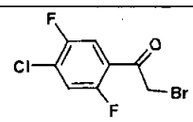
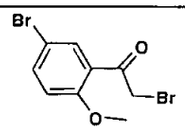
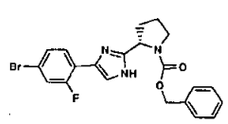


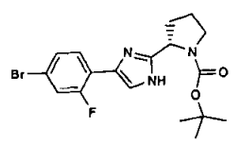
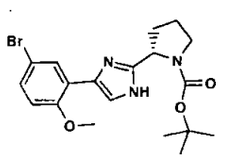
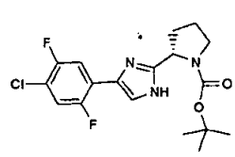
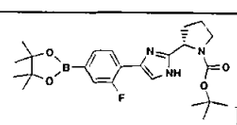
J32.a

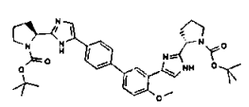
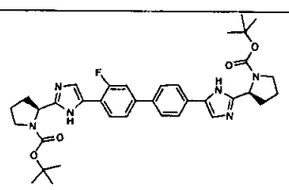
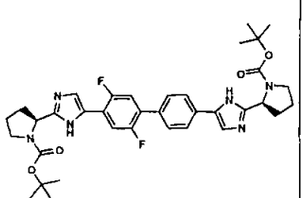
3-(4-bromophenyl)-3-(2,2-dimethylhydrazono)-1,1,1-trifluoropropan-2-one (2.0g, 6.2 mmol) was suspended in 5N sulfuric acid (60 mL) and heated at 45°C for 6 h. The temperature was raised to 85°C for 2 h, and upon cooling a precipitate formed. This material which was isolated by filtration to give 1-(4-bromophenyl)-3,3,3-trifluoropropane-1,2-dione 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 $(M+H)^+$.

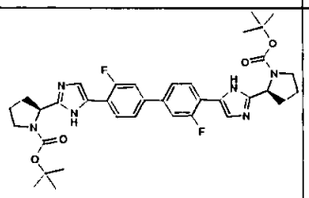
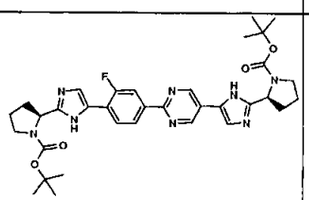
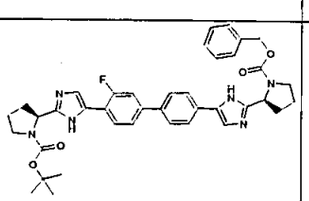
Section D

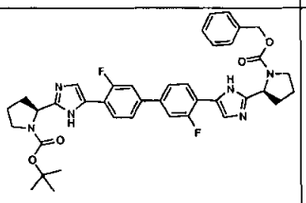
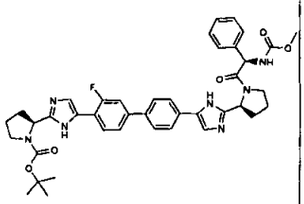
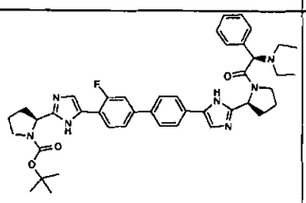
Entry	*Compound Name*	*Structure*	***Data*
D1		 Prepared from 1-(4-bromo-2-fluorophenyl)ethanone (Vendor: Marshalton	t_R = 2.65 min, (86.7%) LCMS: Anal. Calcd. for $C_8H_{15}BrFO$ 296.88; found: 296.91 $(M+H)^+$.

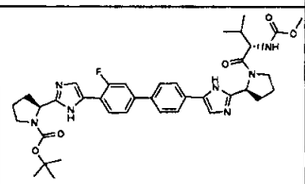
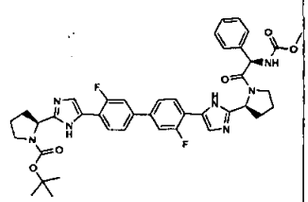
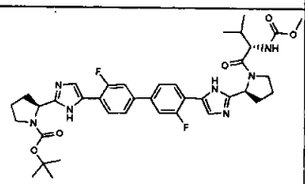
		50043) using bromination conditions outlined in D5.	
D2		 Prepared from 1-(4-chloro-2,5-difluorophenyl)ethanone (Vendor: Oakwood products, 001626) using bromination conditions outlined in D5.	t_R = 2.66 min, (80%) LCMS: Anal. Calcd. for $C_8H_4BrClFO$ 270.92; found: ND $(M+H)^+$.
D3		 Prepared from 2-bromo-1-(5-bromo-2-methoxyphenyl)ethanone (Andersh et al., Synth. Comm. 2000, 30 (12), 2091-98) using bromination conditions outlined in D5.	t_R = 2.57 min, (95%) LCMS: Anal. Calcd. for $C_9H_9BrO_2$ 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 $(M+H)^+$

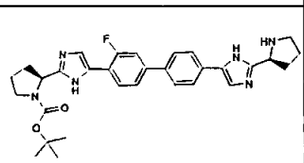
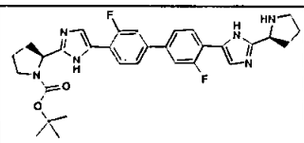
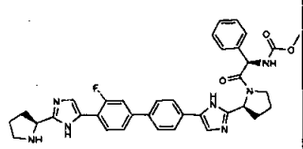
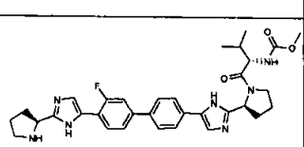
D5		 Experimental conditions in D5	t_R = 2.27min, (95%) LRMS: Anal. Calcd. for $C_{18}H_{22}BrFN_3O_2$ 410.09 and 412.08; found: 410.08 and 412.08 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{18}H_{22}{}^{79}BrFN_3O_2$ 410.0879; found: 410.0893 $(M+H)^+$.
D6		 Prepared from entry D3 (in lieu of entry D1) using experimental conditions outlined in D5.	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 $(M+H)^+$. 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		 Prep	t_R = 2.62 min, (~50%) and 1.95 min (~50%, boronic acid)

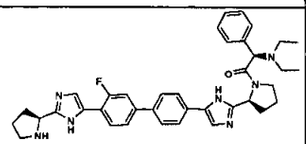
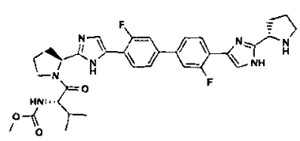
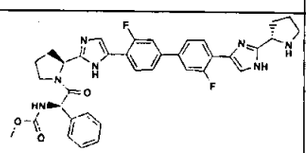
		ared from entry D5 (in lieu of 1b) using experimental conditions outlined in Example 1, Step c.	LRMS: Anal. Calcd. for $C_{24}H_{34}BFN_3O_4$ 458.26; found: 458.23 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{24}H_{34}BFN_3O_4$ 458.2626; found: 458.2610 $(M+H)^+$.
D9	tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-methoxy-3-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry D6 (in lieu of 152e-1) and 1c using experimental conditions outlined in Example 152g-1.	t_R = 2.28 min, (95%) LRMS: Anal. Calcd. for $C_{37}H_{47}N_6O_5$ 655.36; found: 655.37 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{37}H_{47}N_6O_5$ 655.3608; found: 655.3627 $(M+H)^+$.
D10	di-tert-butyl (2S,2'S)-2,2'-((3-fluoro-4,4'-biphenyldiyl)bis(1H-imidazole-4,2-diyl))di(1-pyrrolidinecarboxylate)	 Prepared from entry D5 (in lieu of 152e-1) and 1c using experimental conditions outlined in Example 152g-1.	t_R = 2.21 min, (99.2%) LCMS: Anal. Calcd. for $C_{36}H_{44}FN_6O_4$ 643.34; found: 643.51 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{44}FN_6O_4$ 643.3403; found: 643.3390 $(M+H)^+$.
D11	tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2,5-difluoro-4-		t_R = 2.24 min, (95%) LRMS: Anal. Calcd. for $C_{36}H_{43}F_2N_6O_4$ 661.33; found: 661.35 $(M+H)^+$.

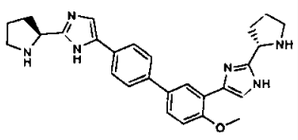
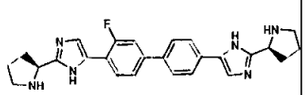
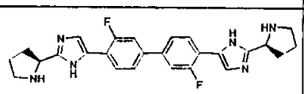
	biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	Prepared from entry D7 (in lieu of 152e-1) and 1c using experimental conditions outlined in Example 152g-1.	HRMS: Anal. Calcd. for $C_{36}H_{43}F_2N_6O_4$ 661.3314; found: 661.3336 $(M+H)^+$.
D12	di-tert-butyl (2S,2'S)-2,2'-((3,3'-difluoro-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl))di(1-pyrrolidinecarboxylate)	 Prepared from entry D5 (in lieu of 152e-1) using experimental conditions outlined in Example 153a-1.	t_R = 2.20min, (95%) LRMS: Anal. Calcd. for $C_{36}H_{43}F_2N_6O_4$ 661.33; found: 661.22 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{43}F_2N_6O_4$ 661.3314; found: 661.3307 $(M+H)^+$.
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-pyrrolidinecarboxylate	 Prepared from entry D8 (in lieu of 1c) and 152b-1 using experimental conditions outlined in Example 152g-1.	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 $C_{34}H_{42}FN_8O_4$ 645.3313; found: 645.3323 $(M+H)^+$.
D14	tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-((benzyloxy)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylat	 Prepared from entry D5 (in lieu of 152e-1) and 1-5c using experimental	t_R = 2.26min, (95%) LRMS: Anal. Calcd. for $C_{39}H_{42}FN_6O_4$ 677.33; found: 677.33 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{39}H_{42}FN_6O_4$

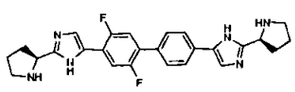
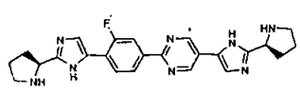
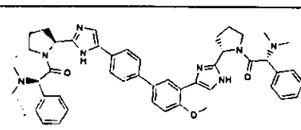
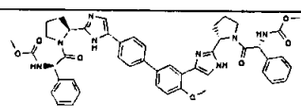
	e	conditions outlined in Example 152g-1.	677.3252; found: 677.3278 $(M+H)^+$.
D15	tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-((benzyloxy)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3,3'-difluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry D8 (in lieu of 1e) and entry D4 using experimental conditions outlined in Example 152g-1.	t_R = 2.36min, (97.3%) LRMS: Anal. Calcd. for $C_{39}H_{41}F_2N_6O_4$ 695.32; found: 695.33 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{39}H_{41}F_2N_6O_4$ 695.3157; found: 695.3151 $(M+H)^+$.
D16	tert-butyl (2S)-2-(5-(3-fluoro-4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry D21 (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	t_R = 2.16 min, (91.0%) LRMS: Anal. Calcd. for $C_{41}H_{45}FN_7O_5$ 734.35; found: 734.36 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{45}FN_7O_5$ 734.3466; found: 734.3474 $(M+H)^+$.
D17	tert-butyl (2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylat	 Prepared from entry D21 (in lieu of 148e) and *Cap*-2 using experimental conditions outlined in	t_R = 1.95 min, (95%) LRMS: Anal. Calcd. for $C_{43}H_{51}FN_7O_3$ 732.40; found: 732.44 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{43}H_{51}FN_7O_3$

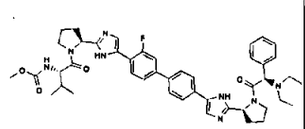
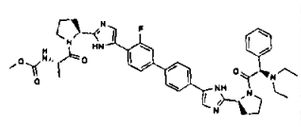
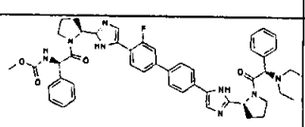
	e	Example 148.	732.4037; found: 732.4065 $(M+H)^+$.
D18	tert-butyl (2S)-2-(5-(3-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry D21 (in lieu of 148e) and *Cap*-51 using experimental conditions outlined in Example 148.	t_R = 2.14 min, (95%) LRMS: Anal. Calcd. for $C_{38}H_{47}FN_7O_5$ 700.36; found: 700.37 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{47}FN_7O_5$ 700.3623; found: 700.3596 $(M+H)^+$.
D19	tert-butyl (2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry D22 (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	t_R = 2.23 min, (95%) LRMS: Anal. Calcd. for $C_{41}H_{44}F_2N_7O_5$ 752.34; found: 752.35 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{44}F_2N_7O_5$ 752.3372; found: 752.3385 $(M+H)^+$.
D20	tert-butyl (2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylat	 Prepared from entry D22 (in lieu of 148e) and *Cap*-51 using experimental conditions outlined in Example 148.	t_R = 2.16 min, (90%) LRMS: Anal. Calcd. for $C_{38}H_{46}F_2N_7O_5$ 718.35; found: 718.36 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{46}F_2N_7O_5$ 718.3528; found: 718.3505 $(M+H)^+$.

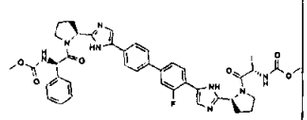
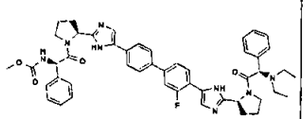
	e		
D21	tert-butyl (2S)-2-(5-(3-fluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate triacetate	 Prepared from entry D14 (in lieu of 152g-8) using experimental conditions outlined in Example 152i-1.	t_R = 1.94 min, (95%) LRMS: Anal. Calcd. for $C_{31}H_{36}FN_6O_2$ 543.29; found: 543.30. HRMS: Anal. Calcd. for $C_{31}H_{36}FN_6O_2$ 543.2884; found: 543.2872 $(M+H)^+$.
D22	tert-butyl (2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from entry D15 (in lieu of 152g-8) using experimental conditions outlined in Example 152i-1.	t_R = 2.14 min, (95%) LRMS: Anal. Calcd. for $C_{31}H_{35}F_2N_6O_2$ 561.28; found: 561.29 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{31}H_{35}F_2N_6O_2$ 561.2790; found: 561.2766 $(M+H)^+$.
D23	methyl ((1R)-2-((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from entry D16 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.90 min, (94%) LRMS: Anal. Calcd. for $C_{36}H_{37}FN_7O_3$ 634.29; found: 634.29 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{37}FN_7O_3$ 634.2942; found: 634.2948 $(M+H)^+$.
D24	methyl ((1S)-1-(((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-2-		t_R = 1.89 min, (95%) LRMS: Anal. Calcd. for for

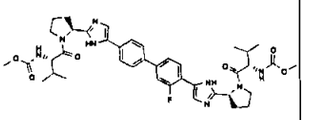
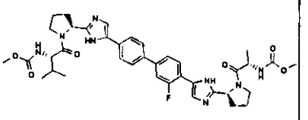
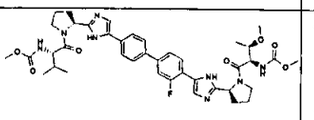
	pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	Prepared from entry D18 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	$C_{33}H_{39}FN_7O_3$ 600.31; found: 600.32 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{33}H_{39}FN_7O_3$ 600.3098; found: 600.3121 $(M+H)^+$.
D25	(1R)-N,N-diethyl-2-((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine	 Prepared from entry D17 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.72 min, (90%) LRMS: Anal. Calcd. for $C_{38}H_{43}FN_7O$ 632.35; found: 632.36 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{43}FN_7O$ 632.3513; found: 632.3527 $(M+H)^+$.
D26	methyl ((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry D20 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.96 min, (95%) LRMS: Anal. Calcd. for $C_{33}H_{38}F_2N_7O_3$ 618.30; found: 618.31 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{33}H_{38}F_2N_7O_3$ 618.3004; found: 618.3024 $(M+H)^+$.
D27	methyl ((1R)-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-	 Prepared from entry D19 (in lieu of 152j-27) using	t_R = 1.63 min, (95%) LRMS: Anal. Calcd. for $C_{36}H_{36}F_2N_7O_3$ 652.28; found: 652.29 $(M+H)^+$.

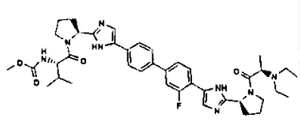
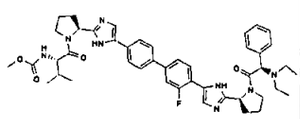
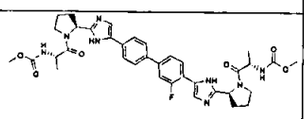
	imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	experimental conditions outlined in Example 152k-1.	HRMS: Anal. Calcd. for $C_{36}H_{36}F_2N_7O_3$ 652.2848; found: 652.2858 $(M+H)^+$.
D28	5,5'-(4-methoxy-3,4'-biphenyldiyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole)	 Prepared from entry D9 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.53 min, (98.2%) LRMS: Anal. Calcd. for $C_{27}H_{31}N_6O$ 455.26; found: 455.26 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{27}H_{31}N_6O$ 455.2559; found: 455.2576 $(M+H)^+$.
D29	5,5'-(3-fluoro-4,4'-biphenyldiyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole) tetraacetate	 Prepared from entry 10 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.55 min, (95%) LRMS: Anal. Calcd. for $C_{26}H_{28}FN_6$ 443.24; found: 443.24 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{26}H_{28}FN_6$ 443.2359; found: 443.2371 $(M+H)^+$.
D30		 Prepared from entry D12 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.72 min, (77.5%) LRMS: Anal. Calcd. for $C_{26}H_{27}F_2N_6$ 461.23; found: 461.25 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{26}H_{27}F_2N_6$ 461.2265; found: 461.2272

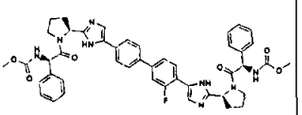
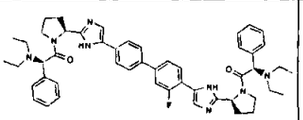
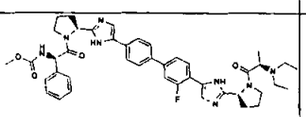
			$(M+H)^+$.
D31	5,5'-(2,5-difluoro-4,4'-biphenyldiyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole)	 Prepared from entry D11 (in lieu of 152j-27) using experimental conditions outlined in Example 152k-1.	t_R = 1.67 min, (95%) LRMS: Anal. Calcd. for $C_{26}H_{27}F_2N_6$ 461.23; found: 461.23 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{26}H_{27}F_2N_6$ 461.2265; found: 461.2287 $(M+H)^+$.
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 $(M+H)^+$.
D33	(1R,1'R)-2,2'-((4-methoxy-3,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)	 Prepared from entry D28 (in lieu of 148e) and *Cap*-1 using experimental conditions outlined in Example 148.	t_R = 1.71 min, (95%) LRMS: Anal. Calcd. for $C_{47}H_{53}N_8O_3$ 777.42; found: 777.41 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{47}H_{53}N_8O_3$ 777.4241; found: 777.4254 $(M+H)^+$.
D34	dimethyl ((4-methoxy-3,4'-biphenyldiyl)bis(1H-imidazole-5,2-	 Prepared from entry D28	t_R = 2.09 min, (95%) LRMS: Anal. Calcd. for $C_{47}H_{49}N_8O_7$ 837.37; found:

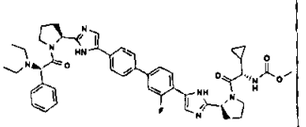
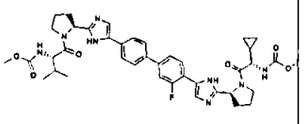
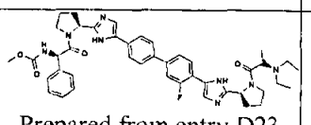
	diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	(in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	837.34 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{47}H_{49}N_8O_7$ 837.3724; found: 837.3690 $(M+H)^+$.
D35	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry D25 (in lieu of 148e) and *Cap*-51 using experimental conditions outlined in Example 148.	t_R = 1.85 min, (97.2%) LRMS: Anal. Calcd. for $C_{45}H_{54}FN_8O_4$ 789.43; found: 789.43 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{45}H_{54}FN_8O_4$ 789.4252; found: 789.4225 $(M+H)^+$.
D36	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 Prepared from entry D25 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148.	t_R = 1.76 min, (97.9%) LRMS: Anal. Calcd. for $C_{43}H_{50}FN_8O_4$ 761.39; found: 761.26 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{43}H_{50}FN_8O_4$ 761.3939; found: 761.3967 $(M+H)^+$.
D37	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-	 Prepared from entry D25	t_R = 1.90 min, (98.6%) LRMS: Anal. Calcd. for $C_{48}H_{52}FN_8O_4$

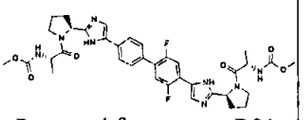
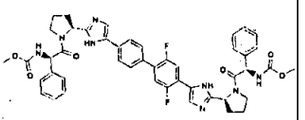
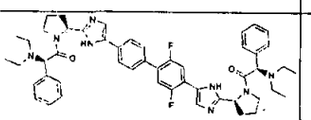
	phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	(in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	823.41; found: 823.42 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{48}H_{52}FN_8O_4$ 823.4096; found: 823.4102 $(M+H)^+$.
D38	methyl ((1R)-2-((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from entry D23 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148.	t_R = 1.89 min, (98.2%) LRMS: Anal. Calcd. for $C_{47}H_{49}N_8O_7$ 763.34; found: 763.32 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{41}H_{44}FN_8O_6$ 763.3368; found: 763.3358 $(M+H)^+$.
D39	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3'-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from entry D23 (in lieu of 148e) and *Cap*-2 using experimental conditions outlined in Example 148.	t_R = 1.88 min, (98.7%) LRMS: Anal. Calcd. for $C_{48}H_{52}FN_8O_4$ 823.41; found: 823.39 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{48}H_{52}FN_8O_4$ 823.4096; found: 823.4127 $(M+H)^+$.

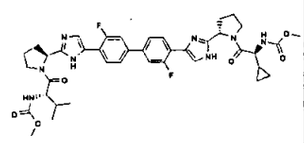
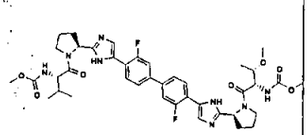
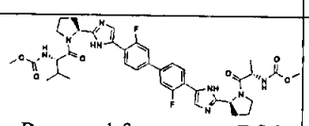
D40	methyl ((1S)-1-(((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry D29 (in lieu of 148e) and *Cap*-51 using experimental conditions outlined in Example 148.	t_R = 1.97 min, (98.4%) LRMS: Anal. Calcd. for $C_{40}H_{50}FN_8O_6$ 757.38; found: 757.32 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{50}FN_8O_6$ 757.3837; found: 757.3815 $(M+H)^+$.
D41	methyl ((1S)-1-(((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry D24 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148.	t_R = 1.82 min, (95.0%) LRMS: Anal. Calcd. for $C_{38}H_{46}FN_8O_6$ 729.35; found: 729.29 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{38}H_{46}FN_8O_6$ 729.3524; found: 729.3523 $(M+H)^+$.
D42	methyl ((1S,2R)-1-(((2S)-2-(5-(3-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-	 Prepared from entry D24 (in lieu of 148e) and *Cap*-86 using experimental conditions outlined in Example 148.	t_R = 1.91 min, (94.0%) LRMS: Anal. Calcd. for $C_{40}H_{50}FN_8O_7$ 773.38; found: 773.31 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{50}FN_8O_7$

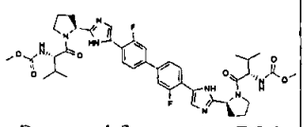
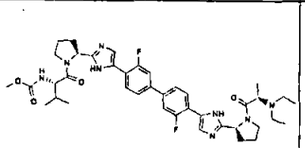
	imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate		773.3786; found: 773.3759 $(M+H)^+$.
D43	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3'-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry D24 (in lieu of 148e) and *Cap*-69b using experimental conditions outlined in Example 148.	t_R = 1.72 min, (97.6%) LRMS: Anal. Calcd. for $C_{40}H_{52}FN_8O_4$ 727.41; found: 727.35 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{52}FN_8O_4$ 727.4096; found: 727.4091 $(M+H)^+$.
D44	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3'-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry D24 (in lieu of 148e) and *Cap*-2 using experimental conditions outlined in Example 148.	t_R = 1.83 min, (96.9%) LRMS: Anal. Calcd. for $C_{45}H_{54}FN_8O_4$ 789.43; found: 789.36 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{45}H_{54}FN_8O_4$ 789.4252; found: 789.4225 $(M+H)^+$.
D45	methyl ((1S)-2-((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-	 Prepared from entry D29 (in lieu of 148e) and *Cap*-	t_R = 1.69 min, (97.7%) LRMS: Anal. Calcd. for for $C_{36}H_{42}FN_8O_6$ 701.32; found: 701.30 $(M+H)^+$.

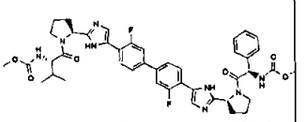
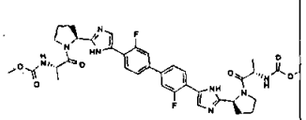
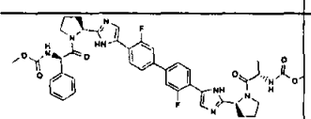
	pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	52 using experimental conditions outlined in Example 148.	HRMS: Anal. Calcd. for $C_{36}H_{42}FN_8O_6$ 701.3222; found: 701.3211 $(M+H)^+$.
D46	dimethyl ((3-fluoro-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 Prepared from entry D29 (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	t_R = 2.05 min, (99.9%) LRMS: Anal. Calcd. for for $C_{46}H_{46}FN_8O_6$ 825.35; found: 825.35 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{46}H_{46}FN_8O_6$ 825.3524; found: 825.3522 $(M+H)^+$.
D47	(1R,1'R)-2,2'-((3-fluoro-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-2-oxo-1-phenylethanamine)	 Prepared from entry D29 (in lieu of 148e) and *Cap*-2 using experimental conditions outlined in Example 148.	t_R = 1.72 min, (99.5%) LRMS: Anal. Calcd. for for $C_{50}H_{58}FN_8O_2$ 821.47; found: 821.44 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{50}H_{58}FN_8O_2$ 821.4667; found: 821.4636 $(M+H)^+$.
D48	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3'-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-	 Prepared from entry D23 (in lieu of 148e) and *Cap*-69b using experimental conditions outlined in Example 148.	t_R = 1.76min, (99.7%) LRMS: Anal. Calcd. for $C_{43}H_{50}FN_8O_4$ 761.39; found: 761.27 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{43}H_{50}FN_8O_4$

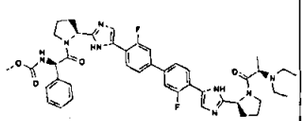
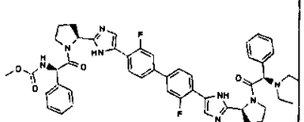
	pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		761.3939; found: 761.3952 $(M+H)^+$.
D49	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 Prepared from entry D25 (in lieu of 148e) and *Cap*-54b using experimental conditions outlined in Example 148.	t_R = 1.92 min, (98.7%) LRMS: Anal. Calcd. for $C_{45}H_{52}FN_8O_4$ 787.41; found: 787.36 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{45}H_{52}FN_8O_4$ 787.4096; found: 787.4074 $(M+H)^+$.
D50	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(3-fluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 Prepared from entry D24 (in lieu of 148e) and *Cap*-54b using experimental conditions outlined in Example 148.	t_R = 1.94 min, (99.0%) LRMS: Anal. Calcd. for $C_{40}H_{48}F_2N_8O_7$ 755.37; found: 755.32 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{48}FN_8O_6$ 755.3681; found: 755.3670 $(M+H)^+$.
D51	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3'-fluoro-4-biphenylyl)-	 Prepared from entry D23 (in lieu of 148e) and *Cap*-69b using experimental conditions outlined in Example 148.	t_R = 1.92 min, (98.3%) LRMS: Anal. Calcd. for $C_{43}H_{50}FN_8O_4$ 761.39; found: 761.35 $(M+H)^+$.

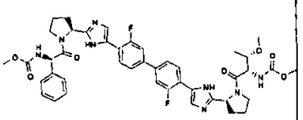
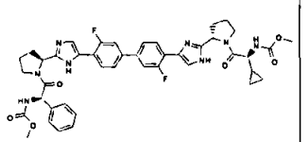
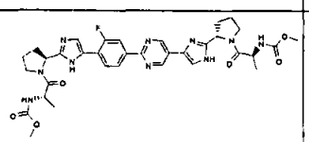
	1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		HRMS: Anal. Calcd. for $C_{43}H_{50}FN_8O_4$ 761.3939; found: 761.3956 $(M+H)^+$.
D52	methyl ((1S)-2-((2S)-2-(5-(2',5'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 Prepared from entry D31 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148.	t_R = 1.69 min, (99.2%) LRMS: Anal. Calcd. for $C_{36}H_{41}F_2N_8O_6$ 719.31; found: 719.29 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{41}F_2N_8O_6$ 719.3117; found: 719.3109 $(M+H)^+$.
D53	dimethyl ((2,5-difluoro-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 Prepared from entry D31 (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148 of 10889PSP.	t_R = 2.08 min, (100.0%) LRMS: Anal. Calcd. for $C_{46}H_{45}F_2N_8O_6$ 843.34; found: 843.34 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{46}H_{45}F_2N_8O_6$ 843.3430; found: 843.3458 $(M+H)^+$.
D54	(1R,1'R)-2,2'-((2,5-difluoro-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-2-oxo-1-	 Prepared from entry D31 (in lieu of 148e) and *Cap*-2 using experimental conditions outlined in Example 148.	t_R = 1.76 min, (99.8%) LRMS: Anal. Calcd. for $C_{50}H_{57}F_2N_8O_2$ 839.46; found: 839.43 $(M+H)^+$.

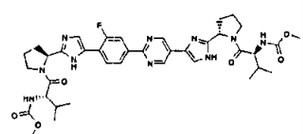
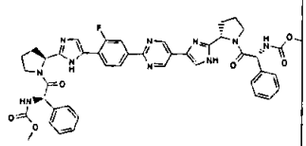
	phenylethanamine)		HRMS: Anal. Calcd. for $C_{50}H_{57}F_2N_8O_2$ 839.4573; found: 839.4585 $(M+H)^+$.
D55	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 Prepared from entry D26 (in lieu of 148e) and *Cap*-54b using experimental conditions outlined in Example 148.	t_R = 1.93 min, (98.5%) LRMS: Anal. Calcd. for $C_{40}H_{47}F_2N_8O_6$ 773.36; found: 773.31 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{47}F_2N_8O_6$ 773.3567; found: 773.3587 $(M+H)^+$.
D56	methyl ((1S,2R)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate	 Prepared from entry D26 (in lieu of 148e) and *Cap*-86 using experimental conditions outlined in Example 148.	t_R = 2.00 min, (98.0%) LRMS: Anal. Calcd. for $C_{40}H_{49}F_2N_8O_7$ 791.37; found: 791.32 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{49}F_2N_8O_7$ 791.3692; found: 791.3682 $(M+H)^+$.
D57	methyl ((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-	 Prepared from entry D26 (in lieu of 148e) and *Cap*-52 using experimental	t_R = 1.86 min, (95.6%) LRMS: Anal. Calcd. for $C_{38}H_{45}F_2N_8O_6$ 747.34; found: 747.30 $(M+H)^+$.

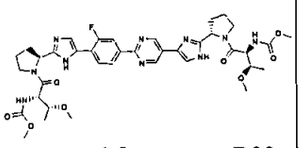
	L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	conditions outlined in Example 148.	HRMS: Anal. Calcd. for $C_{38}H_{45}F_2N_8O_6$ 747.3430; found: 747.3425 $(M+H)^+$.
D58	methyl ((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry D26 (in lieu of 148e) and *Cap*-51 using experimental conditions outlined in Example 148.	t_R = 2.02 min, (96.3%) LRMS: Anal. Calcd. for $C_{40}H_{49}F_2N_8O_6$ 775.37; found: 775.31 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{49}F_2N_8O_6$ 775.3743; found: 775.37.34 $(M+H)^+$.
D59	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3,3'-difluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-	 Prepared from entry D26 (in lieu of 148e) and *Cap*-69b using experimental conditions outlined in Example 148.	t_R = 1.78 min, (98.2%) LRMS: Anal. Calcd. for $C_{40}H_{51}F_2N_8O_4$ 745.40; found: 745.34 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{40}H_{51}F_2N_8O_4$ 745.4001; found: 745.4008 $(M+H)^+$.

	methylpropyl)carbamate		
D60	methyl ((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 Prepared from entry D26 (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 148.	t_R = 2.08 min, (99.1%) LRMS: Anal. Calcd. for $C_{43}H_{47}F_2N_8O_6$ 809.36; found: 809.29 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{43}H_{47}F_2N_8O_6$ 809.3587; found: 809.3568 $(M+H)^+$.
D61	methyl ((1S)-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 Prepared from entry D30 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in Example 148.	t_R = 1.71min, (94.3%) LRMS: Anal. Calcd. for $C_{36}H_{41}F_2N_8O_6$ 719.31; found: 719.19 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{36}H_{41}F_2N_8O_6$ 719.3117; found: 719.3115 $(M+H)^+$.
D62	methyl ((1R)-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-	 Prepared from entry D27 (in lieu of 148e) and *Cap*-52 using experimental conditions outlined in	t_R = 1.94 min, (98.3%) LRMS: Anal. Calcd. for $C_{41}H_{43}F_2N_8O_6$ 781.33; found: 781.26 $(M+H)^+$.

	imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	Example 148.	HRMS: Anal. Calcd. for $C_{41}H_{43}F_2N_8O_6$ 781.3274; found: 781.3264 $(M+H)^+$.
D63	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3,3'-difluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from entry D27 (in lieu of 148e) and *Cap*-69b using experimental conditions outlined in Example 148.	t_R = 1.44 min, (99.0%) LRMS: Anal. Calcd. for $C_{43}H_{49}F_2N_8O_4$ 779.38; found: 779.32 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{43}H_{49}F_2N_8O_4$ 779.3845; found: 779.3842 $(M+H)^+$.
D64	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3,3'-difluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 Prepared from entry D27 (in lieu of 148e) and *Cap*-2 using experimental conditions outlined in Example 148.	t_R = 1.94 min, (95.3%) LRMS: Anal. Calcd. for $C_{48}H_{51}F_2N_8O_4$ 841.40; found: 841.33 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{48}H_{51}F_2N_8O_4$ 841.4001; found: 841.3991 $(M+H)^+$.

D65	methyl ((1S,2R)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate bis(trifluoroacetate)	 Prepared from entry D27 (in lieu of 148e) and *Cap*-86 using experimental conditions outlined in Example 148.	t_R = 2.00 min, (96.2%) LRMS: Anal. Calcd. for $C_{43}H_{47}F_2N_8O_7$ 825.35; found: 825.28 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{43}H_{47}F_2N_8O_7$ 825.3536; found: 825.3527 $(M+H)^+$.
D66	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 Prepared from entry D27 (in lieu of 148e) and *Cap*-54b using experimental conditions outlined in Example 148.	t_R = 2.01 min, (99.5%) LRMS: Anal. Calcd. for $C_{43}H_{45}F_2N_8O_6$ 807.34; found: 807.29 $(M+H)^+$. HRMS: Anal. Calcd. for $C_{43}H_{45}F_2N_8O_6$ 807.3430; found: 807.3409 $(M+H)^+$.
D67	methyl ((1S)-2-((2S)-2-(5-(2-fluoro-4-(5-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-	 Prepared from entry D32 (in lieu of 148e) and *Cap*-	t_R = 1.58 min, (91.1%) LRMS: Anal. Calcd. for $C_{34}H_{40}FN_{10}O_6$ 703.31; found: 703.27 $(M+H)^+$.

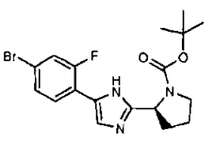
	imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	52 using experimental conditions outlined in Example 148.	HRMS: Anal. Calcd. for $C_{34}H_{40}FN_{10}O_6$ 703.3116; found: 703.3101 $(M+H)^+$.
D68	methyl ((1S)-1-(((2S)-2-(5-(2-fluoro-4-(5-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-pyrimidinyl)phenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 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 $(M+H)^+$.
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)carbamat	 Prepared from entry D32 (in lieu of 148e) and *Cap*-4 using experimental conditions outlined in Example 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 $(M+H)^+$.

	e		
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	 Prepared from entry D32 (in lieu of 148e) and *Cap*-86 using experimental conditions outlined in Example 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.

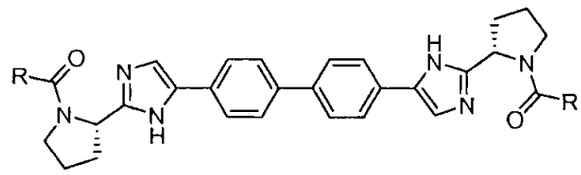
^1H NMR (500 MHz, DMSO-d_6) δ 12.13-11.95 (m, 1H), 7.94 (br s, 1H), 7.54 (d, J = 10.7 Hz, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.36-7.34 (m, 1H), 4.86-4.77 (2m, 1H), 3.54 (m, 1H), 3.38-3.32 (m, 1H), 2.28-2.14 (2m, 1H), 2.05-1.78 (2m, 3H), 1.39 and 1.14 (2s, 9H).

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 $(M+H)^+$.

Examples M1-M27



Example M1-M27 were prepared from 1e and the respective acids using the method described for Example 1. The products were prepared as TFA salts, unless noted otherwise. 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

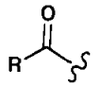
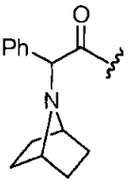
Condition 3

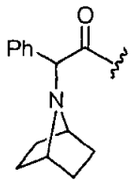
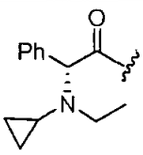
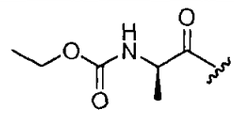
Column = HPLC XTERRA C18 3.0 x 50mm S7
Start %B = 0

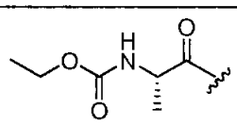
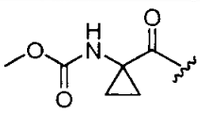
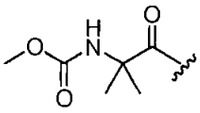
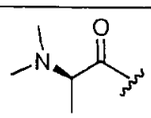
Final %B = 100
Gradient time = 3 min
Stop time = 4 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Slovent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

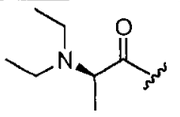
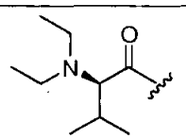
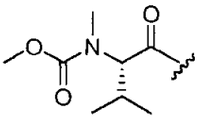
Condition M1

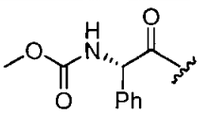
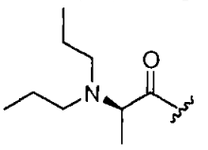
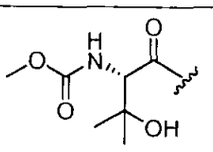
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Final %B = 100
Gradient time = 3 min
Stop time = 4 min
Flow rate = 4 mL/min
Solvent A: = 95% H_20: 5% CH_3CN, 10 mm Ammonium acctate
Solvent B: = 5% H_2O : 95% CH_3CN; 10 mm Ammonium acetate

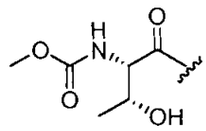
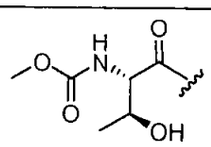
Example	*Compound Name*	 *(Source)*	*RT (LC-Cond.): % homogeneity index: MS data; ^1H NMR data*
M1	7,7'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl(2-oxo-1-phenyl-2,1-ethanediyl)))bis(7-azabicyclo[2.2.1]heptane)	 (*Cap*-77a)	1.04 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{54}H_{59}N_8O_2$: 851.48; found 851.55; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{54}H_{59}N_8O_2$: 851.4761; found 851.4780

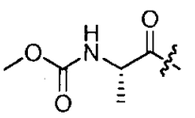
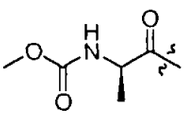
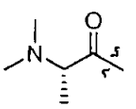
M2	7,7'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl(2-oxo-1-phenyl-2,1-ethanediyl)))bis(7-azabicyclo[2.2.1]heptane)	 (*Cap*-77b)	1.13 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{54}H_{59}N_8O_2$: 851.48; found 851.57; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{54}H_{59}N_8O_2$: 851.4761; found 851.4792
M3	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))bis(N-ethylcyclopropanamine)	 (*Cap*-78)	1.13 min (Cond. 1); >95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{52}H_{59}N_8O_2$: 827.48; found 827.69; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{52}H_{59}N_8O_2$: 827.4761; found 827.4782
M4	ethyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(ethoxycarbonyl)-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-59a)	1.20 min (Cond. 1); >97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.36; found 711.46; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.3619; found 711.3638

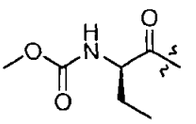
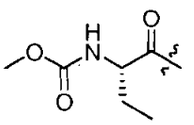
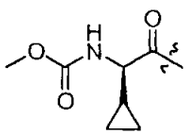
M5	ethyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(ethoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-59b)	1.16 min (Cond. 1); 97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.36; found 711.48; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.3619; found 711.3621
M6	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediylcarbonyl-1,1-cyclopropanediyl))biscarbamate	 (*Cap*-60)	1.12 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{43}N_8O_6$: 707.33; found 707.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{43}N_8O_6$: 707.3306; found 707.3309
M7	methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-(2-((methoxycarbonyl)amino)-2-methylpropanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1,1-dimethyl-2-oxoethyl)carbamate	 (*Cap*-61)	1.21 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.36; found 711.53; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.3619; found 711.3652
M8	(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-		0.91 min (Cond. 1); >80%; LC/MS: Anal. Calcd. for

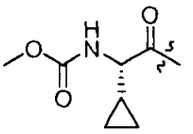
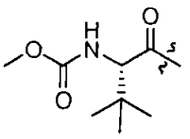
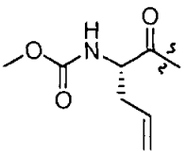
	pyrrolidinediyl))bis(N,N-dimethyl-1-oxo-2-propanamine)	(*Cap*-83)	$[M+H]^+$ $C_{36}H_{47}N_8O_2$: 623.38; found 623.46; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{47}N_8O_2$: 623.3822; found 623.3819
M9	(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-1-oxo-2-propanamine)	 (*Cap*-69a)	1.00 min (Cond. 1); >95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{55}N_8O_2$: 623.38; found 679.67; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{55}N_8O_2$: 679.4448; found 679.4432
M10	(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-3-methyl-1-oxo-2-butanamine)	 (*Cap*-72)	1.03 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{63}N_8O_2$: 735.51; found 735.76; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{63}N_8O_2$: 735.5074; found 735.5060
M11	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)(methyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-	 (*Cap*-62)	1.46 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{55}N_8O_2$: 767.42;

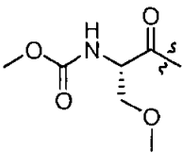
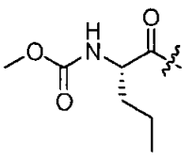
	imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)methylcarbamate		found 767.38; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{55}N_8O_2$: 767.4245; found 767.4252
M12	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 (*Cap*-82)	1.32 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_6$: 807.36; found 807.32; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{47}N_8O_6$: 807.3619; found 807.3651
M13	N,N'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2R)-1-oxo-1,2-propanediyl)))bis(N-propyl-1-propanamine)	 (*Cap*-70a)	1.09 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{63}N_8O_2$: 735.51; found 735.46; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{63}N_8O_2$: 735.5074; found 735.5063
M14	methyl ((1S)-2-hydroxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-	 (*Cap*-65)	1.13 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_8$: 771.38; found 771.21

	imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		
M15	methyl ((1S,2R)-2-hydroxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-hydroxy-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	 (*Cap*-66)	1.10 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_8$: 743.35; found 743.23; ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz), ~14.5 (br s, 4H), 8.15 (s, 2H), 7.97 (d, *J* = 8.5, 4H), 7.89 (d, *J* = 8.4, 4H), 7.10/7.05 (two overlapping d, *J* = 8.0, 8.4, 1.82H), 6.57 (app br s, 0.18H), 5.78 (br d, *J* = 7.9, 0.18H), 5.16 (m, 1.82H), 4.27 (dd, *J* = 8.0, 5.3, 1.82H), 4.10 (m, 0.18H), 3.96-3.81 (m, 6H), 3.55 (s, 5.46H), 3.37 (s, 0.54H), 2.41 (m, 2H), 2.17-2.00 (m, 6H), 1.10 (d, *J* = 6.3, 0.54H), 1.04 (d, *J* = 6.3, 5.46H).
M16	methyl ((1S,2S)-2-hydroxy-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S,3S)-3-hydroxy-2-		1.11 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for

	((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	(*Cap*-67)	$[M+H]^+$ $C_{38}H_{47}N_8O_8$: 743.35; found 743.23
M17	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-52)	1.64 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{43}N_8O_6$: 683.33; found 683.30; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{43}N_8O_6$: 683.3306; found 683.3305.
M18	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-85)	1.70 min (Cond. 2); 97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{43}N_8O_6$: 683.33; found 683.32; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{43}N_8O_6$: 683.3306; found 683.3318.
M19	(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-1-oxo-2-propanamine)	 (*Cap*-13)	1.43 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{47}N_8O_2$: 623.38; found 623.43; HRMS: Anal. Calcd. for $[M+H]^+$

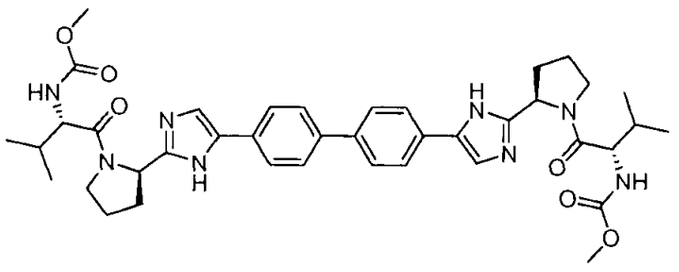
			$C_{36}H_{47}N_8O_2$: 623.3822; found 623.3837.
M20	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2R)-1-oxo-1,2-butanediyl)))biscarbamate	 (*Cap*-53a)	1.82 min (Cond.2); >99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.36; found: 711.35; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.3619; found 711.3649.
M21	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-1-oxo-1,2-butanediyl)))biscarbamate	 (*Cap*-53b)	1.81 min (Cond.2); >99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.36; found 711.35; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.3619; found 711.3643.
M22	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate	 (*Cap*-54a)	1.83 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.36; found 735.44; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.3619; found:

			735.3614.
M23	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate	 (*Cap*-54b)	1.81 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.36; found 735.43; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.3619; found 735.3651.
M24	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate		2.11 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{55}N_8O_6$: 767.42; found 767.58; HRMS: Anal. Calcd. for $C_{42}H_{55}N_8O_6$: 767.4245; found 767.4230.
M25	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((4S)-5-oxo-1-pentene-5,4-diyl)))biscarbamate	 (*Cap*-55)	1.91 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.36; found 735.47; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.3619; found 735.3630.

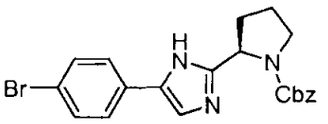
M26	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-seryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(methoxymethyl)-2-oxoethyl)carbamate	 (*Cap*-56)	1.72 min (Cond. 2); 97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_8$: 743.35; found 743.49; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_8$: 743.3517; found 743.3489.
M27	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)pentanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl) carbamate	 (*Cap*-57)	1.98 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.39; found 739.52; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.3932; found 739.3904.

Example M28

methyl ((1S)-1-(((2R)-2-(5-(4'-(2-((2R)-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

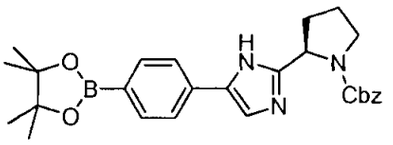


Example M28, Step a



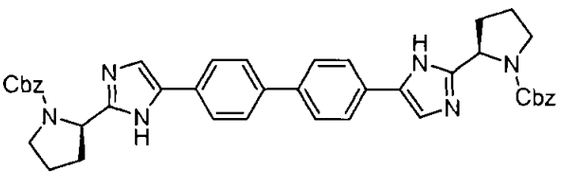
Bromide M28a was prepared from D-Proline according to the procedure described for its enantiomer 28b.

Example M28, Step b



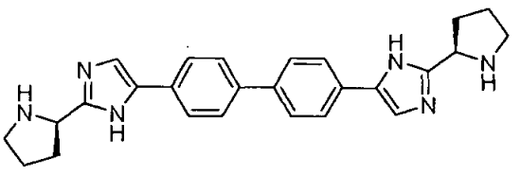
Boronate ester M28b was prepared from bromide M28a according to the procedure described for intermediate 1c. LC: RT = 1.57 min (Cond. 1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{33}BN_3O_4$: 474.26; found 474.24.

Example M28, Step c



Biphenyl M28c was prepared from bromide M28a and boronate M28b according to the procedure described for intermediate 1d. LC: RT = 1.43 min (Cond. 1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_6O_4$: 693.32; found 693.38.

Example M28, Step d



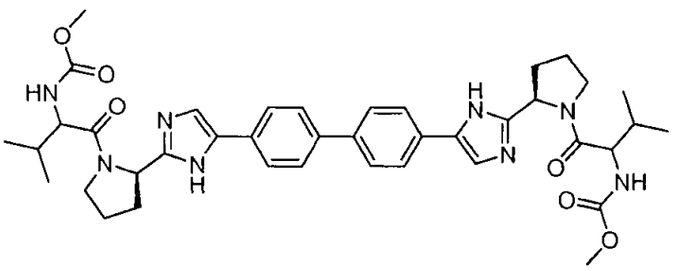
Pyrrolidine M28d was prepared from carbamate M28c according to the procedure described for intermediate 28d. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 11.83 (br s, 2H), 7.80 (d, J = 8.3, 4H), 7.66 (d, J = 8.3, 4H), 7.46 (br s, 2H),

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), 1.82-1.66 (m, 4H). [Note: in the region between 3.2-2.6 ppm there is a broad base-line signal that is believed to be that of the pyrrolidine NH]. LC: RT = 1.02 min (Cond. 1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{29}N_6$: 425.25; found 425.27.

Example M28

Example M28 was prepared as TFA salt from intermediate M28d and *Cap*-51 according to the procedure described for Example 1. LC: RT = 1.33 min (Cond. 1); 96% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.32; found 739.43; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.3932; found 739.3907.

Example M28-1



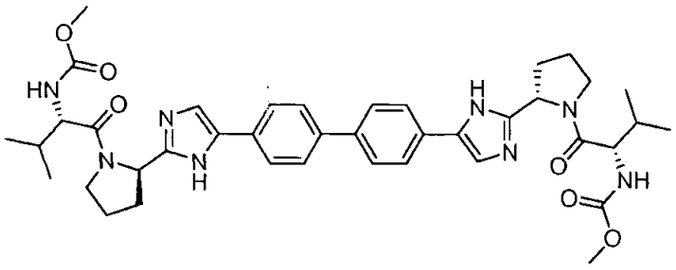
The TFA salt of Example M28-1 was prepared as a mixture of three stereoisomers from intermediate M28d and racemic version of *Cap*-51 according to the procedure described for Example 1. Three peaks with a retention time of 21.74 min, 22.62 min, and 23.40 min, and exhibiting the correct molecular weight, were observed when the sample was analyzed under the following condition:

Waters Acquity HPLC with Micromass ZQ MS (electrospray probe) and Waters 2996 PDA detection. (UV detection @ 315nm)
Column: Acquity UPLC; BEH C18; 1.7um; 100 X 2.1 mm ID; (at approx. 30C)
Mobile phase A: water, 25 mM ammonium acetate at pH=5
Mobile phase B: acetonitrile
Flow rate: 0.50 ml/min
10-50%B 0-35.0 min

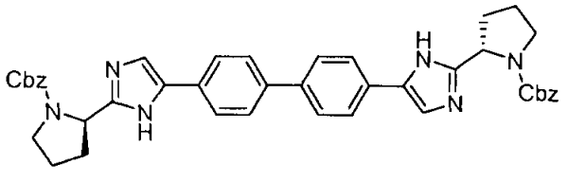
50-98%B	35.0-45.0min
Hold 98%B	45.0-48.0 min
98%B-100%B	48.0-48.5min
Hold 100%B	48.5-50.0min

Example M28-2

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2R)-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

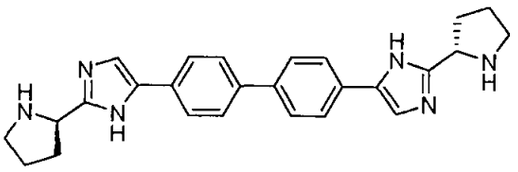


Example M28-2, Step a



Carbamate M28-2a was prepared from boronate ester M28b and bromide 28b according to the procedure described for intermediate 1d. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.25/12.01/11.93 (three br s, 2H), 7.86-6.98 (m, 20H), 5.13-4.88 (m, 6H), 3.63 (m, 2H), 3.47 (m, 2H), 2.35-1.84 (M, 8H). LC: RT = 1.46 min (Cond. 1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{41}N_6O_4$: 693.32; found 693.34.

Example M28-2, Step b

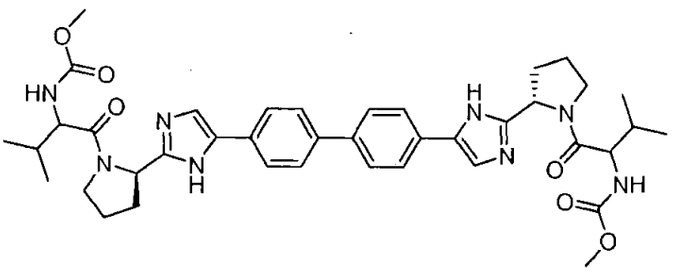


Pyrrolidine M28-2b was prepared from carbamate M28-2a according to the procedure described for intermediate 28d. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 11.84 (br s, 2H), 7.80 (d, J = 8.3, 4H), 7.66 (d, J = 8.3, 4H), 7.46 (br s, 2H), 4.87 (m, 0.05H), 4.16 (app t, J = 7.2, 1.95H), 3.00-2.94 (m, 2H), 2.88-2.82 (m, 2H), 2.10-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.82-1.66 (m, 4H). [Note: in the region between ~3.1-2.6 ppm there is a broad base-line signal that is believed to be that of the pyrrolidine NH]. LC: RT = 0.96 min (Cond. 1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{29}N_6$: 425.25; found 425.28.

Example M28-2

Example M28-2 was prepared as TFA salt from intermediate M28-2b and *Cap*-51 according to the procedure described for Example 1. LC: RT = 1.96 minutes (Cond. 2); 98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_6$ 739.39; found 739.47.

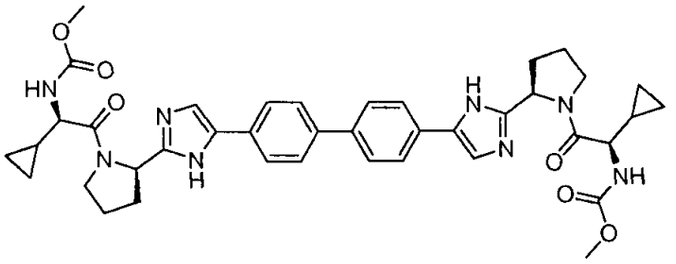
Example M28-3



The TFA salt of Example M28-3 was prepared as a mixture of four stereoisomers from intermediate M28-2b and racemic version of *Cap*-51 according to the procedure described for Example 1. Three peaks with a retention time of 21.28 min, 22.19 min, and 23.01 min, and exhibiting the correct molecular weight, were observed when the sample was analyzed under the LC/MS condition described for Example M28-1.

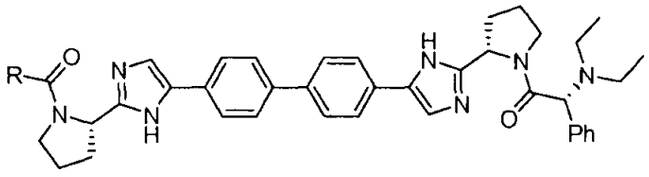
Example M29

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2R)-2,1-pyrrolidinediyl((1R)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate

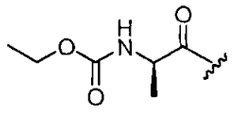


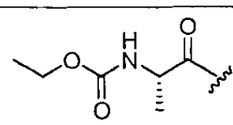
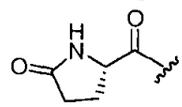
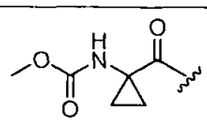
Example M29 was prepared as TFA salt from intermediate M28d and *Cap*-54a according to the procedure described for Example 1. LC: RT = 1.21 min (Cond. 1); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.36; found 735.42; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.3619; found 735.3598.

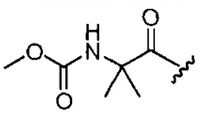
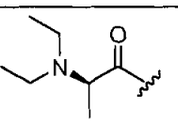
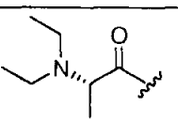
Example M30-M62

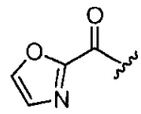
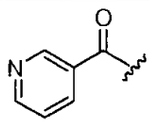
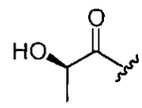


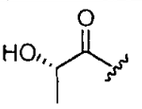
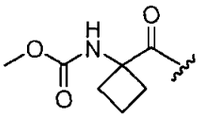
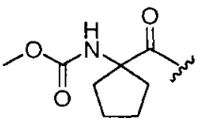
Example M30-M62 were prepared as TFA salts from CJ-24 and the respective caps using the same method described for Example 28.

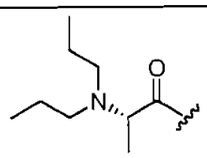
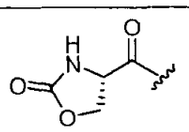
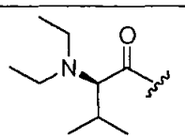
Example	*Compound Name*	 *(Source)*	*RT (LC-Cond.); % homogeneity index; MS data*
M30	ethyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-	 (*Cap*-59a)	1.13 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.42;

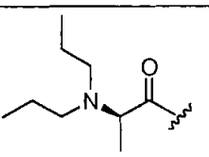
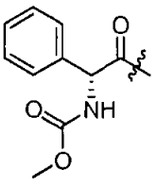
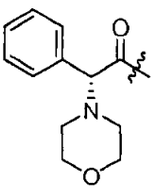
	methyl-2-oxoethyl)carbamate		found 757.50; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.4190; found 757.4181
M31	ethyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-59b)	1.07 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.42; found 757.55; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.4190; found 757.4225
M32	(5S)-5-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-pyrrolidinone		1.02 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_3$: 725.39; found 725.48; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_3$: 725.3928; found 725.3926
M33	methyl (1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopropyl)carbamate	 (*Cap*-60)	1.12 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{51}N_8O_4$: 755.40; found 755.61; HRMS: Anal.

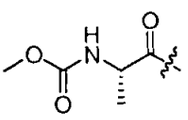
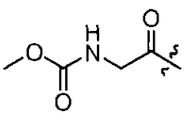
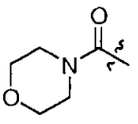
			Calcd. for $[M+H]^+$ $C_{44}H_{51}N_8O_4$: 755.4033; found 755.4066
M34	methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1,1-dimethyl-2-oxoethyl)carbamate	 (*Cap*-61)	1.16 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.42; found 757.63; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.4190; found 757.4164
M35	(2R)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-1-oxo-2-propanamine	 (*Cap*-69a)	1.06 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{57}N_8O_2$: 741.46; found 741.64; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{57}N_8O_2$: 741.4604; found 741.4597
M36	(2S)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-1-oxo-2-propanamine	 (*Cap*-69b)	1.04 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{57}N_8O_2$: 741.46; found 741.63; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{57}N_8O_2$:

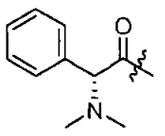
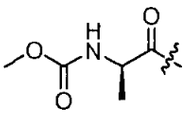
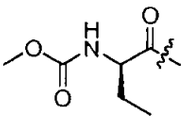
			741.4604; found 741.4581
M37	(1R)-N,N-diethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-2-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine		1.11 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{45}N_8O_3$: 709.36; found 709.51; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{45}N_8O_2$: 709.3615; found 709.3615
M38	(1R)-N,N-diethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-pyridinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine		1.09 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{47}N_8O_2$: 719.38; found 719.51; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{47}N_8O_2$: 719.3822; found 719.3829
M39	(2R)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-propanol		1.09 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{48}N_7O_3$: 686.38; found 686.58; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{48}N_7O_3$: 686.3819; found 686.3843

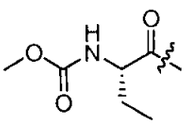
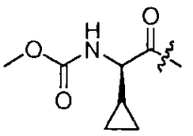
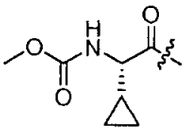
M40	(2S)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-oxo-2-propanol		1.09 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{48}N_7O_3$: 686.38; found 686.57; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{48}N_7O_3$: 686.3819; found 686.3832
M41	methyl (1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclobutyl) carbamate	 (*Cap*-64)	1.19 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 769.42; found 769.66; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 769.419; found 769.4155
M42	methyl (1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)cyclopentyl)carbamate	 (*Cap*-63)	1.25 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{55}N_8O_4$: 783.43; found 783.69; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{55}N_8O_4$: 783.4346; found 783.4357

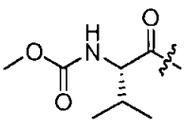
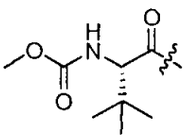
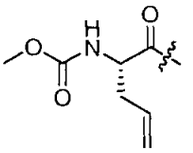
M43	N-((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)-N-propyl-1-propanamine	 (*Cap*-70b)	1.10 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{61}N_8O_2$: 769.49; found 769.69; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{61}N_8O_2$: 769.4917; found 769.4925
M44	(4S)-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-1,3-oxazolidin-2-one	 (*Cap*-81)	1.08 min (Cond.1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.37; found 727.56; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.3720; found 727.3740
M45	(2R)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-3-methyl-1-oxo-2-butanamine	 (*Cap*-72)	1.08 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{61}N_8O_2$: 769.49; found 769.73; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{61}N_8O_2$: 769.4917; found 769.4898

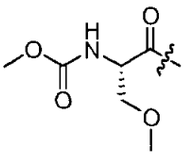
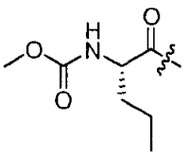
M46	N-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)-N-propyl-1-propanamine	 (*Cap*-70a)	1.12 min (Cond.1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{61}N_8O_2$: 769.49; found 769.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{61}N_8O_2$: 769.4917; found 769.4915
M47	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 (*Cap*-4)	1.85 min (Cond.2); 97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{53}N_8O_4$: 805.42; found 805.4; HRMS: Anal. Calcd. for $[M+H]^+$: $C_{48}H_{53}N_8O_4$ 805.4190; found 805.4196.
M48	(1R)-N,N-diethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(4-morpholinyl)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine	 (*Cap*-6)	1.69 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{57}N_8O_3$: 817.45; found 817.48; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{57}N_8O_3$: 817.4554; found 817.4589.

M49	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-52)	1.67 min (Cond. 2); 92%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.40; found 743.42; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.4033; found 743.4053.
M50	methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		1.63 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{49}N_8O_4$: 729.39; found 729.39; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{49}N_8O_4$: 729.3877; found 729.3888.
M51	(1R)-N,N-diethyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morpholinylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethanamine		1.67 min (Cond.2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_3$: 727.41; found 727.40; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_3$: 727.4084; found

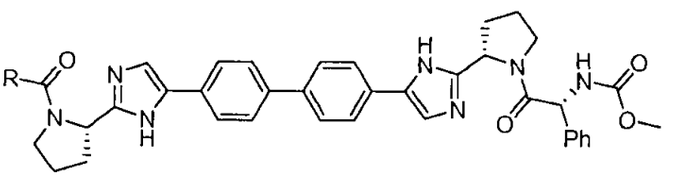
			727.4117.
M52	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine	 (*Cap*-1)	1.65 min (Cond. 2); 92%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{55}N_8O_2$: 775.44; found 775.48; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{55}N_8O_2$: 775.4448; found 775.4433.
M53	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-85)	1.68 min (Cond.2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.40; found 743.42; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.4033; found 743.4055.
M54	methyl ((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	 (*Cap*-53a)	1.78 min; (Cond. 2); >99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.42; found 757.42; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$:

			757.4190; found 757.4216.
M55	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate	 (*Cap*-53b)	1.74 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.42; found 757.41; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.4190; found 757.4212 .
M56	methyl ((1R)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 (*Cap*-54a)	1.74 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 769.42; found 769.52; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 769.4190; found 769.4188 .
M57	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 (*Cap*-54b)	1.72 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 769.42; found 769.53; HRMS: Anal. Calcd. for $[M+H]^+$

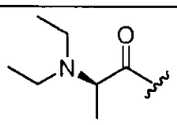
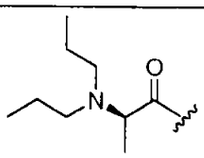
			$C_{45}H_{53}N_8O_4$: 769.4190; found 769.4218.
M58	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-51)	1.76 min (Cond. 2); >99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{55}N_8O_4$: 771.43; found 771.54; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 771.4346; found 771.4379.
M59	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate		1.92 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{57}N_8O_6$: 785.45; found 785.63; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{57}N_8O_4$: 785.4503; found 785.4515.
M60	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-buten-1-yl)carbamate	 (*Cap*-55)	1.81 min (Cond.2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 769.42; found 769.55; HRMS: Anal. Calcd. for

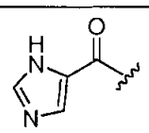
			$[M+H]^+$ $C_{45}H_{53}N_8O_4$: 769.4190; found 769.4157.
M61	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(methoxymethyl)-2-oxoethyl)carbamate	 (*Cap*-56)	1.73 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_5$: 773.41; found 773.55; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_5$: 773.4139; found 773.4107.
M62	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl)carbamate	 (*Cap*-57)	1.73 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{55}N_8O_4$: 771.43; found 771.56 $(M+H)^+$; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{55}N_8O_4$: 771.4346; found 771.4315.

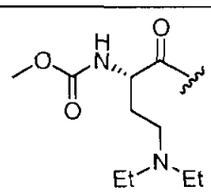
Example M63-M66

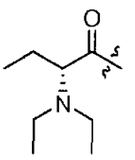


Example M63-M66x were prepared from 28f and the respective acids using the method described for Example 28. Products were prepared as TFA salts unless noted otherwise.

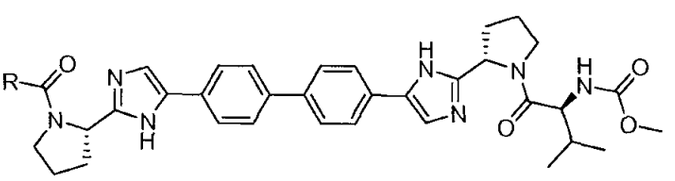
Example	*Compound Name*	 *(Source)*	*RT (LC-Cond.): % homogeneity index; MS data*
M63	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 (*Cap*-69a)	1.17 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.40; found 743.41; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.4033; found 743.4017
M64	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 (*Cap*-70a)	1.22 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for

			$[M+H]^+$ $C_{45}H_{55}N_8O_4$: 771.43; found 771.39; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{55}N_8O_4$: 771.4346; found 771.4361
M65	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-5-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.15 min (Cond. 1); >90%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{40}N_9O_4$: 710.32; found 710.31; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{40}N_9O_4$: 710.3203; found 710.3180

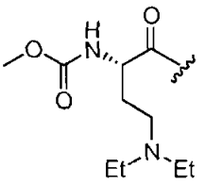
M66a & M66b	M66a: methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(diethylamino)-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate	 (*Cap*-76)	Two fractions enriched with one of two compounds exhibiting very similar spectral data were isolated. M66a: 1.19 min (Cond. 1); 97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{56}N_9O_6$: 830.44; found 830.39 M66b: 1.21 min (Cond. 1); >97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{56}N_9O_6$: 830.44; found 830.39;

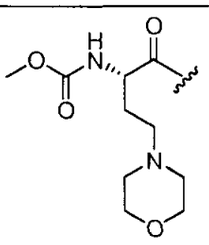
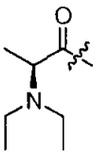
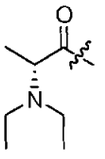
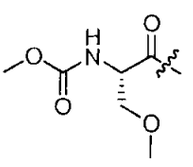
			HRMS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{56}N_9O_6$: 830.4354; found 830.4316
M66x (AcOH)	methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		1.80 minutes (Cond.2); (98%); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$ 757.42; found 757.48; HRMS: Anal. Calcd for $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.4190; found 757.4156

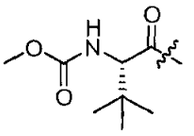
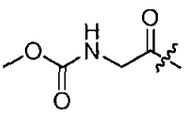
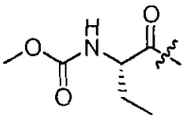
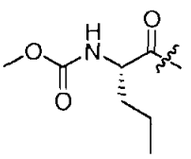
Example M67-M91

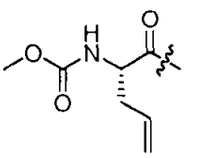
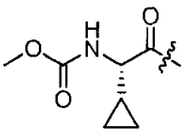
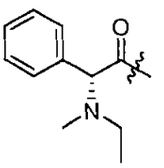
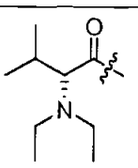


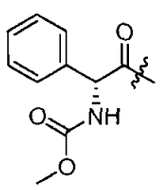
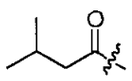
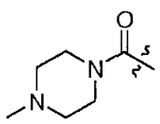
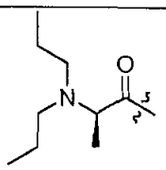
Example M67-M91y were prepared from 28d and the respective acids using the method described for Example 28. Final products were prepared as TFA salts, unless noted otherwise.

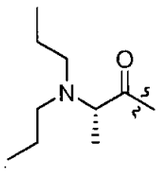
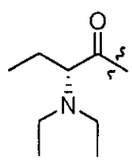
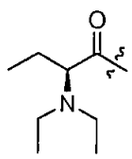
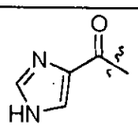
Example	*Compound Name*	 *(Source)*	*RT (LC-Cond.); % homogeneity index; MS data*
M67a & M67b	M67a: methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(4-(diethylamino)-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-76)	Two fractions enriched with one of two compounds exhibiting very similar spectral data were isolated M67a: 1.16 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{58}N_9O_6$: 796.45; found 796.40 M67b: 1.17 min (Cond. 1); >96%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{58}N_9O_6$: 796.45; found 796.40; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{58}N_9O_6$: 796.4510; found 796.4537

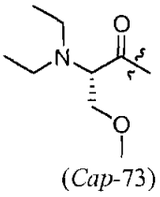
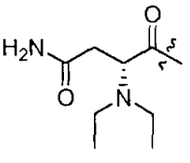
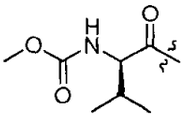
M68 (.AcOH)	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-(4-morpholinyl)propyl)carbamate	 (*Cap*-79)	1.10 min (Cond. 1); >96%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{56}N_9O_7$: 810.43; found 810.44; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{56}N_9O_7$: 810.4303; found 810.4333
M69	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-69b)	1.72 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{53}N_8O_4$: 709.42; found 709.56; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{53}N_8O_4$: 709.4190; found 709.4219.
M70	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-69a)	1.75 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{53}N_8O_4$: 709.42; found 709.55; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{53}N_8O_4$: 709.4190; found 709.4184.
M71	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-	 (*Cap*-56)	1.81 min (Cond. 2); 97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{49}N_8O_7$: 741.37; found 741.48; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{49}N_8O_7$:

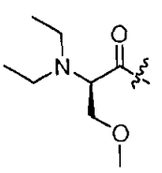
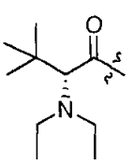
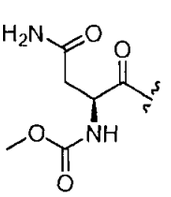
	(methoxymethyl)-2-oxoethyl)carbamate		741.3724; found 741.3738.
M72	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		2.07 min (Cond. 2); 97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{53}N_8O_6$: 753.41; found 753.53; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{53}N_8O_6$: 753.4088; found 753.4111.
M73	methyl (2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		1.80 min (Cond. 2); 97%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{45}N_8O_6$: 697.35; found 697.32; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{45}N_8O_6$: 697.3462; found 697.3443.
M74	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-53b)	1.90 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{49}N_8O_6$: 725.37; found 725.36; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{49}N_8O_6$: 725.3775; found 725.3742.
M75	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-	 (*Cap*-57)	1.96 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.39; found 739.37; HRMS: Anal. Calcd. for

	imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl) carbamate		$[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.3932; found 739.3953.
M76	methyl ((1S)-1-(((2S)-2-(5-(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)-3-buten-1-yl)carbamate	 (*Cap*-55)	1.91 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{49}N_8O_6$: 737.38; found 737.38; HRMS: Anal. Calcd. $C_{40}H_{49}N_8O_6$: 737.3775; found 737.3744.
M77	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-54b)	1.90 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{49}N_8O_6$ 737.38; found 737.34; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{49}N_8O_6$ 737.3775; found 737.3764.
M78	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(ethyl(methyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-3)	1.82 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$ 757.42; found 757.42; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{53}N_8O_4$ 757.4190; found 757.4188.
M79	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-	 (*Cap*-72)	1.78 min (Cond. 2); 94%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{57}N_8O_4$ 737.45; found 737.45; HRMS:

	yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		Anal. Calcd. for $[M+H]^+$ $C_{42}H_{57}N_8O_4$ 737.4503; found 737.4488.
M80	methyl ((1S)-1-(((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-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-4)	2.05 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_6$ 773.37; found 773.40; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{49}N_8O_6$ 773.375; found: 773.3759.
M81	methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		2.05 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{48}N_7O_4$ 666.38; found 666.37; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{48}N_7O_4$ 666.3768; found 666.3785.
M82	methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-((4-methyl-1-piperazinyl)carbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		1.75 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{50}N_9O_4$ 708.40; found 708.38; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{50}N_9O_4$ 708.3986; found 708.3974.
M83	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-		1.81 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{57}N_8O_4$ 737.45;

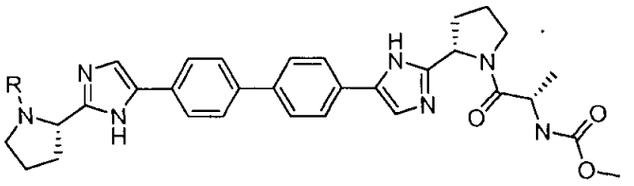
	yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	(*Cap*-70a)	found 737.47; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{57}N_8O_4$ 737.4503; found 737.4480.
M84	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-70b)	1.78 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{57}N_8O_4$ 737.45; found 737.47; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{57}N_8O_4$ 737.4503; found 737.4491 .
M85	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-71a)	1.76 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{55}N_8O_4$ 723.43; found 723.47; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{55}N_8O_4$ 723.4346; found 723.4335 .
M86	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(diethylamino)butanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-71b)	1.73 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{55}N_8O_4$ 723.43; found 723.47; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{55}N_8O_4$ 723.4346; found 723.4343.
M87	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-4-ylcarbonyl)-2-		1.67 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$

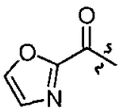
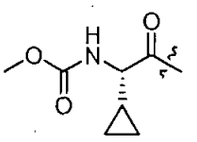
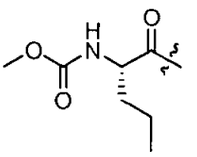
	pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		$C_{37}H_{42}N_9O_4$ 676.34; found 676.45; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{42}N_9O_4$ 676.3360; found 676.3344.
M88	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-O-methyl-L-seryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-73)	1.67 min (Cond. 2); 97%; LCMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{55}N_8O_5$ 739.43; found 739.54; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{55}N_8O_5$ 739.4295; found 739.4327.
M89	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N^2,N^2-diethyl-D-asparaginyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-74)	1.76 min (Cond. 2); 97%; LCMS: Anal. Calcd. for for $[M+H]^+$ $C_{41}H_{54}N_9O_5$ 752.42; found 752.43; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{54}N_9O_5$ 752.4248; found 752.4263.
M90	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2R)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-84)	2.00 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_6$ 739.39; found 739.46; HRMS: Anal. Calcd for $[M+H]^+$ $C_{40}H_{51}N_8O_6$ 739.3932; found 739.3901.

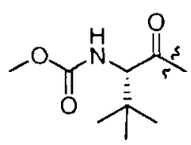
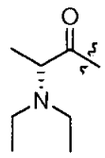
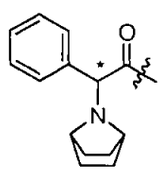
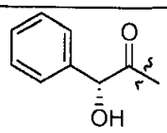
M91	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-O-methyl-D-seryl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-75)	1.73 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{55}N_8O_5$ 739.43; found 739.39; HRMS: Anal. Calcd for $[M+H]^+$ $C_{41}H_{55}N_8O_5$ 739.4295; found 739.4277.
M91x	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-3-methyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		1.78 minutes (Cond. 2); (97%); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{43}H_{59}N_8O_4$ 751.47; found 751.50; HRMS: Anal. Calcd for $[M+H]^+$ $C_{43}H_{59}N_8O_4$: 751.4659; found: 751.4648.
M91y	methyl ((1S)-3-amino-1-(((2S)-2-(5-(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)-3-oxopropyl)carbamate (non-preferred name)	 (*Cap*-58)	1.92 min (Cond. 2); (>97%); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{48}N_9O_7$ 754.37; found 754.42; HRMS: Anal. Calcd for $[M+H]^+$ $C_{39}H_{48}N_9O_7$: 754.3677; found: 754.3676.

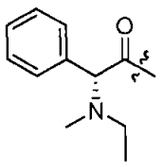
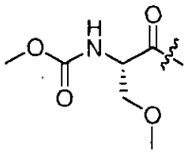
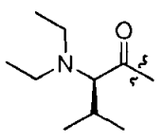
Example M92-M103

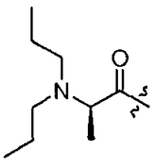
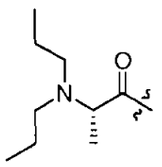
Example M92-M103 were prepared from 28d and the respective acids using the method described for Example 28. Final products were prepared as TFA salts, unless noted otherwise.



Example	*Compound Name*	*R (Source)*	*Analytical Data*
M92	methyl ((1S)-1-methyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-2-ylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate		1.70 min (Cond. 2); 95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{37}N_8O_5$ 649.29; found 649.41; HRMS: Anal. Calcd for $[M+H]^+$ $C_{35}H_{37}N_8O_5$ 649.2887; found 649.2867
M93	methyl ((1S)-1-cyclopropyl-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxoethyl)carbamate	 (*Cap*-54b)	1.76 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{45}N_8O_6$ 709.35; found 709.50; HRMS: Anal. Calcd for $[M+H]^+$ $C_{38}H_{45}N_8O_6$ 709.3462; found 709.3478
M94	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)propanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)butyl)carbamate	 (*Cap*-57)	1.84 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_6$ 711.36; found 711.54; HRMS: Anal. Calcd for $[M+H]^+$ $C_{38}H_{47}N_8O_6$

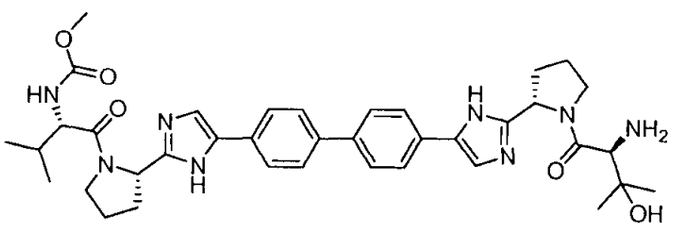
			711.3619; found 711.3590.
M95	methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate		1.91 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{49}N_8O_6$ 725.37; found 725.54; HRMS: Anal. Calcd for $[M+H]^+$ $C_{39}H_{49}N_8O_6$ 725.3775; found 725.3809.
M96	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-69a)	1.61 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{49}N_8O_4$ 681.39; found 681.54; HRMS: Anal. Calcd for $[M+H]^+$ $C_{38}H_{49}N_8O_4$ 681.3877; found 681.3867.
M97	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(7-azabicyclo[2.2.1]hept-7-yl(phenyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-77b)	1.72 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{51}N_8O_4$ 767.40; found 767.59; HRMS: Anal. Calcd for $[M+H]^+$ $C_{45}H_{51}N_8O_4$ 767.4033; found 767.4067.
M98	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hydroxy-2-phenylacetyl)-2-pyrrolidinyl)-		1.80 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$

	1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate		$C_{39}H_{42}N_7O_5$ 688.32; found 688.48; HRMS: Anal. Calcd for $[M+H]^+$ $C_{39}H_{42}N_7O_5$ 688.3247; found 688.3263.
M99	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(ethyl(methyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-3)	1.70 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{49}N_8O_4$ 729.39; found 729.56; HRMS: Anal. Calcd for $[M+H]^+$ $C_{42}H_{49}N_8O_4$ 729.3877; found 729.3887.
M100	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-(methoxymethyl)-2-oxoethyl)carbamate	 (*Cap*-56)	1.75 min (Cond. 2); 99%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{45}N_8O_7$ 713.34; found 713.34; HRMS: Anal. Calcd for $[M+H]^+$ $C_{37}H_{45}N_8O_7$ 713.3411; found 713.3386.
M101	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diethyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-72)	1.66 min (Cond. 2); 94%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{53}N_8O_4$ 709.42; found: 709.42; HRMS: Anal. Calcd for $[M+H]^+$ $C_{40}H_{53}N_8O_4$

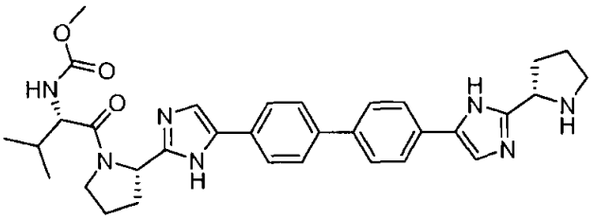
			709.4190; found 709.4166.
M102	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-D-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-70a)	1.71 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{53}N_8O_4$ 709.42; found 709.48; HRMS: Anal. Calcd for $[M+H]^+$ $C_{40}H_{53}N_8O_4$ 709.4190; found 709.4191.
M103	methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropyl-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-70b)	1.66 min (Cond. 2); 98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{53}N_8O_4$ 709.42; found 709.42; HRMS: Anal. Calcd for $[M+H]^+$ $C_{40}H_{53}N_8O_4$ 709.4190; found 709.4198.

Example M104

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(3-hydroxy-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate



Example M104, Step a



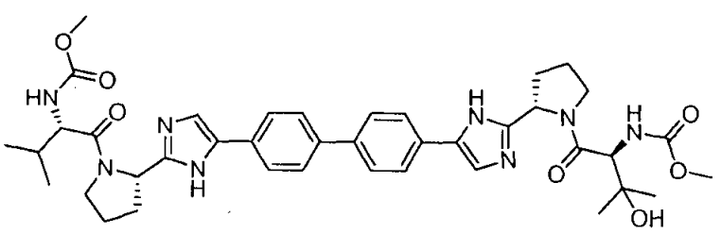
Pyrrolidine M104a was prepared from intermediate 28d and *Cap*-51 according to the procedure described for the synthesis of pyrrolidine 28f.

Example M104

HATU (96.3 mg, 0.253 mmol) was added to a DMF (5.0 mL) solution of pyrrolidine M104a (150 mg, 0.217 mmol), (S)-2-(tert-butoxycarbonylamino)-3-hydroxy-3-methylbutanoic acid (65.8 mg, 0.282 mmol) and *i*-Pr_2EtN (180 uL, 1.03 mmol), and the reaction mixture was stirred at ambient condition for 35 min. The volatile component was removed *in vacuo*, and the residue was purified with a reverse phase HPLC ($MeOH/H_2O/TFA$), and the fractions were concentrated *in vacuo*. The resultant residue was treated with 25% TFA/CH_2Cl_2 (6.0 mL) and stirred for 3.25 hr. 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 Example M104 as an off-white foam (107 mg). LC (Cond. 2): RT = 1.03 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{49}N_8O_5$ = 697.38; found 697.28.

Example M105

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

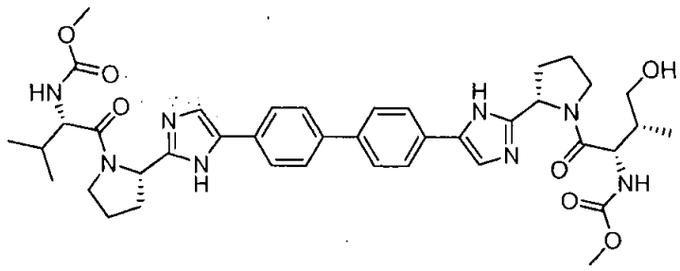


Methyl chloroformate (20 µL, 0.258 mmol) was added to a THF (2.0 mL) solution of Example M104 (82.9 mg, 0.119 mmol) and *i*-Pr_2EtN (50 uL, 0.287 mmol)

and stirred for 65 min. The mixture was then treated with 2.0 M NH_3/MeOH (3 mL), stirred for 2.75 hr, and the volatile component was removed *in vacuo*. The resultant residue was purified with a reverse phase HPLC (MeOH/H_2O/TFA) to afford the TFA salt of Example M105 as a white foam (64.1 mg). LC (Cond. 2): RT = 1.17 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_7$ = 755.39; found 755.25.

Example M106

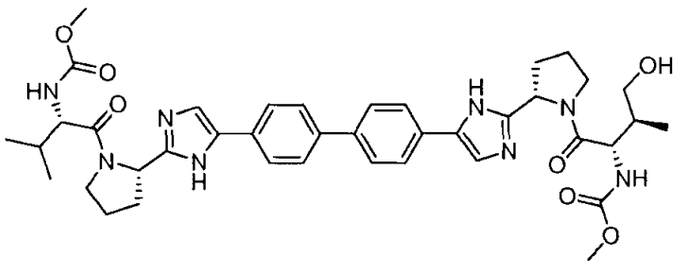
methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-4-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate



HATU (69 mg, 0.181 mmol) was added to a DMF (3.0 mL) solution of pyrrolidine M104a (101 mg, 0.173 mmol), *Cap*-80b (55.9 mg, ~0.183 mmol) and *i*-Pr_2EtN (90 µL, 0.515 mmol), and the reaction mixture was stirred at ambient condition for 70 min. The volatile component was removed *in vacuo* and the residue was purified with a reverse phase HPLC (H_2O/MeOH/TFA) to retrieve the dominant signal. The collected fraction was allowed to stand at ambient condition for a few hours and then the volatile component was removed *in vacuo*, at which time total desilylation of the coupled product was achieved. The resultant product was submitted to a reverse phase HPLC purification (ACN/H_2O/NH_4OAc) to afford Example M106 as an off-white foam (32.2 mg). LC (Cond. 2): RT = 1.19 min; >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_7$ = 755.39; found 755.85.

Example M107

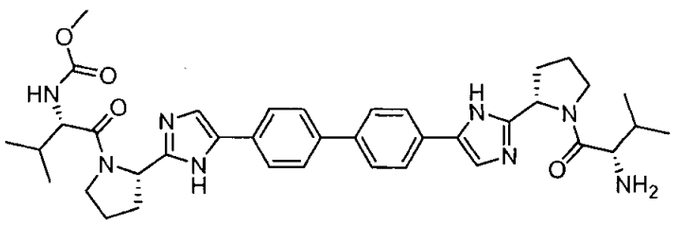
methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S,3S)-4-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate



Example M107 was prepared from pyrrolidine M104a and *Cap*-80a according to the procedure described for the synthesis of Example M106. LC (Cond. 2): RT = 1.20 min; ~95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_7$ = 755.39; found 755.78.

Example M108

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-L-valyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate



HATU (70.1 mg, 0.184 mmol) was added to a DMF (3.0 mL) solution of pyrrolidine M104a (100.7 mg, 0.173 mmol), (L)-Boc-Valine (49.6 mg, 0.228 mmol) and *i*-Pr_2EtN (70 uL, 0.40 mmol), and the reaction mixture was stirred at ambient condition for 65 min. The volatile component was removed *in vacuo* and the residue was purified with a Biotage (60-100% EtOAc/hexanes) to afford 116.6 mg of the coupled product.

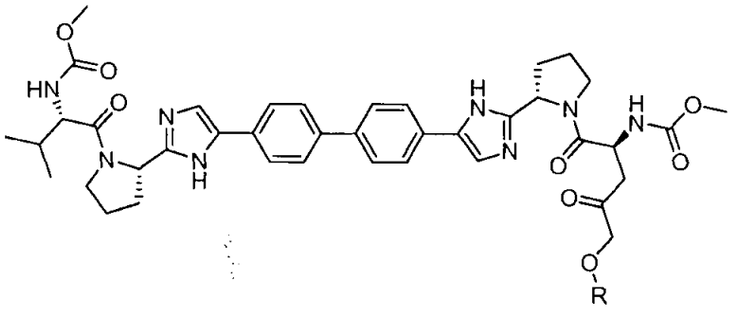
The above product (112 mg) was treated with 25% TFA/CH_2Cl_2 (2 mL) and the reaction mixture was stirred for 6 hr. The volatile component was removed *in vacuo* and the crude material was purified with a combination of MCX resin (MeOH wash; 2.0 M NH_3/MeOH elution) and reverse phase HPLC (H_2O/MeOH/TFA) to

afford the TFA salt of Example M108 as a white foam (98.5 mg). LC (Cond. 2): RT = 1.14 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{49}N_8O_4$ = 681.39; found 681.36. HRMS Calcd. for $[M+H]^+$ $C_{38}H_{49}N_8O_4$: 681.3877; found 681.3865.

Example M109 (R = Bn) & M110 (R = Me)

M109: benzyl (3S)-3-((methoxycarbonyl)amino)-4-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-4-oxobutanoate

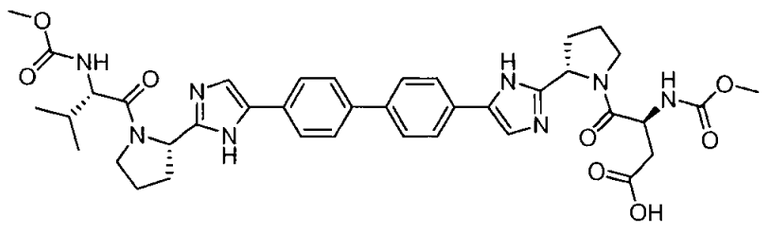
M110: methyl (3S)-3-((methoxycarbonyl)amino)-4-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-4-oxobutanoate



HATU (109 mg, 0.287 mmol) was added to DMF (1.5 ml) solution of pyrrolidine M104a (151 mg, 0.260 mmol), *Cap*-68 (109 mg, 387 mmol), and *i*-Pr_2EtN (100 µl, 0.574 mmol), and the reaction mixture was stirred at ambient condition for 3 hr. The volatile component was removed *in vacuo* and crude material was purified with a combination of MCX resin (MeOH wash; 2.0 M NH_3/MeOH elution) and reverse phase HPLC (H_2O/MeOH/TFA) to afford the TFA salt Example M109 (88.0 mg) and Example M110 (90.2 mg). Example M109: LC (Cond. 2): RT = 2.16; 97% homogenity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{53}N_8O_8$: 845.40; found 845.51. HRMS Calcd. for $[M+H]^+$ $C_{46}H_{53}N_8O_8$: 845.3986; found 845.3983. Example M110: LC (Cond. 2): RT = 1.92; 97% homogenity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{49}N_8O_4$: 769.47; found 769.46. HRMS Calcd. for $[M+H]^+$ $C_{40}H_{49}N_8O_4$: 769.3673; found 769.3682.

Example M111

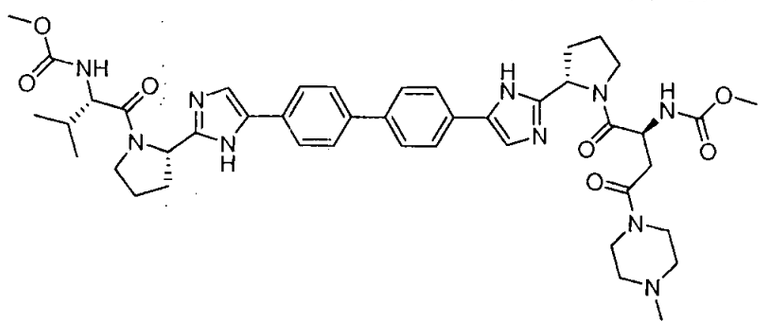
(3S)-3-((methoxycarbonyl)amino)-4-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-4-oxobutanoic acid



A mixture of Example M109 (69.7 mg, 0.082 mmol) and 10% Pd/C (10 mg) in methanol (5 ml) was stirred at room temperature under a balloon of H_2 for 1.5 h. The reaction was filtered through diatomaceous earth (Celite®) and concentrated *in vacuo*, and the resultant material was purified with a reverse phase HPLC (H_2O/MeOH/TFA) to afford the TFA salt of Example M111 as an off-white foam (54.0 mg). LC (Cond. 2): RT = 1.18; 99% homogenity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{39}H_{47}N_8O_8$: 755.35; found 755.32. HRMS Calcd. for $[M+H]^+$ $C_{39}H_{47}N_8O_8$: 755.3517; found 755.3525.

Example M112

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-4-(4-methyl-1-piperazinyl)-4-oxobutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

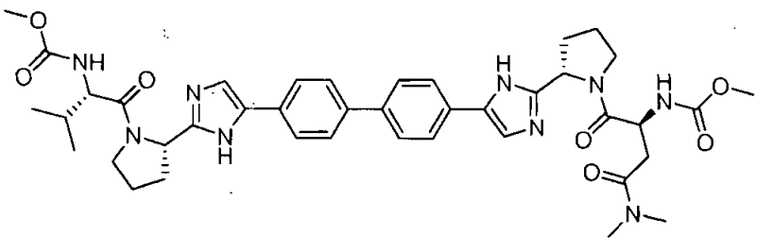


HATU (30.6 mg, 0.080 mmol) was added to a DMF (1.5 ml) solution of Example M111 (55.3 mg, 0.0733 mmol), *N*-methyl piperazine (11.0 mg, 0.11 mmol) and *i*-Pr_2EtN (25 µl, 0.14 mmol), and the reaction mixture was stirred at ambient

condition for 1.5 h. All volatile components were removed *in vacuo*, and the residue was purified with a combination of MCX resin and a reverse phase HPLC (H_2O/MeOH/TFA) to afford the TFA salt of Example M112 as an off-white foam (51.4 mg). LC (Cond. 2): RT = 1.75; 91% homogenity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{57}N_{10}O_7$: 837.44; found 837.59. HRMS Calcd. for $[M+H]^+$ $C_{44}H_{57}N_{10}O_7$: 837.4412; found 837.4453.

Example M113

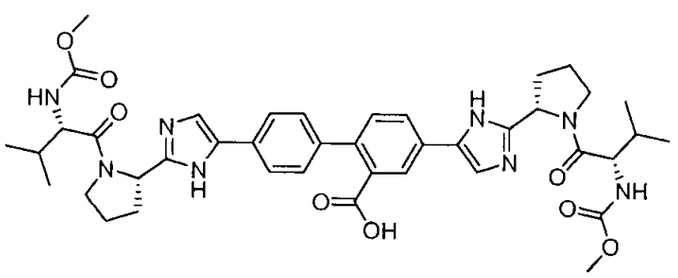
methyl ((1S)-3-(dimethylamino)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-3-oxopropyl)carbamate



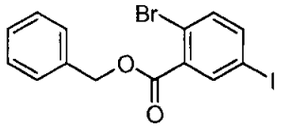
Example M118 was prepared from Example M111 and $Me_2N.HCl$ according to the procedure described for Example M112. LC (Cond. 2): RT = 1.89; 99% homogenity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{52}N_9O_7$: 782.40; found 782.47. HRMS Calcd. for $[M+H]^+$ $C_{41}H_{52}N_9O_7$: 782.3990; found 782.4008.

Example M114

4,4'-bis(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-biphenylcarboxylic acid

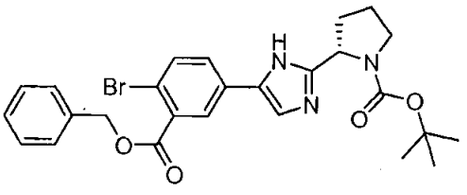


Example M114, Step a



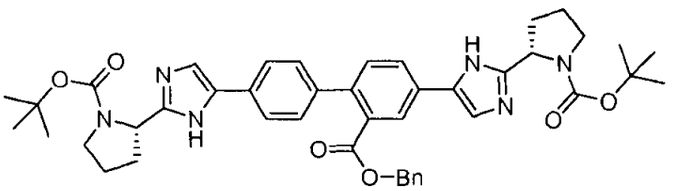
DMF (20 mL) was added to mixture of $KHCO_3$ (1.84g, 18.4 mmol) and 2-bromo-5-iodobenzoic acid (4.99 g, 15.3 mmol) and the resulting mixture was stirred for 15 min. Benzyl bromide (2.4 mL, 20.2 mmol) was added drop-wise over 5 min and stirring was continued at ambient condition for ~20 hr. Most of the 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



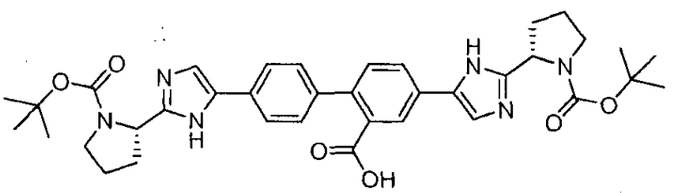
Ester M114a was elaborated to ester M114d by employing a three step protocol employed in the synthesis of bromide 121c from 1-bromo-4-iodo-2-methylbenzene. M114d: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.04/11.97 (br s, 1H), 8.12 (d, J = 2.0, 0.92H), 7.99 (app br s, 0.08H), 7.81 (dd, J = 8.3, 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



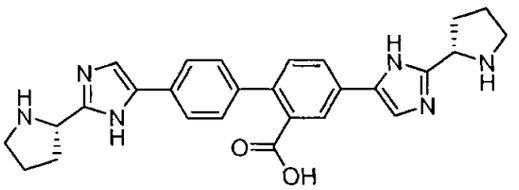
Ester M114e was prepared from bromide M114d and boronate 1c according to the preparation of dimer 1d. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.18/12.00/11.91/11.83 (four br s, 2H), 8.11-7.03 (m, 14H), 5.10 (s, 2H), 4.85-4.78 (m, 2H), 3.55 (app br s, 2H), 3.37 (m, 2H), 2.29-1.80 (m, 8H), 1.41/1.16 (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



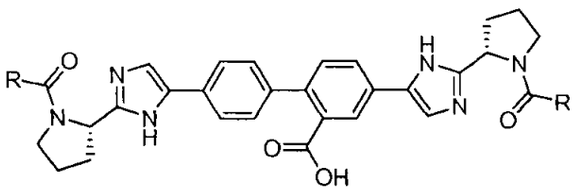
4N HCl/dioxane (8.0 mL) and CH_2Cl_2 (2.0 mL) were sequentially added to carbamate M114f (417 mg, 0.623 mmol), the mixture was vigorously stirred 5.5 hr, and then the volatile component was removed *in vacuo* to afford the HCl (.4x) salt of pyrrolidine M114g (487 mg), contaminated with Ph_3PO impurity. ^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.

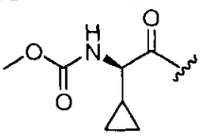
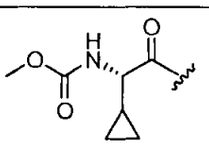
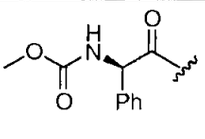
Example M114

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 M115-M116

Examples M115-M116 were prepared using the same method as described for Example M114 and by substituting the appropriate acids for *Cap*-51. The products were isolated as either the acetic acid or TFA salt depending on the nature of the mobile phase of the HPLC purification step.

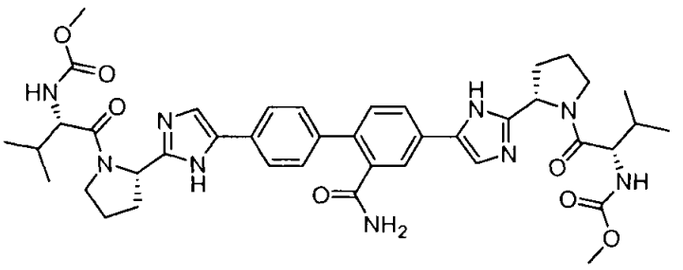


Example	*Compound Name*	 *(Source)*	*RT (LC-Cond.); % homogeneity index; MS data*
M115 (AcOH)	4,4'-bis(2-((2S)-1-((2R)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-biphenylcarboxylic acid	 (*Cap*-54a)	1.17 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_8$: 779.35; found 779.33; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_8$: 779.3517; found 779.3498
M116 (2.TFA)	4,4'-bis(2-((2S)-1-((2S)-2-cyclopropyl-2-((methoxycarbonyl)amino)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-biphenylcarboxylic acid	 (*Cap*-54b)	1.13 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_8$: 779.35; found 779.33; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{47}N_8O_8$: 779.3517; found 779.3551
M117 (2.TFA)	4,4'-bis(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-2-biphenylcarboxylic acid	 (*Cap*-4)	1.29 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{47}N_8O_8$: 851.35; found 851.33; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{47}H_{47}N_8O_8$: 851.3517; found

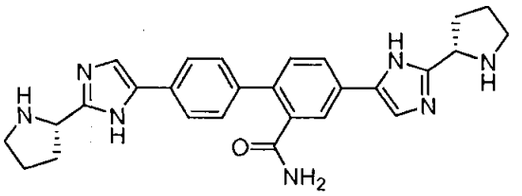
			851.3480

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;

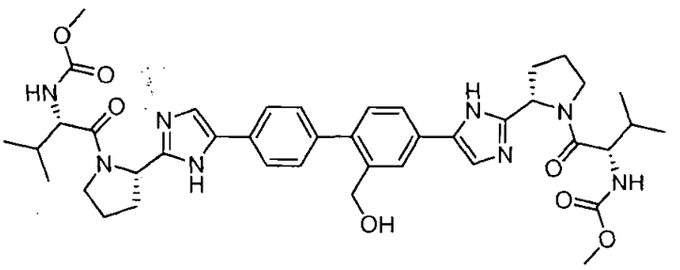
>95 homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{27}H_{30}N_7O$: 468.25; found 468.24.

Example M118

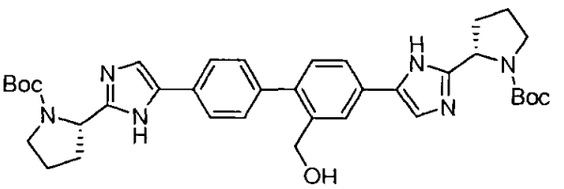
The TFA salt of Example M118 was prepared from intermediate M118a and *Cap*-51 according to the procedure described for Example 1. LC (Cond. 1): RT = 1.16 min; 97% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{52}N_9O_7$: 782.40; found 782.40. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{52}N_9O_7$: 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



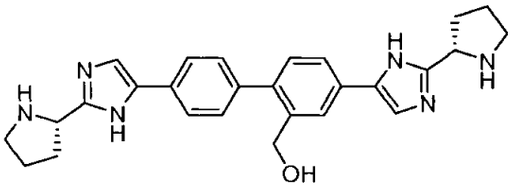
Example M119, step a



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). ^{1}H 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, 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.

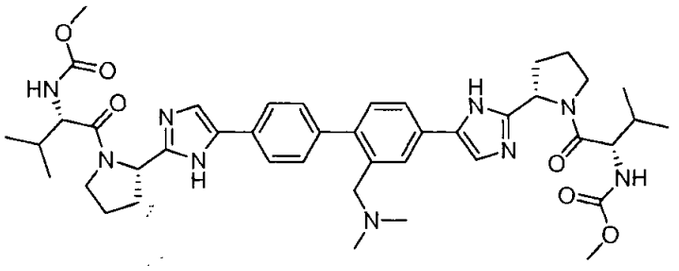
Example M119

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

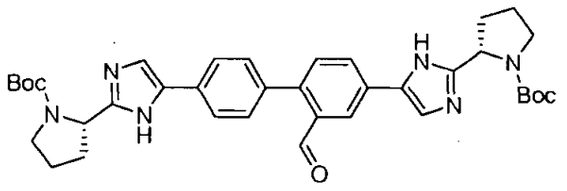
with ACN/H_2O/NH_4OAC solvent system was employed for the purification step. LC (Cond. 1): RT = 1.15 min; 98% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{53}N_8O_7$: 769.40; found 769.40. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{41}H_{53}N_8O_7$: 769.4037; found 769.4023.

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

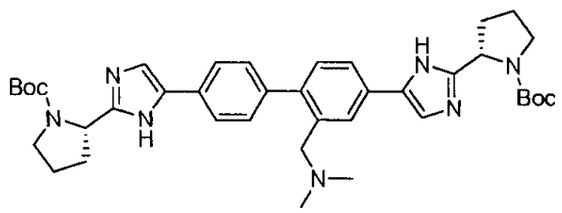


Example M120, step a



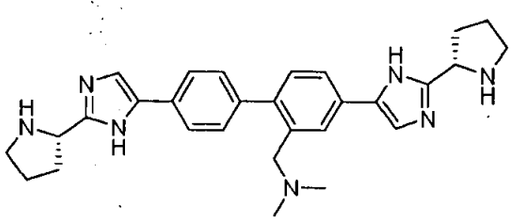
CH_2Cl_2 (6.0 mL) was added to a mixture alcohol M119a (501 mg, 0.765 mmol), TPAP (29.1, 0.083 mmol) and 4-methylmorpholine *N*-oxide (135.8 mg, 1.159 mmol), and the resultant heterogeneous mixture was vigorously stirred at ambient condition for 14.5 hr. Additional TPAP (11.0 mg, 0.031 mmol) and 4-methylmorpholine *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.

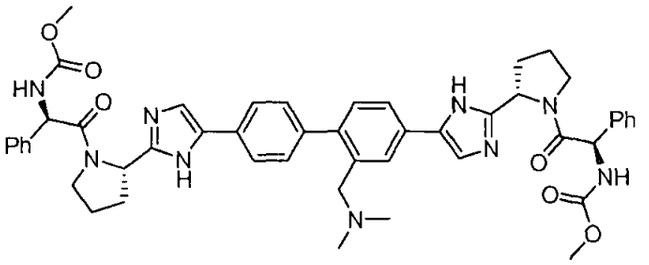
Example M120

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

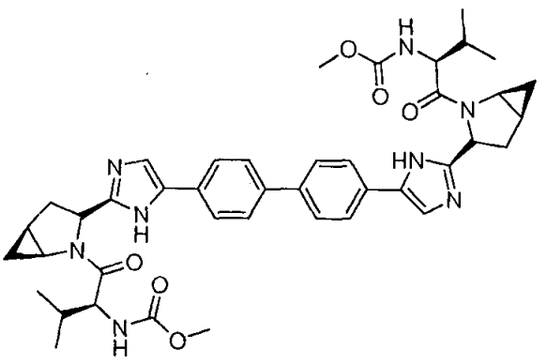
dimethyl ((2-((dimethylamino)methyl)-4,4'-biphenyldiyl)bis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate



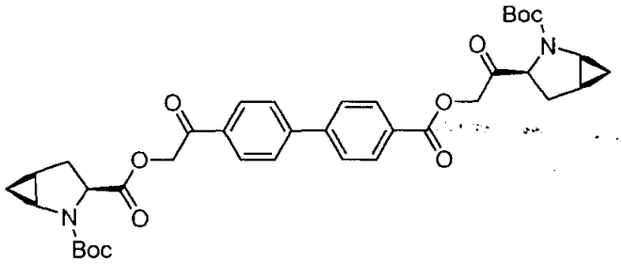
The TFA salt of Example M121 was prepared from M120c and *Cap*-4 according to the procedure described for Example 1. LC (Cond. 1): RT = 1.15 min; >98% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{49}H_{54}N_9O_6$: 796.45; found 864.46. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{49}H_{54}N_9O_6$: 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

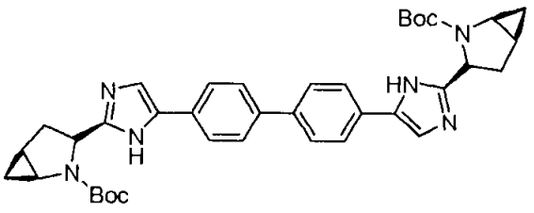


Example M122, step a



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. ^{1}H 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.

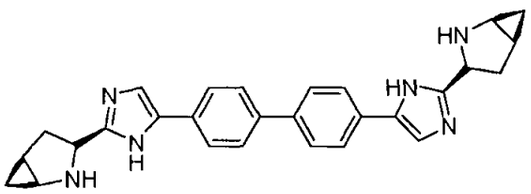
Example M122, Step b



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



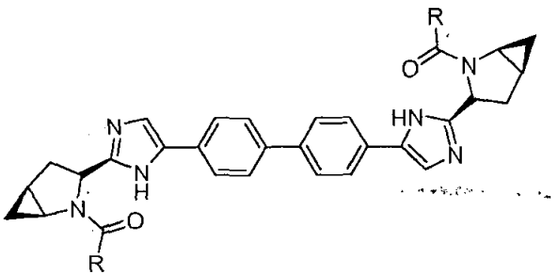
4 N HCl in dioxane (5 mL) was added to a ice-water cooled dioxane (16 mL) solution of carbamate M122b (0.8 g, 1.2 mmol), the ice-water bath was removed and the mixture was stirred at ambient condition for 4 hr. Big chunks of solid that formed during the reaction were broken up with a spatula. Removal 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.

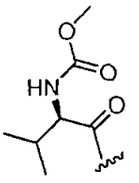
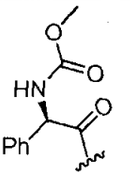
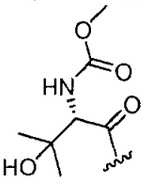
Example M122

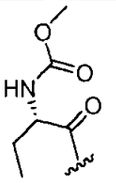
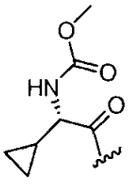
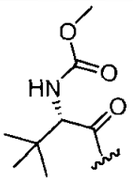
The TFA salt of Example M122 was prepared from M122c and *Cap*-51 according to the procedure described for Example 1. LC (Cond. 1): RT = 1.34 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{51}N_8O_6$: 763.39; found 763.73.

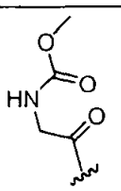
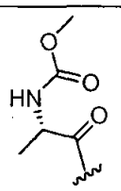
Example M123-M130

Example M123-M130 were prepared according to the procedure described for Example M122. Example M123-M129 were prepared as TFA salts, where as Example M130 was prepared as a free base.



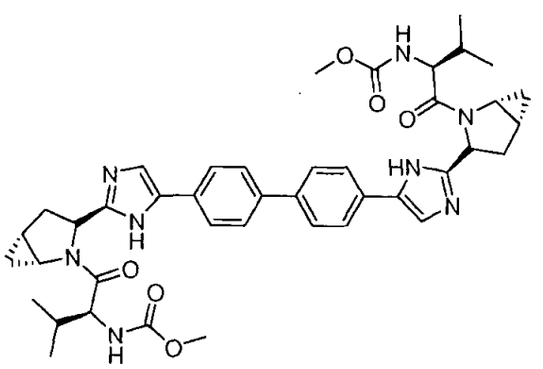
Example	*Compound Name*	 *(Source)*	*RT (LC-Cond.); % homogeneity index; MS data*
M123	methyl ((1R)-1-(((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate	 (*Cap*-84)	1.372 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{51}N_8O_6$: 763.39; found 763.73
M124	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate	 (*Cap*-4)	2.28 minutes (Cond. M1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{47}N_8O_6$: 831.36; found 831.36
M125	methyl ((1S)-2-hydroxy-1-(((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2S)-3-hydroxy-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-		1.76 minutes (Cond. M1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$

	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	(*Cap*-65)	$C_{42}H_{51}N_8O_8$: 795.38; found 795.37
M126	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3,2-diyl((2S)-1-oxo-1,2-butanediyl)))biscarbamate	 (*Cap*-53b)	1.25 minutes (Cond.1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.36; found 735.68
M127	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S,3S,5S)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate	 (*Cap*-54b)	1.27 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_6$: 759.36; found 759.72
M128	methyl ((1S)-1-(((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-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)-2,2-dimethylpropyl)carbamate		2.48 minutes (Cond. M1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{55}N_8O_6$: 791.42; found 791.41

M129	methyl (2-((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-(((methoxycarbonyl)amino)acetyl)-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)-2-oxoethyl)carbamate		1.10 minutes (Cond.1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{39}N_8O_6$: 679.74; found 679.77
M130	methyl ((1S)-2-((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-(N-(methoxycarbonyl)-L-alanyl)-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)-1-methyl-2-oxoethyl)carbamate	 (*Cap*-52)	1.16 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{43}N_8O_6$: 707.33; found 707.69

Example M131

methyl ((1S)-1-(((1R,3R,5R)-3-(5-(4'-(2-((1R,3R,5R)-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

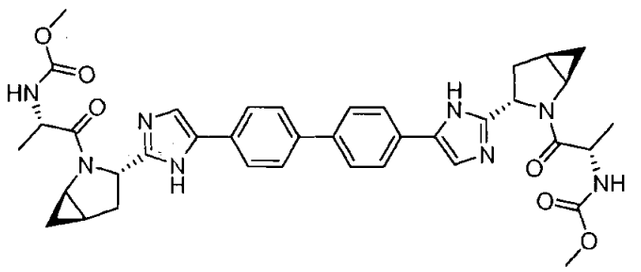


Example M131 was prepared according to the procedure described for its diastereomer Example M122 starting from (1R,3S,5R)-2-(*tert*-butoxycarbonyl)-2-

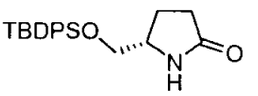
azabicyclo[3.1.0]hexane-3-carboxylic acid, which was in turn synthesized by employing a literature protocol (Hanessian *et al., Angew. Chem., Int. Ed. Engl.* 1997, *36*, 1881-1884). LC (Cond. I): RT = 1.273 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{50}N_8O_6$: 763.39; found 763.94.

Example M132

methyl ((1S)-2-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-(N-(methoxycarbonyl)-L-alanyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-1-methyl -2-oxoethyl)carbamate

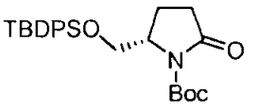


Example M132, Step a



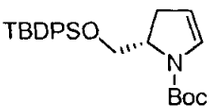
To a solution of (*S*)-5-(hydroxymethyl)pyrrolidin-2-one (10g, 87 mmol) in CH_2Cl_2 (50 mL) was added *tert*-butylchlorodiphenylsilane (25.6 g, 93 mmol), triethylamine (12.1 mL, 87 mmol) and DMAP (1.06 g, 8.7 mmol). The mixture was stirred at room temperature for 5 hours, treated with CH_2Cl_2 (50 mL) and washed with water (50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified with a flash chromatography (30 to 100% of EtOAc/hexanes) to afford ether M132a as colorless oil (22.7 g, 74% yield). ^{1}H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 7.69 (br s, 1H), 7.64-7.61 (m, 4H), 7.50-7.42 (m, 6H), 3.67-3.62 (m, 1H), 3.58-3.51 (m, 2H), 2.24-2.04 (m, 3H), 1.89-1.78 (m, 1H), 1.00 (s, 9H).

Example M132, Step b



Di-*tert*-butyl dicarbonate (28.0 g, 128 mmol) was added slowly to a cooled (ice/water) CH_2Cl_2 (120 mL) solution of ether M132a (22.7 g, 64.2 mmol), triethylamine (8.95 mL, 64.2 mmol), and DMAP (7.84 g, 64.2 mmol). At the end of addition, the cooling bath was removed and stirring continued at ambient condition for 20 hours. The volatile component was removed *in vacuo*, and the crude material was submitted to a flash chromatography (20 to 50 % EtOAc/hexanes) to afford carbamate M132b as off-white solid (29 g, 99% yield). ^{1}H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 7.61-7.54 (m, 4H), 7.50-7.38 (m, 6H), 4.19-4.16 (m, 1H), 3.90 (dd, J = 10.4, 3.6, 1H), 3.68 (dd, J = 10.4, 2.1, 1H), 2.68-2.58 (m, 1H), 2.40-2.33 (m, 1H), 2.22-2.12 (m, 1H), 2.01-1.96 (m, 1H), 1.35 (s, 9H), 0.97 (s, 9H).

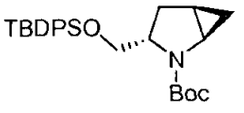
Example M132, Step c



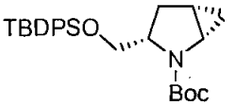
A three-necked flask equipped with a thermometer and a nitrogen inlet was charged with carbamate M132b (10.054 g, 22.16 mmol) and toluene (36 mL), and lowered into -55 °C cooling bath. When the internal temperature of the mixture reached ~ -50 °C, Superhydride (23 mL of 1.0 M in THF, 23.00 mmol) was added dropwise over 30 minutes while maintaining the internal temperature between -50 and -45 °C, and stirred for 35 minutes while maintaining the temperature between -50 and -45 °C. Hunig's Base (16.5 mL, 94 mmol) was added dropwise over 10 minutes. Then DMAP (34 mg, 0.278 mmol) was added in one batch, followed by the addition of trifluoroacetic anhydride (3.6 mL, 25.5 mmol) over 15 minutes, while maintaining the internal temperature between -50 and -45 °C. The bath was removed 10 minutes later, and the reaction mixture was stirred for 14 hours while allowing it to thaw to ambient temperature. It was then diluted with toluene (15 mL), cooled with ice-water bath, and treated slowly with water (55 mL) over 5 minutes. At the end of addition, the phases were separated, and the organic layer was washed with water (50 mL, 2x) and then concentrated *in vacuo*. The crude material was purified with a flash

chromatography (5% EtOAc/hexanes) to afford carbamate M132c as a colorless viscous oil (7.947 g, 82%). ^{1}H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 7.62-7.58 (m, 4H), 7.49-7.40 (m, 6H), 6.47 (br m, 1H), 5.07-5.01 (br m, 1H), 4.18 (br m, 1H), 3.89 (br m, 0.48H), 3.69 (br m, 1.52 H), 2.90-2.60 (br m, 2H), 1.40/1.26 (two overlapping s, 9H), 0.98 (s, 9H).

Example M132, Step d



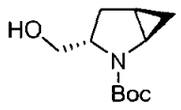
M132d-i



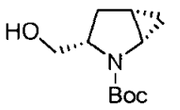
M132d-ii

Diethylzinc (19 mL of ~1.1 M in toluene, 20.90 mmol) was added dropwise over 15 minutes to a cooled (-30 °C) toluene (27 mL) solution of carbamate M132c (3.94 g, 9.0 mmol). Then chloroiodomethane (97%, stabilized over copper; 3 mL, 41.2 mmol) was added dropwise over 10 minutes, and stirred while maintaining the bath temperature around -25 °C for 1 hour and around -21 °C for 18.5 hours. The reaction was then opened to air and quenched by a slow addition of 50% saturated $NaHCO_3$ solution (40 mL), and then removed from the cooling bath and stirred at ambient condition for 20 minutes. It was filtered through a filter paper and the white cake was washed with 50 mL of toluene. The organic phase of the filtrate was separated, and washed with water (40 mL, 2x), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified with a Biotage system (350 g silica gel; sample was loaded with 7% EtOAc/hexanes; eluted with 7-20% EtOAc/hexanes) to afford methanopyrrolidine M132d as a colorless viscous oil, mainly as the trans isomer (3.691 g, 90.7%). [Note: the exact trans/cis ratio has not been determined yet at this stage]. ^{1}H NMR (DMSO-d_6, δ = 2.50, 400 MHz) of M132d-i: 7.62-7.60 (m, 4H), 7.49-7.40 (m, 6H), 3.76 (br m, 1H), 3.67 (br m, 2H), 3.11-3.07 (m, 1H), 2.23 (br m, 1H), 2.03 (br m, 1H), 1.56-1.50 (m, 1H), 1.33 (br s, 9H), 1.00 (s, 9H), 0.80-0.75 (m, 1H), 0.30 (br m, 1H).

Example M132, Step e



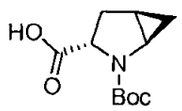
M132e-i



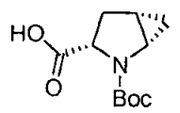
M132e-ii

TBAF (7.27 mL of 1.0 M in THF, 7.27 mmol) was added dropwise over 5 minutes to a THF (30 mL) solution of the ether M132d (3.13 g, 6.93 mmol) and the mixture was stirred at ambient condition for 4.75 hours. After it was treated with saturated NH_4Cl solution (5 mL), most of the volatile component was removed *in vacuo*, and the residue was partitioned between CH_2Cl_2 (70 mL) and 50% saturated NH_4Cl solution (30 mL). The aqueous phase was extracted with CH_2Cl_2 (30 mL), and the combined organic phase was dried ($MgSO_4$), filtered, concentrated *in vacuo*, and then exposed to high vacuum overnight. The resulting crude material was purified with a Biotage (40-50% EtOAc/hexanes) to afford alcohol M132e as colorless oil, mainly as the trans isomer, contaminated with traces of lower Rf impurities (1.39 g, 94%). [Note: the exact trans/cis ratio has not been determined yet at this stage]. ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz) of M132e-i: 4.70 (app t, J = 5.7, 1H), 3.62-3.56 (m, 1H), 3.49-3.44 (m, 1H), 3.33-3.27 (m, 1H), 3.08-3.04 (m, 1H), 2.07 (br m, 1H), 1.93-1.87 (m, 1H), 1.51-144 (m, 1H), 1.40 (s, 9H), 0.76-0.71 (m, 1H), 0.26 (br m, 1H).

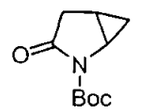
Example M132, Step f



M132f-i



M132f-ii

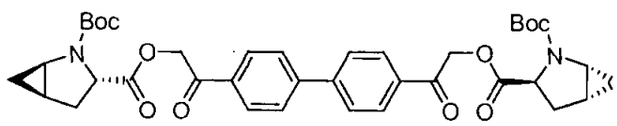


M132f-iii

A semi-solution of $NaIO_4$ (6.46 g, 30.2 mmol) in H_2O (31 mL) was added to CH_3CN (20 mL) and CCl_4 (20 mL) solution of alcohol M132e (2.15 g, 10.08 mmol) prepared above, and $RuCl_3$ (0.044 g, 0.212 mmol) was added immediately and the heterogeneous reaction mixture was vigorously stirred for 75 minutes. The reaction mixture was diluted H_2O (60 mL) and extracted with CH_2Cl_2 (50 mL, 3x). The combined organic phase was treated with 1 mL CH_3OH, allowed to stand for about 5 minutes, and then filtered through a pad of diatomaceous earth (Celite®). The pad was washed with CH_2Cl_2 (50 mL), and the filtrate was rotervaped to afford a light

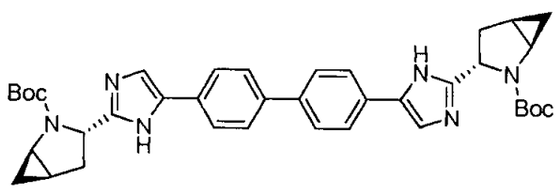
charcoal-colored solid. ^{1}H NMR of the crude material indicated a 1.00 : 0.04 : 0.18 mole ratio among *trans* acid M132f-i: presumed *cis* acid M132f-ii: side product M132f-iii. The crude material was dissolved in EtOAc (~10 mL) with heating, and allowed to stand at ambient condition with seeding. About 15 minutes into the cooling phase, a rapid crystal formation was observed. About 1 hour later, hexanes (~6 mL) was added and the mixture was refrigerated overnight (it does not appear that additional compound has precipitated out). The mixture was filtered and washed with ice/water cooled hexanes/EtOAc (2:1 ratio; 20 mL) and dried under high vacuum to afford the first crop of acid M132f-i (off-white crystals, 1.222 g). The mother liquor was rotervaped, and the residue was dissolved in ~3 ml of EtOAc (with heating), allowed to stand at ambient condition for 1 hour, and then 3 mL hexanes was added and stored in a refrigerator for ~15 hours. A second crop of acid M132f-i (grey crystals, 0.133 g) was retrieved similarly. ^{1}H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 12.46 (br s, 1H), 3.88 (br m, 1H), 3.27 (br m, 1H; partially overlapped with the signal of water), 2.28 (br m, 1H), 2.08 (br m, 1H), 1.56 (br m, 1H), 1.40/1.34 (two overlapped br s, 9H), 0.73-0.68 (m, 1H), 0.46-0.43 (m, 1H). Optical rotation (10 mg/mL of $CHCl_3$): $[\alpha]_D$ = -216 for first crop & -212 for the second crop.

Example M132, Step g



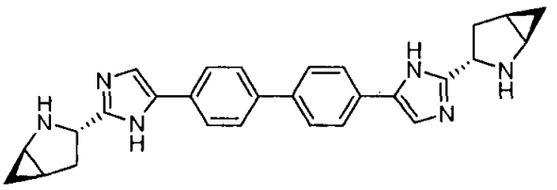
Ketoester M132g was prepared from acid M132f-i and 1,1'-(biphenyl-4,4'-diyl)bis(2-bromoethanone) by employing the procedure described for the preparation of ketoester M122a. LC (Cond. 1): RT = 2.09 minutes. LC/MS: Anal. Calcd. for $[M+H-Boc]^+$ $C_{33}H_{37}N_2O_8$: 589.26; found 589.29.

Example M132, Step h



Carbamate M132h was prepared from ketoester M132g according to the procedure described for the preparation of imidazole 1b from ketoamide 1a, with the exception that 20 mol equiv of NH_4OAc was employed for the thermal cyclization, and that CH_2Cl_2 was employed during the work up step. LC (Cond. I): RT = 1.48 minutes. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{45}N_6O_4$: 649.35; found 649.40.

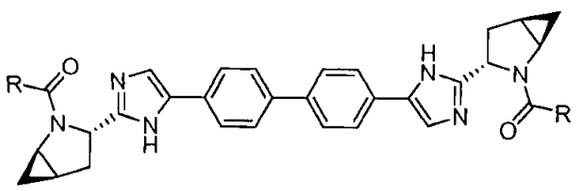
Example M132, Step i

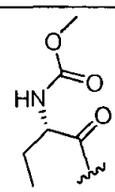
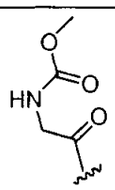


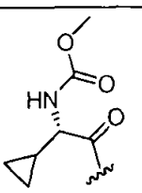
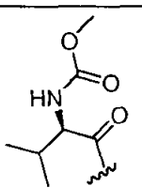
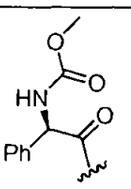
Pyrrolidine M132i (.4HCl) was prepared from carbamate M132h according to the procedure described for the preparation of pyrrolidine M122c. The crude material was submitted to subsequent acylation step without purification. ^1H NMR (DMSO-d_6, δ = 2.50, 400 MHz): 10.5-10.0 (br signal, not integratable), 8.02 (s, 2H), 7.95 (d, J = 8.6, 4H), 7.85 (d, J = 8.3, 4H), 4.75 (m, 2H), 3.43 (m, 2H), 2.67-2.50 (m, 4H), 1.95 (m, 2H), 1.11 (m, 2H), 0.86 (m, 2H). RT = 1.00 minutes. LC/MS: Anal. Calcd. for $[M+H]^+$ C28H20N6: 449.25 ; found 49.27.

Example M132

Example M132, along with its analogs Example M133-M137 highlighted in the table below, were prepared as TFA salts from pyrrolidine M132i (.4HCl) by employing the procedure described for the synthesis of Example M122 and appropriate acids. Example M132: LC (Cond. I): RT = 1.14 min; >95% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{43}N_8O_6$: 707.33; found 707.43.



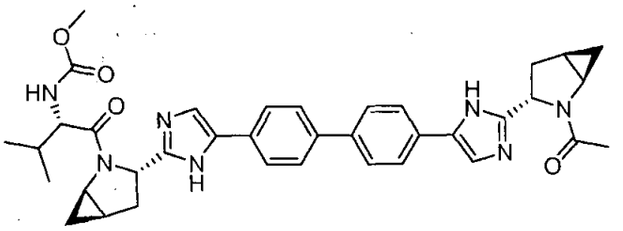
Example	*Compound Name*		*RT (LC-Cond.); % homogeneity index; MS data*
M133	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((2S)-1-oxo-1,2-butanediyl)))biscarbamate		1.22 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.36; found 735.48
M134	methyl (2-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-(((methoxycarbonyl)amino)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxoethyl) carbamate		1.12 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{39}N_8O_6$: 679.30; found 679.38

M135	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate		1.25 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{47}N_8O_6$: 759.36; found 759.45
M136	methyl ((1R)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate		1.34 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{50}N_8O_6$: 763.39; found 763.46
M137	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate		1.38 minutes (Cond. I); >98%; LC/MS:

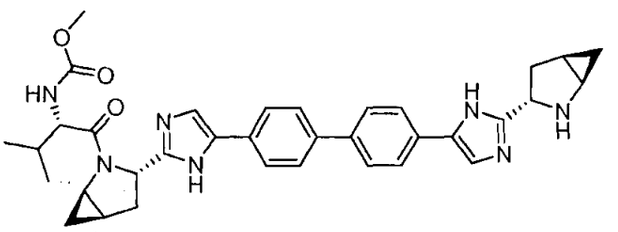
			Anal. Calcd. for $[M+H]^+$ $C_{48}H_{47}N_8O_6$: 831.36; found 831.37

Example M138

methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-acetyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate



Example M138, Step a



To a slurry of pyrrolidine M132i (.4HCl) (0.3 g, 0.32 mmol) in DMF (4 mL), (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (97 mg, 0.55 mmol) and *i*-Pr_2EtN (0.26 mL, 1.5 mmol) were added. After the mixture became a clear solution, HATU (0.2 g, 0.53 mmol) was added, and it was stirred at room temperature for 3 hours. The volatile component was removed *in vacuo*, and the resulting residue (which was a mixture of starting material, and mono- and bis-acylated products) was dissolved in methanol and purified with a reverse phase HPLC (CH_3OH/H_2O/TFA) to isolate the TFA salt of pyrrolidine M138a as white foam (80 mg). LC (Cond. I):

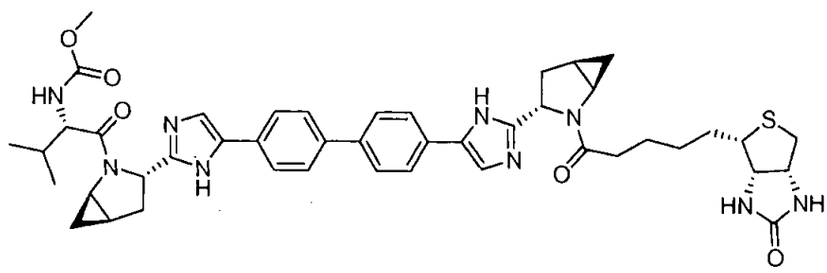
RT = 1.17 minutes. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{35}H_{40}N_7O_3$: 606.32; found 606.36.

Example M138

Acetic acid (7.6 mg, 0.13 mmol), *i*-Pr_2EtN (32 mg, 0.25 mmol), and HATU (53 mg, 0.14 mmol) were sequentially added to a DMF (2 mL) solution of the TFA salt of pyrrolidine M138a (40 mg, 0.04 mmol), and the reaction mixture was stirred at room temperature for 3 hours. The volatile component was removed *in vacuo*, and the residue was dissolved in methanol and purified with a reverse phase HPLC (CH_3OH/H_2O/TFA) to afford the TFA salt of Example M138 as white foam (8 mg). LC (Cond. I): RT = 1.20 min; >95% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{42}N_7O_4$: 648.33; found 648.36.

Example M139

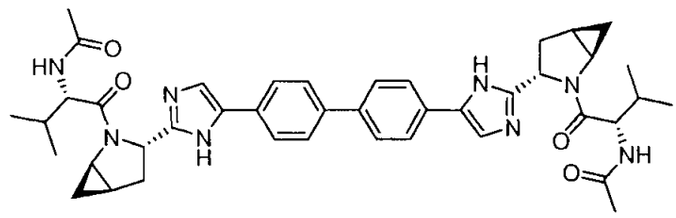
methyl ((1S)-2-methyl-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl- 2-methylpropyl)carbamate



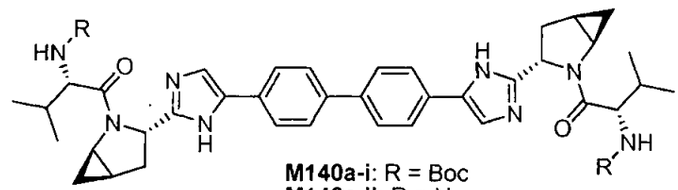
HATU (53 mg) was added to a mixture of the TFA salt of pyrrolidine M138a (40 mg, 0.042 mmol), *d*-Biotin (10.3 mg, 0.042 mmol) and *i*-Pr_2EtN (0.044 mL, 0.253 mmol), and the reaction mixture was stirred at room temperature for 3 hours. The volatile component was removed *in vacuo*, and the residue was dissolved in methanol and purified with a reverse phase HPLC (CH_3OH/H_2O/TFA) to afford the TFA salt of Example M139 as a light yellow solid (7 mg). LC (Cond. I): RT = 1.28 min; >95% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{45}H_{54}N_9O_5S$: 832.40; found 832.34.

Example M140

N-((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-acetamido-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)acetamide



Example M140, Step a



M140a-i: R = Boc
M140a-ii: R = H

HATU (852 mg, 2.24 mmol) was added to a DMF (20 mL) solution of pyrrolidine M132i (.4HCL) (650 mg, 1.09 mmol), Boc-*L*-Valine (523 mg, 2.41 mmol), *i*-Pr_2EtN (1.15 mL, 6.56 mmol), and the reaction mixture was stirred at room temperature for 1 hour. The volatile component was removed *in vacuo*, and the crude was dissolved in CH_3OH and purified with a reverse phase HPLC (CH_3OH/H_2O/TFA) to afford 0.96 g of acylated product. A portion of the product (0.72 g) was dissolved in CH_2Cl_2 (4 mL), treated with TFA (0.26 mL, 3.35 mmol), and the resulting mixture was stirred at ambient condition for 4 hours. The volatile component was removed *in vacuo* to afford the TFA salt of M140a-ii, *tert-butyl ((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-((tert-butoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate*, which was used in the next step without purification. LC (Cond. 1): RT = 0.93 minutes. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_2$: 647.38; found 647.26.

The free base form of carbamate M140a-i could be isolated at the coupling stage as follows: the HPLC fraction was neutralized with excess 2.0 N NH_3/CH_3OH, the volatile component was removed *in vacuo* and the residue was partitioned

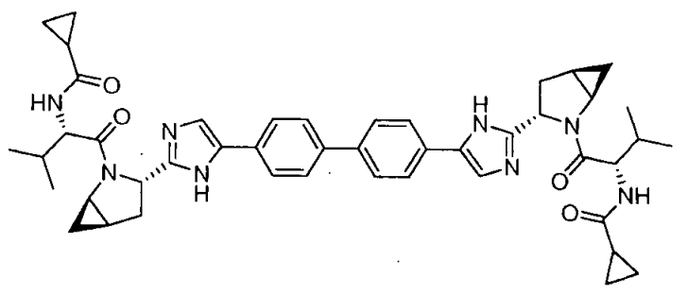
between CH_2Cl_2 and ~5% saturated $NaHCO_3$ solution. The organic layer was dried (Na_2SO4), filtered, and concentrated *in vacuo* to afford M140a-i, *(2S)-1-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-amino-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-3-methyl-1-oxo-2-butanamine*, as a light yellow foam. LC (Cond. I): RT = 1.64 min; >95% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{63}N_8O_6$: 847.49; found 847.54.

Example M140

Acetic anhydride (21 mg, 0.204 mmol) and *i*-Pr_2EtN (0.083 mL, 0.476 mmol) were sequentially added to a DMF (3 mL) solution of the TFA salt of M140a-ii (75 mg, 0.068 mmol), and the reaction mixture was stirred at ambient condition until completion, as determined by LC/MS analysis. The volatile component was removed *in vacuo*, and the residue was dissolved in CH_3OH and submitted to a reverse phase HPLC (CH_3OH/H_2O/TFA) to afford the TFA salt of Example M140 as white foam (35 mg). LC (Cond. I): RT = 1.18 min; >98% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{51}N_8O_4$: 731.40; found 731.34.

Example M141

N-((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-((cyclopropylcarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)cyclopropanecarbamate

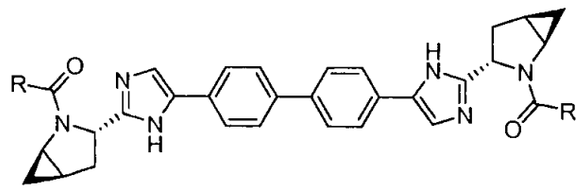


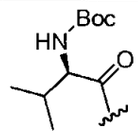
Example M141 was prepared as a TFA salt from amine M140a-ii (TFA salt) and cyclopropanecarboxylic acid according to the coupling procedure described for the synthesis of carbamate M140a-i. LC (Cond. I): RT = 1.33 min; >95%

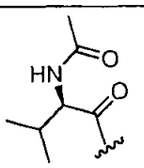
homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{55}N_8O_4$: 783.42; found 783.36.

Example M142-M143

Example M142 (free base) and Example M143 (TFA salt) were prepared by employing the procedures described for the synthesis of Example M140 and appropriate materials.

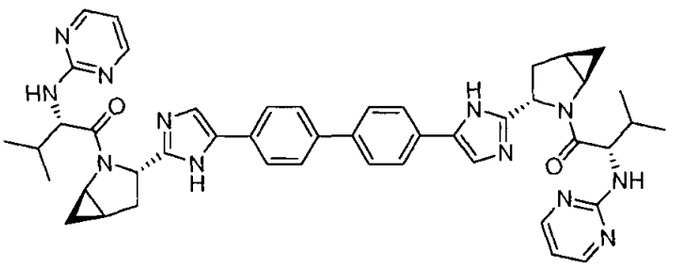


Example	*Compound Name*		*RT (LC-Cond.); % homogeneity index; MS data*
M142	tert-butyl ((1R)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2R)-2-((tert-butoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate		1.65 minutes (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{48}H_{63}N_8O_6$: 847.49; found 847.54

M143	N-((1R)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2R)-2-acetamido-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)acetamide		1.26 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{51}N_8O_4$: 731.40; found 731.34

Example M144

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((2S)-3-methyl-1-oxo-1,2-butanediyl)))di(2-pyrimidinamine)



A mixture of the TFA salt of amine M140a-ii (75 mg, 0.068 mmol), 2-bromopyrimidine (32.4 mg, 0.204 mmol), and *i*-Pr_2EtN (0.048 mL, 0.272 mmol) in DMSO (0.2 mL)/toluene (1.2 mL) was heated at 90 °C for 20 hours. Additional 2-bromopyrimidine (32.4 mg, 0.204 mmol) was added and heating continued for 8 hours. Most of the volatile component was removed *in vacuo* and the residue was purified twice by a reverse phase HPLC system, (CH_3OH/H_2O/TFA) followed by (ACN/H_2O/TFA), to afford the TFA salt of Example M144, contaminated with unknown minor impurities, as a yellow foam (10 mg). RT = 20.9 minutes (see the LC method detail below); >95% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{46}H_{51}N_{12}O$: 803.43; found 803.70.

Method details for analysis of Example M144:

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

Column: Waters Acquity BEH C18; 1.7um ; 150 X 2.1 mm ID; (at 35C)

Mobile phase A: Water/ acetonitrile (97.5/2.5) with 5 mM ammonium formate; 0.05% formic acid at pH 3.3

Mobile phase B: : Acetonitrile/Water (97.5/2.5) with 5 mM ammonium formate; 0.05% formic acid

Flow: 0.35 ml/min

Hold 10%B 0-1min

10-35%B 1-20 min

35-98%B 20-32 min

hold 98% 32-35 min

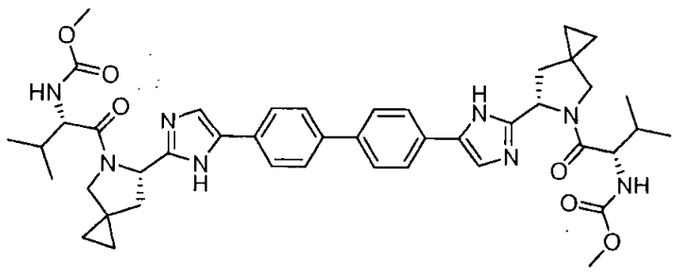
98-10%B 35- 35.5 min

hold 10%B 35.5-40.0 min

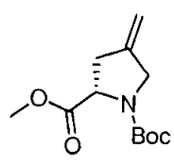
UV detection: @ 260 nm

Example M145

methyl ((1S)-1-(((6S)-6-(4-(4'-(2-((6S)-5-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-azaspiro[2.4]hept-6-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-5-azaspiro[2.4]hept-5-yl)carbonyl)-2-methylpropyl)carbamate

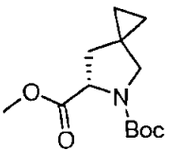


Example M145, Step a



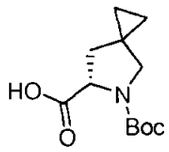
$TMSCHN_2$ (3.63 mL of 2.0 M/ether, 7.26 mmol) was added dropwise to a CH_3OH (33 mL) / benzene (33 mL) solution of (*S*)-1-*tert*-butyl 4-methylenepyrrolidine-1,2-dicarboxylate (1.5 g, 6.60 mmol), and the reaction mixture was stirred at ambient condition for 3.5 hours. Removal of the volatile component *in vacuo* afforded ester M145a as a tan oil (1.57 g). ^{1}H NMR ($CDCl_3$, δ = 7.26 ppm, 500 MHz): 5.01-4.98 (m, 2H), 4.50-4.48 (m, 0.5H), 4.39-4.37 (m, 0.5H), 4.07-4.04 (m, 2H), 3.71 (s, 3H), 3.01-2.87 (m, 1H), 2.66-2.55 (m, 1H), 1.46/1.41 (two overlapping s, 9H).

Example M145, Step b



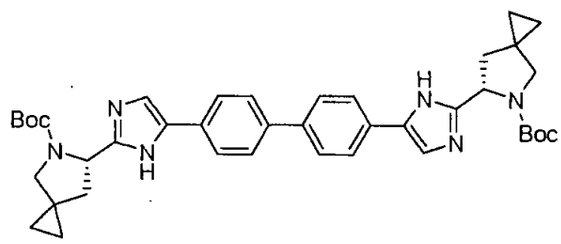
Diethylzinc (5.65 mL of 1.1 M in toluene, 6.22 mmol) was added dropwise over 20 minutes to a cooled (-22 °C) toluene (4 mL) solution of ester M145a (0.50 g, 2.07 mmol). Cloroiodomethane (0.90 mL, 12.4 mmol) was added dropwise over 10 minutes, and the reaction mixture was stirred at -22 °C for 18 hours. The reaction was quenched with saturated solution of $NaHCO_3$ (aq.) (5 mL) at similar temperature and was then allowed to thaw to ambient temperature. The mixture was filtered, and the precipitate was washed with EtOAc (100 mL). The layers of the filtrate were separated, and the organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified with a Biotage (10-20% EtOAc/hexanes) to afford ester M145b as colorless oil (0.139 g). ^{1}H NMR ($CDCl_3$, δ = 7.26 ppm, 500 MHz): 4.47-4.44 (m, 0.5H), 4.47-4.34 (m, 0.5H), 3.73 (s, 3H), 3.39-3.27 (m, 2H), 2.25-2.18 (m, 1H), 1.86-1.84 (m, 0.5H), 1.78-1.75 (m, 0.5H), 1.44/1.40 (two overlapping s, 9H), 0.63-0.48 (m, 4H). LC (Cond. II): RT = 2.26 minutes. LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{12}H_{19}NNaO_4$: 264.12; found 264.22.

Example M145, Step c



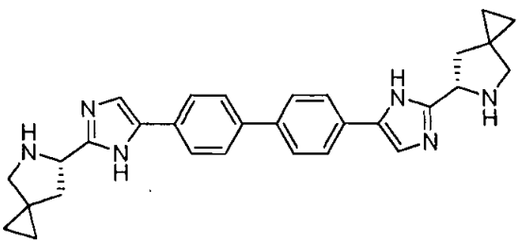
A water (0.61 mL) solution of LiOH (0.016 g, 0.65 mmol) was added to an ethanol (1.2 mL) solution of ester M145b (0.139 g, 0.544 mmol), and the reaction mixture was stirred at ambient condition for 19 hours. The volatile component was removed *in vacuo*, and the residue was dissolved in water (5 mL), cooled (ice/water), acidified to a pH region of 3.0 with 1N HCl (aq.), and then extracted with EtOAc (50 mL, 3x). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford acid M145c as viscous oil which solidified upon standing (0.129 g). ^{1}H NMR ($CDCl_3$, δ = 7.26 ppm, 500 MHz): 4.48-4.40 (m, 1H), 3.55-3.05 (m, 2H), 2.37-1.87 (m, 2H), 1.47/1.44 (two overlapping s, 9H), 0.78-0.50 (m, 4H). LC (Cond. II): RT = 2.26 minutes. LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{12}H_{19}NNaO_4$: 264.12; found 264.22.

Example M145, Step d



Carbamate M145d was prepared starting from acid M145c and 1,1'-(biphenyl-4,4'-diyl)bis(2-bromoethanone) and employing the general procedure described for the synthesis of M122b with the exception that the ketoester-cyclization step was conducted under microwave conditions (140 °C; 90 min). LC (Cond. II): RT = 2.54 minutes. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{49}N_6O_4$: 677.38; found 677.45.

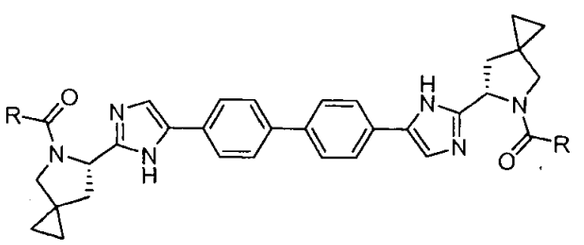
Example M145, Step e

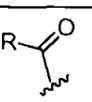


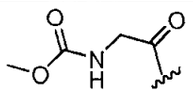
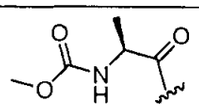
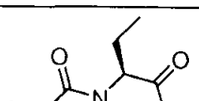
25% TFA/CH_2Cl_2 (5.3 mL) was added to carbamate M145d (0.718 g, 1.06 mmol) and the resultant mixture was stirred at ambient condition for 5 hours. The volatile component was removed *in vacuo*, and the residue was free-based with MCX (6 g, CH_3OH washing; 1:1 $CHCl_3$ / 2 N NH_3/CH_3OH elution) to afford pyrrolidine M145e as a light yellow solid (406 mg). ^1H NMR (DMSO-d_6, d = 2.5 ppm, 500 MHz): 11.89 (br s, 2H), 7.82 (d, J = 7.9, 4H), 7.67 (d, J = 7.9, 4H), 7.50 (br s, 2H), 4.37 (m, 2H), 2.92 (app d, J = 9.8, 2H), 2.81 (app d, J = 10.1, 2H), 2.09-2.05 (m, 2H), 1.98-1.94 (m, 2H), 0.62-0.49 (m, 8H). LC (Cond. II): RT = 1.75 minutes. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{30}H_{33}N_6$: 477.28; found 477.35.

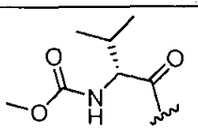
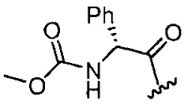
Example M145

Example M145, along with its analogs Example M146-M147 highlighted in the table below, were prepared as TFA salts starting from pyrrolidine M145 and appropriate acids, by employing the general HATU coupling condition outlined for Example-1, with the exception that the reaction mixture was diluted with CH_3OH and directly submitted to a reverse phase HPLC (CH_3OH/H_2O/TFA) purification. Example M145: LC (Cond. II), RT = 2.27 min); >95% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+ = C_{44}H_{55}N_8O_6$: 791.42; found 791.44.



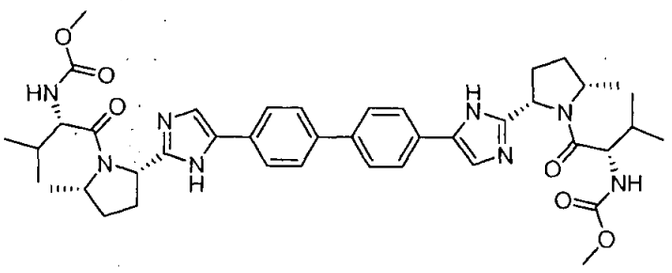
Example	*Compound Name*		*RT (LC-Cond.); %*

			homogeneity index; MS data
M146	methyl (2-(((6S)-6-(4-(4'-(2-(((6S)-5-(((methoxycarbonyl)amino)acetyl)-5-azaspiro[2.4]hept-6-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-5-azaspiro[2.4]hept-5-yl)-2-oxoethyl)carbamate		1.97 minutes (Cond. II); >95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{43}N_8O_6$: 707.33; found 707.36
M147	methyl ((1S)-2-((6S)-6-(4-(4'-(2-((6S)-5-(N-(methoxycarbonyl)-L-alanyl)-5-azaspiro[2.4]hept-6-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-5-azaspiro[2.4]hept-5-yl)-1-methyl-2-oxoethyl)carbamate		2.01 minutes (Cond. II); >95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.36; found 735.41
M148	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(6S)-5-azaspiro[2.4]heptane-6,5-diyl((2S)-1-oxo-1,2-butanediyl)))biscarbamate		2.14 minutes (Cond. II); >95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{51}N_8O_6$: 763.39; found 763.46

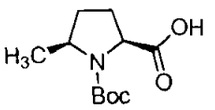
M149	methyl ((1R)-1-(((6S)-6-(4-(4'-(2-((6S)-5-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-azaspiro[2.4]hept-6-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-5-azaspiro[2.4]hept-5-yl)carbonyl)-2-methylpropyl)carbamate		2.44 minutes (Cond. II); >95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{44}H_{55}N_8O_6$: 791.42; found 791.44
M150	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(6S)-5-azaspiro[2.4]heptane-6,5-diyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate		2.52 minutes (Cond. II); >95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{50}H_{51}N_8O_6$: 859.39; found 859.42

Example M151

methyl ((1S)-1-(((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate

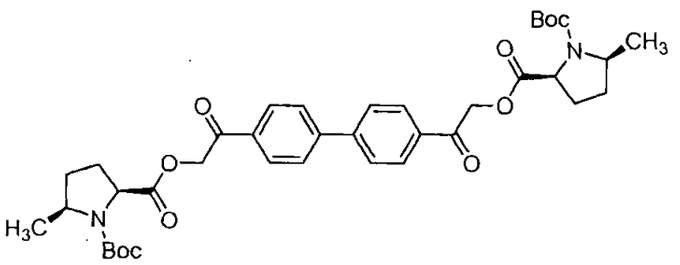


Example M151, Step a



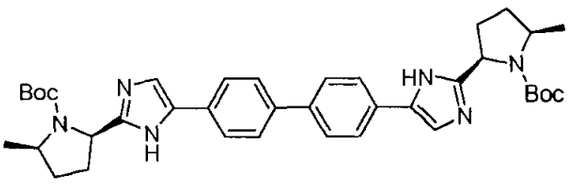
The title compound was synthesized according to a literature protocol (*J. Med. Chem.*, 2006, *49*, 3520) with the following purification modifications: the crude material (2.7 g) was recrystallized from EtOAc/hexanes at ambient temperature to afford acid M151a as a white crystal (2.2 g). ^{1}H NMR ($CDCl_3$, δ = 7.24 ppm, 400 MHz): 4.32 (br m, 1H), 3.89 (br m, 1H), 2.40 (br m, 1H), 2.00 (m, 2H), 1.65 (m, 1H), 1.45 (s, 9H), 1.20 (d, J = 5.6, 3H). LC (Cond. 1): RT = 1.40 minutes. LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{11}H_{20}NO_4Na$: 252.12; found 252.21.

Example M151, Step b



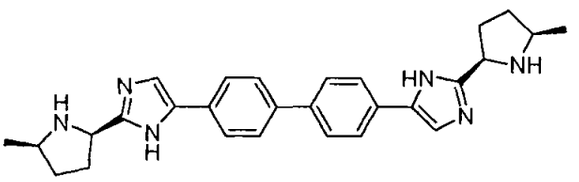
To a mixture of acid M151a and 1,1'-(biphenyl-4,4'-diyl)bis(2-bromoethanone) (1.85 g, 4.66 mmol) in acetonitrile (50 mL), *i*-Pr_2EtN (1.24 g, 9.6 mmol) was added dropwise, and the reaction was stirred at room temperature for 7 hr. The volatile component was removed *in vacuo* and the residue was partitioned between ethyl acetate and water (1:1, 100 mL). The organic layer was separated and washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford ketoester M151b as white foam (3.19 g), which was used in the next step without purification. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 8.10 (d, J = 8.5, 4H), 7.95 (d, J= 8.5, 4H), 5.70-5.50 (br m, 4H), 4.40 (br m, 2H), 3.90 (br m, 2H), 2.25 (m, 2H), 2.15 (m, 4H), 1.60 (m, 2H), 1.41 (s, 8H), 1.39 (s, 10H), 1.20 (m, 6H). LC (Cond. 1): RT = 2.15 minutes. LC/MS: parent ion was not observed.

Example M151, Step c



A mixture of ketoester M151b (2.94 g, 4.24 mmol) and ammonium acetate (6.54 g, 85 mmol) in xylene (40 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 between CH_2Cl_2 (100 mL) and water (50 mL). The organic layer was washed with saturated $NaHCO_3$ (20 mL), dried (Na_2SO_4), concentrated *in vacuo*. The resultant crude material was purified with a Biotage (0-100% EtOAc/hexanes) to afford imidazole M151c as light brown solid (1.72 g). LC (Cond. I): RT = 1.03 minutes. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{49}N_6O_4$: 653.37; found 653.40.

Example M151, Step d

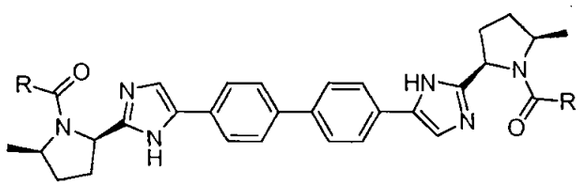


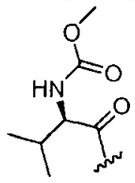
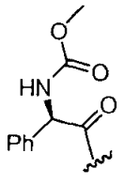
4 N HCl in dioxane (14 mL, 56 mmol) was added dropwise to a dioxane (70 mL) solution of carbamate M151c (1.72 g, 2.63 mmol), and the reaction mixture was stirred at room temperature for 4 hours. Removal of the volatile component *in vacuo* afforded the HCl salt of pyrrolidine M151d as a yellow solid (1.58 g). ^{1}H NMR (DMSO-d_6, δ=2.5 ppm, 400 MHz): δ 9.85 (br s, 1H), 8.80 (br s, 1H), 7.89 (d, J = 8.3, 4H), 7.77 (s, 2H), 7.75 (d, J = 8.6, 4H), 4.70 (br m, 2H), 3.75 (br m, 2H), 2.45-2.35 (m, 4H), 2.25 (m, 2H), 1.75 (m, 2H), 1.50 (d, J = 6.6, 6H). LC (Cond. I): RT = 1.03 minutes. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{28}H_{33}N_6$: 453.28 ; found 453.28.

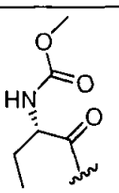
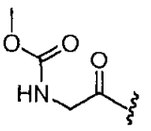
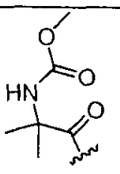
Example M151

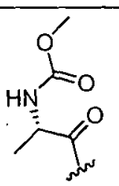
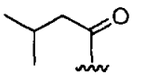
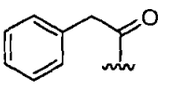
Example M151, along with its analogs Example M152-M161 highlighted in the table below, were prepared as TFA salts starting from pyrrolidine M151d and appropriate acids, by employing the general HATU coupling condition outlined for Example-1, with the exception that the reaction mixture was diluted with CH_3OH and

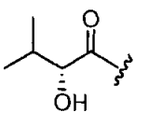
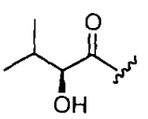
directly submitted to a reverse phase HPLC purification (CH_3OH/H_2O/TFA). Example M151: LC (Cond. I): RT = 1.41 min; >95% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{55}N_8O_6$: 767.42; found 767.40.



Example	*Compound Name*		*RT (LC-Cond.); % homogeneity index; MS data*
M152	methyl ((1R)-1-(((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		1.38 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{55}N_8O_6$: 767.42; found 767.33
M153	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S,5S)-5-methyl-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate		1.46 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$

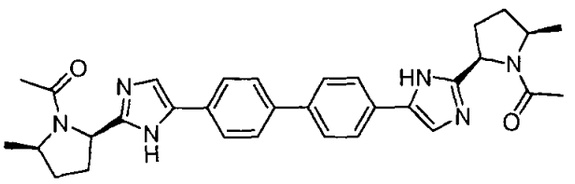
			$C_{48}H_{51}N_8O_6$: 835.39; found 835.31
M154	dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S,5S)-5-methyl-2,1-pyrrolidinediyl)((2S)-1-oxo-1,2-butanediyl)))biscarbamate		1.27 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.39; found 739.28
M155	methyl (2-((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-(((methoxycarbonyl)amino)acetyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)-2-oxoethyl)carbamate		1.19 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{43}N_8O_6$: 683.33; found 683.32
M156	methyl (2-((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-(2-((methoxycarbonyl)amino)-2-methylpropanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-5-		1.33 minutes (Cond. I); >98%; LC/MS: Anal. Calcd.

	methyl-1-pyrrolidinyl)-1,1-dimethy l-2-oxoethyl)carbamate		for $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.39; found 739.28
M157	methyl ((1S)-2-((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-(N-(methoxycarbonyl)-L-alanyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate		1.21 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.36; found 711.23
M158	4,4'-(4,4'-biphenyldiyl)bis(2-((2S,5S)-5-methyl-1-(3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazole)		1.42 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{49}N_6O_2$: 621.39; found 621.28
M159	4,4'-(4,4'-biphenyldiyl)bis(2-((2S,5S)-5-methyl-1-(phenylacetyl)-2-pyrrolidinyl)-1H-imidazole)		1.46 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$

			$C_{44}H_{45}N_6O_2$: 689.36; found 689.26
M160	(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S,5S)-5-methyl-2,1-pyrrolidinediyl)))bis(3-methyl-1-oxo-2-butanol)		1.27 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{49}N_6O_4$: 653.38; found 653.27
M161	(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S,5S)-5-methyl-2,1-pyrrolidinediyl)))bis(3-methyl-1-oxo-2-butanol)		1.267 minutes (Cond. I); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{49}N_6O_4$: 653.38; found 653.34

Example M162

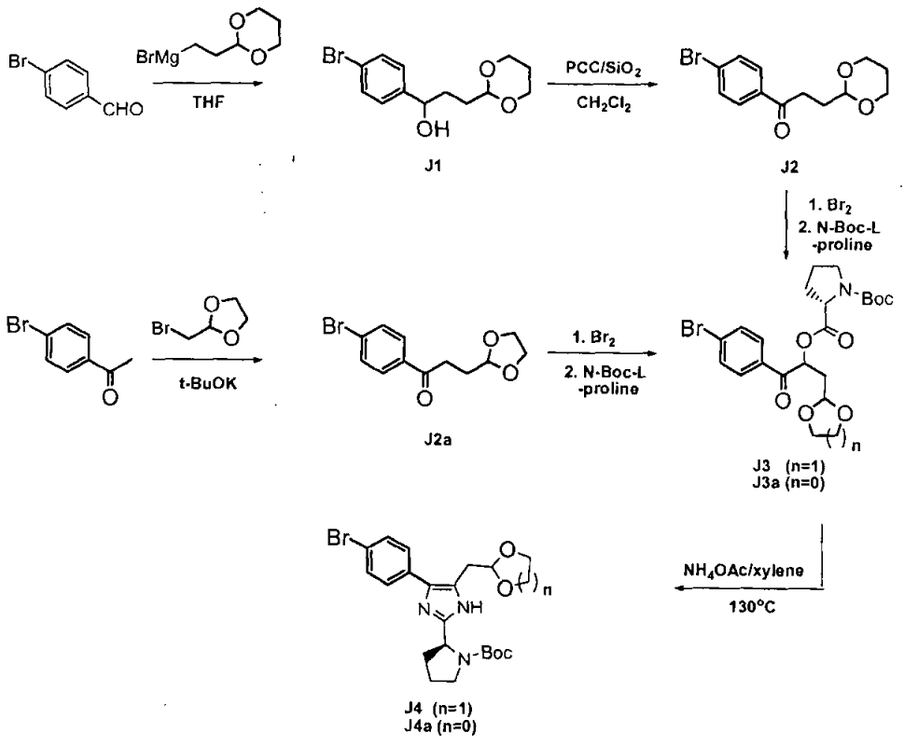
2-((2S,5S)-1-acetyl-5-methyl-2-pyrrolidinyl)-4-(4'-(2-((2S,5S)-1-acetyl-5-methyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole



Acetic anhydride (38.4 mg, 0.376 mmol) and *i*-Pr_2EtN (0.153 mL, 0.877 mmol) were added to a DMF (3 mL) solution of the HCl salt of pyrrolidine M151d (75 mg, 0.125 mmol), and the mixture was stirred at room temperature for 2 hours. The volatile component was removed *in vacuo*, and the residue was dissolved in CH_3OH and purified with a reverse phase HPLC (CH_3OH/H_2O/TFA) to afford the TFA salt of M162 as a white foam (55 mg). LC (Cond. I): RT = 1.13 min; >95% homogeneity index. LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{32}H_{37}N_6O_2$: 537.30 ; found 537.21.

Examples J1-J14.f and E1-E5m

Synthetic Scheme 1

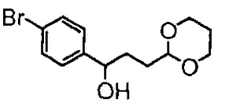


LCMS conditions 1: Phenomenex-Luna 4.6 x 50 mm S10, 0 to 100%B over 2 min, 3 min stop time, 4 mL/min, 220nm, A: 10% CH_3OH-90%H2O - 0.1% TFA; B: 90% CH_3OH-10%H2O-0.1% TFA.

LCMS conditions 2: 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% CH_3OH-90%H2O - 0.1% TFA; B: 90% CH_3OH-10%H2O-0.1% TFA.

LCMS conditions 3: Luna 4.6 x 30 mm C18, 0 to 100%B over 2 min, 3 min stop time, 5 mL/min, 220nm, A: 5% Acetonitrile-90%H2O – 10 Mm NH_4OAc; B: 90% Acetonitrile -10%H2O-0.1% 10 Mm NH_4OAc.

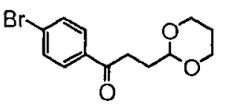
Reference: *J.Org.Chem.* (1992) *57*,1784.



J1

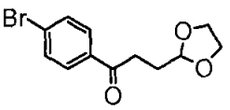
108 mL of (1,3-dioxan-2-ylethyl) magnesium bromide (0.5M) was added to a solution of 4-bromobenzaldehyde (10g, 54.0 mmol) in THF (350 mL) at -78 °C under nitrogen and stirred for 2 hours before warming to 0 °C. The reaction was quenched with sat NH_4Cl soln, diluted with diethyl ether and washed with brine. The crude product was charged (CH_2Cl_2) to a 40M Biotage silica gel cartridge; Gradient elution 15 - 100% B over 750 mL (A = Hexanes; B = ethyl acetate) to give Example J1, 1-(4-bromophenyl)-3-(1,3-dioxan-2-yl)propan-1-ol (quantitative yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 4.70-4.66 (m, 1H), 4.57 (t, *J* = 4.9 Hz, 1H), 4.12-4.19 (m, 2H), 3.76 (tt, *J* = 11.9, 2.7 Hz, 2H), 2.87 (d, *J* = 3.7 Hz, 1H), 2.12-2.03 (m, 1H), 1.86-1.87 (m, 2H), 1.74-1.68 (m, 2H), 1.36-1.32 (m, 1H). RT = 1.8 minutes (condition 1); LRMS: No parent ion evident.

Reference: *JOC* (1989) *54* 5387.



J2

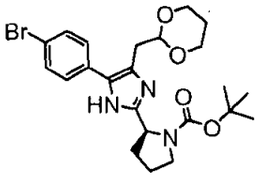
PCC (8.16g, 59.8 mmol) was admixed with 9 g SiO_2 and ground (mortar & pestle) and suspended in Dichloromethane (360 mL). To the suspension was added in one portion Example J1, 1-(4-bromophenyl)-3-(1,3-dioxan-2-yl)propan-1-ol (9g, 29.9 mmol) dissolved in 5 mL of the same solvent. The reaction mixture was stirred for 2 hours an filtered through celite (rinse with (CH_2Cl_2). After being czoncentrated the residue was charged (CH_2Cl_2) to a 40 M Biotage silica gel cartridge. Gradient elution 15-70% B over 750 mL mL (A = Hexanes; B = ethyl acetate) gave Example J2, 1-(4-bromophenyl)-3-(1,3-dioxan-2-yl)propan-1-one 7.7 g (86 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 8.7 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 4.65 (t, J = 4.9 Hz, 1H), 4.09-4.06 (m, 2H), 3.74 (dt, J = 11.0, 2.4 Hz, 2H), 3.06 (t, J = 7.3 Hz, 2H), 2.07-2.01 (m, 3H), 1.35-1.31 (m, 1H). LCMS: RT = 1.9 minutes (condition 1); C13H15BrO3 Calcd.: 299; found: 299 $(M+H)^+$.



J2a

The potassium *tert*-butoxide (15 mL, 1M in THF) was added dropwise to a solution of 1-(4-bromophenyl)ethanone (3 g, 15.07 mmol) in DMSO (60 mL) at 0 °C and stirred for 30 min under nitrogen. The enolate was cannulated into a solution of 2-(bromomethyl)-1,3-dioxolane (2.52 g, 15.07 mmol) in DMSO (10 mL) at 0 °C and the reaction allowed to warm to 24°C and stirred 6 hours. Concentrate to remove solvent (high vacuum rotory evaporation) and charge (CH_2Cl_2) of residue to a 40 (M) Biotage silica gel cartridge and gradient elution 5- 35% B over 1 L (A = Hexanes; B = ethyl acetate) gave Example J2a, 1-(4-bromophenyl)-3-(1,3-dioxolan-2-yl)propan-1-one 327 mg (7.6%) and 571 mg of a bis addition product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 4.97 (t, J = 4.3 Hz, 1H), 3.96-3.94 (m, 2H), 3.87-3.84 (m, 2H), 3.08-3.05 (m, 2H), 2.15-2.11 (m, 2H).

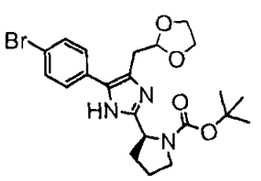
Reference: Bromination *JACS* (1952) *74* 6263. Displacement/Cyclization *J.Med.Chem.* (2001) *44* 2990.



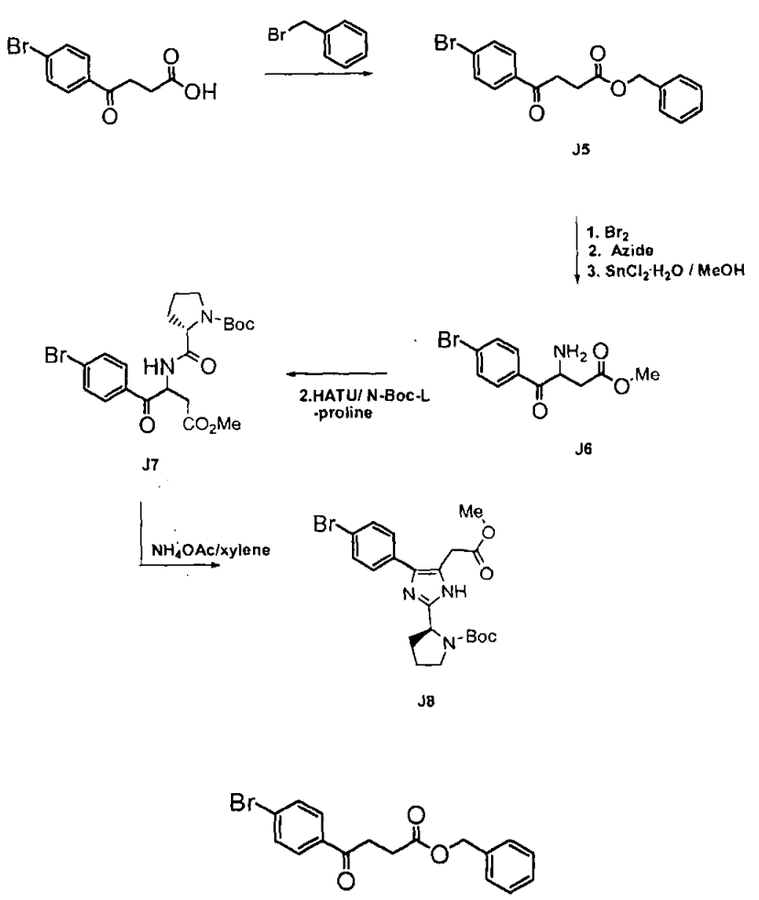
J4

Bromine (1.3 mL, 25.2 mmol) was added to a solution of Example J2, 1-(4-bromophenyl)-3-(1,3-dioxan-2-yl)propan-1-one (7.7g, 25.7 mmol) in diethyl ether (60 mL) and 1,4-dioxane (40 mL) and the solution stirred 30 min at 24 °C (Until TLC indicated reaction complete). The solvent was removed by rotory evaporation and the residue was taken up in acetonitrile (350 mL). (S)-N-Boc-Proline (5.54g, 25.7 mmol) was added followed by dropwise addition of Hunig's base (8.5 mL, 51.5 mmol) and the reaction was stirred 6 hours before being concentrated. The crude product was taken up in CH_2Cl_2 and charged to a 40 (M) Biotage silica gel cartridge. Gradient elution 15 - 100% B over 1 L (A = hexanes; B = ethyl acetate) gave Example J3, 2-(1-(4-bromophenyl)-3-(1,3-dioxan-2-yl)-1-oxopropan-2-yl) 1-*tert*-butyl pyrrolidine-1,2-dicarboxylate 13 g (100%).). RT = 2.2 minutes (condition 1); LCMS: Anal. C23H30BrNO7 Calcd. 534; found: 534 $(M+Na)^+$.

Ammonium acetate (6.45 g, 107 mmol) was added to a solution of Example J3, 2-(1-(4-bromophenyl)-3-(1,3-dioxan-2-yl)-1-oxopropan-2-yl) 1-*tert*-butyl pyrrolidine-1,2-dicarboxylate (5.5 g, 10.7 mmol) in xylene (120 mL) and stirred for 3 hours at 130 °C in a screw capped 500 mL pressure vessel. After being cooled, the reaction mixture was diluted with ethyl acetate (600 mL) and washed with sat $NaHCO_3$ and brine before being concentrated by rotory evaporation under high vacuum. The crude product was taken up in CH_2Cl_2 and charged to a 40 (M) Biotage silica gel cartridge. Gradient elution 15 - 100% B over 2 L (A = CH_2Cl_2; B = ethyl acetate) gave Example J4, (S)-*tert*-butyl 2-(4-((1,3-dioxan-2-yl)methyl)-5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate 2.22 g (40%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 4H), 4.94-4.92 (m, 1H), 4.77 (t, J = 4.9 Hz, 1H), 4.15-4.12 (m, 2H), 3.81-3.75 (m, 2H), 3.3-3.37 (m, 2H), 3.0-2.90 (m, 2H), 2.10-2.05 (m, 4H), 1.94-1.91 (m, 1H), 1.49 (s, 9H) 1.36-1.34 (m, 1H). RT = 1.8 minutes (condition 1); HRMS: Anal. C23H30BrN3O4 Calcd. 492.1492; found: 492.1505 $(M+H)^+$.

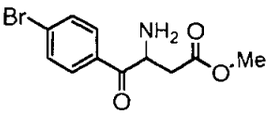
J4a Derived from example J2a		RT = 1.68 min, (Cond 1) HRMS: Anal. Calcd. for $C_{22}H_{29}BrN_3O_4$ 478.1336; found: 478.1356 $(M+H)^+$.

Synthetic Scheme 2



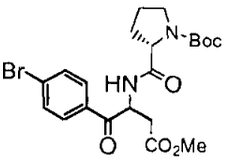
Benzyl bromide (9.98 g, 58.3 mmol) was added to a solution of 4-(4-bromophenyl)-4-oxobutanoic acid (15.0 g, 58.3 mmol) and K_2CO_3 (3.5 g, 58.3 mmol) in DMF (300 mL) and stirred for 18 hours. The reaction mixture was partitioned between water (200 mL) and ethyl acetate (500 mL). Sat'd $NaHCO_3$ soln

(20 mL) was added and the aqueous layer extracted with ethyl acetate (2x) and the combined organic layers were washed with brine and dried and filtered. Concentration gave Example J5, benzyl 4-(4-bromophenyl)-4-oxobutanoate 16 g (79%) which was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 8.6 Hz, 2H), 7.61 (d, J = 8.5 Hz, 2H), 7.35-7.34 (m, 5H), 5.14 (s, 2H), 3.27 (t, J = 6.7 Hz, 2H), 2.81 (t, J = 6.7 Hz, 2H). HRMS: Anal. C17H16BrNO3 Calcd. 347.0277; found: 347.0283 $(M+H)^+$.



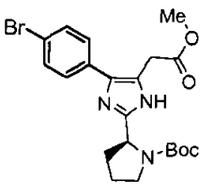
J6

Bromine (2.5 mL, 46.1 mmol) was added to a solution of Example J5, benzyl 4-(4-bromophenyl)-4-oxobutanoate (16 g, 46.1 mmol) in ether (200 mL) and 1,4-Dioxane (50 mL) and the solution was stirred for 6 hours before being concentrated by rotory evaporation and taken up in acetonitrile (450 mL). Sodium azide (3.0 g, 46.1 mmol) was added and the reaction mixture stirred 18 hours. The solvent was removed upon concentration and the residue taken up in ethyl acetate and wash with water, brine, dried Na_2SO_4, and filtered. Concentration gave benzyl 3-azido-4-(4-bromophenyl)-4-oxobutanoate 17g (95%) which was carried forward without further purification. Tin (II) chloride dehydrate (24.9 g, 131 mmol) was added to a solution of benzyl 3-azido-4-(4-bromophenyl)-4-oxobutanoate (17 g, 43.8 mmol) in CH_3OH (550 mL) and stirred for 14 hours at 65 °C. The reaction was concentrated by rotory evaporation and dried under high vacuum for 18 hours to give a mixture of benzyl and Example J6, methyl 3-amino-4-(4-bromophenyl)-4-oxobutanoate, (transesterifcation had occurred) and carried forward with purification. RT = 1.3 minutes (condition 1); LCMS: Anal. C11H12BrNO3 Calcd. 286.0; found: 286.14 $(M+H)^+$.



J7

HATU (10.5 g, 27.6 mmol) was added to a solution of Example J6, methyl 3-amino-4-(4-bromophenyl)-4-oxobutanoate (10 g, 27.6 mmol), (S)-N-Boc-proline (7.13 g, 33.1 mmol), and Hunig'sBase (45 mL, 276 mmol) in DMF (150 mL) and stirred for 18 hours at 24 °C. The reaction was diluted with ethyl acetate (2 vol) and H2O (1/4 vol) and sat $NaHCO_3$ (1/8 vol). Filter through diatomaceous earth (Celite®) to remove tin salts. Extract aqueous layer (2x) with ethyl acetate, and concentrate combined organic to remove solvents (high vacuum on rotory evaporator). The residue was subject to a short silica gel chromatography to remove by-products, and the resultant crude product was charged (CH_2Cl_2) a 65 (M) Biotage silica gel cartridge. Gradient elution 15 - 70% B over 2 L (A = Hexanes; B = ethyl acetate) gave a less polar band of (2S)-*tert*-butyl 2-(4-(benzyloxy)-1-(4-bromophenyl)-1,4-dioxobutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate 1.35 g (8.7%) and more polar Example J7, (2S)-*tert*-butyl 2-(4-(methoxy)-1-(4-bromophenyl)-1,4-dioxobutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate 7.6 g (49%). RT = 2.0 minutes (condition 1); LCMS: Anal. C21H27BrN2O6 Calcd. 383; found: 383 (M-Boc).

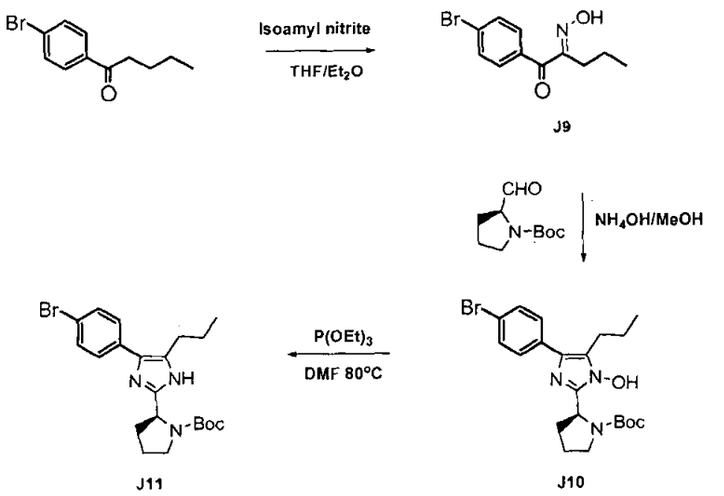


J8

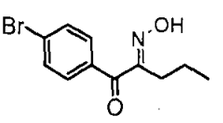
Ammonium acetate (9.4 g, 157 mmol) was added to a solution of Example J7, (2S)-*tert*-butyl 2-(4-(methoxy)-1-(4-bromophenyl)-1,4-dioxobutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (7.6 g, 15.7 mmol) in xylene (80 mL) and stirred for 4 hours at 140 °C in a screw capped 150 mL pressure vessel. After being cooled, the reaction mixture was diluted with ethyl acetate and washed with sat $NaHCO_3$ and brine before being concentrated by rotory evaporation under high vacuum. The crude product was taken up in CH_2Cl_2 and charged to a 40 (M) Biotage silica gel cartridge. Gradient elution 15 - 100% B over 2 L (A = CH_2Cl_2; B = ethyl acetate) gave Example J8, (S)-*tert*-butyl 2-(4-(4-bromophenyl)-5-(2-methoxy-2-oxoethyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate 3.38 g (46%).^{1}H NMR (500

MHz, DMSO-d_6) δ 7.54 (s, 4H), 4.83-4.73 (m, 1H), 3.81 (br. s, 1H), 3.62 (s, 3H), 3.53-3.51 (m, 1H), 3.38-3.31 (m, 2H), 2.25-2.15 (m, 1H), 1.99-1.83 (m, 3H), 1.41/1.16 (s, 9H). RT = 1.6 minutes (Condition 1). LCMS: Anal. Calcd. for C21H26BrN3O4 464.11; found: 464.40 $(M+H)^+$.

Synthetic Scheme 3

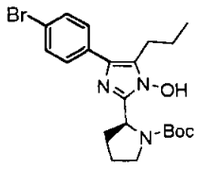


Reference: *J.Med.Chem.*(84), *27*, 20. *Syn. Lett.* (2004) 2315.



The conc. HCl (40 mL) was added dropwise to a solution of 1-(4-bromophenyl)pentan-1-one (4.68g, 19.41 mmol) and sodium nitrite (4.02 g, 58.2 mmol) in THF (80 ml) at 0 °C and allowed to warm to room temperature and stirred 18 hours. The reaction mixture was diluted with diethyl ether and the organic phase washed with sat'd $NaHCO_3$ and brine. Concentration gave (Z)-1-(4-bromophenyl)-2-(hydroxyimino)pentan-1-one 3.1g (33%) as an oil which was used without further purification.). RT = 2.1 min, (Condition 1) LCMS: Anal. Calcd. for C11H12BrN1O2 270.01; found: 270.15 $(M+H)^+$.

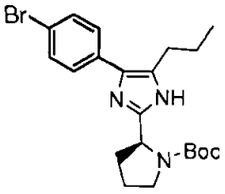
Reference: *Bioorg. Med.Chem.Lett* (2002) 1009.



J10

The 28% ammonium hydroxide (15 mL) was added to a solution of (Z)-1-(4-bromophenyl)-2-(hydroxyimino)pentan-1-one (1.5g, 5.55 mmol) and (S)-N-BOC-prolinal (1.1g, 5.55 mmol) in methanol (60 mL) and stirred for 18 hours at 24 °C. The reaction mixture was partitioned between CH_2Cl_2 and water and the organic phase concentrated and applied (CH_2Cl_2) to a 40 (M) Biotage silica gel column. Gradient elution, 5-100%, over 1L (A = Hexanes; B = ethyl acetate) gave (S)-*tert*-butyl 2-(4-(4-bromophenyl)hydroxy-5-propyl-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (863 mg, 34.5 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.54 (m, 4H), 5.0-4.88 (m, 1H), 3.53-3.41 (m, 1H), 3.41-3.36 (m, 1H), 2.72 (t, J = 7.0 Hz, 2H), 2.24-2.03 (m, 2H), 1.96-1.91 (m, 1H), 1.89-1.81 (m, 1H), 1.60 (h, J = 7.6 Hz, 2H), 1.39/1.17 (s, 9H). 0.92 (t, J = 7.0 Hz, 3H). RT = 1.9 min, (Condition 1) LCMS: Anal. Calcd. for C21H28BrN3O3 450.13; found: 450.33 $(M+H)^+$.

Reference: *Chem. Pharm. Bull.* (1994) *42*, 560.

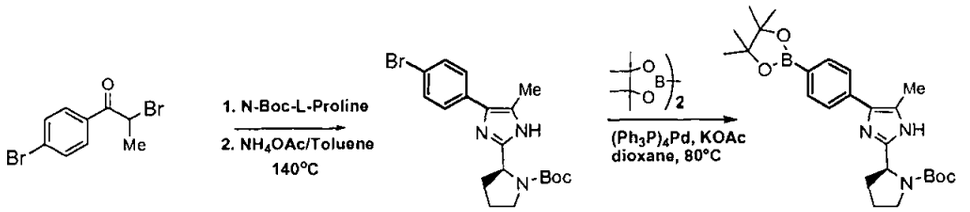


J11

The triethyl phosphite (0.9 mL, 5.33 mmol) was added to a solution of (S)-*tert*-butyl 2-(4-(4-bromophenyl)hydroxy-5-propyl-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (800 mg, 1.776 mmol) in DMF (2 mL) and stirred for 18 hours at 80 °C. Add second 0.8 mL and the reaction was continued an additional 8 hours, cooled, and taken up in ethyl acetate (400 mL) and washed with water and brine. Apply in CH_2Cl_2 to a 25 (M) Biotage silica gel column. Gradient elution, 15-100%, over 750

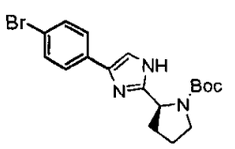
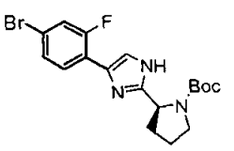
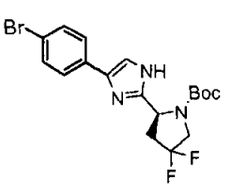
mL (A = Hexanes; B = ethyl acetate) gave (S)-*tert*-butyl 2-(4-(4-bromophenyl)-5-propyl-1H-imidazol-2-yl)pyrrolidine-1-carboxylate 585 mg (76 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.55-7.53 (m, 4H), 4.80-4.69 (m, 1H), 3.53-3.51 (m, 1H), 3.38-3.32 (m, 1H), 2.71 (t, J = 7.0 Hz, 2H), 2.24-2.11 (m, 1H), 2.0-1.79 (m, 1H), 1.89-1.79 (m, 2H), 1.63-1.59 (m, 2H), 1.41/1.17 (s, 9H). 0.91 (t, J = 7.6 Hz, 3H). RT = 1.8 min, (Condition 1) LRMS: Anal. Calcd. for C21H28BrN3O2 434.14; found: 434.0 $(M+H)^+$.

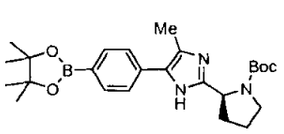
Synthetic Scheme 4



To a mixture of 2,4'-dibromopropiophenone (4.96 g, 0.017 mol) and N-Boc-L-proline (4.09 g, 0.019 mol) in dry CH_3CN (75 mL) was added DIEA (3.30 mL, 0.019 mol) and the mixture was stirred at room temperature under Ar for 16 hours. The mixture was then concentrated under reduced pressure and the concentrate was partitioned with CH_2Cl_2-10% saturated $NaHCO_3$. The organic phase was washed (brine), dried (Na_2SO_4), filtered, and concentrated to give the proline ester (7.28 g, >100%) as a colorless gum which was used as such in the next step. LCMS: Anal. Calcd. for C19H24BrNO5: 426; found: 426 $(M+H)^+$.

A mixture of the proline ester (0.435 g, 1.0 mmol) and ammonium acetate (0.308 g, 4.0 mmol) in toluene (5 mL) was heated at 140°C (bath temperature) in a sealed tube for 5 hours. The cooled reaction mixture was evaporated and the residue was chromatographed (SiO_2/ ethyl acetate-hexane, 3:2) to give Example E1 (0.320 g, 79%) as a nearly colorless foam. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.53 (s, 4H), 4.98 (m, 0.3H), 4.87 (m, 0.7H), 3.65 (m, 1H), 3.4-3.6 (m, 1H), 2.50 (s, 3H), 2.32 (m, 1H), 2.13 (m, 2H), 1.94 (m, 1H), 1.47 (s, 3H), 1.31 (s, 6H). LCMS: Anal. Calcd. for C19H24BrN3O2: 405, 407; found: 406, 408 $(M+H)^+$.

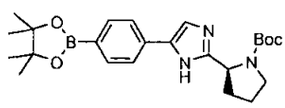
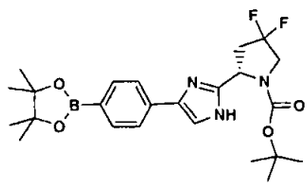
E1a		RT = 1.71 min (condition 1); LCMS: Anal. Calcd. for $C_{18}H_{23}BrN_3O_2$: 392.10; found 391.96 [M+H]+
E1b		RT = 2.27 min, (Cond 2) LRMS: Anal. Calcd. for $C_{18}H_{22}BrFN_3O_2$ 410.09 and 412.09; found: 410.08 and 412.08 $(M+H)^+$.
E1c		RT = 2.19 min, (Cond 2) LCMS: Anal. Calcd. for $C_{18}H_{21}BrF_2N_3O_2$ 428.08 and 430.08; found: 428.07 and 430.07 $(M+H)^+$.



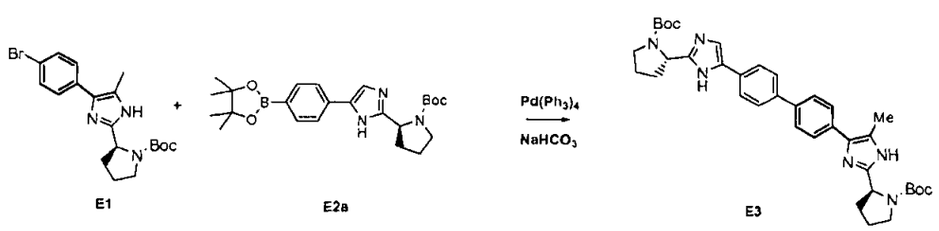
E2

A mixture of Example E1, (S)-*tert*-butyl 2-(4-(4-bromophenyl)-5-methyl-1H-imidazol-2-yl)-pyrrolidine-1-carboxylate (1.568 g, 3.86 mmol), bis(pinacolato)diboron (2.058 g, 8.10 mmol) and potassium acetate (0.947 g, 9.65 mmol) in dioxane (25 mL) was purged with a stream of Ar bubbles for 10 min and then $(Ph_3P)_4Pd$ (0.223 g, 0.19 mmol) was added and purging with Ar was continued

for another 10 min. The reaction vessel was then sealed and heated at 80°C (bath temperature) for 18 hours. The cooled mixture was diluted with dichloromethane and then it was washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated. The residue was triturated with ethyl acetate and the resulting solid was filtered, washed with a little ethyl acetate and dried in vacuo to give the title compound (quantitative) as a solid. It was used as such in the next step without further purification. ^{1}HNMR (400 MHz, DMSO-d_6) δ 11.93 (br s, 0.3H), 11.71 (br s, 0.7H), 7.65 (br s, 4H), 4.79 (m, 0.4H), 4.69 (m, 0.6H), 3.52 (m, 1H), 3.36 (m, 2H), 2.38 (s, 3H), 1.78-2.26 (m, 4H), 1.41 (s, 4H), 1.30 (s, 10H), 1.17 (m, 6H). LCMS: Anal. Calcd. for C25H36BN3O4: 453; found: 454 $(M+H)^+$.

E2a		RT = 1.64 min (condi 1); LCMS: Anal. Calcd. for C24H35BN3O4: 440.27; found 440.23. [M+H]+
E2b		RT = 2.44 min, (Cond 2) LCMS: Anal. Calcd. for C24H33BF2N3O4 476.25; found: 476.51 $(M+H)^+$.

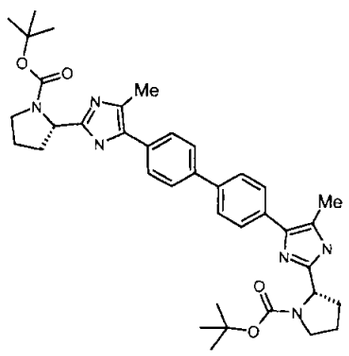
Synthetic Scheme 5

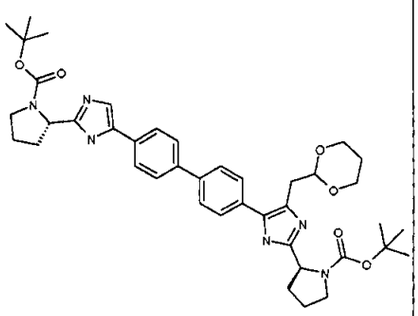
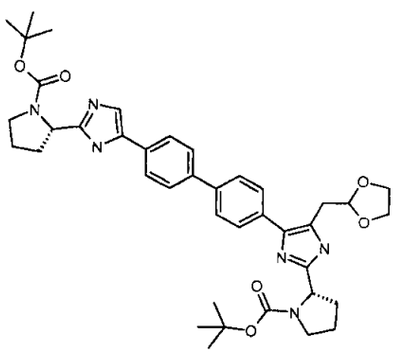


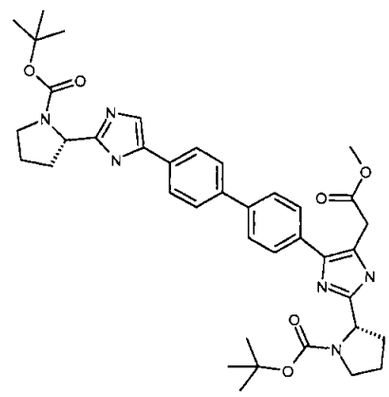
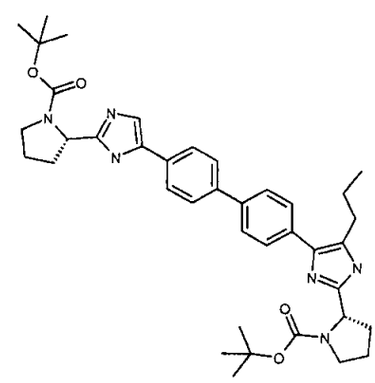
E1 E2a E3

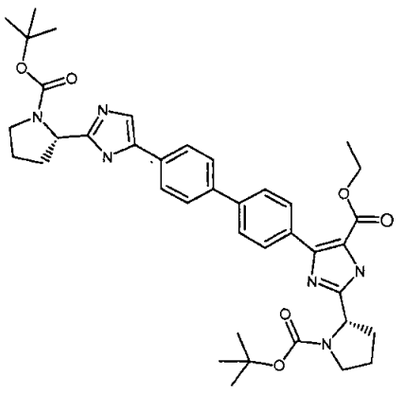
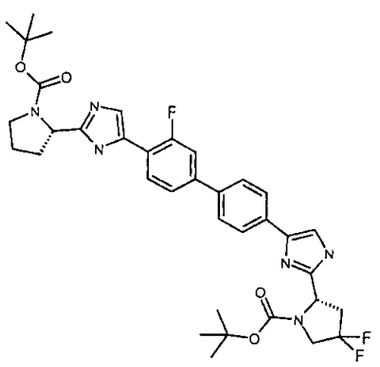
A mixture of Example E1, (S)-*tert*-butyl 2-(4-(4-bromophenyl)-5-methyl-1H-

imidazol-2-yl)-pyrrolidine-1-carboxylate (0.682 g, 1.68 mmol), Example E2a, (S)-*tert*-butyl 2-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (0.764 g, 1.74 mmol) and $NaHCO_3$ (0.465 g, 5.53 mmol) in a mixture of DME (20 mL) and H_2O (5 mL) was purged with a stream of Ar bubbles for 10 min. To this mixture was added $(Ph_3P)_4Pd$ (0.091 g, 0.08 mmol) and purging with Ar was continued for another 10 min. The reaction vessel was then sealed and heated at 80 °C (bath temperature) for 18 hours. The cooled mixture was concentrated under reduced pressure and the concentrate was diluted with ethyl acetate and washed with H_2O. The aqueous phase was back-extracted with ethyl acetate and the combined organic phase was washed (brine), dried (Na_2SO_4), filtered, and concentrated to give a gum. The residue was chromatographed (SiO_2/ ethyl acetate-hexane, 7:3) to give Example E3 (0.592 g, 59%) as a foam. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.37-7.88 (m, 8H), 7.27 (s, 1H), 5.10 (t, *J* = 7.65 Hz, 2H), 3.45 (m, 4H), 3.00 (m, 2H), 2.44 (s, 3H), 2.20 (br s, 4H), 1.99 (m, 2H), 1.53 (s, 18H). LCMS: Anal. Calcd. for C37H46N6O4: 638; found: 639 $(M+H)^+$.

E3a Derived from example E2 and E3			LCMS: Anal. Calcd. for C38H48N6O4: 652; found: 653 $(M+H)^+$.

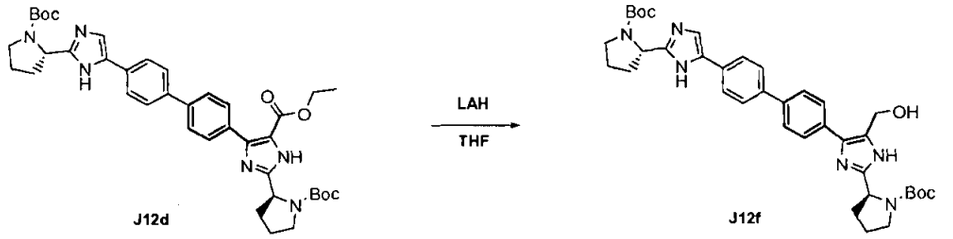
J12 Derived from example E2a and J4	tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-4-(1,3-dioxan-2-ylmethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate		RT = 1.65 min, (cond 3) HRMS: Anal. Calcd. for $C_{41}H_{53}N_6O_6$ 725.4021; found: 725.4026 $(M+H)^+$.
J12a Derived from example E2a and J4a	tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-4-(1,3-dioxolan-2-ylmethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate		RT = 1.62 min, (cond 1) HRMS: Anal. Calcd. for $C_{40}H_{51}N_6O_6$ 711.3865; found:

			711.3874 $(M+H)^+$.
J12b Derived from example E2a and J8	tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-5-(2-methoxy-2-oxoethyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate		RT = 1.72 min, (cond 1) HRMS: Anal. Calcd. for $C_{39}H_{48}N_6O_6$ 697.3087; found: 697.3721 $(M+H)^+$.
J12c Derived from example E2a and J11	tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-5-propyl-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate		RT = 1.72 min, (cond 1) LCMS: Anal. Calcd. for $C_{39}H_{50}$

			N_6O_4 667.40; found: 667.30 $(M+H)^+$.
J12d	ethyl 2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate		RT = 1.70 min, (95%) (Cond 2); LRMS: Anal. Calcd. for C38H47N6O6 683.36; found: 683.42 $(M+H)^+$
J12e Derived from example E2b and E1b	tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-3'-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinecarboxylate		RT = 2.24 min, (cond 2) LCMS: Anal. Calcd. for $C_{36}H_{42}$

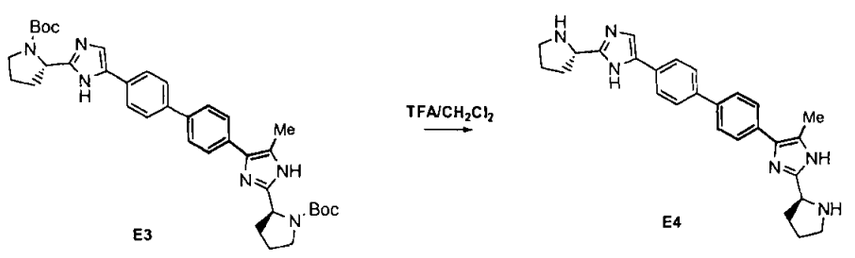
			$F_3N_6O_4$ 679.32; found: 679.57 $(M+H)^+$.

Synthetic Scheme 6

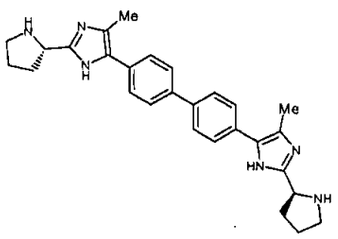
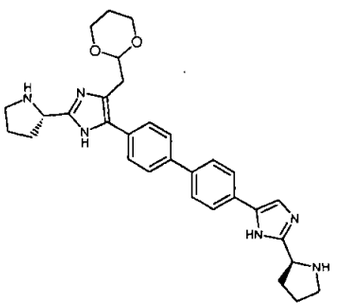
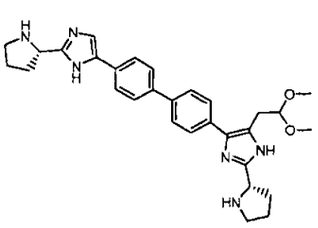


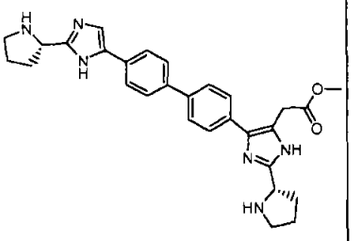
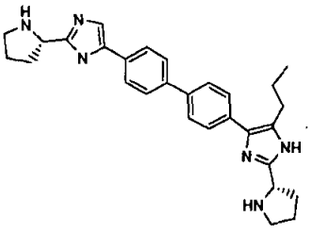
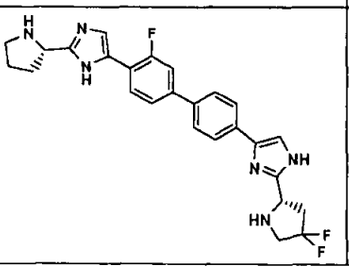
The LAH (0.7 mL, 1M in THF) was added to a solution of Example J12d, (466 mg, 0.669 mmol) in THF (50 mL) and stirred at 0°C for 1.5 hours before slowly allowing to warm to room temperature. After 3 hours the reaction was quenched with water (0.4 mL), 15% NaOH (0.4 mL) and water (0.4 mL) and the aluminum salts removed by filtration. The salts were rinsed with THF, the combined filtrates were concentrated, and the residue charged (CH_2Cl_2) to a 25 (S) Biotage silica gel cartridge and gradient eluted 15 - 100% over 1L solvent (A = CH_2Cl_2; B = 10% CH_3OH/ ethyl acetate) to give Example J12f, tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-4-(hydroxymethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate, 88 mg (20%) in addition to recovered J12d and over reduction. RT = 1.7 minutes (Condition 1); LCMS Anal. Calcd. for C37H46N6O5 665.36; found: 665.46 $(M+H)^+$.

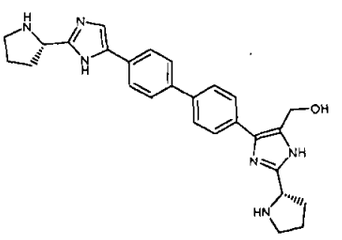
Synthetic Scheme 7



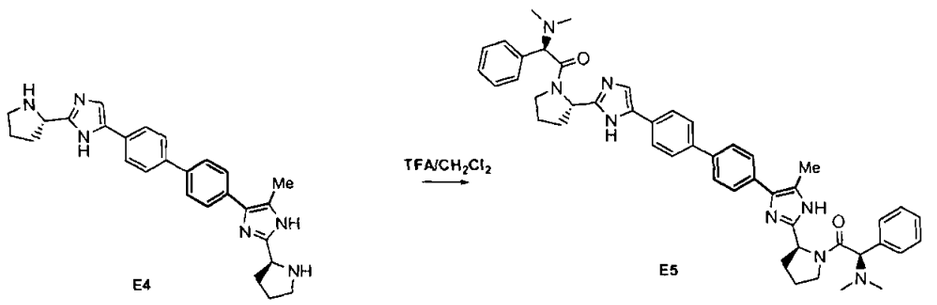
A solution of Example E3 (0.240 g, 0.376 mmol) in 5 mL of TFA-CH_2Cl_2 (4:1) was stirred at room temperature for 2 hours and then the volatiles were removed under reduced pressure. The resulting gum was taken up in a minimum volume of CH_3OH and adsorbed on an MCX LP cartridge (6 g, pre-conditioned with CH_3OH). The cartridge was washed with CH_3OH and then eluted with 2M NH_3 in CH_3OH. The product-containing fractions were combined and evaporated to give E4 (quantitative) as a gum which was used as such in the next step. LCMS: Anal. Calcd. for C27H30N6: 438; found: 439 $(M+H)^+$.

E4a			LCMS: Anal. Calcd. for $C_{28}H_{32}N_6$: 452; found: 453 $(M+H)^+$.	
J13 Derived from example J12			RT = 1.18 min, (cond 1) LCMS: Anal. Calcd. for $C_{31}H_{36}N_6O_2$ 525.29; found: 525.31 $(M+H)^+$.	Prepared using experimental conditions from example 152k-1.
J13a Derived from example J12a			RT = 1.14 min, (cond 1) LCMS: Anal. Calcd. for	Prepared using experimental conditions in

			$C_{30}H_{36}N_6O_2$ 513.29; found: 513.42 $(M+H)^+$.	example 152k-1.
J13b Derived from example J12b			RT = 1.19 min, (cond 1) LCMS: Anal. Calcd. for $C_{29}H_{32}N_6O_2$ 497.26; found: 497.48 $(M+H)^+$.	Prepared using experimental conditions as outlined in example 152k-1.
J13c Derived from example J12c			RT = 1.26 min, (cond 1) LCMS: Anal. Calcd. for $C_{39}H_{50}N_6O_4$ 467.28; found: 467.55 $(M+H)^+$.	Prepared using experimental conditions from example 152k-1.
J13e Derived from example J12e	2-((2S)-4,4-difluoro-2-pyrrolidinyl)-4-(3'-fluoro-4'-(2-((2S)-2-		RT = 1.77 min, (Cond 2) LCMS: Anal.	Prepared using experimental conditio

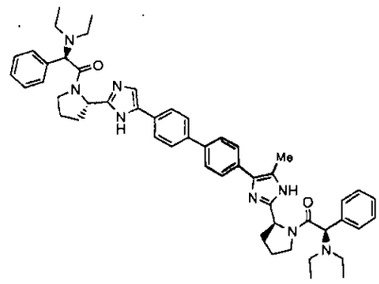
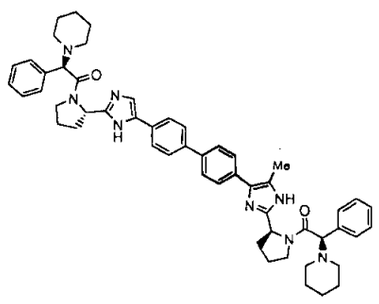
	pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazole		Calcd. for $C_{26}H_{26}F_3N_8$ 479.22; found: 479.39 $(M+H)^+$.	ns from example 152k-1.
J13f Derived from example J12f			RT = 1.02 min, (cond 1) LCMS: Anal. Calcd. for $C_{27}H_{30}N_6O$ 455.25; found: 455.47 $(M+H)^+$.	Prepared using experimental conditions from example 152k-1.

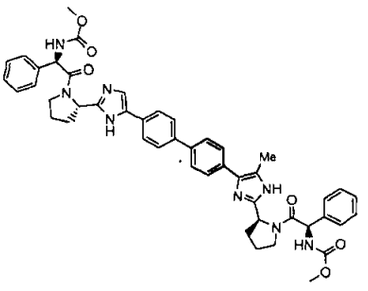
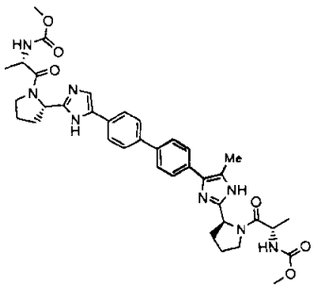
Synthetic Scheme 8

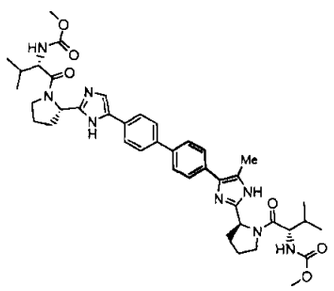
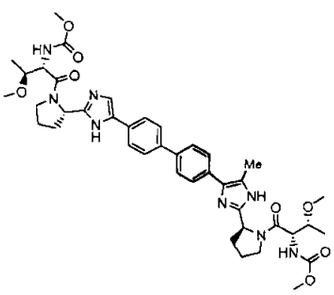


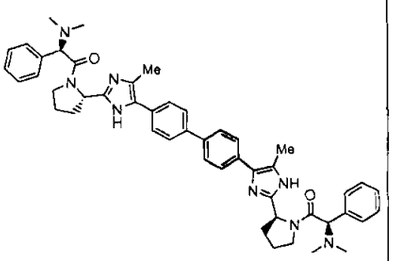
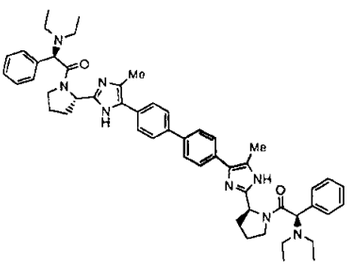
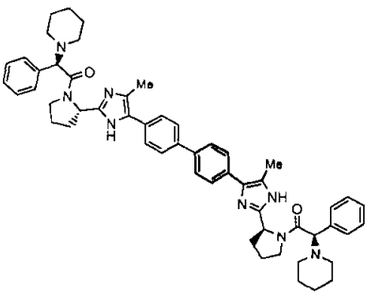
A solution of (R)-2-(dimethylamino)-2-phenylacetic acid hydrochloride (0.047 g, 0.220 mmol), HATU (0.084 g, 0.220 mmol) and DIEA (0.17 mL, 0.70 mmol) in dry DMF (1 mL) was stirred at room temperature for 5 min and then a solution of E4 (0.041 g, 0.094 mmol) in dry DMF (0.5 mL) was added. The mixture was stirred at room temperature for 18 hours and then it was quenched with AcOH (0.2 mL) and a few drops of TFA. This solution was submitted directly to preparative HPLC (C-18/ CH_3CN-H2O+0.1% TFA) to give the TFA salt of Example

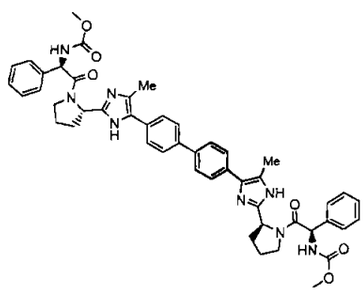
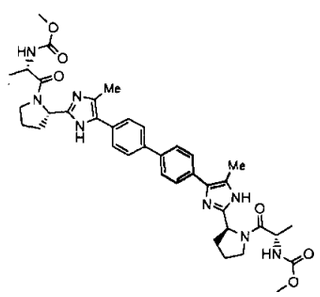
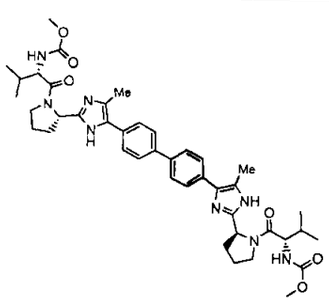
E5, (1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-5-methyl-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-dimethyl-2-oxo-1-phenylethanamine (0.011 g, 10%) as a white solid. ^{1}HNMR (400 MHz, CH_3OH-d_4) δ 7.80-7.93 (m, 6H), 7.71-7.74 (m, 2H), 7.50-7.67 (m, 10H), 5.37-5.51 (m, 2H), 5.30 (m, 2H), 4.04 (br s, 3H), 3.00-3.13 (m, 4H), 2.81 (br s, 8H), 2.55 (s, 2H), 2.49 (s, 1H), 2.36 (m, 2H), 2.12-2.25 (m, 5H), 1.96 (br s, 2H). LCMS: Anal. Calcd. for C47H52N8O2: 760; found: 761 $(M+H)^+$.

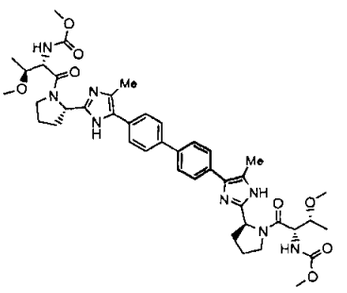
E5a Derived from example E4	(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-5-methyl-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine		LCMS: Anal. Calcd. for $C_{51}H_{60}N_8O_2$: 816; found: 817 $(M+H)^+$.
E5b Derived from example E4	1-((1R)-2-((2S)-2-(4-(4'-(4-methyl-2-((2S)-1-((2R)-2-phenyl-2-(1-piperidinyl)acetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)piperid		LCMS: Anal. Calcd. for $C_{53}H_{60}N_8O_2$: 840; found: 841 $(M+H)^+$.

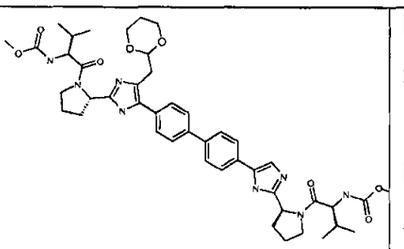
	ine		
E5c Derived from example E4	methyl ((1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-((methoxycarbonyl)amino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-5-methyl-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate		LCMS: Anal. Calcd. for $C_{47}H_{48}N_8O_6$: 820; found: 821 $(M+H)^+$.
E5d Derived from example E4	methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-4-methyl-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for $C_{37}H_{44}N_8O_6$: 696; found: 697 $(M+H)^+$.

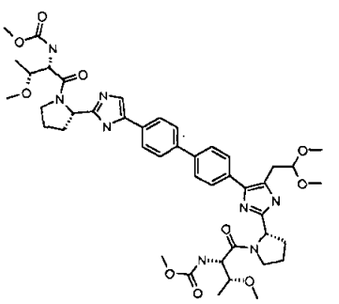
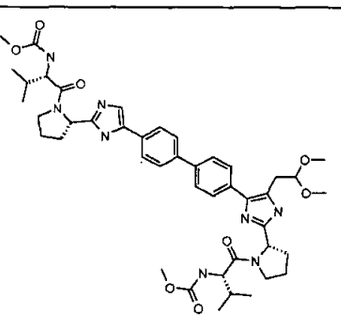
E5e Derived from example E4	methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-5-methyl-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{52}N_8O_6$: 752; found: 753 $(M+H)^+$.
E5f Derived from example E4	methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-4-methyl-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		LCMS: Anal. Calcd. for $C_{41}H_{52}N_8O_8$: 784; found: 785 $(M+H)^+$.

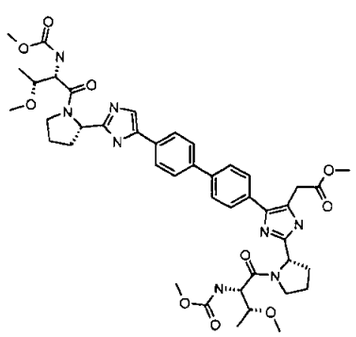
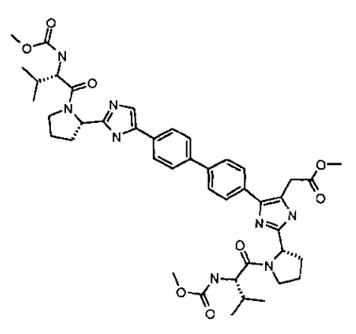
E5g Derived from example E4a	(1R,1'R)-2,2'-(4,4'-biphenyldiylbis((4-methyl-1H-imidazole-5,2-diyl)(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)		LCMS: Anal. Calcd. for $C_{48}H_{54}N_8O_2$: 774; found: 775 $(M+H)^+$.
E5h Derived from example E4a	(1R,1'R)-2,2'-(4,4'-biphenyldiylbis((4-methyl-1H-imidazole-5,2-diyl)(2S)-2,1-pyrrolidinediyl))bis(N,N-diethyl-2-oxo-1-phenylethanamine)		LCMS: Anal. Calcd. for $C_{52}H_{62}N_8O_2$: 830; found: 831 $(M+H)^+$.
E5i Derived from example E4a	1,1'-(4,4'-biphenyldiylbis((4-methyl-1H-imidazole-5,2-diyl)(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))dipiperidine		LCMS: Anal. Calcd. for C54H62N8O2: 854; found: 855 $(M+H)^+$.

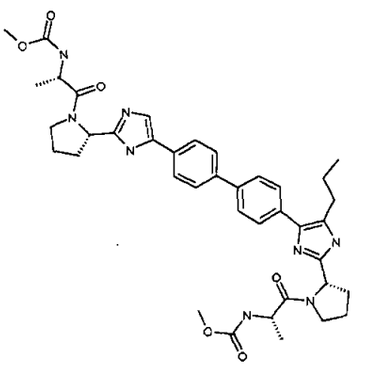
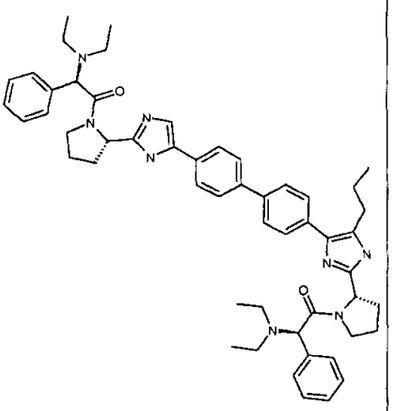
E5j Derived from example E4a	dimethyl (4,4'-biphenyldiylbis((4-methyl-1H-imidazole-5,2-diyl)(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate		LCMS: Anal. Calcd. for C48H50N8O6: 834; found: 835 $(M+H)^+$.
E5k Derived from example E4a	methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-5-methyl-1H-imidazol-4-yl)-4-biphenylyl)-5-methyl-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate		LCMS: Anal. Calcd. for C38H46N8O6: 710; found: 711 $(M+H)^+$.
E5l Derived from example E4a	methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-4-		LCMS: Anal. Calcd. for C42H54N8O6: 766; found: 767 $(M+H)^+$.

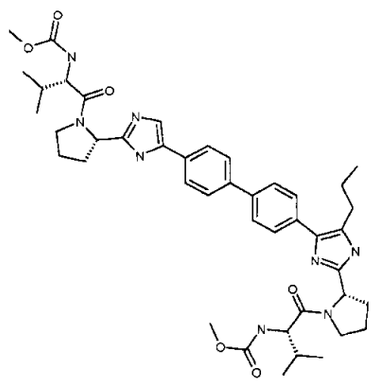
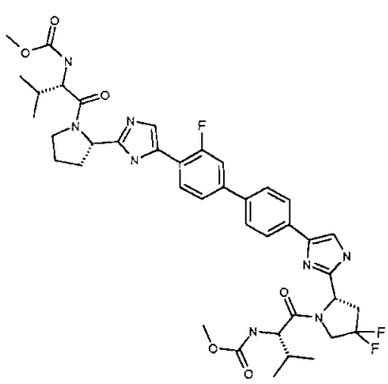
	methyl-1H-imidazol-5-yl)-4-biphenylyl)-5-methyl-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		
E5m Derived from example E4a	methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-5-methyl-1H-imidazol-4-yl)-4-biphenylyl)-5-methyl-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate		LCMS: Anal. Calcd. for C42H54N8O8: 798; found: 799 $(M+H)^+$.

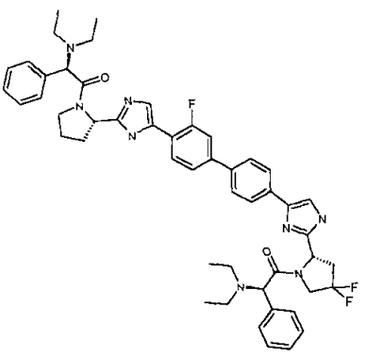
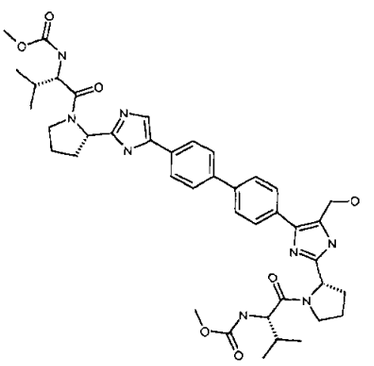
J14 Derived from example J13	methyl ((1S)-1-(((2S)-2-(4-(1,3-dioxan-2-ylmethyl)-5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)		RT = 1.37 min, (Cond 1); HRMS: Anal. Calcd. for

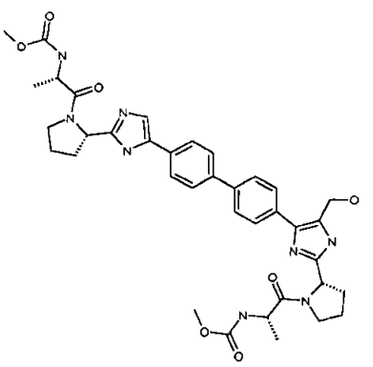
	amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		$C_{45}H_{58}N_8O_8$ 839.4450; found: 839.4456 $(M+H)^+$.
J14a Derived from example J13a	methyl ((1S,2R)-1-(((2S)-2-(4-(2,2-dimethoxyethyl)-5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate		RT = 1.44 min, (Cond 1); HRMS: Anal. Calcd. for $C_{44}H_{58}N_8O_{10}$ 859.4349; found: 859.4352 $(M+H)^+$.
J14a.1 Derived from example J13a	methyl ((1S)-1-(((2S)-2-(4-(2,2-dimethoxyethyl)-5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-		RT = 1.44 min, (Cond 1); HRMS: Anal. Calcd. for $C_{44}H_{58}N_8O_8$

	methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		827.4450; found: 827.4449 $(M+H)^+$.
J14b Derived from example J13b	methyl (2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-5-yl)acetate		HRMS: Anal. Calcd. for $C_{43}H_{54}N_8O_{10}$ 843.4036; found: 843.4046 $(M+H)^+$.
J14b.1 Derived from example J13b	methyl (2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-		RT = 1.42 min, (Cond 1); HRMS: Anal. Calcd. for $C_{43}H_{54}N_8O_8$ 811.4137;

	pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-5-yl)acetate		found: 811.4154 $(M+H)^+$.
J14c Derived from example J13c	methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-4-propyl-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate		RT = 1.42 min, (Cond 1); HRMS: Anal. Calcd. for $C_{39}H_{49}N_8O_6$ 725.3775; found: 725.3758 $(M+H)^+$.
J14c.1 Derived from example J13c	(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-5-propyl-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine		RT = 1.39 min, (Cond 1); HRMS: Anal. Calcd. for $C_{53}H_{65}N_8O_2$ 845.5225; found: 845.5207 $(M+H)^+$.

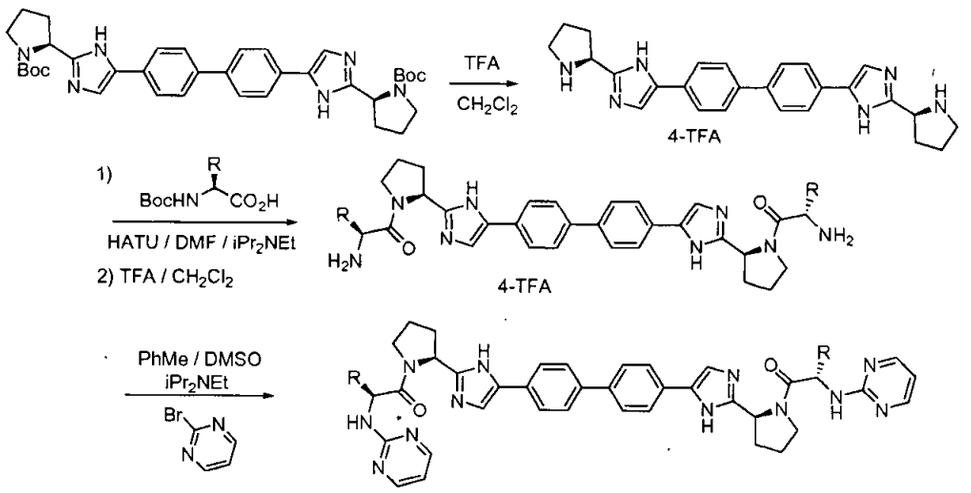
J14c.2 Derived from example J13c	methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-5-propyl-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		RT = 1.59 min, (Cond 1); HRMS: Anal. Calcd. for $C_{43}H_{57}N_8O_6$ 781.4317; found: 781.4377 $(M+H)^+$.
J14e Derived from example J13e	methyl ((1S)-1-(((2S)-4,4-difluoro-2-(4-(3'-fluoro-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		RT = 1.99 min, (Cond 2) HRMS: Anal. Calcd. for $C_{40}H_{48}F_3N_8O_6$ 793.3643; found: 793.3653 $(M+H)^+$.

J14e.1 Derived from example J13e	(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-4,4-difluoro-2-pyrrolidinyl)-1H-imidazol-4-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine		RT = 1.79 min, (Cond 2) HRMS: Anal. Calcd. for $C_{50}H_{56}F_3N_8O_2$ 857.4473; found: 857.4478 $(M+H)^+$.
J14f Derived from example J13f	methyl ((1S)-1-(((2S)-2-(4-(hydroxymethyl)-5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate		RT = 1.40 min, (Cond 1); HRMS: Anal. Calcd. for $C_{41}H_{53}N_8O_7$ 769.4037; found: 769.4020 $(M+H)^+$.

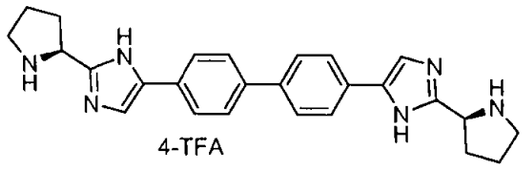
J14f.1 Derived from example J13f	methyl ((1S)-2-((2S)-2-(4-(4'-(4-(hydroxymethyl)-2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate		RT = 1.21 min, (Cond 1); HRMS: Anal. Calcd. for $C_{37}H_{45}N_8O_7$ 713.3411; found: 713.3391 $(M+H)^+$.

Section PY

Scheme 1



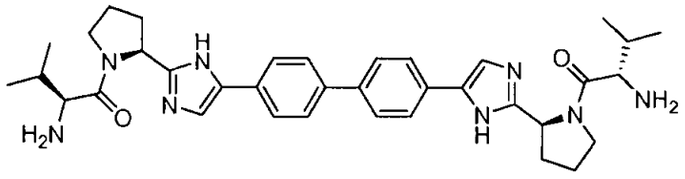
Example PY1. 4,4'-bis(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl trifluoroacetic acid salt



4-TFA

To a solution of (2S,2'S)-tert-butyl 2,2'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))dipyrrolidine-1-carboxylate (2.61 g, 4.18 mmol) in CH_2Cl_2 (25 mL) was added TFA (12 mL) and the mixture was allowed to stir at room temperature. After allowing the reaction to stir for 2 hours it was concentrated to dryness *in vacuo*. The material was used withouth further purification in subsequent steps. LCMS: Anal. Calcd. for $C_{26}H_{28}N_6$: 424; found: 425 $(M+H)^+$.

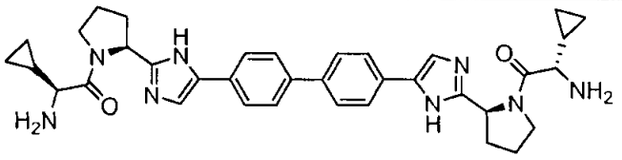
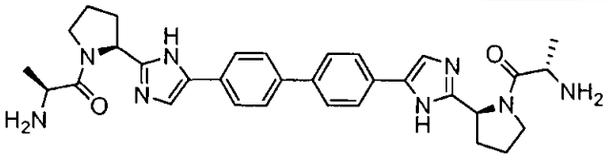
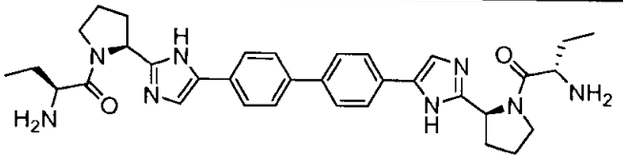
Example PY2. (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(2-amino-3-methylbutan-1-one).

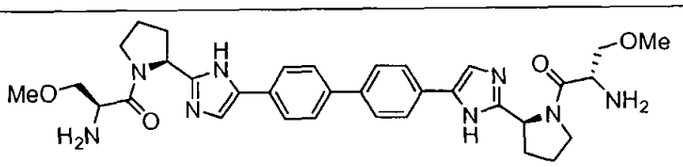
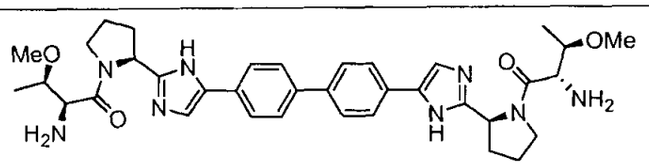


To a solution of 4,4'-bis(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)biphenyl tetrakis(2,2,2-trifluoroacetate) (2.695 g, 3.06 mmol), (S)-2-(tert-butoxycarbonylamino)-3-methylbutanoic acid (1.60 g, 7.34 mmol) and DIEA (5.3 mL, 30.6 mmol) in DMF (15 mL) was added HATU (2.39 g, 6.27 mmol) and the mixture was allowed to stir at room temperature for 14 h. MeOH (5 mL) was added and the mixture was allowed to stir for 4h. It was then poured into ca. 150 mL of cold water and allowed to stand for 20 min. The solid was filtered and dried under vacuum overnight and then purified by biotage (40+M, 0 to 25% MeOH in EtOAc) to give a yellow brown foam (1.76 g, 70%). ^{1}HNMR (300 MHz, DMSO-d_6) δ 12.11 – 12.17 (m, 1H), 11.76 (s, 1H), 7.73 – 7.94 (m, 4H), 7.62 – 7.70 (m, 4H), 7.49 (d, J = 1.8 Hz, 1H), 6.76 (d, J = 8.5 Hz, 1H), 5.06 (dd, J = 2.7, 6.3 Hz, 2H), 4.00 – 4.07 (m, 2H), 3.77 (s, br, 3H), 2.07 – 2.15 (m, 4H), 1.88 – 2.00 (m, 6H), 1.37 (s, 18H), 0.88 (d, J = 6.6 Hz, 6H), 0.82 (d, J = 6.6 Hz, 6H). LCMS: Anal. Calcd. for $C_{46}H_{62}N_8O_6$: 822; found: 823 $(M+H)^+$. The material was suspended in CH_2Cl_2 (15 mL) and TFA (6 mL) was added. After stirring for 2h the solvents were removed *in vacuo* giving a yellow orange solid. The solid was partitioned between sat $NaHCO_3$ and EtOAc however the

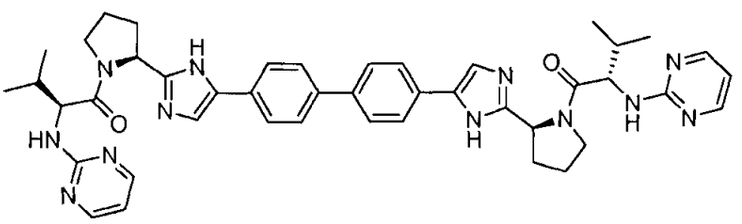
material was insoluble in EtOAc. Therefore the volatiles were removed *in vacuo* and the residue was loaded on to an SCX cation exchange cartridge and eluted with MeOH and then NH_3 in MeOH (2M). The appropriate fractions were concentrated *in vacuo* to give a yellow foam (1.24 g, 65%). LCMS: Anal. Calcd. for $C_{36}H_{46}N_8O_2$: 622; found: 623 $(M+H)^+$. The material was used as is in subseqent steps.

The following were prepared similarly. Note that in some cases the TFA salt obtained from the Boc deprotection was carried forward directly.

Example	*Structure*	*Analytical Data*
Example PY3		LCMS: Anal. Calcd. for $C_{36}H_{42}N_8O_2$: 618; found: 619 $(M+H)^+$.
Example PY4		LCMS: Anal. Calcd. for $C_{32}H_{38}N_8O_2$: 566; found: 567 $(M+H)^+$.
Example PY5		LCMS: Anal. Calcd. for $C_{34}H_{42}N_8O_2$: 594; found:

		595 $(M+H)^+$.
Example PY6		LCMS: Anal. Calcd. for $C_{34}H_{42}N_8O_4$: 626; found: 627 $(M+H)^+$.
Example PY7		LCMS: Anal. Calcd. for $C_{36}H_{42}N_8O_2$: 618; found: 619 $(M+H)^+$.

Example PY8 (N,N'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-3-methyl-1-oxo-1,2-butanediyl)))di(2-pyrimidinamine)

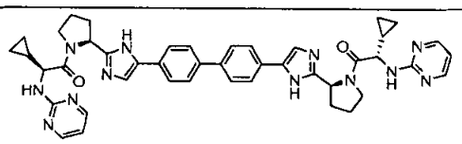


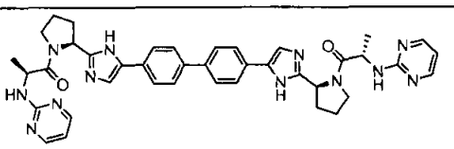
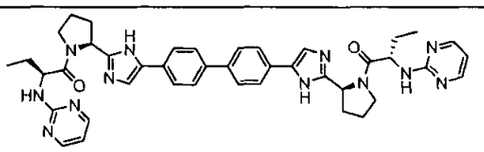
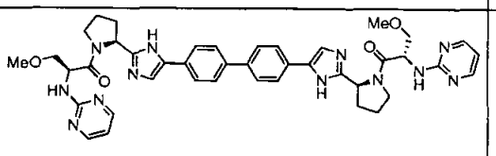
A mixture of (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(2-amino-3-methylbutan-1-one) (222 mg, 0.36 mmol), 2-bromopyrimidine (0.170 g, 1.07 mmol) and iPr_2NEt (0.25 mL, 1.432 mmol) in toluene (3 mL) and DMSO (0.5 mL) was heated at 90°C overnight. LCMS indicated the reaction to be incomplete therefore heating was continued for a further 12 hours. The volatiles were removed *in vacuo* and the residue was diluted with MeOH and purified by prep HPLC (CH_3CN-H_2O-NH_4OAc). The appropriate

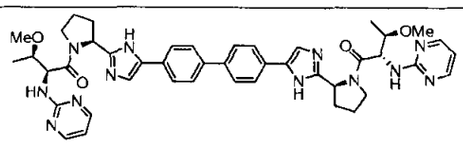
fractions were concentrated *in vacuo* and subsequently re-purified by prep HPLC (CH_3CN-H_2O-TFA). The appropriate fractions were adsorbed onto an MCX cation exchange resin cartridge (Oasis) and the resin was washed with MeOH and eluted with 2M NH3 in MeOH. The solvent was removed *in vacuo* and the residue was lyophyllized to give a colorless solid (17.2 mg, 6%). ^{1}HNMR (300 MHz, DMSO-d_6) δ 12.15, 12.28 (s, 1H, rotamers, 1:1 ratio), 8.28 (d, J = 4.8 Hz, 4H), 7.79 (app d, J = 8.1 Hz, 4H), 7.62 – 7.70 (m, 4H), 7.49 (d, J = 1.5 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 6.60 (t, J = 4.8 Hz, 2H), 5.05 (dd, J = 6.9, 4.0 Hz, 2H), 4.50 (app t, unresolved dd, J = 8.5, 8.0 Hz, 2H), 3.98 – 4.06 (m, 2H), 3.78 – 3.85 (m, 2H), 1.98 – 2.23 (m, 10H), 0.96 (d, J= 6.6 Hz, 6H), 0.92 (d, J= 6.6 Hz, 6H). LCMS: Anal. Calcd. for $C_{44}H_{50}N_{12}O_2$: 778; found: 779 $(M+H)^+$.

The following were prepared similarly:

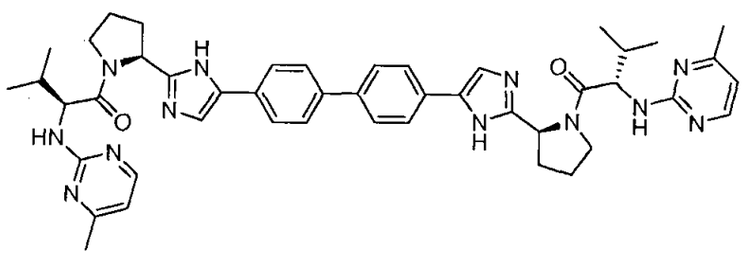
Note that in some cases the TFA salt obtained from the Boc deprotection was carried forward directly and an appropriate amount of iPr_2NEt was added to the reaction mixture.

Compound Name	*Example*	*Structure*	*Analytical Data*
N,N'-(4,4'-biphenyldiyl bis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl))) di(2-pyrimidinami	*Example PY 9*		LCMS: Anal. Calcd. for $C_{36}H_{42}N_8O_2$: 618; found: 619 $(M+H)^+$.

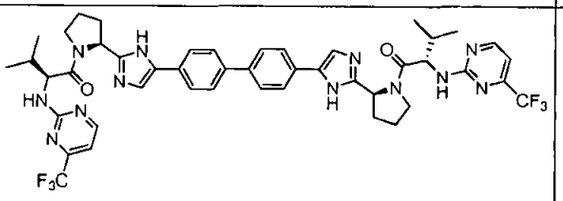
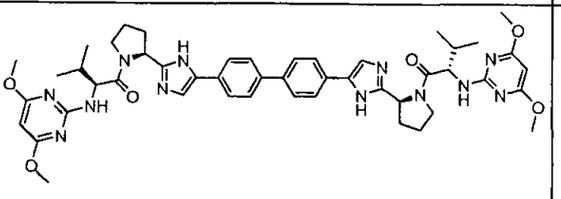
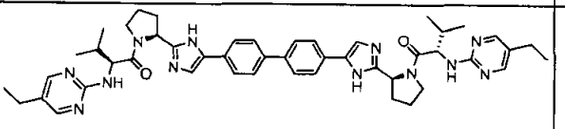
ne)			
N,N'-(4,4'-biphenyldiyl bis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-1-oxo-1,2-propanediyl)))di(2-pyrimidinamine)	*Example PY10*		LCMS: Anal. Calcd. for $C_{32}H_{38}N_8O_2$: 566; found: 567 $(M+H)^+$.
N,N'-(4,4'-biphenyldiyl bis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-1-oxo-1,2-butanediyl))) di(2-pyrimidinamine)	*Example PY11*		LCMS: Anal. Calcd. for $C_{34}H_{42}N_8O_2$: 594; found: 595 $(M+H)^+$.
N,N'-(4,4'-biphenyldiyl bis(1H-imidazole-4,2-diyl(2S)-	*Example PY12*		LCMS: Anal. Calcd. for $C_{34}H_{42}N_8O_4$: 626;

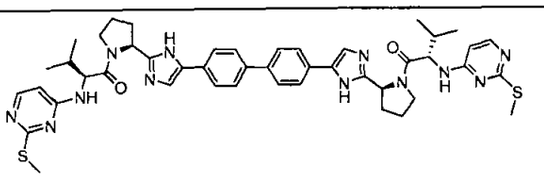
2,1-pyrrolidinediyl((2S)-3-methoxy-1-oxo-1,2-propanediyl))di(2-pyrimidinamine)			found: 627 $(M+H)^+$.
N,N'-(4,4'-biphenyldiyl bis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((2S,3R)-3-methoxy-1-oxo-1,2-butanediyl))) di(2-pyrimidinamine)	*Example PY13*		LCMS: Anal. Calcd. for $C_{36}H_{42}N_8O_2$: 618; found: 619 $(M+H)^+$.

Example PY14. (Modified method)

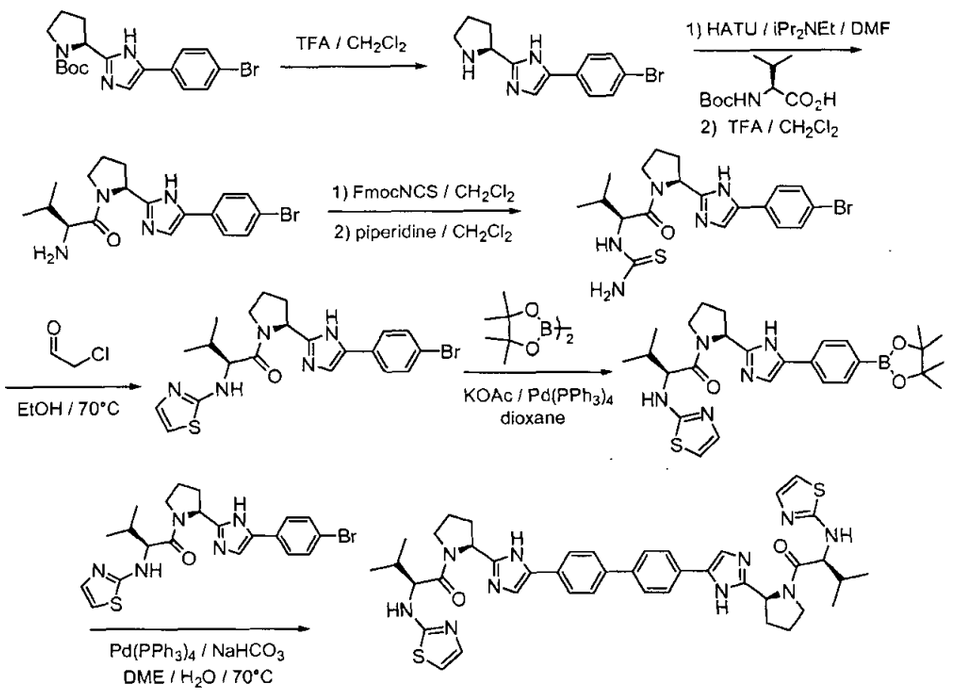


A mixture of (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(2-amino-3-methylbutan-1-one) (50 mg, 0.080 mmol), 2-chloro-4-methylpyrimidine (103 mg, 0.803 mmol), and DIPEA (0.140 mL, 0.803 mmol) in NMP (3 mL) was heated in a sealed tube for 4h at 140°C using a Microwave. The volatiles were removed *in vacuo* and the residue was diluted with MeOH and filtered through a Strata XC MCX cartridge. The cartridge was washed with methanol. The compound was release from the cartridge by washing with a solution of 2M of Ammonia/Methanol. The filtrate was evaporated under reduced pressure to give an orange oil. The crude material was purified HPLC (CH_3CN-H_2O-NH_4OAc). The appropriate fractions were concentrated *in vacuo* and subsequently re-purified by prep HPLC (CH_3CN-H_2O-TFA). The appropriate fractions were concentrated *in vacuo* to give a Yellow solid (21.5 mg, 31.9%). LCMS: Anal. Calcd. for $C_{46}H_{54}N_{12}O_2$:807; found: 807.5 $(M+H)^+$.

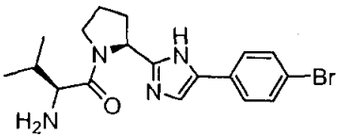
Example	Structure	Analytical Data
Example PY15		LCMS: Anal. Calcd. for $C_{46}H_{48}F_6N_6O_2$:914; found:915.16 $(M+H)^+$.
Example PY16		LCMS: Anal. Calcd. for $C_{48}H_{58}N_{12}O_6$:898; found: $(M+H)^+$899.21. 16
Example PY17		LCMS: Anal. Calcd. for $C_{48}H_{58}N_{12}O_2$:834; found: $(M+H)^+$835.45.

Example PY18		LCMS: Anal. Calcd. for $C_{46}H_{54}N_{12}O_4S_2$: 870; found:$(M+H)^+$ 871.24.

Scheme 2



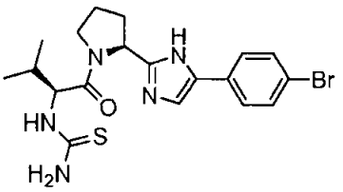
Example PY19. (S)-2-amino-1-((S)-2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methylbutan-1-one.



The title compound was prepared from (S)-tert-butyl 2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate and (S)-2-amino-3-methylbutanoic acid by the procedures detailed in Examples 1 and 2. ^{1}HNMR (300 MHz, DMSO-d_6) δ

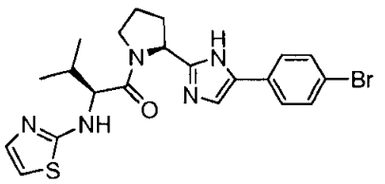
11.73 (s, 1H), 7.68 (d, J = 5.9 Hz, 1H), 7.65 (d, J = 5.9 Hz, 1H), 7.46 – 7.58 (m, 3H), 5.14, 5.05 (dd, J = 7.0, 3.0 Hz, 1H, rotamers, 1:1 ratio), 3.66 (app t, J = 6.5 Hz, 1H), 3.53 – 3.61 and 3.38 – 3.47 (m, 1H, rotamers, 1:1 ratio), 3.28 (s, 2H), 1.70 – 2.21 (m, 6H), 0.75 – 0.88 (m, 6H). LCMS: Anal. Calcd. for $C_{18}H_{23}BrN_4O$: 390, 392; found: 391, 393 $(M+H)^+$.

Example PY20. 1-((S)-1-((S)-2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)thiourea.



To a solution of (S)-2-amino-1-((S)-2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methylbutan-1-one (1.530 g, 3.91 mmol) in CH_2Cl_2 (10 mL) was added O-(9H-fluoren-9-yl)methyl carbonisothiocyanatidate (1.100 g, 3.91 mmol) as a solid in one portion. The mixture was allowed to stir at room temperature for 12 h. Piperidine (2 mL) was added to the mixture and it was allowed to stir at room temperature for 1 h. A further portion of piperidine (2 mL) was added and the solution allowed to stir 1 h. The solution was concentrated to dryness and the residue was purified by column chromatography (biotage, eluting with 5:4.5:0.5 hex:EtOAc:MeOH, and then 5% MeOH in EtOAc). The title compound as obtained as a light yellow glass (1.30 g, 74%). ^{1}HNMR (300 MHz, DMSO-d_6) δ 11.81 (s, H), 7.65 (d, J = 8.8 Hz), 7.63 – 7.71 (m, overlap with previous peak, 2H total), 7.42 – 7.56 (m, 2H), 7.10 – 7.14 (m, 1H), 5.06 (dd, J = 7.0, 3.0 Hz, 1H), 4.94 (app t, J = 8.0 Hz, 1H), 4.72 – 4.76 and 4.56 – 4.62 (m, 1H, rotamers, 1:1 ratio), 3.77 – 3.90 (m, 1H), 2.07 – 2.14 (m, 2H), 1.90 – 1.98 (m, 3H), 0.93 (d, J = 7.0 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H). LCMS: Anal. Calcd. for $C_{19}H_{24}BrN_5OS$: 449, 451; found: 450, 452 $(M+H)^+$.

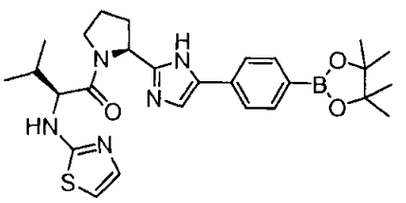
Example PY21. (S)-1-((S)-2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-2-(thiazol-2-ylamino)butan-1-one.



A solution of 1-((S)-1-((S)-2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)thiourea (1.29 g, 2.86 mmol) was dissolved in EtOH (50 mL) and 2-chloroacetaldehyde (0.4 mL, 3.15 mmol) was added. The mixture was heated at 70°C overnight. A further portion of 2-chloroacetaldehyde (0.4 mL, 3.15 mmol) was added and heating continued for a further 12 h. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (biotage), eluting with 50% EtOAc in hexanes and then 10% MeOH in EtOAc. The desired product was isolated as a orange-brown foam (557.2 mg). LCMS (NH_4OAc) shows this to be of sufficient purity. Eluting further with 100% MeOH gave a second fraction (980.8 mg) which was shown to contain the product by TLC (5:4.5:0.5 hex:EtOAc:MeOH). This second fraction from the column was re-purified to give a light orange-brown foam (426.6 mg). The two fractions were combined to afford the title compound as a orange brown foam (983.8 mg, 72%).

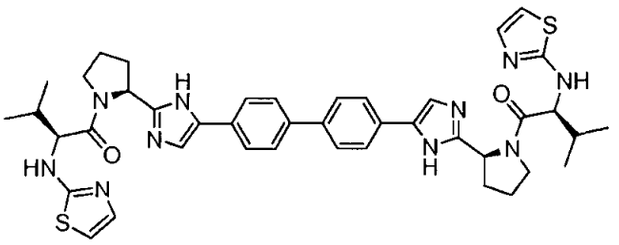
^{1}HNMR (300 MHz, CD_3OD) δ 7.57 (app d, J = 8.0 Hz, 2H), 7.47 (app d, J = 8.0 Hz, 2H), 7.32 (s, 1H), 6.98 (d, J = 3.6 Hz, 1H), 6.55 (d, J = 3.6 Hz, 1H), 5.32 – 5.35 and 5.10 – 5.15 (m, 1H, rotamers, 1:3 ratio), 4.08 – 4.15 (m, 1H), 3.82 – 3.90 (m, 1H), 3.03 – 3.15 (m, 1H), 2.03 – 2.33 (m, 4H), 1.06 and 0.99 (d, J = 7.0 Hz, 3H, rotamers 1:3 ratio), 1.04 and 0.94 (d, J = 7.0 Hz, 3H, rotamers 1:3 ratio). LCMS: Anal. Calcd. for $C_{21}H_{24}BrN_5OS$: 473, 475; found: 474, 476 $(M+H)^+$.

Example PY22. (S)-3-methyl-1-((S)-2-(5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-2-(thiazol-2-ylamino)butan-1-one.



A mixture of (S)-1-((S)-2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-2-(thiazol-2-ylamino)butan-1-one (87.5 mg, 0.184 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (141 mg, 0.553 mmol), potassium acetate (91 mg, 0.922 mmol) and $Pd(Ph_3P)_4$ (21.31 mg, 0.018 mmol) was suspended in dioxane and degassed by bubbling N_2 through the mixture. It was then heated at 85°C. After heating for 4 h the mixture was concentrated and purified by passing through a pad of silica gel eluting with 1:1 hex:EtOAc, and then EtOAc (neat) to give afforded the desired product as a light yellow film (101 mg). LCMS (CH_3CN-H_2O-NH_4OAc) showed that the product was contaminated with ca. 10% PPh_3O. The material was used as is in subsequent steps. LCMS: Anal. Calcd. for $C_{27}H_{36}BN_5O_3S$: 521; found: 522 $(M+H)^+$.

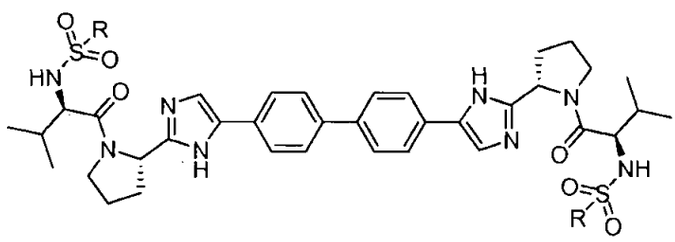
Example PY23. (N,N'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-3-methyl-1-oxo-1,2-butanediyl)))bis(1,3-thiazol-2-amine)



A mixture of (S)-3-methyl-1-((S)-2-(5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-2-(thiazol-2-ylamino)butan-1-one (275 mg, 0.527 mmol), (S)-1-((S)-2-(5-(4-bromophenyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-2-(thiazol-2-ylamino)butan-1-one (250 mg, 0.527 mmol), $NaHCO_3$ (133 mg, 1.582 mmol) and $Pd(Ph_3P)_4$ (60.9 mg, 0.053 mmol) in DME (3 mL) and Water (1 mL) was degassed by passing a stream of N_2 through the mixture. The vessel was sealed and the reaction was heated at 80°C overnight. The reaction mixture was diluted with H_2O and extracted with EtOAc containing ca. 5% MeOH (X3). The combined org layers were concentrated, dissolved in MeOH and loaded onto an MCX cartridge. The cartridge was washed with MeOH and then NH_3 in MeOH (2M). The appropriate fractions were concentrated *in vacuo* and the residue was purified by prep HPLC (CH_3CN-H_2O-NH_4OAc). The material was purified by column chromatography (biotage) eluting with 0 to 20% MeOH in

EtOAc. Further purification by prep HPLC (CH_3CN-H_2O-NH_4OAc) followed by lyophilization afforded the title compound as a colorless solid (6.9 mg, 2%). ^{1}HNMR (300 MHz, DMSO-d_6) δ 13.41 (s, 1H), 11.75 (s, 2H), 7.75 – 7.80 (m, 4H), 7.68 – 7.71 (m, 4H), 7.49 (s, 2H), 6.99 (d, J = 3.7 Hz, 2H), 6.57 (d, J = 3.7 Hz, 2H), 5.34 – 5.36 (m, 1H), 5.07 (app dd, J = 3.7, 7.0Hz, 2H), 4.42 (t, J = 8.4 Hz, 2H), 3.98 – 4.05 (m, 2H), 3.79 – 3.85 (m, 2H), 3.44 – 3.56 (m, 1H), 1.97 – 2.21 (m, 8H), 1.01 and 0.95 (d, J = 7.0 Hz, 6H, rotamers, 1:3 ratio), 0.99 and 0.92 (d, J = 7.0 Hz, 6H, rotamers, 1:3 ratio). LCMS: Anal. Calcd. for $C_{42}H_{48}N_{10}O_2S_2$: 788; found: 789 $(M+H)^+$.

Examples FY1-FY3



Examples FY1-FY3 were prepared according to the protocols described for the synthesis of Example F66 and by employing appropriate materials.

LC/MS Condition:

Column: Phenomenex 10u 3.0 X 50 mm

Start % B = 0

Final % B = 100

Gradient Time = 3min

Flow Rate = 4 mL/Min

Wavelength = 220

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

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

Example	*R*	*RT (LC-Cond. is noted above); % homogeneity index; MS data*
FY1		2.03 min; > 95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{38}H_{51}N_8O_6S_2$ 779.34;

		found: 779.72
FY2		2.19 min; > 95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{40}H_{55}N_8O_6S_2$ 807.37; found: 807.78
FY3		2.24 min; > 95%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{42}H_{55}N_8O_6S_2$ 831.37; found: 832.02

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

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
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'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
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
cj-84	D
cj-85	D
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
cj-113	D
cj-114	D
cj-115	D
cj-116	D
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
J21	D
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

M131	D
M132	D
M133	D
M134	C
M135	D
M136	C

M137	D
M138	D
M139	D
M140	D
M140a-ii	C
M140a-i	C

M141	C
M142	C
M143	C
M144	D
M145	D
M146	D

M147	D
M148	D
M149	C
M150	D
M151	D
M152	
M153	D
M154	D
M155	C
M156	C
M157	D
M158	C
M159	D
M160	C

M161	C
M162	C
E5	D
E5a	D
E5b	D
E5c	D
E5d	D
E5e	D
E5f	D
E5g	D
E5h	D
E5i	D
E5j	D
E5k	D

E5l	D
E5m	D
J14	D
J14a	D
J14a.1	D
J14b	D
J14b.1	D
J14c	D
J14c.1	D
J14c.2	D
J14e	D
J14e.1	D
J14f	D
J14f.1	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

methyl ((1S)-2-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-(N-(methoxycarbonyl)-L-alanyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-1-methyl-2-oxoethyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((2S)-1-oxo-1,2-butanediyl)))biscarbamate;

methyl (2-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-(((methoxycarbonyl)amino)acetyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)-2-oxoethyl) carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))biscarbamate;

methyl ((1R)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-acetyl-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-methyl-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl- 2-methylpropyl)carbamate;

N-((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-acetamido-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)acetamide;

tert-butyl ((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-((tert-butoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

(2S)-1-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-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)-3-methyl-1-oxo-2-butanamine;

N-((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-((cyclopropylcarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)cyclopropanecarbamate;

tert-butyl ((1R)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2R)-2-((tert-butoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

N-((1R)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2R)-2-acetamido-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)acetamide;

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(1R,3S,5R)-2-azabicyclo[3.1.0]hexane-3,2-diyl((2S)-3-methyl-1-oxo-1,2-butanediyl)))di(2-pyrimidinamine);

methyl ((1S)-1-(((6S)-6-(4-(4'-(2-((6S)-5-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-azaspiro[2.4]hept-6-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-5-azaspiro[2.4]hept-5-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl (2-((6S)-6-(4-(4'-(2-((6S)-5-(((methoxycarbonyl)amino)acetyl)-5-azaspiro[2.4]hept-6-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-5-azaspiro[2.4]hept-5-yl)-2-oxoethyl)carbamate;

methyl ((1S)-2-((6S)-6-(4-(4'-(2-((6S)-5-(N-(methoxycarbonyl)-L-alanyl)-5-azaspiro[2.4]hept-6-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-5-azaspiro[2.4]hept-5-yl)-1-methyl-2-oxoethyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(6S)-5-azaspiro[2.4]heptane-6,5-diyl((2S)-1-oxo-1,2-butanediyl)))biscarbamate;

methyl ((1R)-1-(((6S)-6-(4-(4'-(2-((6S)-5-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-azaspiro[2.4]hept-6-yl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-5-azaspiro[2.4]hept-5-yl)carbonyl)-2-methylpropyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(6S)-5-azaspiro[2.4]heptane-6,5-diyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

methyl ((1R)-1-(((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-((2R)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S,5S)-5-methyl-2,1-pyrrolidinediyl)((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S,5S)-5-methyl-2,1-pyrrolidinediyl)((2S)-1-oxo-1,2-butanediyl)))biscarbamate;

methyl (2-((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-(((methoxycarbonyl)amino)acetyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)-2-oxoethyl)carbamate;

methyl (2-((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-(2-((methoxycarbonyl)amino)-2-methylpropanoyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)-1,1-dimethyl-2-oxoethyl)carbamate;

methyl ((1S)-2-((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-(N-(methoxycarbonyl)-L-alanyl)-5-methyl-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-5-methyl-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

4,4'-(4,4'-biphenyldiyl)bis(2-((2S,5S)-5-methyl-1-(3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazole);

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

(2R,2'R)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S,5S)-5-methyl-2,1-pyrrolidinediyl)))bis(3-methyl-1-oxo-2-butanol);

(2S,2'S)-1,1'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl((2S,5S)-5-methyl-2,1-pyrrolidinediyl)))bis(3-methyl-1-oxo-2-butanol);

2-((2S,5S)-1-acetyl-5-methyl-2-pyrrolidinyl)-4-(4'-(2-((2S,5S)-1-acetyl-5-methyl-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole;

tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-4-(1,3-dioxan-2-ylmethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-4-(1,3-dioxolan-2-ylmethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate;

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

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

ethyl 2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-5-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazole-4-carboxylate;

tert-butyl (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-3'-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinecarboxylate;

2-((2S)-4,4-difluoro-2-pyrrolidinyl)-4-(3'-fluoro-4'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazole;

(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-5-methyl-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine;

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

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

methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-4-methyl-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-5-methyl-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-4-methyl-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

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

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

1,1'-(4,4'-biphenyldiylbis((4-methyl-1H-imidazole-5,2-diyl)(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))dipiperidine;

dimethyl (4,4'-biphenyldiylbis((4-methyl-1H-imidazole-5,2-diyl)(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-5-methyl-1H-imidazol-4-yl)-4-biphenylyl)-5-methyl-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-4-methyl-1H-imidazol-5-yl)-4-biphenylyl)-5-methyl-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S,2R)-2-methoxy-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-5-methyl-1H-imidazol-4-yl)-4-biphenylyl)-5-methyl-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(1,3-dioxan-2-ylmethyl)-5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S,2R)-1-(((2S)-2-(4-(2,2-dimethoxyethyl)-5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methoxypropyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(2,2-dimethoxyethyl)-5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl (2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-O-methyl-L-threonyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-5-yl)acetate;

methyl (2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-valyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-5-yl)acetate;

methyl ((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-4-propyl-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-5-propyl-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-5-propyl-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((2S)-4,4-difluoro-2-(4-(3'-fluoro-4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-4,4-difluoro-2-pyrrolidinyl)-1H-imidazol-4-yl)-3-fluoro-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-N,N-diethyl-2-oxo-1-phenylethanamine;

methyl ((1S)-1-(((2S)-2-(4-(hydroxymethyl)-5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-2-((2S)-2-(4-(4'-(4-(hydroxymethyl)-2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

(N,N'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-3-methyl-1-oxo-1,2-butanediyl)))di(2-pyrimidinamine);

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((1S)-1-cyclopropyl-2-oxo-2,1-ethanediyl)))di(2-pyrimidinamine);

N,N'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-1-oxo-1,2-propanediyl)))di(2-pyrimidinamine);

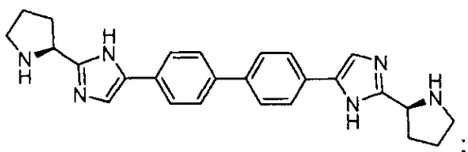
N,N'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-1-oxo-1,2-butanediyl)))di(2-pyrimidinamine);

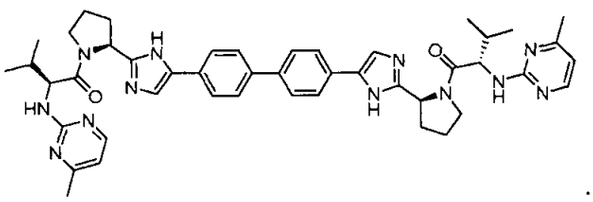
N,N'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((2S)-3-methoxy-1-oxo-1,2-propanediyl)))di(2-pyrimidinamine); and

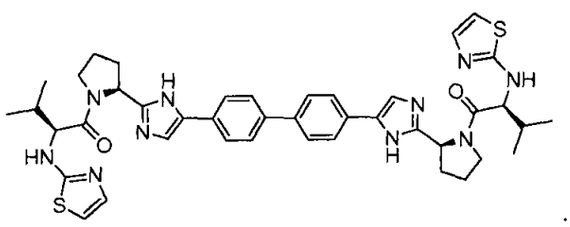
N,N'-(4,4'-biphenyldiylbis(1H-imidazole-4,2-diyl(2S)-2,1-pyrrolidinediyl((2S,3R)-3-methoxy-1-oxo-1,2-butanediyl)))di(2-pyrimidinamine);

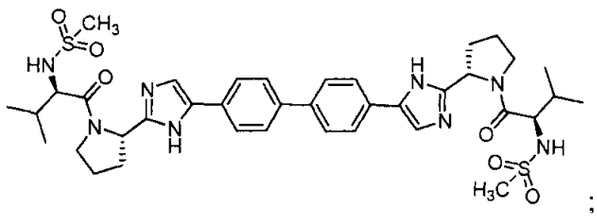
or a pharmaceutically acceptable salt thereof.

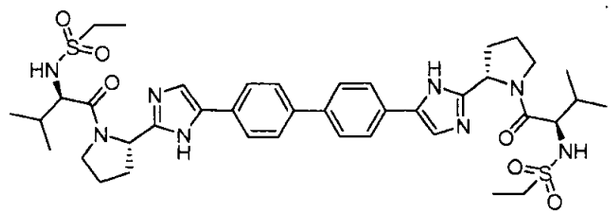
2. A compound selected from

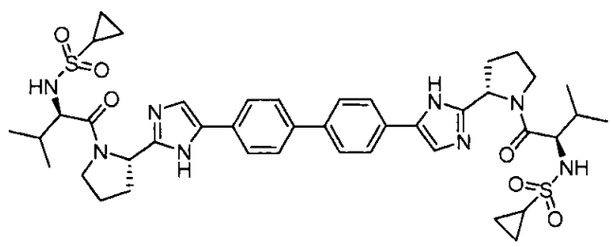

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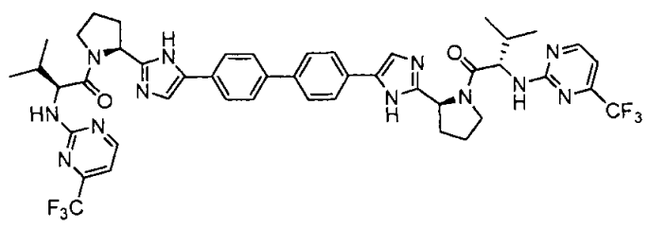

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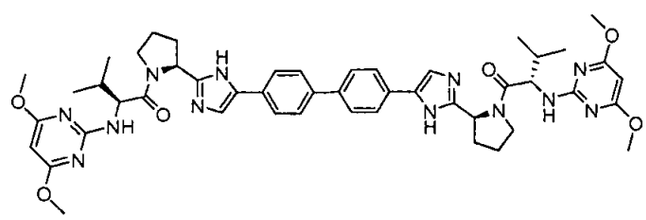

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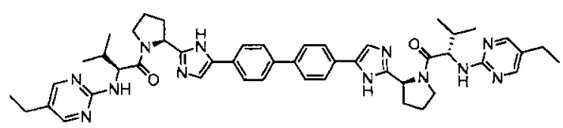

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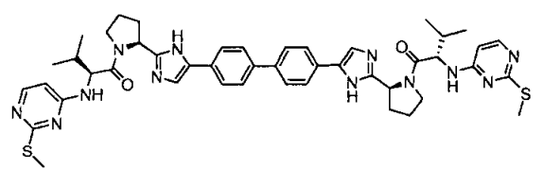

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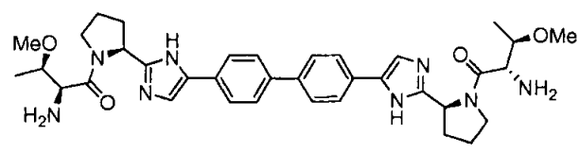

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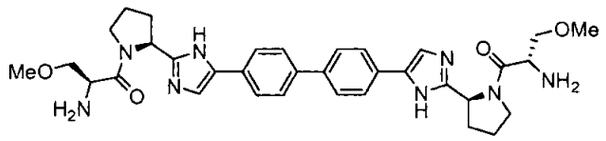

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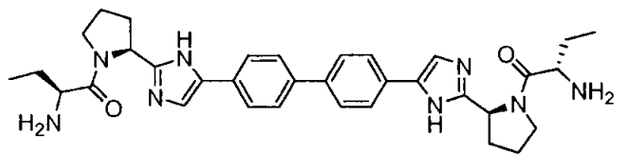

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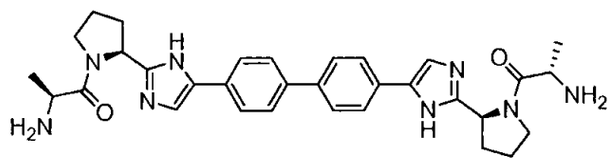

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N
H
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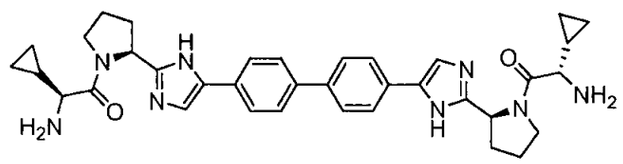
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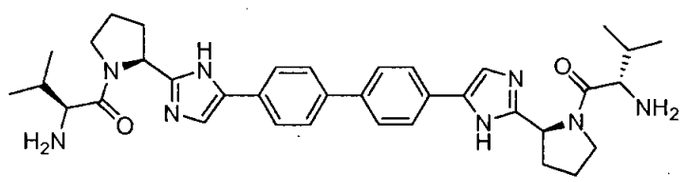
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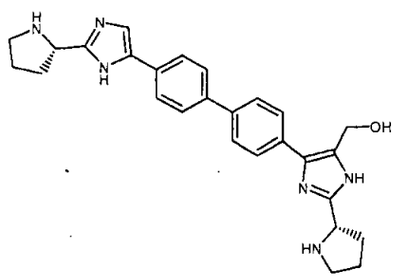
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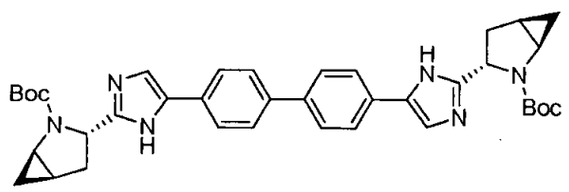
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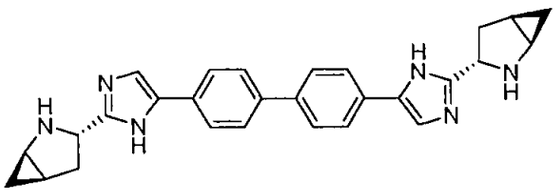
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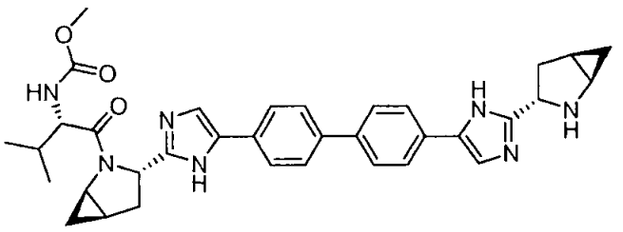

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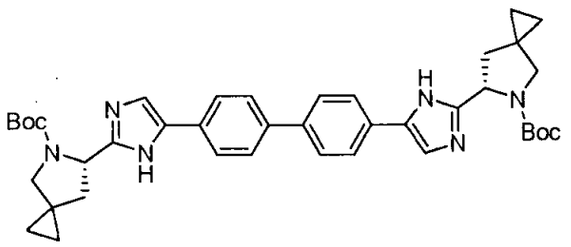
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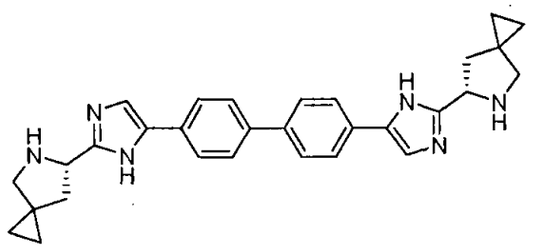

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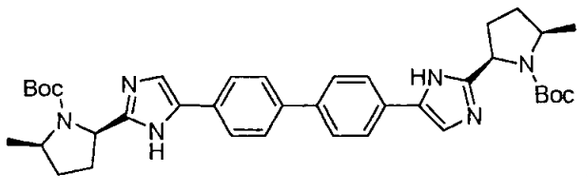
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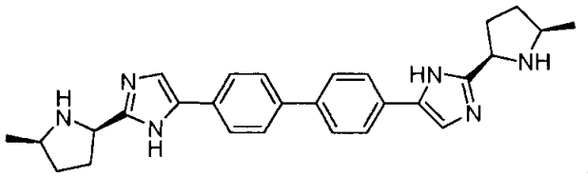

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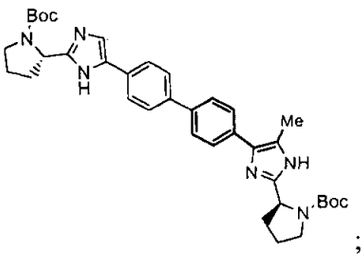

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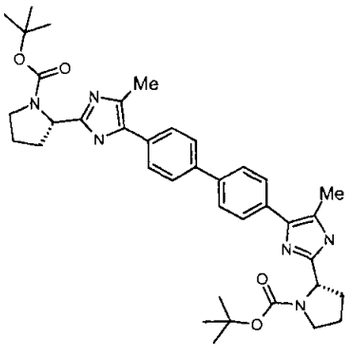

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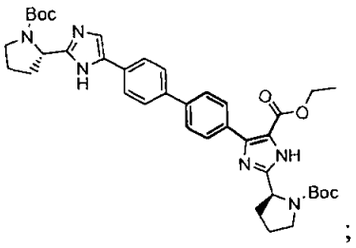

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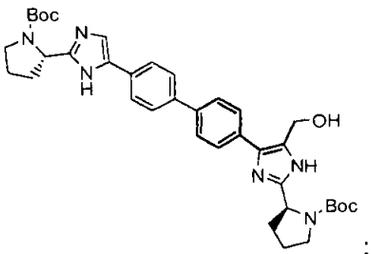

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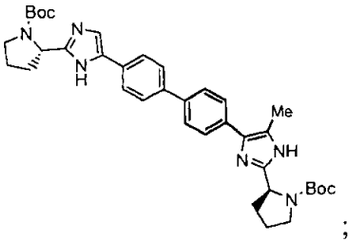

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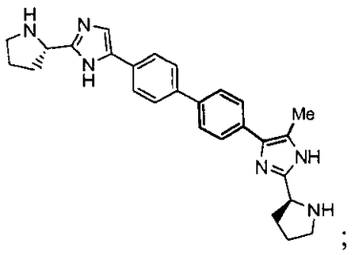

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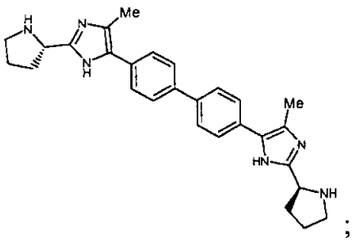

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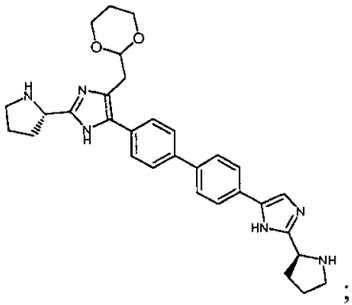

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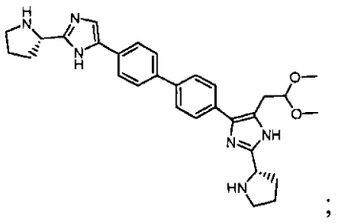

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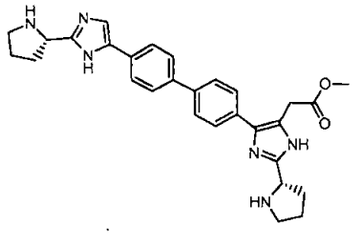

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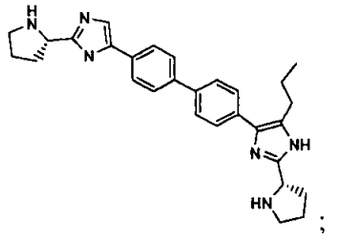

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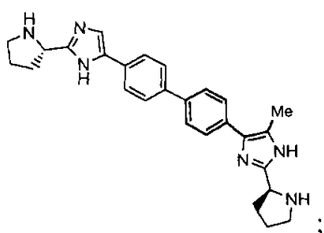

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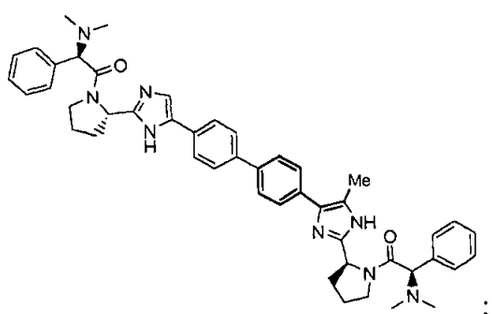

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or a pharmaceutically acceptable salt thereof.

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.

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.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-099269- -00000-0000
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Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 1917

PATENTE DE INVENCIÓN ☐ **MODELO DE UTILIDAD** ☐ **Art 33 Decisión 486/00**

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☐ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

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

Completa ☑ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ **(Art. 92 Decisión 486/00)**

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

Completa ☐ Incompleta ☐

2/2

Solicitante:
Bristol-Myers
Squibb Company

PCT/US2008/
053779

Apoderado:
Alvaro Correa
Ordoñez

P2010/50

IMIDAZOLIL-BIFENIL-IMIDAZOLES COMO INHIBIDORES DEL VIRUS DE LA HEPATITIS C

Descripción de la Invención

La presente invención se dirige generalmente a compuestos antivíricos, y se dirige más específicamente a compuestos que inhiben el funcionamiento de la proteína NS5A codificada por el virus de la hepatitis C (HCV, por sus siglas en inglés), composiciones que comprenden tales compuestos y métodos para inhibir el funcionamiento de la proteína NS5A.

El HCV es un patógeno humano principal, que infecta un estimado de 170 millones de personas en el mundo, aproximadamente cinco veces el número infectado por el virus de la inmunodeficiencia humana de tipo 1. Una fracción substancial de estos individuos infectados con HCV desarrollan un enfermedad progresiva del hígado seria, incluyendo cirrosis y carcinoma hepatocelular.

Actualmente, la terapia más efectiva del HCV emplea una combinación del alfa interferón y ribavirina, conduciendo a una eficacia sostenida en 40% de los pacientes. Los resultados clínicos recientes demuestran que el alfa interferón pegilado es superior al alfa interferón sin modificar como monoterapia. Sin embargo, aún con los regímenes terapéuticos experimentales que involucran combinaciones del alfa interferón pegilado y la ribavirina,

una fracción substancial de los pacientes no tiene una reducción sostenida en la carga viral. Así, hay una necesidad clara que se sostiene desde hace mucho para desarrollar terapéuticos efectivos para el tratamiento contra la infección por HCV.

El HCV es un virus del ARN de hebra positiva. Con base en la comparación de la secuencia deducida de aminoácidos y la amplia similitud en la región 5' sin traducir, el HCV se ha clasificado como un género separado en la familia Flaviviridae. Todos los miembros de la familia Flaviviridae han envuelto viriones que contienen un genoma de ARN de hebra positiva que codifica todas las proteínas conocidas específicas del virus, por medio de la traducción de una estructura de lectura abierta sencilla sin interrumpir.

Se encuentra una heterogeneidad considerable dentro del nucleótido y de la secuencia codificada de aminoácidos a través del genoma de HCV. Al menos se han caracterizado seis principales genotipos, y se han descrito más de 50 subtipos. Los principales genotipos del HCV difieren en su distribución a nivel mundial, y la importancia clínica en la heterogeneidad genética del HCV permanece elusiva a pesar de diversos estudios sobre el efecto posible de los genotipos en la patogénesis y la terapia.

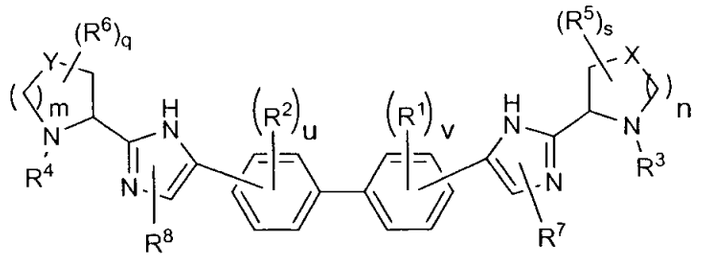
El genoma del ARN del HCV de hebra sencilla, es de aproximadamente 9500 nucleótidos de longitud y tiene una

estructura sencilla de lectura abierta (ORF, por sus siglas en inglés) que codifica una poliproteína grande sencilla de alrededor de 3000 aminoácidos. En las células infectadas, esta poliproteína se desdobla en sitios múltiples por proteasas celulares y virales, para producir proteínas estructurales y no estructurales (NS). En el caso del HCV, la generación de proteínas maduras no estructurales (NS2, NS3, NS4A, NS4B, NS5A, y NS5B) se efectúa por dos proteasas virales. La primera, se cree que es una metaloproteasa y desdobla una unión NS2-NS3; la segunda es una serina proteasa contenida dentro de la región terminal N del NS3 (de aquí en adelante referida como NS3 proteasa) y media todos los desdoblamientos posteriores en la dirección descendente del NS3, tanto en el sitio cis, en el sitio de desdoblamiento NS3-NS4A, y en trans, para el resto de los sitios NS4A-NS4B, NS4B-NS5A, NS5A-NS5B. La proteína NS4A parece servir a funciones múltiples actuando como un factor para la proteasa NS3, y ayudando posiblemente en la localización de membrana de NS3 y de otros componentes virales de la replicasa. La formación compleja de la proteína NS3 con el NS4A, parece necesaria para los eventos de procesamiento, incrementando la eficiencia proteolítica en todos los sitios. La proteína NS3 también muestra una nucleósido trifosfatasa y actividades de la ARN helicasa. La NS5B (también referida en la presente como polimerasa de HCV) es una polimerasa de ARN dependiente

del ARN que se involucra en la replicación del HCV.

Los compuestos útiles para tratar pacientes infectados con HCV son deseados los cuales selectivamente inhiben la replicación viral del HCV. En particular, los compuestos que son efectivos para inhibir la función de la proteína NS5A son deseados. La proteína NS5A del HCV se describe por ejemplo, en Tan, S.-L., Katzel, M.G. Virology 2001, 284, 1-12; and in Park, K.-J.; Choi, S.-H, J. Biological Chemistry 2003.

En un primer aspecto la presente descripción proporciona un compuesto de la fórmula (I)



(I),

o una sal farmacéuticamente aceptable del mismo, en donde

m y n son independientemente 0, 1 ó 2;

q y s son independientemente 0, 1, 2, 3 ó 4;

u y v son independientemente 0, 1, 2 ó 3;

X se selecciona de O, S, S(O), SO_2, CH_2, CHR^5, y $C(R^5)_2$; con la afección de que cuando n es 0, X se selecciona de CH_2, CHR^5, y $C(R^5)_2$;

Y se selecciona de O, S, S(O), SO_2, CH_2, CHR^6, y $C(R^6)_2$; con la afección de que cuando m es 0, Y se selecciona de CH_2,

CHR^6, y $C(R^6)_2$;

cada R^1 y R^2 se selecciona independientemente de alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, arilalcoxicarbonilo, 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 indpendientemente de hidrógeno, R^9-C(O)-, y R^9-C(S)-;

cada R^5 y R^6 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 hasta seis miembros fusionado con un átomo de carbono adyacente, en donde el anillo de tres hasta seis miembros está opcionamente substituido con uno o dos grupos alquilo;

R^7 y R^8 se seleccionan cada uno indpendientemente de hidrógeno, alcoxicarbonilo, alquilo, arilalcoxicarbonilo, carboxi, haloalquilo, (NR^aR^b)carbonilo, y trialquilsililalcoxialquilo; y

cada R^9 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.

En una primera modalidad del primer aspecto de la presente descripción, se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde m y n son cada uno 1.

En una segunda modalidad del primer aspecto de la presente descripción, se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde

u y v son cada uno independientemente 0, 1, ó 2; y

cada R^1 y R^2 se selecciona independientemente de alcoxi, alcoxialquilo, alquilo, arilalcoxicarbonilo, carboxi, formilo, halo, haloalquilo, hidroxialquilo, (NR^aR^b)alquilo, y (NR^aR^b)carbonilo.

En una tercera modalidad del primer aspecto de la presente descripción, se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde

u y v son cada uno independientemente 0 ó 1; y

cuando está presente, R^1 y/o R^2 son halo.

En una cuarta modalidad del primer aspecto de la presente descripción, se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde

u y v son cada uno independientemente 0 ó 1; y

cuando está presente, R^1 y/o R^2 son halo, en donde el halo es fluoro.

En una quinta modalidad del primer aspecto de la presente descripción, se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde al menos uno de X e Y es S.

En una sexta modalidad del primer aspecto de la presente descripción, se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde X e Y son cada uno S.

En una séptima modalidad del primer aspecto de la presente descripción, se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde X se selecciona de CHR^5, y $C(R^5)_2$; e Y se selecciona de CH_2, CHR^6, y $C(R^6)_2$.

En una octava modalidad del primer aspecto de la presente descripción, se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde R^7 y R^8 son independientemente seleccionados de hidrógeno, alcoxicarbonilo, alquilo, arilalcoxicarbonilo, carboxi, haloalquilo, y (NR^aR^b)carbonilo.

En una novena modalidad del primer aspecto de la presente descripción, se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde R^7 y R^8 son cada uno hidrógeno.

En una décima modalidad del primer aspecto de la presente descripción, se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde

q y s son independientemente 0, 1, ó 2; y

cada R^5 y R^6 se selecciona independientemente de alquilo, arilo, halo, y hidroxi, en donde el alquilo puede formar opcionalmente un anillo de tres hasta seis miembros fusionado con un átomo de carbono adyacente, en donde el anillo de tres hasta seis miembros está opcionamente substituido con uno o dos grupos alquilo.

En una decimoprimera modalidad del primer aspecto de la presente descripción, se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde

q y s son independientemente 0 ó 1; y

cuando está presente, R^5 y/o R^6 son cada uno halo.

En una decimosegunda modalidad del primer aspecto de la presente descripción, se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde

q y s son independientemente 0 ó 1; y

cuando está presente, R^5 y/o R^6 son cada uno halo, en donde el halo es fluoro.

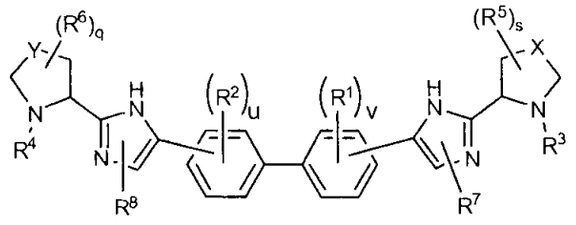
En una decimotercera modalidad del primer aspecto de la

presente descripción, se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde al menos uno de R^3 y R^4 es hidrógeno.

En una decimocuarta modalidad del primer aspecto de la presente descripción, se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde R^3 y R^4 son cada uno R^9-C(O)-.

En una decimoquinta modalidad del primer aspecto de la presente descripción, se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde cada R^9 se selecciona independientemente de alcoxi, alcoxialquilo, 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 un segundo aspecto, la presente descripción proporciona un compuesto de la Fórmula (II)



(II),

o una sal farmacéuticamente aceptable del mismo, en donde

q y s son independientemente 0, 1, ó 2;

u y v son independientemente 0, 1, ó 2;

X se selecciona de S, CH_2, CHR^5, y $C(R^5)_2$;

Y se selecciona de S, CH_2, CHR^6, y $C(R^6)_2$;

cada R^1 y R^2 se selecciona independientemente de alcoxi, alcoxialquilo, alquilo, arilalcoxicarbonilo, carboxi, formilo, halo, haloalquilo, hidroxialquilo, (NR^aR^b)alquilo, y (NR^aR^b)carbonilo;

R^3 y R^4 se seleccionan cada uno indpendientemente de hidrógeno y R^9-C(O)-;

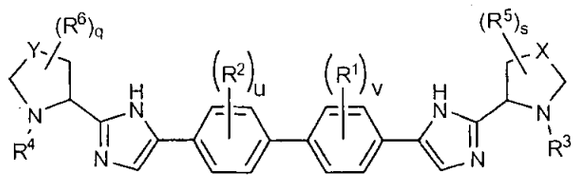
cada R^5 y R^6 se selecciona independientemente de alquilo, arilo, halo, y hidroxi, en donde el alquilo puede formar opcionalmente un anillo de tres hasta seis miembros fusionado con un átomo de carbono adyacente, en donde el anillo de tres hasta seis miembros está opcionamente substituido con uno o dos grupos alquilo;

R^7 y R^8 se seleccionan cada uno independientemente de hidrógeno, alcoxicarbonilo, alquilo, arilalcoxicarbonilo, carboxi, haloalquilo, y (NR^aR^b)carbonilo; y

cada R^9 se selecciona independientemente de alcoxi, alcoxialquilo, 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 un tercer aspecto, la presente descripción

proporciona un compuesto de la Fórmula (III)



(III),

o una sal farmacéuticamente aceptable del mismo, en donde

q y s son independientemente 0, 1, ó 2;

u y v son independientemente 0 ó 1;

X se selecciona de CH_2, CHR^5, y $C(R^5)_2$;

Y se selecciona de CH_2, CHR^6, y $C(R^6)_2$;

cuando está presente, R^1 y/o R^2 son halo, en donde el halo es fluoro;

R^3 y R^4 son cada uno R^9-C(O)-;

cuando está presente, R^5 y/o R^6 son halo, en donde el halo es fluoro; y

cada R^9 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.

En un cuarto aspecto, la presente descripción

proporciona un compuesto seleccionado de ((1S)-1-(((2S)-2-(5-(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; (1R,1'R)-2,2'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidinediil))bis(N,N-dimetil-2-oxo-1-feniletanamina); ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo; ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-4,4-difluoro-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo; ((1S)-1-(((1R,3R,5R)-3-(5-(4'-(2-((1R,3R,5R)-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; ((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)carbamato de metilo; ((1S)-2-metil-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pirimidinil-

D-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo;

((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo;

(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidinediil((1R)-2-oxo-1-fenil-2,1-etanediil)))biscarbamato de dimetilo;

(1R)-N,N-dimetil-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etanamina;

((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo; y

((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3,3-dimetilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2,2-dimetilpropil)carbamato de metilo;

o una sal farmacéuticamente aceptable del mismo.

En una primera modalidad del quinto aspecto la sal farmacéuticamente aceptable es una sal de diclorohidrato.

En un sexto aspecto, la presente descripción 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 sexto aspecto la composición comprende además uno o dos compuestos adicionales que tiene actividad anti-HCV. En una segunda modalidad al menos uno de los compuestos adicionales es un interferón o una ribavirina. En una tercera modalidad el interferón se selecciona de interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A, e interferón tau linfoblastoide.

En una cuarta modalidad del sexto aspecto la composición comprende además uno o dos compuestos adicionales que tiene actividad anti-HCV en donde al menos uno de los compuestos adicionales se selecciona de interleucina 2, interleucina 6, interleucina 12, un compuesto que aumenta el desarrollo de una respuesta de célula T auxiliar tipo 1, ARN de interferencia, ARN antisentido, Imiquimod, ribavirina, un inhibidor de inosina 5'-monofosfato deshidrogenasa, amantadina, y rimantadina.

En una quinta modalidad del sexto aspecto la composición comprende además uno o dos compuestos adicionales que tiene actividad anti-HCV en donde al menos uno de los compuestos adicionales es efectivo para inhibir la función de un

direcconador 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 contra una infección por HCV.

En un séptimo aspecto, la presente descripción proporciona un método de tratamiento contra 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 séptimo aspecto el método comprende administrar uno o dos compuestos adicionales que tiene 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 al menos uno de los compuestos adicionales es un interferón o una ribavirina. En una tercera modalidad el interferón se selecciona de interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A, y interferón tau linfoblastoide.

En una cuarta modalidad el método comprende además administrar uno o dos compuestos adicionales que tiene 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 se selecciona de interleucina 2, interleucina 6, interleucina 12, un compuesto que aumenta el desarrollo de una respuesta de célula T auxiliar tipo 1, ARN de interferencia, ARN antisentido, Imiquimod, ribavirina, un inhibidor de inosina 5'-monofosfato deshidrogenasa, amantadina, y rimantadina.

En una quinta modalidad el método comprende además administrar uno o dos compuestos adicionales que tienen 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 direccionador seleccionado de metaloproteasa de HCV, serina proteasa de HCV, polimerasa de HCV, helicasa de HCV, HCV NS4B portein, entrada de HCV, ensamble de HCV, salida de HCV, proteína NS5A de HCV, e IMPDH para el tratamiento contra una infección por HCV.

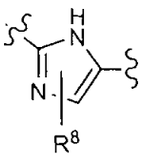
Otras modalidades de la presente descripción pueden comprender combinaciones apropiadas de dos o más de las modalidades y/o aspectos descritos en la presente.

Aún otras modalidades y aspectos de la descripción serán aparentes de conformidad con la descripción proporcioanda a continuación.

Los compuestos de la presente descripción también pueden existir como tautómeros; por lo tanto la presente descripción

también abarca todas las formas tautoméricas.

La descripción de la presente descrita aquí deberá construirse en congruencia con las leyes y principios del enlace químico. En algunos casos, puede ser necesario remover un átomo de hidrógeno con objeto de acomodar un substituyente en cualquier ubicación dada. Por ejemplo, en la estructura mostrada abajo



R^8 puede enlazarse ya sea al átomo de carbono en el anillo de imidazol o, alternativamente, R^8 puede tomarse en lugar del átomo de hidrógeno en el anillo de nitrógeno para formar un imidazol N substituido.

Se deberá entender que los compuestos abarcados por la presente descripción son aquellos que son adecuadamente estables para uso como agente farmacéutico.

Se pretende que la definición de cualquier substituyente o variable (por ejemplo, R^1, R^2, R^5, R^6, etc.) en una locación particular en una molécula, sea independiente de sus definiciones en cualquier otro lugar de la molécula. Por ejemplo, cuando u es 2, cada uno de los dos grupos R^1 puede ser el mismo o diferente.

Todas las patentes, solicitudes de patente y referencia de literatura citadas en la especificación se incorporan en

la presente para referencia en su totalidad. En el caso de inconsistencias, la presente descripción, incluye las definiciones que se revisaran.

Como se usa en la presente especificación, los siguientes términos tienen los significados indicados:

Como se usa en la presente, las formas singulares "un", "uno" y "los" incluye referencia plurales a menos que el contexto claramente dicte lo contrario.

A menos que se establezca de otra manera, todos los grupos arilo, cicloalquilo y heterociclilo de la presente descripción pueden substituirse como se describe en cada una de sus definiciones respectivas. Por ejemplo, la parte arilo de un grupo arilalquilo puede substituirse como se describe en la definición del término 'arilo'.

El término "alquenilo," como se usa en la presente, se refiere a un grupo de cadena recta o ramificada de dos hasta seis átomos de carbono que contiene al menos un enlace doble carbono-carbono.

El término "alqueniloxi," como se usa en la presente, se refiere a un grupo alquenilo enlazado a la porción molecular precursora a través de un átomo de oxígeno.

El término "alqueniloxicarbonilo," como se usa en la presente, se refiere a un grupo alqueniloxi enlazado a la porción molecular precursora a través de un grupo carbonilo.

El término "alcoxi," como se usa en la presente, se refiere a un grupo alquilo enlazado a la porción molecular precursora a través de un átomo de oxígeno.

El término "alcoxialquilo," como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos o tres grupos alcoxi.

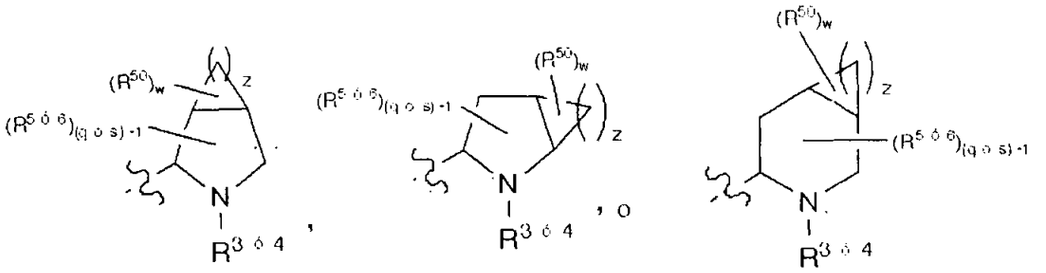
El término "alcoxialquilcarbonilo," como se usa en la presente, se refiere a un grupo alcoxialquilo enlazado a la porción molecular precursora a través de un grupo carbonilo.

El término "alcoxicarbonilo," como se usa en la presente, se refiere a un grupo alcoxi enlazado a la porción molecular precursora a través de un grupo carbonilo.

El término "alcoxicarbonilalquilo," como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos, o tres grupos alcoxicarbonilo.

El término "alquilo," como se usa en la presente, se refiere a un grupo derivado de un hidrocarburo saturado de cadena recta o ramificada que contiene desde uno hasta seis átomos de carbono. En los compuestos de la presente descripción, 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 opcionalmente formar un anillo de tres hasta 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 R^{50} grupos alquilo pueden ser los mismos o diferentes.

El término "alquilcarbonilo" como se usa en la presente, se refiere a un grupo alquilo enlazado a la porción molecular precursora a través de un grupo carbonilo.

El término "alquilcarbonilalquilo" como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos, o tres grupos alquilcarbonilo.

El término "alquilcarboniloxi" como se usa en la presente, se refiere a un grupo alquilcarbonilo enlazado a la porción molecular precursora a través de un átomo de oxígeno.

El término "alquilsulfanilo," como se usa en la presente, se refiere a un grupo alquilo enlazado a la porción molecular precursora a través de un átomo de azufre.

El término "alquilsulfonilo", como se usa en la presente, se refiere a un grupo alquilo enlazado a la porción molecular precursora a través de un grupo sulfonilo.

El término "arilo," como se usa en la presente, se

refiere a un grupo fenilo, o un sistema de anillo fusionado bicíclico en donde uno o más de los anillos es un grupo fenilo. Los sistemas de anillo fusionado bicíclico que consiste de un grupo fenilo fusionado a un anillo carbocíclico de cuatro hasta seis miembros aromático y no aromático. Los grupos arilo de la presente invención pueden enlazarse a la porción molecular precursora a través de cualquier átomo de carbono sustituible en el grupo. Los ejemplos representativos de grupos arilo incluyen, pero no se limitan a, indanilo, indenilo, naftilo, fenilo, y tetrahidronaftilo. Los grupos arilo de la presente descripción son opcionalmente substituidos con uno, dos, tres, cuatro o cinco substituyentes independientemente seleccionados de alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, alquilcarbonilo, un segundo grupo arilo, arilalquilo, arilcarbonilo, ciano, halo, haloalcoxi, haloalquilo, heterociclilo, heterociclilalquilo, heterociclilcarbonilo, hidroxi, hidroxialquilo, nitro, $-NR^xR^y$, (NR^xR^y)alquilo, oxo, y $-P(O)OR_2$, en donde cada R es independientemente seleccionado de hidrógeno y alquilo; y en donde la parte alquilo del arilalquilo y el heterociclilalquilo son no substituidos 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 opcionalmente substituidos además con uno, dos, o tres substituyentes independientemente seleccionados de alcoxi, alquilo, ciano, halo, haloalcoxi, haloalquilo, y nitro.

El término "arilalquenilo," como se usa en la presente, se refiere a un grupo alquenilo substituido con uno, dos o tres grupos arilo.

El término "arilalcoxi" como se usa en la presente, se refiere a un grupo arilo enlazado a la porción molecular precursora a través de un grupo alcoxi.

El término "arilalcoxialquilo," como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos o tres grupos arilalcoxi.

El término "arilalcoxialquilcarbonilo," como se usa en la presente, se refiere a un grupo arilalcoxialquilo enlazado a la porción molecular precursora a través de un grupo carbonilo.

El término "arilalcoxicarbonilo," como se usa en la presente, se refiere a un grupo arilalcoxi enlazado a la porción molecular precursora a través de un grupo carbonilo.

El término "arilalquilo", como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos, o tres grupos arilo. La parte alquilo del arilalquilo es opcionalmente substituido además con uno o dos grupos

adicionales independientemente seleccionados de alcoxi, alquilcarboniloxi, halo, haloalcoxi, haloalquilo, heterociclilo, hidroxi, y $-NR^cR^d$, en donde el heterociclilo es opcionalmente substituido además con uno o dos substituyentes independientemente seleccionados de alcoxi, alquilo, arilo no substituido, arilalcoxi no substituido, arilalcoxicarbonilo no substituido, halo, haloalcoxi, haloalquilo, hidroxi, y $-NR^xR^y$.

El término "arilalquilcarbonilo," como se usa en la presente, se refiere a un grupo arilalquilo enlazado a la porción molecular precursora a través de un grupo carbonilo.

El término "arilcarbonilo", como se usa en la presente, se refiere a un grupo arilo enlazado a la porción molecular precursora a través de un grupo carbonilo.

El término "ariloxi", como se usa en la presente, se refiere a un grupo arilo enlazado a la porción molecular precursora a través de un átomo de oxígeno.

El término "ariloxialquilo," como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos o tres grupos ariloxi.

El término "ariloxicarbonilo," como se usa en la presente, se refiere a un grupo ariloxi enlazado a la porción molecular precursora a través de un grupo carbonilo.

El término "arilsulfonilo," como se usa en la presente,

se refiere a un grupo arilo enlazado a la porción molecular precursora a través de un grupo sulfonilo.

Los términos "Extremo" y "extremo" como se usa en la presente, se refiere al grupo que se coloca en el átomo de nitrógeno del anillo que contiene nitrógeno terminal, esto es, los anillos de pirrolidina del compuesto 1e. Se deberá entender que "Extremo" o "extremo" puede referirse al reactivo usado para anexar el grupo al anillo que contiene nitrógeno terminal o para el fragmento en el producto final, esto es, "Extremo-51" o "el fragmento extremo-51 encontrado en LS-19".

El término "carbonilo", como se usa en la presente, se refiere a -C(O)-.

El término "carboxi", como se usa en la presente, se refiere a $-CO_2H$.

El término "ciano", como se usa en la presente, se refiere a -CN.

El término "cicloalquilo," como se usa en la presente, se refiere a un sistema de anillo hidrocarburo monocíclico saturado que tiene tres hasta siete átomos de carbono y cero heteroátomos. Los ejemplos representativos de grupos cicloalquilo incluyen, pero no se limitan a, ciclopropilo, ciclopentilo, y ciclohexilo. Los grupos cicloalquilo de la presente descripción son opcionalmente substituidos con uno, dos, tres, cuatro o cinco substituyentes independientemente

seleccionados de alcoxi, alquilo, arilo, ciano, halo, haloalcoxi, haloalquilo, heterociclilo, hidroxi, hidroxialquilo, nitro, y $-NR^xR^y$, en donde el arilo y el heterociclilo son opcionalmente substituidos además con uno, dos o tres substituyentes independientemente seleccionados de alcoxi, alquilo, ciano, halo, haloalcoxi, haloalquilo, hidroxi, y nitro.

El término "(cicloalquil)alquenilo," como se usa en la presente, se refiere a un grupo alquenilo substituido con uno, dos, o tres grupos cicloalquilo.

El término "(cicloalquil)alquilo," como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos, o tres grupos cicloalquilo. La parte alquilo del (cicloalquil)alquilo es opcionalmente substituido además con uno o dos grupos independientemente seleccionados de hidroxi y $-NR^cR^d$.

El término "cicloalquiloxi," como se usa en la presente, se refiere a un grupo cicloalquilo enlazado a la porción molecular precursora a través de un átomo de oxígeno.

El término "cicloalquiloxialquilo," como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos, o tres grupos cicloalquiloxi.

El término "cicloalquilsulfonilo," como se usa en la presente, se refiere a un grupo cicloalquilo enlazado a la porción molecular precursora a través de un grupo sulfonilo.

El término "formilo," como se usa en la presente, se refiere a -CHO.

Los términos "halo" y "halógeno," como se usa en la presente, se refiere a F, Cl, Br, o I.

El término "haloalcoxi", como se usa en la presente, se refiere a un grupo haloalquilo enlazado a la porción molecular precursora a través de un átomo de oxígeno.

El término "haloalcoxicarbonilo," como se usa en la presente, se refiere a un grupo haloalcoxi enlazado a la porción molecular precursora a través de un grupo carbonilo.

El término "haloalquilo", como se usa en la presente, se refiere a un grupo alquilo substituido por uno, dos, tres o cuatro átomos de halógeno.

El término "heterociclilo," como 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 independientemente seleccionados de nitrógeno, oxígeno y azufre. El anillo de cuatro miembros tiene cero hasta dos enlaces dobles, el anillo de cinco miembros tiene cero hasta dos enlaces dobles, y los anillos de seis y siete miembros tiene cero hasta tres enlaces dobles. El término "heterociclilo" también incluye grupos bicíclicos en los cuales el anillo heterociclilo se fusiona a otro grupo heterociclilo monocíclico, o un

anillo carbocíclico aromático o no aromático de cuatro hasta seis miembros; así como grupos bicíclicos puenteados tales como 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 descripción pueden enlazarse a la porción molecular precursora a través de cualquier átomo de carbono o átomo de nitrógeno en el grupo. Los ejemplos de grupos heterociclilo incluyen, pero no se limitan 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 descripción son opcionalmente substituidos con uno, dos, tres, cuatro, o cinco substituyentes independientemente seleccionados 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 heterociclilalquil son no substituidos 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 opcionalmente substituidos además con uno, dos, o tres substituyentes independientemente seleccionados de alcoxi, alquilo, ciano, halo, haloalcoxi, haloalquilo, y nitro.

El término "heterociclilalquenilo", como se usa en la presente se refiere a un grupo alquenilo substituido con uno, dos, o tres grupos heterociclilo.

El término "heterociclilalcoxi", como se usa en la presente, se refiere a un grupo heterociclilo enlazado a la porción molecular precursora a través de un grupo alcoxi.

El término "heterociclilalcoxicarbonilo," como se usa en la presente, se refiere a un grupo heterociclilalcoxi enlazado a la porción molecular precursora a través de un grupo carbonilo.

El término "heterociclilalquilo," como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos, o tres grupos heterociclilo. La parte alquilo del heterociclilalquilo es opcionalmente substituido además con uno o dos grupos adicionales independientemente seleccionados de alcoxi, alquilcarboniloxi, arilo, halo, haloalcoxi, haloalquilo, hidroxi, y $-NR^cR^d$, en donde el

arilo es opcionalmente substituido además con uno o dos substituyentes independientemente seleccionados de alcoxi, alquilo, arilo no substituido, arilalcoxi no substituido, arilalcoxicarbonilo no substituido, halo, haloalcoxi, haloalquilo, hidroxi, y $-NR^XR^Y$.

El término "heterociclilalquilcarbonilo," como se usa en la presente, se refiere a un grupo heterociclilalquilo enlazado a una porción molecular precursora a través de un grupo carbonilo.

El término "heterociclilcarbonilo," como se usa en la presente, se refiere a un grupo heterociclilo enlazado a la porción molecular precursora a través de un grupo carbonilo.

El término "heterocicliloxi," como se usa en la presente, se refiere a un grupo heterociclilo enlazado a la porción molecular precursora a través de un átomo de oxígeno.

El término "heterocicliloxialquilo," como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos, o tres grupos heterocicliloxi.

El término "heterocicliloxicarbonilo," como se usa en la presente, se refiere a un grupo heterocicliloxi enlazado a la porción molecular precursora a través de un grupo carbonilo.

El término "hidroxi," como se usa en la presente, se refiere a -OH.

El término "hidroxialquilo," como se usa en la

presente, se refiere a un grupo alquilo substituido con uno, dos o tres grupos hidroxi.

El término "hidroxialquilcarbonilo," como se usa en la presente, se refiere a un grupo hidroxialquilo enlazado a la porción molecular precursora a través de un grupo carbonilo.

El término "nitro," como se usa en la presente, se refiere a $-NO_2$.

El término "$-NR^aR^b$," como se usa en la presente, se refiere a dos grupos, R^a y R^b, los cuales se enlazan a la porción molecular precursora a través de un átomo de nitrógeno. R^a y R^b son independientemente seleccionados de hidrógeno, alquenilo, y alquilo.

El término "(NR^aR^b)alquilo," como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos o tres grupos $-NR^aR^b$.

El término "(NR^aR^b)carbonilo," como se usa en la presente, se refiere a un grupo $-NR^aR^b$ enlazado a la porción molecular precursora a través de un grupo carbonilo.

El término "$-NR^cR^d$," como se usa en la presente, se refiere a dos grupos, R^c y R^d, los cuales se enlazan a la porción molecular precursora a través de un átomo de nitrógeno. R^c y R^d son independientemente seleccionados de hidrógeno, alqueniloxicarbonilo, alcoxialquilcarbonilo, alcoxicarbonilo, alquilo, alquilcarbonilo,

alquilsulfonilo, arilo, arilalcoxicarbonilo, arilalquilo, arilalquilcarbonilo, arilcarbonilo, arilsulfonilo, cicloalquilo, cicloalquilsulfonilo, formilo, haloalcoxicarbonilo, heterociclilo, heterociclilalcoxicarbonilo, 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 substituido, y en donde la parte alquilo del arilalquilo, el arilalquilcarbonilo, el heterociclilalquilo, y el heterociclilalquilcarbonilo son opcionalmente substituidos además con un grupo $-NR^eR^f$; y en donde el arilo, la parte arilo del arilalcoxicarbonilo, 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 son opcionalmente substituidos además con uno, dos o tres substituyentes independientemente seleccionados de alcoxi, alquilo, ciano, halo, haloalcoxi, haloalquilo, y nitro.

El término "(NR^cR^d)alquenilo," como se usa en la presente, se refiere a un grupo alquenilo substituido con

uno, dos o tres grupos $-NR^cR^d$.

El término "(NR^cR^d)alquilo," como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos o tres grupos $-NR^cR^d$. La parte alquilo del (NR^cR^d)alquilo es opcionalmente substituido además 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 opcionalmente substituido además con uno, dos, tres, cuatro, o cinco substituyentes independientemente seleccionados de alcoxi, alquilo, ciano, halo, haloalcoxi, haloalquilo, y nitro.

El término "(NR^cR^d)carbonilo," como se usa en la presente, se refiere a un grupo $-NR^cR^d$ enlazado a la porción molecular precursora a través de un grupo carbonilo.

El término "$-NR^eR^f$," como se usa en la presente, se refiere a dos grupos, R^e y R^f, los cuales se enlazan a la porción molecular precursora a través de un átomo de nitrógeno. R^e y R^f son independientemente seleccionados de hidrógeno, alquilo, arilo no substituido, arilalquilo no substituido, cicloalquilo no substituido, (ciclolalquil)alquilo no substituido, heterociclilo no substituido, heterociclilalquilo no substituido, (NR^xR^y)alquilo, y (NR^xR^y)carbonilo.

El término "(NR^eR^f)alquilo," como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos o tres grupos $-NR^eR^f$.

El término "(NR^eR^f)alquilcarbonilo," como se usa en la presente, se refiere a un grupo (NR^eR^f)alquilo enlazado a la porción molecular precursora a través de un grupo carbonilo.

El término "(NR^eR^f)carbonilo," como se usa en la presente, se refiere a un grupo $-NR^eR^f$ enlazado a la porción molecular precursora a través de un grupo carbonilo.

El término "(NR^eR^f)sulfonilo," como se usa en la presente, se refiere a un grupo $-NR^eR^f$ enlazado a la porción molecular precursora a través de un grupo sulfonilo.

El término "$-NR^xR^y$," como se usa en la presente, se refiere a dos grupos, R^x y R^y, los cuales se enlazan a la porción molecular precursora a través de un átomo de nitrógeno. R^x y R^y son independientemente seleccionados de hidrógeno, alcoxicarbonilo, alquilo, alquilcarbonilo, arilo no substituido, arilalcoxicarbonilo no substituido, arilalquilo no substituido, cicloalquilo no substituido, heterociclilo no substituido, y $(NR^{x'}R^{y'})$carbonilo, en donde $R^{x'}$ y $R^{y'}$ son independientemente seleccionados de hidrógeno y alquilo.

El término "(NR^xR^y)alquilo," como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos o tres grupos $-NR^xR^y$.

El término "oxo", como se usa en la presente, se refiere a =O.

El término "sulfonilo" como se usa en la presente, se refiere a $-SO_2-$.

El término "trialquilsililo", como se usa en la presente, se refiere a $-SiR_3$, en donde R es alquilo. Los grupos R pueden ser los mismos o diferentes.

El término "trialquilsililalquilo", como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos o tres grupos trialquilsililo.

El término "trialquilsililalcoxi," como se usa en la presente, se refiere a un grupo trialquilsililalquilo enlazado a la porción molecular precursora a través de un átomo de oxígeno.

El término "trialquilsililalcoxialquilo" como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos o tres grupos trialquilsililalcoxi.

Los centros asimétricos existen en los compuestos de la presente descripción. Estos centros se designan por los símbolos "R" o "S", dependiendo de la configuración de substituyentes alrededor del átomo de carbono quiral. Deberá entenderse que la descripción abarca todas las formas isoméricas estereoquímicas, o mezclas de los mismos, las cuales poseen la capacidad para inhibir NS5A. Los estereoisómeros individuales de los compuestos pueden

prepararse sintéticamente de materiales de partida comercialmente disponibles los cuales contienen centros quirales o por la preparación de mezclas de productos enantioméricos seguido por la separación tal como la conversión de una mezcla de diastereómeros seguido por la separación o recristalización, técnicas cromatográficas, o separación directa de enantiómeros en columnas cromatográficas quirales. Los compuestos de partida de la estereoquímica particular son ya sea comercialmente disponibles o pueden hacer y resolverse por técnicas conocidas en el arte.

Ciertos compuestos de la presente descripción también pueden existir en formas conformacionales estables diferentes las cuales pueden separarse. La asimetría torsional debido a la rotación restingida alrededor de un enlace sencillo asimétrico, por ejemplo debido a la cadena del anillo u obstrucción estérica, pueden permitir la separación de conformeros diferentes. La presente descripción incluye cada isómero conformacional de estos compuestos y mezclas de los mismos.

El término "compuestos de la presente descripción", y expresiones equivalentes, significa que abarca compuestos de la fórmula (I), y enantiómeros, diastereómeros y sales farmacéuticamente aceptables de los mismos. Similarmente, las referencias a intermediarios significa que abarcan sus sales

donde el contexto se permite.

Los compuestos de la presente descripción pueden existir como sales farmacéuticamente aceptables. El término "sal farmacéuticamente aceptable", como se usa en la presente, representa sales o formas de iones anfotéricos de los compuestos de la presente descripción que son solubles o dispersables en agua o aceite, que son, dentro del alcance del juicio médico sólido, apropiadas para usarse en contacto con los tejidos de pacientes sin una toxicidad, irritación, respuesta alérgica excesiva, u otro problema o complicación correspondientes con una relación beneficio/riesgo razonable, y son efectivos para su uso proyectado. Las sales se pueden preparar durante el aislado y purificación final de los compuestos o separadamente al hacer reaccionar un átomo de nitrógeno apropiado con un ácido apropiado. Las sales de adición ácida representativas incluyen acetato, adipato, alginato, citrato, aspartato, benzoato, bencenosulfonato, bisulfato, butirato, camforato, camforsulfonato; digluconato, dibromohidrato, diclorohidrato, diyodohidrato, glicerofosfato, hemisulfato, heptanoato, hexanoato, formato, fumarato, clorohidrato, bromohidrato, yodohidrato, 2-hidroxietansulfonato, lactato, maleato, mesitilensulfonato, metansulfonato, naftilensulfonato, nicotinato, 2-naftalensulfonato, oxalato, palmoato,

pectinato, persulfato, 3-fenilproprionato, picrato, pivalato, propionato, succinato, tartrato, tricloroacetato, trifluoroacetato, fosfato, glutamato, bicarbonato, para-toluensulfonato, y undecanoato. Ejemplos de ácidos los cuales se pueden emplear 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 aislado y purificación final de los compuestos al hacer reaccionar un grupo carboxi con una base apropiada tal como el hidróxido, carbonato, o bicarbonato de un catión de metal o con amoniaco o una amina primaria, secundaria, o terciaria orgánica. Los cationes de sales farmacéuticamente aceptables incluyen litio, sodio, potasio, calcio, magnesio, y aluminio, así como cationes de amina cuaternaria no tóxica tales como amonio, tetrametilamonio, tetraetilamonio, metilamina, dimetilamina, trimetilamina, trietilamina, dietilamina, etilamina, tributilamina, piridina, N,N-dimetilanilina, N-metilpiperidina, N-metilmorfolina, diciclohexilamina, procaina, dibencilamina, N,N-dibencilfenetilamina, y N,N'-dibenciletilendiamina. Otras aminas orgánicas representativas útiles para la formación de sales de

adición base incluyen etilendiamina, etanolamina, dietanolamina, piperidina, y piperazina.

Cuando es posible que, para usarse en la terapia, las cantidades terapéuticamente efectivas de un compuesto de la fórmula (I), así como sales farmacéuticamente aceptables de las mismas, puedan administrarse como el químico puro, es posible que presentan el ingrediente activo como la composición farmacéutica. En consecuencia, la descripción proporciona además composiciones farmacéuticas, que incluyen cantidades terapéuticamente efectivas de 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" como se usa en la presente, se refiere a la cantidad total de cada componente activo que es suficiente para mostrar un beneficio significativo en el paciente, por ejemplo, una reducción en la carga viral. Cuando se aplica a un ingrediente activo individual, administrado solo, el término se refiere sólo al ingrediente. Cuando se aplica a una combinación, el término se refiere a cantidades combinadas de los ingredientes activos que resultan del efecto terapéutico, ya sea administrado en combinación, sucesivamente o simultáneamente. Los compuestos de la fórmula (I) y las sales farmacéuticamente

aceptables del mismo son como se describen arriba. Los portador(es), diluyente(s), o excipiente(s) deben ser aceptables en el sentido de que sean compatibles con los otros ingredientes de la formulación y no perniciosos para el receptor de los mismos. De acuerdo con otro aspecto de la presente descripción, se proporciona también un proceso para la preparación de una formulación farmacéutica que incluye mezclar un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, con uno o más portadores, diluyentes o excipientes farmacéuticamente aceptables. El término "farmacéuticamente aceptable" como se usa en la presente, se refiere a aquellos compuestos, materiales, composiciones y/o formas de dosificación que se encuentran dentro del alcance del juicio médico sólido, adecuados para el uso en contacto con los tejidos de pacientes sin toxicidad excesiva, irritación, respuesta alérgica u otros problemas o complicaciones correspondientes con una relación beneficio/riesgo razonable, y son efectivos para su uso proyectado.

Las formulaciones farmacéuticas pueden estar presentes en formas de dosificación unitarias que contienen una cantidad predeterminada del ingrediente activo por dosis unitaria. Los niveles de dosificación de entre alrededor de 0.01 y alrededor de 250 miligramos por kilogramo ("mg/kg") de peso corporal por día, preferiblemente entre

alrededor de 0.05 y alrededor de 100 mg/kg de peso corporal por día de los compuestos de la descripción, son típicos en una monoterapia para la prevención y tratamiento contra las enfermedades mediadas por HCV. Típicamente, las composiciones farmacéuticas de la descripción se administrarán desde alrededor de 1 hasta alrededor de 5 veces por día o alternativamente, como una infusión continua. Tal administración puede ser usada como una terapia aguda o crónica. La cantidad de ingrediente activo que puede ser combinada con los materiales portadores para producir una forma de dosificación sencilla variarán dependiendo de la afección de que se trate, la severidad de la afección, el tiempo de administración, la ruta de administración, la relación de excreción del compuesto empleado, la duración del tratamiento, la edad, género, peso y afección del paciente. Las formulaciones de la dosificación unitaria preferida son aquellas que contienen una dosis diaria o sub-dosis, como se mencionó arriba, o una fracción apropiada de la misma, de un ingrediente activo. El tratamiento se inicia con dosificaciones pequeñas sustancialmente menos óptimas que la dosis del compuesto. Posteriormente, la dosificación se incrementa mediante pequeños incrementos hasta que se alcanza el efecto óptimo bajo las circunstancias. En general, el compuesto se

administra más deseablemente en un nivel de concentración que producirá generalmente resultados efectivos antivíricos sin provocar cualquier daño o efectos secundarios perniciosos.

Cuando las composiciones de esta descripción comprenden una combinación de un compuesto de la descripción y uno o más agentes profilácticos o terapéuticos adicionales, tanto el compuesto como el agente adicional se presentan usualmente en niveles de dosificación de entre aproximadamente 10 a 150%, y más probablemente entre alrededor de 10 y 80% de la dosificación administrada normalmente en un régimen de monoterapia.

Las formulaciones farmacéuticas pueden adaptarse para la administración mediante cualquier ruta apropiada, por ejemplo, mediante la ruta oral (que incluye bucal o sublingual), rectal, nasal, tópica (que incluye bucal, sublingual o transdermal), vaginal o parenteral (que incluye subcutánea, intracutánea, intramuscular, intra-articular, intrasinovial, intraesternal, intratecal, intralesional, intravenosa o inyecciones o infusiones intradermales). Tales formulaciones pueden prepararse mediante cualquier método conocido en el arte de la farmacia, por ejemplo, al poner en asociación el ingrediente activo con el portador (es) o el excipiente(s). La administración oral o administración por

inyección son preferidas.

Las formulaciones farmacéuticas adaptadas para la administración oral pueden ser presentadas como unidades discretas tales como cápsulas o tabletas, polvos o gránulos, soluciones o suspensiones en líquidos acuosos y no acuosos, espumas comestibles o batidos, o en emulsiones líquidas aceite en agua o emulsiones agua en aceite.

Por ejemplo, para la administración oral en la forma de una tableta o cápsula, el componente del fármaco activo puede ser combinado con un portador inerte farmacéuticamente aceptable no tóxico tal como etanol, glicerol, agua y similares. Los polvos se preparan mediante la pulverización del compuesto hasta un tamaño fino adecuado y mezclarlo con un portador farmacéutico similarmente pulverizado tal como un carbohidrato comestible, como por ejemplo, almidón o manitol. Puede también estar presente como saborizante, conservador, dispersante y agente colorante.

Las cápsulas se elaboran preparando una mezcla de polvos como se describe arriba, y se llenan con vainas formadas de gelatina. Los agentes mejoradores de flujo y lubricantes tales como sílice coloidal, talco, estearato de magnesio, estearato de calcio o polietilen glicol sólido pueden agregarse a la mezcla en polvo antes de realizar la operación de relleno. Puede también añadirse un agente desintegrante o de solubilización tal como agar-

agar, carbonato de calcio, o carbonato de sodio para mejorar la disponibilidad del medicamento cuando se ingiere la cápsula.

Por otra parte, cuando se desee o sea necesario, los aglutinantes adecuados, lubricantes, agentes desintegrantes y agentes colorantes pueden también ser incorporados en la mezcla. Los aglutinantes adecuados incluyen almidón, gelatina, azúcares naturales tales como glucosa o beta-lactosa, edulcorantes de maíz, gomas sintéticas y naturales tales como acacia, tragacanto, o alginato de sodio, carboximetilcelulosa, polietilen glicol y similares. Los lubricantes usados en estas formas de dosificación incluyen oleato de sodio, cloruro de sodio y similares. Los desintegradores incluyen sin limitación, almidón, metil celulosa, agar, betonita, goma xantana y similares. Las tabletas se formulan, por ejemplo, mediante la preparación de una mezcla de polvo, granulados o sedimentos añadiendo un lubricante y desintegrante, y comprimir en tabletas. Una mezcla de polvos se prepara al mezclar el compuesto, pulverizado adecuado, con un diluyente o una base como la descrita arriba, y opcionalmente con un aglutinante tales como carboximetilcelulosa, un alginato, agente de gelificación o polivinil pirrolidona, una solución retardante tal como una parafina, un acelerador de la resorción tal como una

sal cuaternaria y/o un agente de absorción tal como bentonita, caolín o fosfato de dicalcio. La mezcla del polvo puede ser granulada mediante un humedecimiento con un aglutinante tal como un jarabe, pasta de almidón, mucílago de acadia o soluciones de materiales poliméricos o celulósicos y forzada a través de un tamiz. Como una alternativa para la granulación, la mezcla del polvo puede realizarse por medio de la máquina para elaborar tabletas dando como resultado trozos de forma imperfecta fragmentados como gránulos. Los gránulos pueden ser lubricados para prevenir la adherencia a los troqueles que forman la tableta por medio de la adición de ácido esteárico, una sal de estearato, talco o aceite mineral. La mezcla lubricada se comprime entonces en tabletas. Los compuestos de la presente descripción pueden también ser combinados con un portador inerte que fluye libremente y comprimirse en tabletas directamente sin ir a través de las Extremos de granulación o sedimentación. Puede proporcionarse un revestimiento protector opaco o claro que consiste de un revestimiento de sellado con laca, un revestimiento de azúcar o material polimérico y un revestimiento de pulido de cera. Los colorantes pueden añadirse a aquellos revestimientos para distinguir diferentes dosificaciones unitarias.

Los fluidos orales tales como una solución, jarabe y

elixires pueden prepararse en formas de dosificación unitarias tal que una cantidad dada contenga una cantidad predeterminada del compuesto. Los jarabes pueden prepararse disolviendo el compuesto en una solución acuosa saborizada adecuadamente mientras que los elíxires se preparan a través del uso de un vehículo no tóxico. Pueden añadirse solubilizadores y emulsificadores tales como alcoholes de isoestearilo etoxilados y éteres de polioxietilen sorbitol, conservadores, aditivos de condimentación tales como edulcorantes naturales o aceite de menta, o sacarina u otros edulcorantes artificiales y similares.

Cuando sea apropiado, las formulaciones de dosificación unitarias para la administración oral pueden ser microencapsuladas. La formulación puede también ser preparada para prolongar o sostener la liberación mediante por ejemplo, material particulado de revestimiento o incrustación en polímeros, ceras o similares.

Los compuestos de la fórmula (I) y sales farmacéuticamente aceptables de los mismos, pueden también administrarse en la forma de sistemas de suministro de liposomas, tales como vesículas unilamelares pequeñas, vesículas unilamelares grandes y vesículas multilamelares. Los liposomas pueden formarse a partir de una variedad de fosfolípidos tales como colesterol, estearilamina o

fosfatidilcolinas.

Los compuestos de la fórmula (I) y las sales farmacéuticamente aceptables de los mismos pueden suministrarse mediante el uso de anticuerpos monoclonales como portadores individuales en los que se acoplan las moléculas del compuesto. Los compuestos pueden también ser acoplados con polímeros solubles como portadores de fármacos dirigibles. Tales polímeros pueden incluir polivinilpirrolidona, copolímero de pirano, polihidroxipropilmetacrilamidafenol, polihidroxietilaspartamidafenol, o polietilenoxidepolilisina sustituida con residuos de palitoilo. Además, los compuestos pueden ser acoplados a una clase de polímeros biodegradables útiles en obtener una liberación controlada de un fármaco, por ejemplo, ácido poliláctico, poliepsilon caprolactona, ácido polihidroxi butírico, poliortoésteres, poliacetales, polidihidropiranos, policianoacrilatos y copolímeros de bloque anfifáticos o reticulados de hidrogeles.

Las formulaciones farmacéuticas adaptadas para la administración transdermal pueden ser presentadas como parches discretos para permanecer en contacto íntimo con la epidermis del receptor durante un periodo de tiempo prolongado. Por ejemplo, el ingrediente activo puede ser suministrado a partir de un parche mediante la iontofóresis

como se describe generalmente en Pharmaceutical Research 1986, 3(6), 318.

Las formulaciones farmacéuticas adaptadas para la administración tópica pueden ser formuladas como ungüentos, cremas, suspensiones, lociones, polvos, soluciones, pastas, geles, rocíos, aerosoles o aceites.

Las formulaciones farmacéuticas adaptadas para la administración rectal pueden presentarse como supositorios o como enemas.

Las formulaciones farmacéuticas adaptadas para la administración nasal, en donde el portador es un sólido, incluye un polvo del curso que tiene un tamaño de partícula, por ejemplo, en el intervalo de 20 hasta 500 micrones, que se administra en la forma en la que se inhala, es decir, mediante la inhalación rápida a través de un pasaje nasal de un recipiente que se mantiene próximo a la nariz. Las formulaciones adecuadas en donde el portador es un líquido, para la administración como un rociador nasal o gotas nasales, incluye soluciones en aceite o acuosas del ingrediente activo.

Las formulaciones farmacéuticas adaptadas para la administración mediante inhalación incluyen polvos o neblinas de partículas finas que pueden ser generadas por medio de varios tipos de aerosoles presurizados de dosis medidas, nebulizadores o insufladores.

Las formulaciones farmacéuticas adaptadas para la administración vaginal pueden ser presentadas como pesarios, tampones, cremas, geles, pastas, espumas o formulaciones de rocío.

Las formulaciones farmacéuticas adaptadas para la administración parenteral incluyen soluciones de inyecciones estériles acuosas y no acuosas que pueden contener antioxidantes, soluciones amortiguadoras, bacteriostatos y solutos que suministran la formulación isotónica con la sangre del receptor pretendido; y las suspensiones estériles acuosas y no acuosas que pueden incluir agentes de suspensión y agentes de espesamiento. Las formulaciones pueden estar presentes en contenedores de dosis unitarias y dosis múltiples, por ejemplo, ampolletas selladas y frascos, y pueden ser almacenados en una afección de deshidratación por secado (liofilizadas) que requiere solo de la adición del portador líquido estéril, por ejemplo, agua para inyecciones, inmediatamente previo a su uso. Las soluciones de inyecciones extemporáneas y suspensiones pueden estar presentes a partir de polvos estériles, gránulos y tabletas.

Se entenderá que además de los ingredientes mencionados arriba en particular, las formulaciones pueden incluir otros agentes convencionales en el arte, haciendo referencia al

tipo de formulación en cuestión, por ejemplo, aquellas adecuadas para la administración oral pueden incluir agentes saborizantes.

El término "paciente" incluye tanto a los humanos como a otros mamíferos.

El término "tratar" se refiere a: (i) prevenir una enfermedad, trastorno o afección que se presenta en un paciente que puede estar predispuesto a las enfermedades, trastornos y/o afección pero que no ha sido aún diagnosticado como para (ii) inhibir la enfermedad, trastorno o afección, es decir, interrumpe su desarrollo, y (iii) alivia la enfermedad, trastorno o afección, es decir, provoca la regresión de la enfermedad, trastorno y/o afección.

Los compuestos de la presente descripción también pueden ser administrados con una ciclosporina, por ejemplo, ciclosporina A. La ciclosporina A ha demostrado ser activa contra el HCV en ensayos clínicos (*Hepatology* 2003, *38*, 1282; *Biochem. Biophys. Res. Commun.* 2004, 313, 42; *J. Gastroenterol.* 2003, 38, 567).

La tabla 1 a continuación enlista algunos ejemplos ilustrativos de los compuestos que pueden ser administrados con los compuestos de esta descripción. Los compuestos de la presente descripción pueden ser administrados con otros compuestos con actividad anti-HCV en combinación con una terapia, ya sea en conjunto o por separado, o combinando los

compuestos en una composición.

Tabla 1

Nombre Comercial	*Clase Fisiológica*	*Tipo de Inhibidor o Direccionador*	*Compañía Fuente*
NIM811		Inhibidor de Ciclofilina	Novartis
Zadaxin		Inmunomodulador	Sciclone
Suvus		Azul de metileno	Bioenvision
Actilon (CPG10101)		Agonista TLR9	Coley
Batabulin (T67)	Anticáncer	Agonista de β-tubulina	Tularik Inc., South San Francisco, CA

Nombre Comercial	*Clase Fisiológica*	*Tipo de Inhibidor o Direccionador*	*Compañía Fuente*
ISIS 14803	Antivírico	antisentido	ISIS Pharmaceuticals Inc, Carlsbad, CA/Elan Phamaceuticals Inc., New York, NY
Summetrel	Antivírico	antivírico	Endo Pharmaceuticals Esperarings Inc., Chadds Ford, PA
GS-9132 (ACH-806)	Antivírico	Inhibidor del HCV	Achillion / Gilead
Compuestos y sales de pirazolo-pirimidina de WO-2005047288 26 May 2005	Antivírico	Inhibidores del HCV	Arrow Therapeutics Ltd.

Nombre Comercial	*Clase Fisiológica*	*Tipo de Inhibidor o Direccionador*	*Compañía Fuente*
Levovirin	Antiviral	Inhibidor del IMPDH	Ribapharm Inc., Costa Mesa, CA
Merimepodib (VX-497)	Antiviral	Inhibidor del 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

Nombre Comercial	*Clase Fisiológica*	*Tipo de Inhibidor o Direccionador*	*Compañía Fuente*
GL-59728	Antiviral	Inhibidor de Replicasa NS5B	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 RdRp	Japan Tobacco Inc., Tokio, Japón
Levovirin	Antiviral	ribavirina	ICN Pharmaceuticals, Costa Mesa, CA
Ribavirina	Antiviral	ribavirina	Schering-Plough Corporation, Kenilworth, NJ

Nombre Comercial	*Clase Fisiológica*	*Tipo de Inhibidor o Direccionador*	*Compañía Fuente*
Viramidine	Antiviral	Profármaco de Ribavirina	Ribapharm Inc., Costa Mesa, CA
Heptazyme	Antiviral	ribozima	Ribozima Pharmaceuticals Inc., Boulder, CO
BILN-2061	Antiviral	Inhibidor de serina proteasa	Boehringer Ingelheim Pharma KG, Ingelheim, Alemania
SCH 503034	Antiviral	Inhibidor de serina proteasa	Schering Plough
Zadazim	Modulador inmunitario	Modulador inmunitario	SciClone Pharmaceuticals Inc., San Mateo, CA
Ceplene	Inmunomo-dulador	modulador inmunitario	Maxim Pharmaceuticals Inc., San Diego, CA

Nombre Comercial	*Clase Fisiológica*	*Tipo de Inhibidor o Direccionador*	*Compañía Fuente*
CellCept	Inmunodepresor	Inmunodepresor IgG de HCV	F. Hoffmann-La Roche LTD, Basilea, Suiza
Civacir	Inmunodepresor	Inmunodepresor 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

Nombre Comercial	*Clase Fisiológica*	*Tipo de Inhibidor o Direccionador*	*Compañía Fuente*
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

Nombre Comercial	*Clase Fisiológica*	*Tipo de Inhibidor o Direccionador*	*Compañía Fuente*
Interferón-β	Interferón	Interferón-β-1a	Serono
Multiferon	Interferón	IFN de larga duración IFN	Viragen/Valentis
Wellferon	Interferón	linfoblastoide IFN-αn1	GlaxoSmithKline plc, Uxbridge, RU
Omniferon	Interferón	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/ modulador inmune	Maxim Pharmaceuticals Inc., San Diego, CA
Pegasys y Ribavirina	Interferón	IFN-α2a PEGilado/ribavirina	F. Hoffmann-La Roche LTD, Basilea, Suiza

Nombre Comercial	*Clase Fisiológica*	*Tipo de Inhibidor o Direccionador*	*Compañía Fuente*
PEG-Intron	Interferón	IFN-α2b PEGilado	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron / Ribavirina	Interferón	IFN-α2b PEGilado/ ribavirina	Schering-Plough Corporation, Kenilworth, NJ
IP-501	Protección de hígado	antibiótico	Indevus Pharmaceuticals Inc., Lexington, MA
IDN-6556	Protección de hígado	Inhibidor de caspasa	Idun Pharmaceuticals Inc., San Diego, CA
ITMN-191 (R-7227)	Antiviral	Inhibidor de serine protease	InterMune Pharmaceuticals Inc., Brisbane, CA
GL-59728	Antiviral	Inhibidor de Replicasa NS5B	Genelabs
ANA-971	Antiviral	TLR-7 agonist	Anadys

Los compuestos de la presente descripción también pueden usarse como reactivos de laboratorio. Los compuestos pueden ser instrumentos que proporcionen herramientas de investigación para diseñar ensayos de replicación viral, validación de los sistemas de ensayo para animales y estudios de biología estructural para perfeccionar el conocimiento de los mecanismos de la enfermedad de HCV. Además, los compuestos de la presente descripción son útiles para establecer o determinar el sitio de enlace de otros compuestos antivíricos, por ejemplo, mediante la inhibición competitiva.

Los compuestos de esta descripción pueden ser usados también para tratar o prevenir la contaminación viral de los materiales y por lo tanto, reducir el riesgo de una infección viral del personal médico o de laboratorio, o pacientes que están en contacto con tales materiales, por ejemplo, sangre, tejido, instrumentos quirúrgicos y vestimenta, instrumentos de laboratorio y vestimenta, y colección sanguínea o aparatos para transfusión y materiales.

Esta descripción se pretende que abarque los compuestos que tienen la fórmula (I) cuando se preparan por procesos sintéticos o por procesos metabólicos incluyendo aquellos que se presentan naturalmente en el cuerpo humano o animal (in vivo) o procesos que se presentan in vitro.

Las abreviaturas usadas en la presente solicitud, incluyendo particularmente en los esquemas de reacción ilustrativos y ejemplos son como sigue, son bien conocidos para aquellos expertos en la técnica. Algunas de las abreviaturas usadas son como siguen: HATU para hexafluorofosfato de O-(7-azabenzottriazol-1-il)-N,N,N',N'-tetrametiluronio; Boc para tert-butoxicarbonil; NBS para N-bromosuccinimida; tBu o t-Bu para tert-butilo; SEM para -(trimetilsilil)etoximetilo; DMSO para dimetilsulfóxido; MeOH para metanol; TFA para ácido trifluoroacético; TA/TR para temperatura ambiente o tiempo de retención (como lo dicta el contexto); tR para tiempo de retención; EDCI para clorohidrato 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 dimetilsulfuro; 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 carbobenciloxi; n-BuLi para n-butilitio; ACN para acetonitrilo; h o hr para horas; m o min para minutos; s para segundos; LiHMDS para hexametildisilazida de litio; DIBAL para hidruro diisobutil

aluminio; TBDMSCl para cloruro de tert-butildimetilsililo; Me para metilo; ca. para alrededor; OAc para acetato; iPr para isopropilo; Et para etilo; Bn para bencilo; y HOAT para 1-hidroxi-7-azabenzotriazol.

Las abreviaturas usadas en la solicitud actual, incluyendo particularmente en los esquemas de reacción ilustrativos y ejemplo los cuales siguen son bien conocidos para aquellos expertos en la técnica. Algunas de las abreviaturas son como siguen:

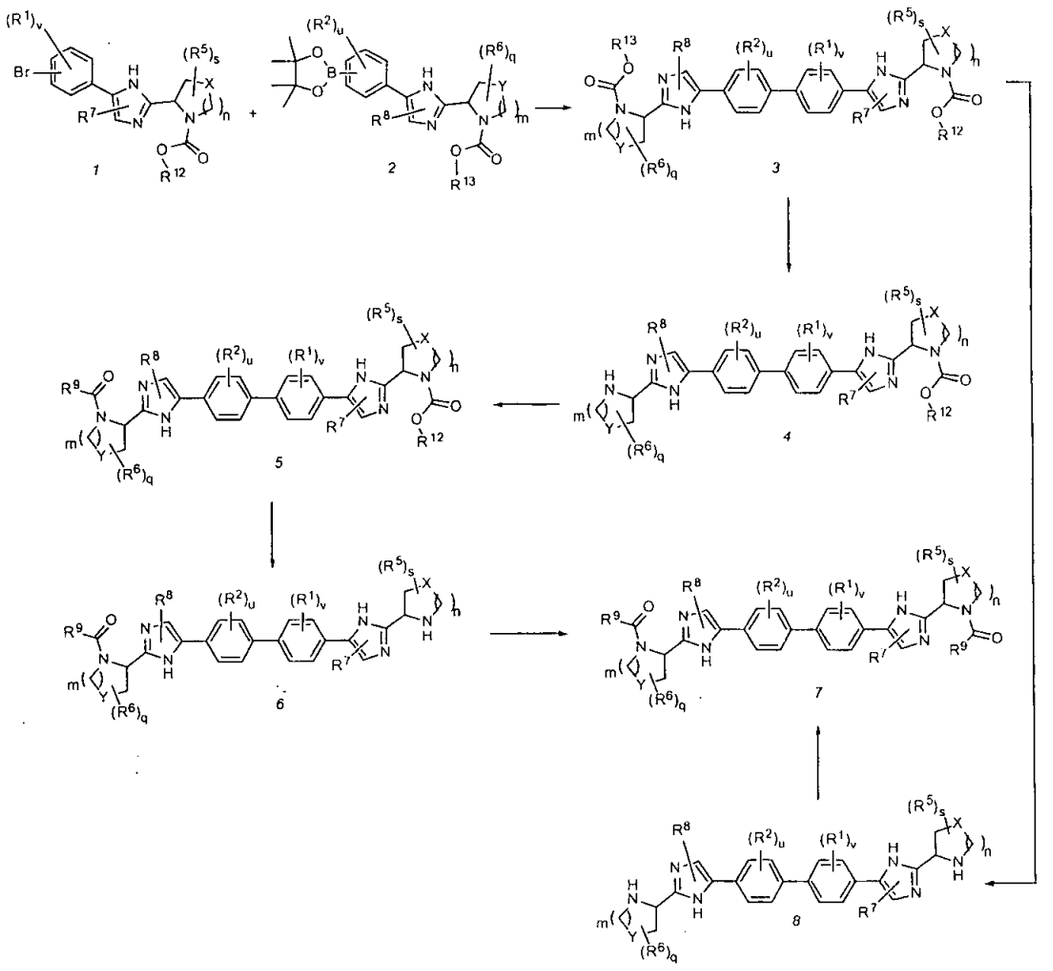
Los compuestos y procesos de la presente descripción serán mejor entendidos en conexión con los siguientes esquemas sintéticos que ilustran los métodos para los cuales los compuestos de la presente descripción pueden prepararse. Los materiales de partida pueden obtenerse de fuentes comerciales o prepararse por métodos conocidos bien establecidos en la literatura para aquellos de experiencia ordinaria en la técnica. Será fácilmente aparente para alguien experto en la técnica que los compuestos definidos arriba pueden sintetizarse por substitución de los reactivos y agentes apropiados en la síntesis mostrada a continuación. También será fácilmente aparente para alguien experto en la técnica que las Extremos de protección y desprotección selectiva, así como el orden de las Extremos por sí mismas, pueden llevarse a cabo en orden variado, dependiendo de la naturaleza de las variables para completar exitosamente la

síntesis mencionada a continuación. Las variables son como se definen arriba a menos que se denote de otra manera a continuación.

Esquema de reacción 1: Bifenilos simétricos o asimétricos

El haluro de arilo 1 y éster borónico 2 puede acoplarse para producir biarilo 3 usando condiciones de acoplamiento Suzuki-Miayura estándar (*Angew Chem. Int. Ed. Engl* 2001, 40, 4544). Se deberá notar que el análogo de ácido borónico de 2 puede usarse en lugar de éster. La mono-desprotección de la porción de pirrolidina puede completarse cuando R^{12} y R^{13} son diferentes. Cuando R^{12} = bencilo, y R^{13} = t-butilo el tratamiento para condiciones hidrogenolíticas produce 4. Por ejemplo, El catalizador Pd/C en la presencia de una base tal como carbonato de potasio puede usarse. La acilación del 4 puede completarse bajo condiciones de acilación estándar. Un reactivo de acoplamiento tal como HATU en combinación con una base amina tal como base Huning puede usarse en este aspecto. Alternativamente, el 4 puede hacerse reaccionar con un isocianato o cloruro de carbamoilo para proporcionar los compuestos de la fórmula 5 donde R^9 es una amina. Además la desprotección del 5 puede completarse por el tratamiento con ácido fuerte tal como HCl o ácido trifluoroacético. Las condiciones estándar análogas a aquellas usadas para convertir el 4 hasta 5 pueden usarse para preparar el 7 a partir del 6. En otra modalidad en donde R^{12} = R^{13} = t-Bu, la conversión directa al 8 puede completarse por el

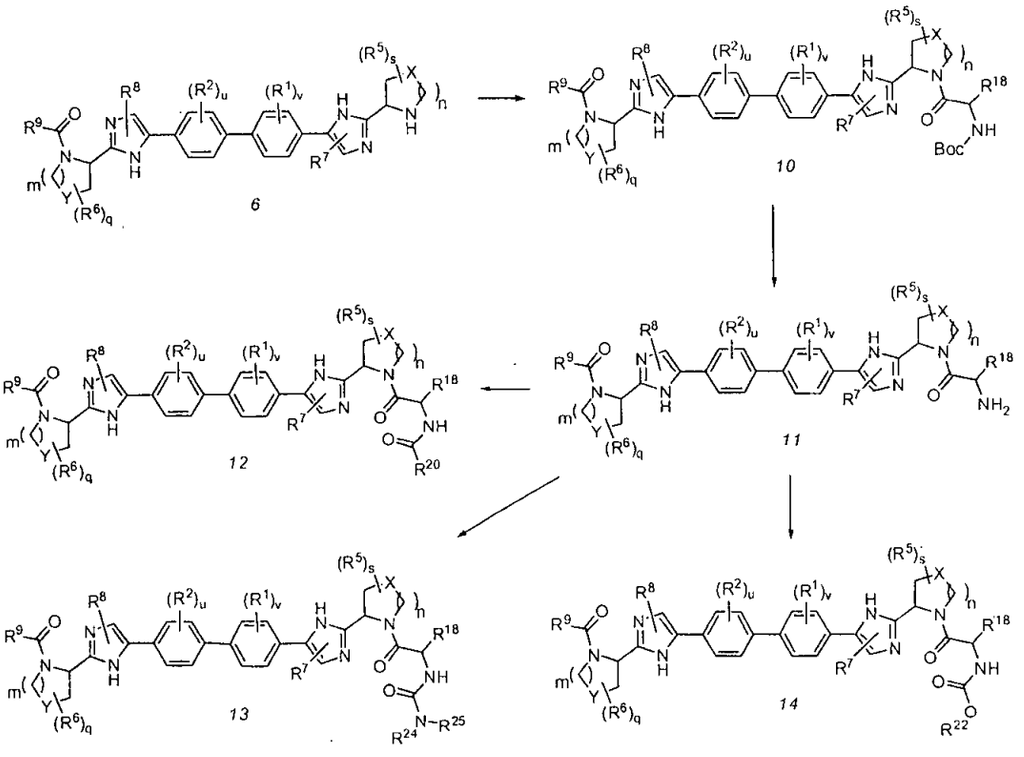
tratamiento contral 3 con ácido fuerte tal como HCl o ácido trifluoroacético. La conversión del 8 hasta 7 se completa en una manera análoga a los métodos usados para preparar el 5 a partir del 4 ó 7 a partir del 6. En esta instancia sin embargo, los extremos en 7 serán idénticas.



Esquema de reacción 2: Bifenilos con extremo asimétrico

La conversión del 6 (a partir del Esquema de reacción 1) hasta 10 puede ser usando condiciones de acoplamiento

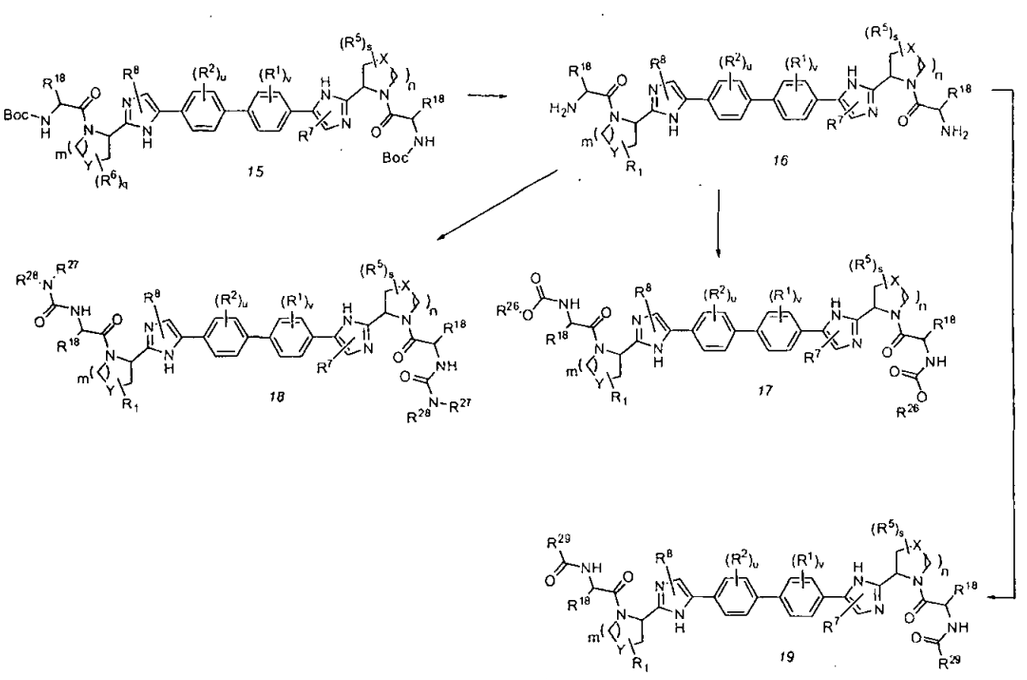
de amida estándar tales como HATU con una base amina, tal como base Huning. La desprotección puede completarse con ácido fuerte tal como HCl o ácido trifluoroacético proporcionando el 11. El compuesto 11 puede luego convertirse al 12, 13, ó 14 usando un cloruro ácido, un isocianato o cloruro de carbamoilo, o un cloroformiato respectivamente.



Esquema de reacción 3: Bifenilos elaborados con extremo simétrico

El compuesto 15 (15 = 7 (Esquema de reacción 1) en donde cada R^9 es $-CH(NHBoc)R^{18}$) pueden convertirse al 16 por medio de tratamiento con ácido fuerte tal como HCl o ácido

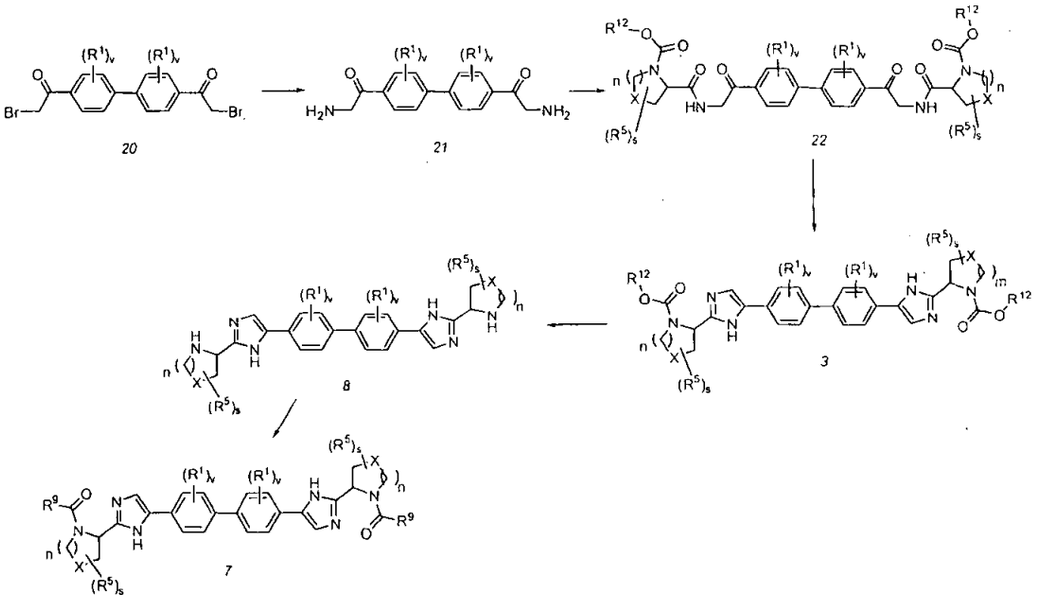
trifluoroacético. Los compuestos 17, 18, y 19 pueden prepararse a partir del 16 por tratar el 16 con un cloroformiato, isocianato o cloruro de carbamoilo apropiado, o un cloruro ácido respectivamente.



Esquema de reacción 4: Bifenilos simétricos

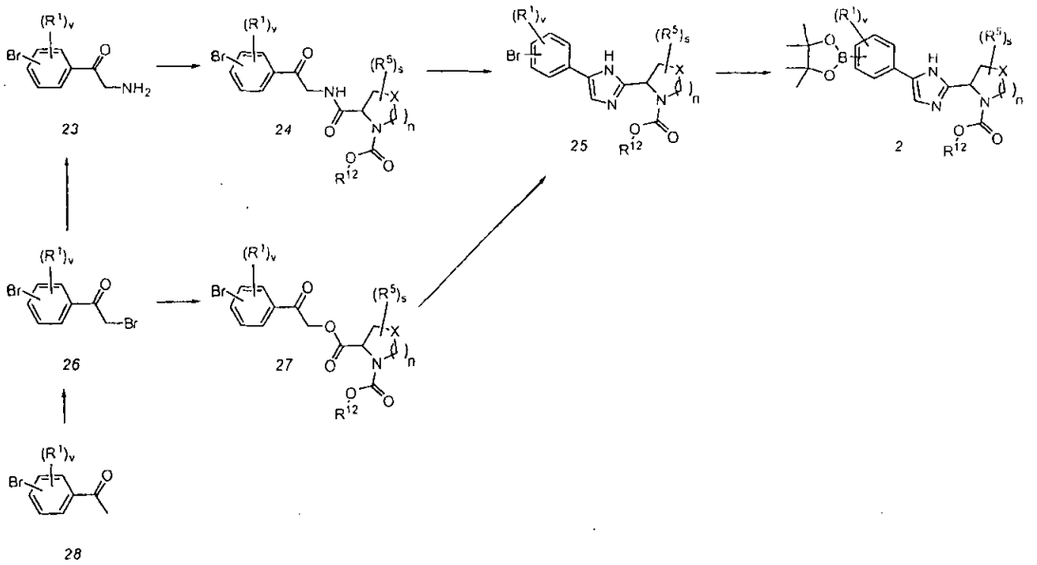
Los análogos de bifenilo simétricos (compuestos de la fórmula 7 donde ambas mitades de la molécula son equivalentes) pueden sintetizarse partiendo de la bromocetona 20. La aminación por el desplazamiento con un nucleofilo tal como azida, ftalimida o preferiblemente diformilamida de sodio (Yinglin and Hongwen, Synthesis, (1990), página 122) seguido por desprotección proporcionando el 21. La condensación bajo condiciones de aminación estándar tales

como HATU y Base Hunig con un aminoácido apropiadamente protegido proporciona el 22. El calentamiento con acetato de amonio bajo condiciones de microondas o térmicas resulta en la formación del 3 el cual puede desprotegerse con ácido fuerte tal como HCl o ácido trifluoroacético (R^{12} = R^{13} = t-Bu) o por hidrogenolisis con gas de hidrógeno y un catalizador de metal de transición tal como Pd/C (R^{12} = R^{13} = bencilo). La acilación puede afectarse con un ácido carboxílico (R^9CO_2H) en una manera similar a la conversión del 21 hasta 22. La formación de urea puede completarse por el tratamiento con un isocianato apropiado (R^9 = $R^{24}R^{25}N$; R^{25} =H) o cloruro de carbamoilo (R^9 = $R^{24}R^{25}N$; R^{25} es diferente a hidrógeno).



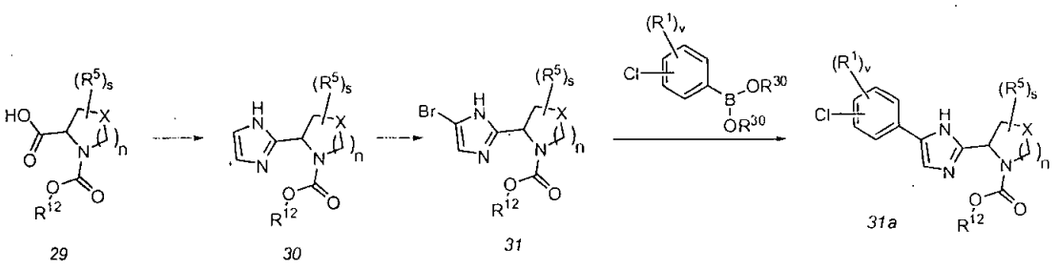
Esquema de reacción 5: Materiales de partida 25 y 2

El esquema de reacción 5 describe la preparación de algunos de los materiales de partida requeridos para las secuencias sintéticas detalladas en los esquemas de reacción 1-4. El intermediario clave 25 (análogo al 1 en el esquema de reacción 1) se prepara a partir de la ceto-amida 24 o ceto-éster 27 por medio del calentamiento con acetato de amonio bajo condiciones de microondas o térmicas. La ceto-amida 24 puede prepararse a partir del 23 por medio de condensación con un aminoácido cíclico o acíclico apropiado bajo condiciones de formación de amida estándar. El bromuro 26 puede darse enjuagando al 23 por el tratamiento con un nucleofilo tal como azida, ftalimida o diformilamida de sodio (Synthesis 1990, 122) seguido por desprotección. El bromuro 26 puede también convertirse al 27 por hacerse reaccionar con un aminoácido N protegido cíclico o acíclico apropiado en la presencia de la base tal como carbonato de potasio o bicarbonato de sodio. La brominación del 28 con una fuente de ión de bromonio tal como bromuro, NBS, o CBr_4 resulta en la formación del 26. El bromuro 25 puede convertirse al éster borónico 2 por medio de tratamiento con bis-pinacalotodiboro bajo catalisis de paladio de conformidad al método descrito en Journal of Organic Chemistry 1995, 60, 7508, o variaciones del mismo.



Esquema de reacción 6: Material de partida 31a

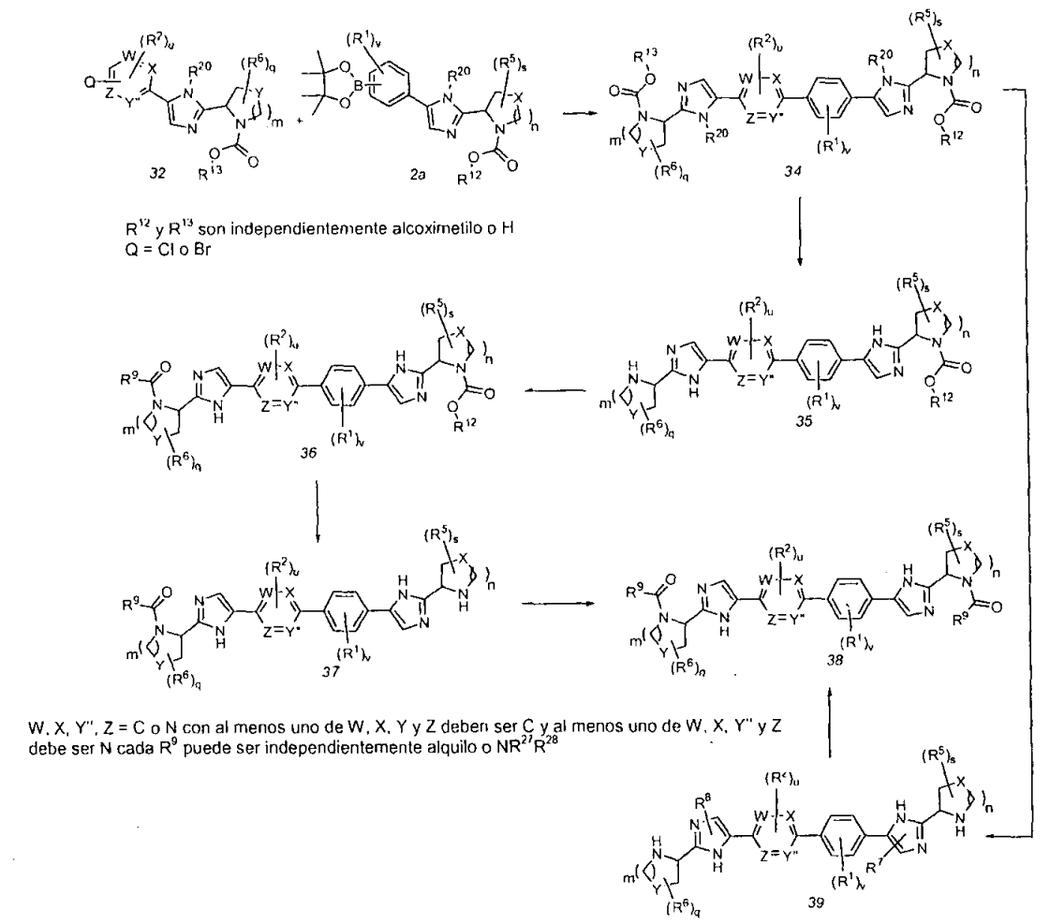
En otra modalidad, los materiales de partida tales como el 31a (análogo al 25 en el Esquema de reacción 5 y 1 en el Esquema de reacción 1) pueden prepararse por haćerse reaccionar los derivados de bromoimidazol 31 bajo condiciones de acoplamientode tipo Suzuki con una variedad de ácido de aril borónicos cloro substituidos los cuales pueden prepararse por metodologías estándar (ver, por ejemplo, Organic Letters 2006, 8, 305 y referencias citadas en la presente) u obtenerse de fuentes comerciales. El bromoimidazol 31 puede obtenerse por el imidazol bromado 30 con una fuente de ión de bromonio tal como bromo, CBr_4, o N-bromosuccinimida. El Imidazol 30 puede prepararse a partir de aminoácidos protegidos en N los cuales son apropiadamente substituidos por hacerse reaccionar con glioxal en una solución metanólica de hidróxido de amonio.



Esquema de reacción 7: Heteroarilos

Todavía en otra modalidad de la presente descripción, el haluro de arilo 32 puede acoplarse bajo condiciones catalizadas de paladio Suzuki-Miyaura para formar el derivado de heteroarilo 34. El compuesto 34 puede elaborar al 35 por el tratamiento por condiciones hidrogenolíticas con hidrógeno y un catalizador de metal de transición tal como paladio sobre carbono (R^{13} = bencilo). La acilación del 35 puede completarse con un cloruro ácido apropiado (R^9COCl) en la presencia de una base tal como trietilamina, con un ácido carboxílico apropiadamente substituido (R^9CO_2H) en la presencia de un reactivo de acoplamiento estándar tal como HATU, o con un isoscianato ($R^{27}NCO$ en donde R^9 = $R^{27}R^{28}N$-; R^{28} =H) o cloruro de carbamoilo ($R^{27}R^{29}NCOCl$ en donde R^9 = $R^{27}R^{28}N$-). El compuesto 37 puede prepararse a partir del 36 (R^{12} = t-Bu) por medio de tratamiento con ácido fuerte tal como HCl o ácido trifluoroacético. La acilación de la amina resultante en el 37 para dar el 38 puede completarse como en la transformación del 35 al 36. En casos en donde R^{12} = R^{13}, el 34 puede directamente transformarse en el 39 por el tratamiento con

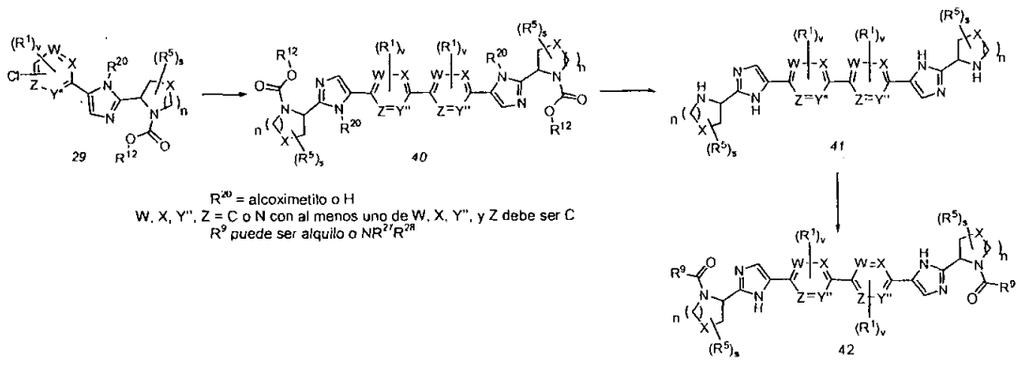
ácido fuerte tal como HCl o ácido trifluoroacético (R^{12} = R^{13} = t-Bu) o puede emplear condiciones hidrogenoliticas con hidrógeno y un catalizador de metal de transición tal como paladio en carbono (R^{12} = R^{13} = bencilo). La acilación del 39 puede completarse en una manera análoga a aquella descrita por la transformación del 35 al 36.



Esquema de reacción 8

El cloruro de heteroarilo 29 puede convertirse al análogo simétrico 40 por medio de tratamiento con una fuente

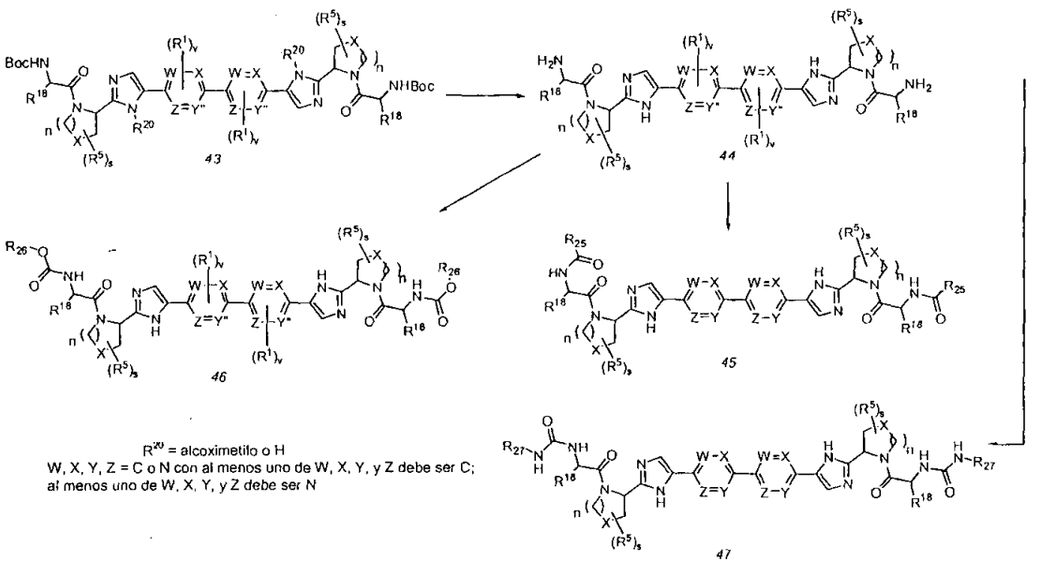
de paladio tal como diclorobis(benzonitrilo)paladio en la presencia de tetraquis(dimetilamino)etileno a temperatura elevada. El removido del éter SEM y carbamatos de Boc encontró que el 40 puede completarse en una Extremo por el tratamiento con un ácido fuerte tal como HCl o ácido trifluoroacético proporcionando el 41. La conversión al 42 puede completarse en una manera similar a las condiciones usadas para convertir el 38 al 39 en el Esquema de reacción 7.



Esquema de reacción 9: Heteroarilos substituidos con extremo simétrica

El compuesto 43 (análogo al 42 en donde R_{23} = -CH(NHBoc)R_{24}) puede elaborar al 45, 46, y 47 por medio de metodologías similares a aquellas descritas en el esquema de reacción 3. En casos en donde R_{20} = alcoximetilo (ie; SEM), el removido puede completarse simultáneamente con el removido del carbamato Boc (cf; 43 hasta 44) usando ácido fuerte tal como HCl o

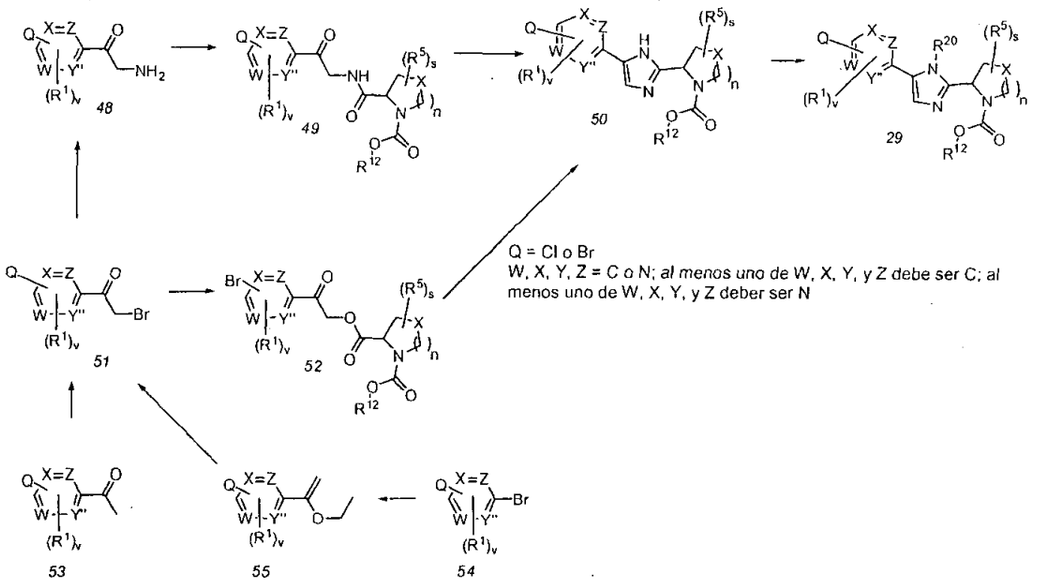
ácido trifluoroacético.



Esquema de reacción 10: Material de partida 29

Los bromuros de heteroarilo 54 pueden hacerse reaccionar con un estanano de vinilo tal como tributil(1-etoxivinil)estaño en la presencia de una fuente de paladio tal como diclorobis(trifenilfosfina)paladio (II) para proporcionar el 55 el cual puede subsecuentemente transformarse en la bromocetona 51 por medio de tratamiento con una fuente de ión de bromonio tal como N-bromosuccinimida, CBr_4, o bromuro. Alternativamente, los bromuros de heteroarilo ceto substituidos 53 pueden directamente convertirse al 51 por medio de tratamiento con una fuente de ión de bromonio tal como bromuro, CBr_4, o N-bromosuccinimida.

El bromuro 51 puede convertirse a la aminocetona 48 por medio de la adición de azida de sodio, ftalimida de potasio o diformilamida de sodio (Synthesis 1990, 122) seguido por desprotección. La aminocetona 48 puede luego acoplarse con un aminoácido apropiadamente substituido bajo condiciones de formación de amida estándar (ie; un reactivo de acoplamiento tal como HATU en la presencia de una base suave tal como base Huning) para proporcionar el 49. El compuesto 49 puede luego además transformarse en el imidazol 50 por medio de hacerse reaccionar con acetato de amonio bajo condiciones de microondas o térmicas. Alternativamente, el 51 puede hacerse reaccionar directamente con un aminoácido apropiadamente substituido en la presencia de una base tal como bicarbonato de sodio o carbonato de potasio proporcionando el 52 el cual puede volver a hacerse reaccionar con acetato de amonio bajo condiciones de microondas o térmicas para proporcionar el 50. El imidazol 50 puede protegerse con un grupo de alcoximetilo por el tratamiento con el haluro de alcoximetilo apropiado tal como cloruro de 2-(trimetilsilil)etoximetilo después de primero desprotonarse con una base fuerte tal como hidruro de sodio.

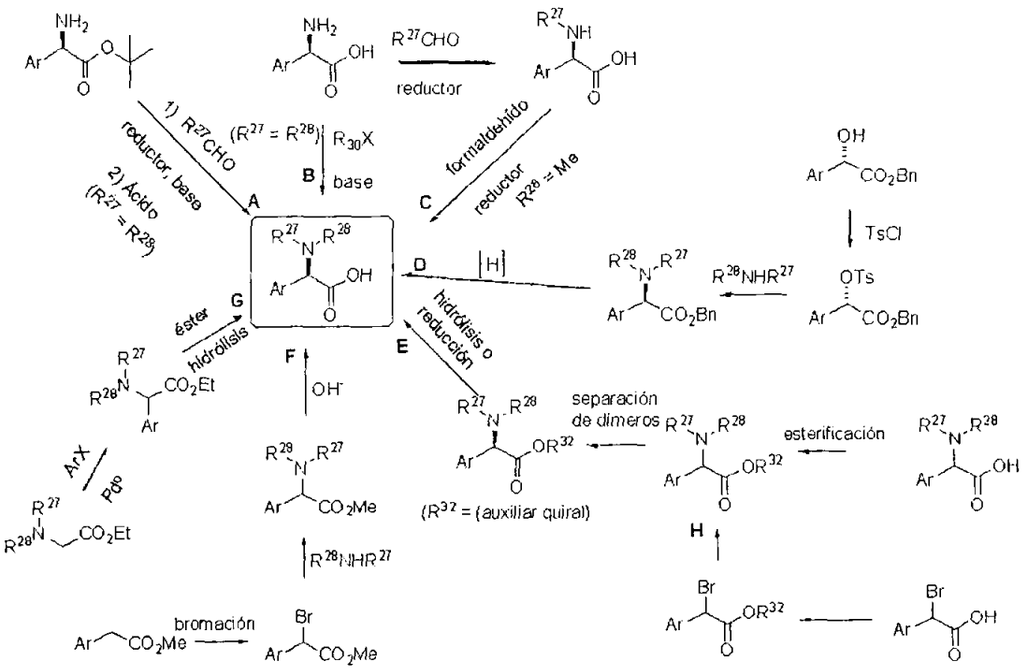


Esquema de reacción 11: Derivados de fenilglicina substituidos

Los derivados de fenilglicina substituidos pueden prepararse por un número de métodos mostrados a continuación. El éster de t-butil fenilglicina puede alquilarse reductivamente (trayectoria A) con un aldehído apropiado y un reductor tal como cianoborohidruro de sodio en un medio ácido. La hidrólisis del éster de t-butilo puede completarse con ácido fuerte tal como HCl o ácido trifluoroacético. Alternativamente, la 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 (trayectoria B). La trayectoria C ilustra la alquilación reductiva de la

fenilglicina como en la trayectoria A seguida por una segunda alquilación reductiva con un aldehído alternativo tal como formaldehído en la presencia de un agente reductor y ácido. La trayectoria D ilustra la síntesis de las fenilglicinas substituidas por medio de los análogos de ácido mandelico correspondientes. La conversión del alcohol secundario a un grupo dado competente puede completarse con cloruro de p-toluensulfonilo. El desplazamiento del grupo de tosilato con una amina apropiada seguido por el remivido reductivo del éster de bencilo puede proporcionar los derivados de fenilglicina substituidos. En la trayectoria E un derivado de fenilglicina substituido racémico se resolvió por la esterificación con un auxiliar quiral enantiomericamente puro tal como pero limitado a (+)-1-feniletanol, (-)-1-feniletanol, una oxazolidinona Evan, o pantolactona enantioméricamente pura. La separación de los diastereómeros se completa por medio de cromatografía (gel de sílice, HPLC, cristalización, etc) seguido por el removido del quiral auxiliar proporcionando derivados de fenilglicina enantiomericamente puros. La trayectoria H ilustra una secuencia sintética la cual se intersecta con la trayectoria E en donde el auxiliar

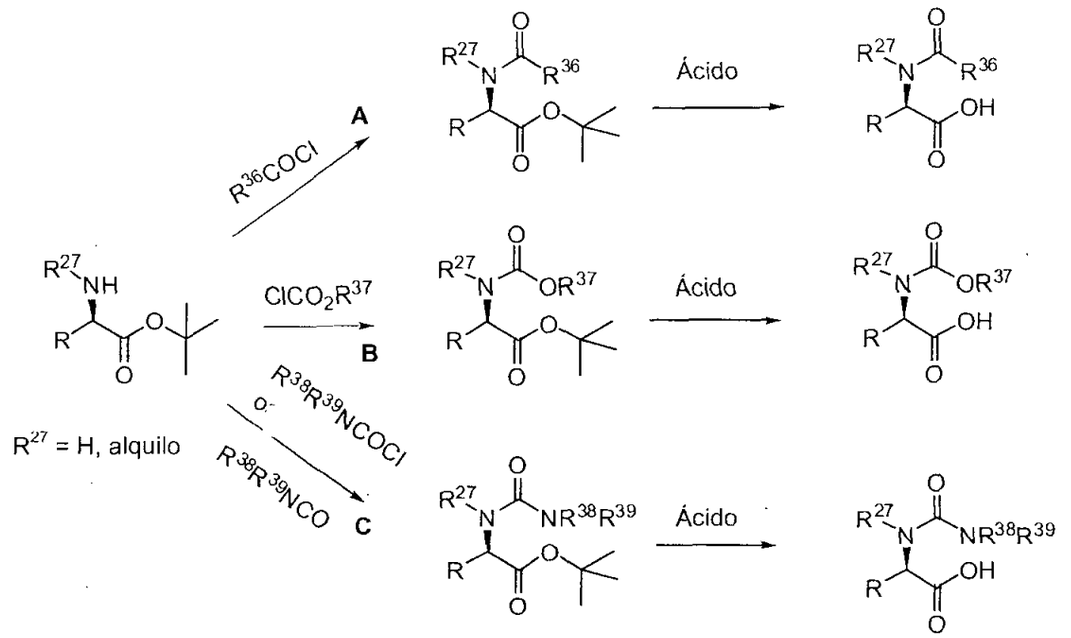
quiral anteriormente mencionado se instala previo a la adición de la amina. Alternativamente, un éster de un ácido arilacético puede brominarse con una fuente de ión de bromonio tal como bromuro, N-bromosuccinimida, o CBr_4. El bromuro bencílico resultante puede desplazarse con una variedad de aminas mono o disubstituidas en la presencia de una base de amina terciaria tal como trietilamina o Base Hunig. La hidrólisis del éster de metilo por medio de tratamiento con hidróxido de litio a temperatura baja o 6N HCl a temperatura elevada proporciona los derivados de fenilglicina substituidos. Otro método se muestra en la trayectoria G. Los análogos de glicina pueden derivarse con una variedad de haluros de arilo en la presencia de una fuente de paladio (0) tal como bis(tributilfosfina)paladio y base tal como fosfato de potasio. El éster resultante puede luego hidrolizarse por el tratamiento con una base o ácido. Se entenderá que otros métodos conocidos para preparar derivados de fenilglicina existen en el arte y pueden enmendarse para proporcionar los compuestos deseado en esta descripción. Se deberá también entender que los derivados de fenilglicina finales pueden purificarse para una pureza enantiomerica mayor de 98%ee por medio de HPLC preparativa.



Esquema de reacción 12: Derivados de aminoácido acilados

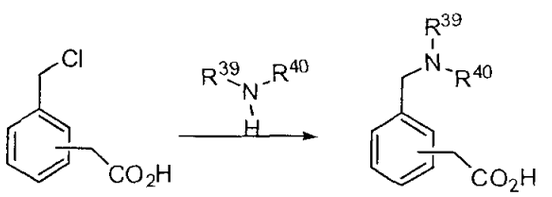
En otra modalidad de la presente descripción, los derivados de fenilglicina acilados pueden prepararse como se ilustra a continuación. Los derivados de fenilglicina en donde el ácido carboxílico se protegió como un éster removido fácilmente, pueden acilarse con un cloruro ácido en la presencia de una base tal como trietilamina para proporcionar las amidas correspondientes (trayectoria A). La trayectoria B ilustra la acilación del derivado de fenilglicina de partida con un cloroformiato apropiado mientras la trayectoria C muestra la reacción con un isocianato o cloruro de carbamoilo apropiado. Cada uno de los tres intermediarios mostrados en las trayectorias A - C puede desprotegerse por métodos conocidos por aquellos

de habilidad en el arte (ie; el tratamiento contra éster de t-butilo con una base fuerte tal como HCl o ácido trifluoroacético).



Esquema de reacción 13

Los ácidos fenilacéticos substituidos con amino pueden prepararse por el tratamiento contra un ácido clorometilfenilacético con un exceso de una amina.



Condiciones de análisis del compuesto

La evaluación de pureza y el análisis de baja resolución de masas se conducen en un sistema Shimadzu LC con el sistema Waters

Micromass ZQ MS. Se deberá notar que los tiempos de retención pueden variar ligeramente entre las máquinas. Las condiciones CL empleadas en determinar el tiempo de retención (TR) fueron:

Condición 1

Columna = Phenomenex-Luna 3.0X 50 mm S10

Inicio %B = 0

Final %B = 100

Tiempo de gradiente = 2 min

Tiempo de paro = 3 min

Relación de flujo = 4 mL/min

Longitud de onda = 220 nm

Solvente A = 0.1% TFA en 10% metanol/90%H_2O

Solvente B = 0.1% TFA en 90% metanol/10% H_2O

Condición 2

Columna = Phenomenex-Luna 4.6X50 mm S10

Inicio %B = 0

Final %B = 100

Tiempo de gradiente = 2 min

Tiempo de paro = 3 min

Relación de flujo = 5 mL/min

Longitud de onda = 220 nm

Solvente A = 0.1% TFA en 10% metanol/90%H_2O

Solvente B = 0.1% TFA en 90% metanol/10% H_2O

Condición 3

Columna = HPLC XTERRA C18 3.0 x 50mm S7

Inicio %B = 0

Final %B = 100

Tiempo de gradiente = 3 min

Tiempo de paro = 4 min

Relación de flujo = 4 mL/min

Longitud de onda = 220 nm

Solvente A = 0.1% TFA en 10% metanol/90%H_2O

Solvente B = 0.1% TFA en 90% metanol/10% H_2O

Afección M1

Columna : Luna 4.6 x 50 mm S10

Inicio %B = 0

Final %B = 100

Tiempo de gradiente = 3 min

Tiempo de paro = 4 min

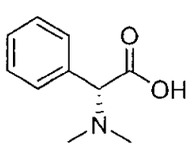
Relación de flujo = 4 mL/min

Solvente A = 95% H_2O:5% CH_3CN, 10 mm acetato de amonio

Solvente B = 5% H_2O: 95% CH_3CN; 10 mm acetato de amonio

Síntesis de los extremos comunes

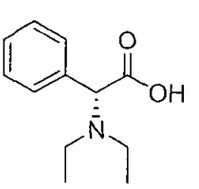
Extremo 1



Una suspensión de 10% Pd/C (2.0g) en metanol (10 mL) se agregó a una mezcla de (R)-2-fenilglicina (10g, 66.2 mmol), formaldehído (33 mL de 37% en peso

en agua), HCl 1N (30 mL) y metanol (30 mL), y se expuso a H_2 (60 psi)(4.218 kg/cm^2) durante 3 horas. La mezcla de reacción se filtró a través de tierra diatomácea (Celite®), y el filtrado se concentró in vacuo. El material crudo resultante se recristalizó a partir del isopropanol para proporcionar la sal HCl del extremo 1 como una aguja blanca (4.0 g). Rotación óptica: -117.1° [c = 9.95 mg/mL en H_2O; λ = 589 nm]. ^{1}H 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); CL (Cond. I): TR = 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.

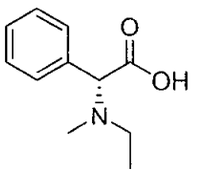
Extremo 2



El $NaBH_3CN$ (6.22g, 94 mmol) se agregó en porciones durante algunos minutos a una mezcla fría (hielo/agua) de (R)-2-Fenilglicina (6.02 g, 39.8 mmol) y MeOH (100 mL), y se agitó durante 5 min. Acetaldehído (10 mL) se agregó en porciones durante 10 min y se continuó agitando a la misma temperatura fría durante 45 min y a temperatura ambiente durante ~6.5 hr. La mezcla de reacción se volvió a enfriar

con un baño de agua con hielo, se trató con agua (3 mL) y luego se apagó con una adición gota a gota de HCl concentrado durante ~ 45 min hasta que el pH de la mezcla es ~ 1.5 - 2.0. El baño frío se removió y la agitación continuó mientras se agregó HCl concentrado en el orden 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 in vacuo. El material crudo se recristalizó a partir del etanol para proporcionar la sal HCl del 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). CL (Cond. I): TR = 0.43 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{12}H_{18}NO_2$: 208.13; encontrado 208.26

Extremo 3



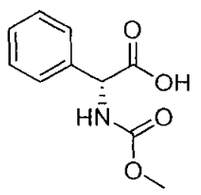
El acetaldehído (5.0 mL, 89.1 mmol) y una suspensión de 10% Pd/C (720 mg) en metanol/H_2O (4mL/1 mL) se agregó secuencialmente a una mezcla fría (~ 15°C) de (R)-2-fenilglicina (3.096g, 20.48 mmol), HCl 1N (30 mL) y metanol

(40 mL). El baño frío se removió y la mezcla de reacción se agitó bajo un globo de H_2 durante 17 horas. Un acetaldehído adicional (10 mL, 178.2 mmol) se agregó y se continuó agitando bajo una atmósfera de H_2 durante 24 horas [Nota: el suministró de H_2 se reabasteció como sea necesario a través de la reacción]. La mezcla de reacción se filtró a través de tierra diatomácea (Celite®), y el filtrado se concentró in vacuo. El material crudo resultante se recristalizó a partir del isopropanol para proporcionar la sal HCl del ácido (R)-2-(etilamino)-2-fenilacético como un sólido blanco brillante (2.846g). ^{1}H 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). CL (Cond. I): TR = 0.39 min; >95 % 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% Pd/C (536 mg) en metanol/H_2O (3 mL/1 mL) se agregó a una mezcla de ácido (R)-2-(etilamino)-2-fenilacético/HCl (1.492g, 6.918 mmol), formaldehído (20 mL de 37% en peso en agua), HCl 1N (20 mL) y metanol (23 mL). La mezcla de reacción se agitó bajo un globo de H_2 durante ~72 horas, en donde el H_2 suministrado se restableció como se necesario. La mezcla de reacción se filtró a través de tierra diatomácea (Celite®) y el filtrado se concentró in vacuo. El material crudo resultante se

recristalizó a partir del isopropanol (50 mL) para proporcionar la sal HCl del extremo 3 como un sólido blanco (985 mg). ^{1}H 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). CL (Cond. I): TR = 0.39 min; >95 % 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

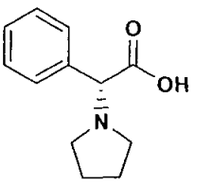


El $ClCO_2Me$ (3.2 mL, 41.4 mmol) se agregó en porciones a una semi-solución de THF (410 ml) frío (hielo/agua) de 2-amino-2-fenilacetato de (R)-tert-butilo/HCl (9.877 g, 40.52 mmol) y diisopropiletilamina (14.2 mL, 81.52 mmol) durante 6 min, y se agitó a temperatura similar durante 5.5 horas. El componente volátil se removió in vacuo, y el residuo se dividió entre agua (100 mL) y acetato de etilo (200 mL). La capa orgánica se lavó con HCl 1N (25 mL) y una solución de $NaHCO_3$ saturado (30 mL), se secó ($MgSO_4$), se filtró y se concentró in vacuo. El aceite incoloro resultante se trituró a partir de los hexanos, se filtró y se lavó con hexanos (100

mL) para proporcionar 2-(metoxicarbonilamino)-2-fenilacetato de (R)-tert-butilo como un sólido blanco (7.7 g). ^{1}H 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). CL (Cond. 1): TR = 1.53 min; ~90 % índice de homogeneidad; LC/MS: Análisis calculado para $[M+Na]^+$ $C_{14}H_{19}NNaO_4$: 288.12; encontrado 288.15.

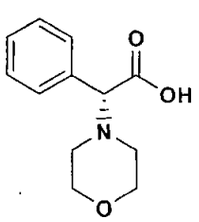
El TFA (16 mL) se agregó en porciones a una solución de CH_2Cl_2 (160 mL) (hielo/agua) del producto de arriba durante 7 minutos, y el baño frío se removió y la mezcla de reacción se agitó durante 20 horas. Ya que la desprotección no se completó, un TFA adicional (1.0 mL) se agregó y se continuó agitando durante 2 horas adicionales. El componente volátil se removió in vacuo, y el residuo de aceite resultante se trató con dietil éter (15 mL) y hexanos (12 mL) para proporcionar un precipitado. El precipitado se filtró y se lavó con dietil éter/hexanos (~1:3 ratio; 30 mL) y se secó in vacuo para proporcionar el 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]. ^{1}H 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). CL (Cond. I): TR = 1.01 min; >95 % 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



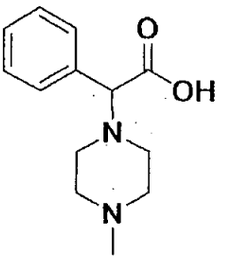
Una mezcla de (R)-2-fenilglicina (1.0 g, 6.62 mmol), 1,4-dibromobutano (1.57 g, 7.27 mmol) y Na_2CO_3 (2.10 g, 19.8 mmol) en etanol (40 mL) se calentó a 100°C durante 21 horas. La mezcla de reacción se enfrió a temperatura ambiente y se filtró, y el filtrado se concentró in vacuo. El residuo se disolvió en etanol y se acidificó con HCl 1N hasta pH 3-4, y el componente volátil se removió in vacuo. El material crudo resultante se purificó por HPLC de fase inversa (agua/metanol/TFA) para proporcionar la sal TFA del extremo 5 como una espuma blanca semi-viscosa (1.0 g). ^{1}H RMN (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); TR = 0.30 min (Cond. 1); >98% 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 del extremo 6 se sintetizó a partir de (R)-2-fenilglicina y 1-bromo-2-(2-bromoetoxi)etano usando el método de la preparación del extremo 5. ^{1}H 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); TR = 0.32 min (Cond. I); >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



Tapa-7a: enantiómero-1
Tapa-7b: enantiómero-2

Una solución CH_2Cl_2 (200 mL) de cloruro de p-toluensulfonilo (8.65 g, 45.4 mmol) se agregó en porciones a una solución CH_2Cl_2 (200 mL) (-5 °C) de 2-hidroxi-2-fenilacetato de (S)-bencilo (10.0 g, 41.3 mmol), trietilamina (5.75 mL, 41.3 mmol) y 4-dimetilaminopiridina (0.504 g, 4.13 mmol), mientras se mantuvo 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. Esto se permitió que se derritiera a 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 in vacuo para proporcionar 2-fenil-2-(tosiloxi)acetato de bencilo como un aceite viscoso el cual se solidificó durante el reposo (16.5 g). La integridad quiral del producto no se verificó y el producto se usó para la siguiente Extremo 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). TR = 3.00 (Cond. II); >90% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{22}H_{20}NaO_5S$: 419.09; encontrado 419.04.

Una solución THF (75 mL) de 2-fenil-2-(tosiloxi)acetato de bencilo (6.0 g, 15.1 mmol), 1-metilpiperazina (3.36 mL, 30.3 mmol) y N,N-diisopropiletilamina (13.2 mL, 75.8 mmol) se calentó a 65°C durante 7 horas. La reacción se permitió enfriar a temperatura ambiente y el componente volátil se removió in vacuo. 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 in vacuo. El material crudo resultante se purificó por cromatografía instantánea (gel de sílice, acetato de etilo) para proporcionar 2-(4-metilpiperazin-1-il)-2-fenilacetato de bencilo como un aceite viscoso café-anaranjado (4.56 g). El análisis HPLC quiral (Quiralcel OD-H) indico que la muestra es una mezcla de enantiómeros en un intervalo de 38.2 hasta

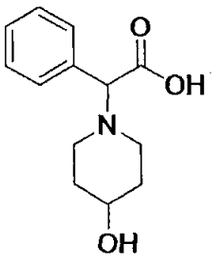
58.7. La separación de los enantiómeros se efectuó como sigue: el producto se disolvió en 120 mL de etanol/heptano (1:1) y se inyectó (5 mL/inyección) en una columna HPLC quiral (Quiracel OJ, 5 cm ID x 50 cm L, 20 μm) eluida con 85:15 Heptano/etanol a 75 mL/min, y se monitoreó a 220 nm. El Enantiómero-1 (1.474 g) y el enantiómero-2 (2.2149 g) se recuperó como un aceite viscoso. ^{1}H 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* = 12.5, 1H), 4.02 (s, 1H), 2.65-2.38 (app br s, 8H), 2.25 (s, 3H). TR = 2.10 (Cond. III); >98% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{20}H_{25}N_2O_2$: 325.19; encontrado 325.20.

Una solución metanol (10 mL) de ya sea un enantiómero de 2-(4-metilpiperazin-1-il)-2-fenilacetato de bencilo (1.0 g, 3.1 mmol) se agregó a una suspensión de 10% Pd/C (120 mg) en metanol (5.0 mL). La mezcla de reacción se expusó a un globo de hidrógeno, bajo un monitoreó cuidadoso durante <50 min. Inmediatamente después de que se completó la reacción, el catalizador se filtró a través de tierra diatomácea (Celite®) y el filtrado se concentró in vacuo para proporcionar el extremo 7, contaminada con ácido fenilacético como una espuma color canela (867.6 mg; la masa es como arriba el rendimiento teórico). El producto se usó para la siguiente Extremo 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); TR = 0.31 (Cond. II); >90% 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 del extremo 8 y Extremo 9 se llevo a cabo de conformidad con la síntesis del extremo 7 usando las aminas apropiadas para la Extremo de desplazamiento SN_2 (esto es, 4-hidroxipiperidina para el extremo 8 y (S)-3-fluoropirrolidina para el extremo 9) y condiciones modificadas para la separación de los intermediarios estereoisómericos respectivos, como se describe a continuación.

Extremo 8

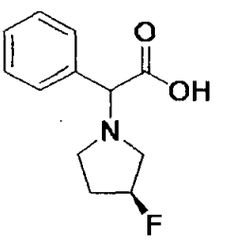


8a: enantiómero-1
8b: enantiómero-2

La separación enantiómerica del intermediario de 2-(4-hidroxipiperidin-1-il)-2-fenilacetato de bencilo se efectuó 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 HPLC quiral (Quiracel OJ, 2 cm ID x 25 cm L, 10 µm) eluida con 80:20 heptano/etanol a 10 mL/min, se monitoreó a 220 nm, para

proporcionar 186.3 mg de enantiómero-1 y 209.1 mg del enantiómero-2 como aceites viscosos ligeramente amarillos. Este éster de bencilo se hidrogenolizó de conformidad a la preparación del extremo 7 para proporcionar el 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). TR = 0.28 (Cond. II); >98% 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

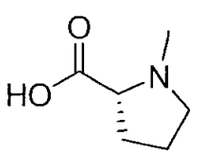


9a: diastereómero-1
9b: diastereómero-2

La separación diastereómerica del intermediario 2-((S)-3-fluoropirrolidin-1-il)-2-fenilacetato de bencilo se efectuó al emplear las siguientes condiciones: el éster (220 mg) se separó en una columna HPLC quiral (Quiracel OJ-H, 0.46 cm ID x 25 cm L, 5 µm) eluida con 95% CO_2/5% metanol con 0.1% TFA, a una presión de 10 barias, 70 mL/min relación de flujo, y una temperatura de 35°C. El HPLC eluido para los estereoisómeros respectivos se concentró, y el residuo se disolvió en CH_2Cl_2 (20 mL) y se lavó con un medio acuoso

(10 mL agua + 1 mL de una solución de $NaHCO_3$ suturado). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró in vacuo para proporcionar 92.5 mg de la fracción-1 y 59.6 mg de la fracción-2. Estos ésteres de bencilo se hidrogenizaron de conformidad a la preparación del extremo 7 para preparar las Extremos 9a y 9b. El extremo 9a (diastereómero-1; la muestra es una sal TFA como un resultado de la purificación en HPLC de fase inversa usando H_2O/metanol/TFA Solvente): ^1H RMN (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). TR = 0.42 (Cond. I); >95% 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, 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). TR = 0.44 (Cond. I); LC/MS: Análisis calculado para $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; encontrado 224.14.

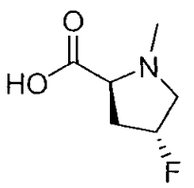
Extremo 10



A una solución de D-prolina (2.0 g, 17 mmol) y formaldehído (2.0 mL de 37% en peso en H_2O) en metanol (15 mL) se agregó una suspensión de 10% Pd/C (500 mg) en metanol

(5 mL). La mezcla se agitó bajo un globo de hidrógeno durante 23 horas. La mezcla de reacción se filtró a través de tierra diatomácea (Celite®) y se concentró in vacuo para proporcionar el extremo 10 como un sólido blanco opaco (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). TR = 0.28 (Cond. II); >98% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_6H_{12}NO_2$: 130.09; encontrado 129.96.

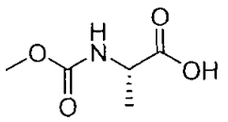
Extremo 11



Una mezcla de ácido (2S,4R)-4-fluoropirrolidina-2-carboxílico (0.50 g, 3.8 mmol), formaldehído (0.5 mL de 37% en peso en H_2O), 12 N HCl (0.25 mL) y 10% Pd/C (50 mg) en metanol (20 mL) se agitó bajo un globo de hidrógeno durante 19 horas. La mezcla de reacción se filtró a través de tierra diatomácea (Celite®) y el filtrado se concentró in vacuo. El residuo se recristalizó a partir del isopropanol para proporcionar la sal HCl del 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,

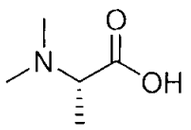
13.4, 1H), 2.85 (s, 3H), 2.60-2.51 (m, 1H), 2.39-2.26 (m, 1H). TR = 0.28 (Cond. II); >98% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_6H_{11}FNO_2$: 148.08; encontrado 148.06.

Extremo 12



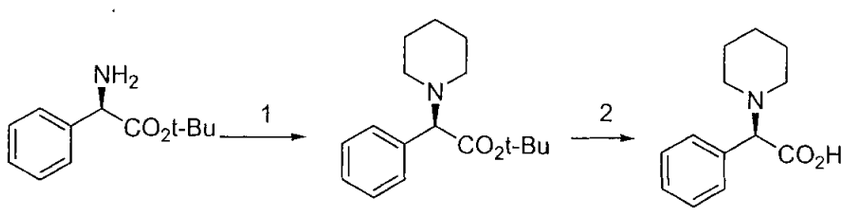
La L-Alanina (2.0 g, 22.5 mmol) se disolvió en 10% de una solución de carbonato de sodio acuoso (50 mL), y una solución en THF (50 mL) de cloroformiato de metilo (4.0 mL) se agregó a esto. La mezcla de reacción se agitó bajo condiciones ambientales durante 4.5 horas y se concentró in vacuo. El sólido blanco resultante se disolvió en agua y se acidificó con HCl 1N hasta un pH ~ 2-3. La solución resultante se extrajo con acetato de etilo (3 x 100 mL), y la fase orgánica combinada se secó (Na_2SO_4), se filtró y se concentró in vacuo para proporcionar un aceite incoloro (2.58 g). 500 mg de este material se purificó por HPLC de fase inversa (H_2O/metanol/TFA) para proporcionar 150 mg del extremo 12 como un aceite incoloro. ^1H 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 mmol), formaldehído (8.4 g, 37 % en peso), HCl 1N (30 mL) y 10% Pd/C (500 mg) en metanol (30 mL) se agitó bajo una atmósfera de hidrógeno (50 psi)(3.515 kg/cm^2) durante 5 horas. La mezcla de reacción se filtró a través de tierra diatomácea (Celite®) y el filtrado se concentró in vacuo para proporcionar la sal HCl del extremo 13 como un aceite el cual se solidificó durante el reposo bajo vacío (4.4 g; la masa es como arriba el 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

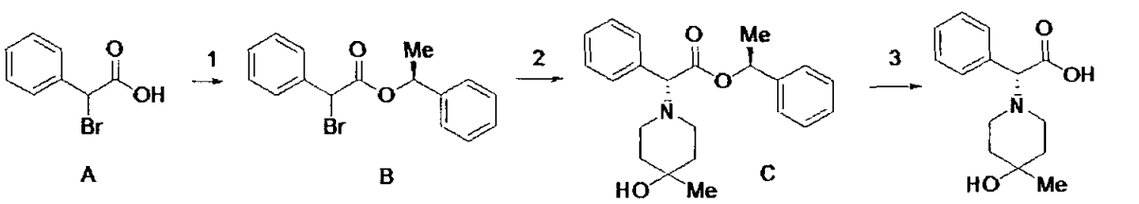
Extremo 1: Una mezcla éster de tert-butil (R)-(-)-D-fenilglicina (3.00 g, 12.3 mmol), $NaBH_3CN$ (0.773 g, 12.3 mmol), KOH (0.690 g, 12.3 mmol) y ácido acético (0.352 mL, 6.15 mmol) se agitó en metanol a 0°C. A esta mezcla se agregó dialdehído glutárico (2.23 mL, 12.3 mmol) en porciones durante 5 minutos. La mezcla de reacción se agitó esto se

permitió calentar a 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% NaOH acuoso y acetato de etilo. La fase orgánica se separó, se secó ($MgSO_4$), se filtró y se concentró hasta secarse para proporcionar un aceite claro. Este material se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0.1% TFA) para dar el intermediario éster (2.70 g, 56%) como un aceite claro. ^{1}HRMN (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 $(M+H)^+$.

Extremo 2: A una solución agitada del intermediario éster (1.12g, 2.88mmol) en diclorometano (10 mL) se agregó TFA (3 mL). La mezcla de reacción se agitó a temperatura ambiente durante 4 horas y luego esto se concentró hasta secarse para dar un aceite amarillo ligero. El aceite se purificó usando HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0.1% TFA). Las fracciones apropiadas se combinaron y se concentraron hasta secarse in vacuo. El residuo luego se disolvió en una cantidad mínima de metanol y se aplicó para aplicar los cartuchos de extracción MCX LP (2 x 6 g). Los cartuchos se

enjuagaron con metanol (40 mL) y luego el compuesto deseado se eluyó usando amoniaco 2M en metanol (50 mL). Las fracciones que contienen el producto se combinaron y se concentraron y el residuo se tomó en agua. La liofilización de esta solución proporcionó el compuesto del título (0.492 g, 78%) como un sólido amarillo ligero. ^{1}HRMN (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



A B C (R)-EXTREMO-15

Extremo 1; 2-bromo-2-fenilacetato de (S)-1-Feniletilo: A una mezcla de ácido α-bromofenilacético (10.75 g, 0.050 mol), (S)-(-)-1-feniletanol (7.94 g, 0.065 mol) y DMAP (0.61 g, 5.0 mmol) en diclorometano seco (100 mL) se agregó EDCI sólido (12.46 g, 0.065 mol) todas de una vez. La solución resultante se agitó a temperatura ambiente bajo Ar durante 18 horas y luego esto 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 instantánea (SiO_2/hexano-acetato de etilo, 4:1) de este aceite

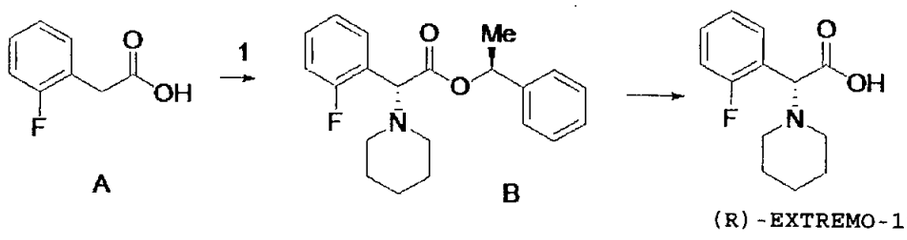
proporcionó el compuesto del título (11.64 g, 73%) como un sólido blanco. ^{1}HRMN (400 MHz, $CDCl_3$) δ 7.53-7.17 (m, 10H), 5.95 (q, J = 6.6 Hz, 0.5H), 5.94 (q, J = 6.6 Hz, 0.5H), 5.41 (s, 0.5H), 5.39 (s, 0.5H), 1.58 (d, J = 6.6 Hz, 1.5H), 1.51 (d, J = 6.6 Hz, 1.5H).

Extremo 2; (R)-2-(4-hidroxi-4-metilpiperidin-1-il)-2-fenilacetato de (S)-1-Feniletilo: A una solución de 2-bromo-2-fenilacetato (S)-1-feniletilo (0.464 g, 1.45 mmol) en THF (8 mL) se agregó trietilamina (0.61 mL, 4.35 mmol), seguido por yoduro de tetrabutilamonio (0.215 g, 0.58 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 5 minutos y luego una solución de 4-metil-4-hidroxipiperidina (0.251 g, 2.18 mmol) en THF (2 mL) se agregó. La mezcla se agitó durante 1 hora a temperatura ambiente y luego esto se calentó a 55-60°C (temperatura del baño de aceite) durante 4 horas. La mezcla de reacción fría luego se diluyó con acetato de etilo (30 mL), se lavó (H_2O x2, salmuera), se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó por cromatografía de gel de sílice (0-60% acetato de etilo-hexano) para proporcionar primero el (S,R)-isómero del compuesto del título (0.306 g, 60%) como un sólido blanco y luego el (S,S)-isómero correspondiente (0.120 g, 23%), también como un sólido blanco. (S,R)-isómero: ^{1}HRMN (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 $(M+H)^+$. (S,S)-isómero: ^{1}HRMN (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: Análisis calculado para $C_{22}H_{27}NO_3$: 353; encontrado: 354 $(M+H)^+$.

Extremo 3; ácido (R)-2-(4-Hidroxi-4-metilpiperidin-1-il)-2-fenilacético: A una solución de (R)-2-(4-hidroxi-4-metilpiperidin-1-il)-2-fenilacetato de (S)-1-feniletilo (0.185 g, 0.52 mmol) en diclorometano (3 mL) se agregó ácido trifluoroacético (1 mL) y la mezcla se agitó a temperatura ambiente durante 2 horas. Los volátiles se removieron subsecuentemente in vacuo y el residuo se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 20 x 100mm; CH_3CN-H_2O-0.1% 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

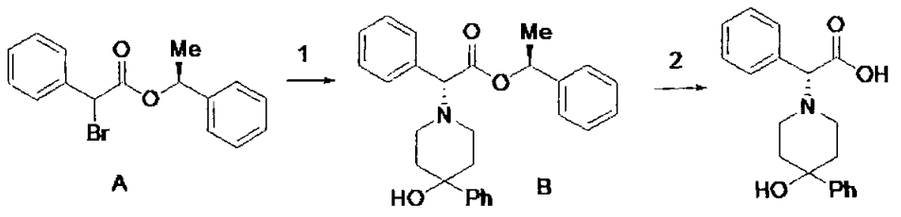
Extremo 1; 2-(2-fluorofenil)acetato de (S)-1-Feniletilo: Una mezcla de ácido 2-fluorofenilacético (5.45 g, 35.4 mmol), (S)-1-feniletanol (5.62 g, 46.0 mmol), EDCI (8.82 g, 46.0 mmol) y DMAP (0.561 g, 4.60 mmol) en CH_2Cl_2 (100 mL) se agitó a temperatura ambiente durante 12 horas. El solvente luego se concentró y el residuo se dividió con H_2O-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 in vacuo. El residuo se purificó por cromatografía de gel de sílice (Biotage/ 0-20% acetato de etilo-hexano) para proporcionar el compuesto del título como un aceite incoloro (8.38 g, 92%). ^{1}HRMN (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).

Extremo 2; 2-(2-fluorofenil)-2-(piperidin-1-il)acetato de (R)-((S)-1-Feniletilo): A una solución de 2-(2-fluorofenil)acetato de (S)-1-feniletilo (5.00 g, 19.4 mmol) en THF (1200 mL) a 0°C se agregó DBU (6.19 g, 40.7 mmol) y la solución se permitió calentar a temperatura ambiente mientras se agitó durante 30 minutos. La solución luego se enfrió a -78°C y una solución de CBr_4 (13.5 g, 40.7 mmol) en THF (100 mL) se agregó y la mezcla se permitió calentar a -10°C y se agitó a esta temperatura durante 2 horas. La mezcla de reacción se apagó 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 in vacuo. Al residuo se agregó piperidina (5.73 mL,

58.1 mmol) y la solución se agitó a temperatura ambiente durante 24 horas. Los volátiles luego se concentraron in vacuo y el residuo se purificó por cromatografía de gel de sílice (Biotage/ 0-30% dietil éter-hexano) para proporcionar una mezcla pura de diastereómeros (2:1 relación por ^{1}HRMN) como un aceite amarillo (2.07 g, 31%), junto con material de partida sin reacción (2.53 g, 51%). Además la cromatografía de la mezcla diastereómerica (Biotage/ 0-10% dietil éter-tolueno) proporcionó el compuesto del título como un aceite incoloro (0.737 g, 11%). ^{1}HRMN (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 $(M+H)^+$.

Extremo 3; ácido (R)-2-(2-fluorofenil)-2-(piperidin-1-il)acético: Una mezcla de 2-(2-fluorofenil)-2-(piperidin-1-il)acetato de (R)-((S)-1-feniletilo) (0.737 g, 2.16 mmol) y 20% $Pd(OH)_2/C$ (0.070 g) en etanol (30 mL) se hidrogenó a temperatura ambiente y presión atmosférica (H_2 globo) durante 2 horas. La solución luego se purgó con Ar, se filtró a través de tierra diatomácea (Celite®), y se concentró in vacuo. Esto proporcionó el compuesto del título como un sólido incoloro (0.503 g, 98%). ^{1}HRMN (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

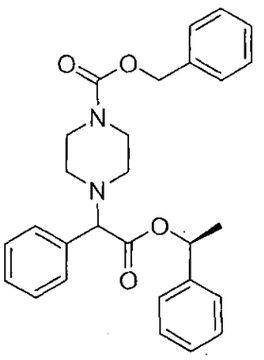


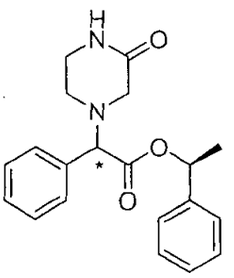
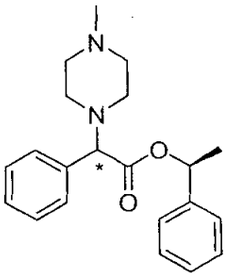
(R)-EXTREMO-17

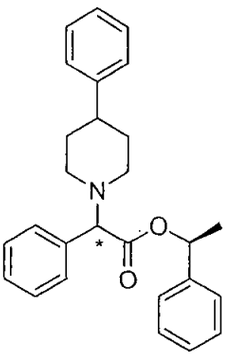
Extremo 1; (R)-2-(4-hidroxi-4-fenilpiperidin-1-il)-2-fenilacetato de (S)-1-Feniletilo: A una solución de 2-bromo-2-fenilacetato de (S)-1-feniletilo (1.50 g, 4.70 mmol) en THF (25 mL) se agregó trietilamina (1.31 mL, 9.42 mmol), seguido por yoduro de tetrabutilamonio (0.347 g, 0.94 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 5 minutos y luego una solución de 4-fenil-4-hidroxipiperidina (1.00 g, 5.64 mmol) en THF (5 mL) se agregó. La mezcla se agitó durante 16 horas y luego esto 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% acetato de etilo-hexano) para proporcionar una mezcla 2:1 aproximadamente de diastereómeros, como se juzga por ^{1}HRMN. La separación de estos isómeros se llevó a cabo usando cromatografía de fluido supercrítico (Quiralcel OJ-H, 30 x 250mm; 20% etanol en CO_2 a 35°C), para dar

primero el (R)-isómero del compuesto del título (0.534 g, 27%) como un aceite amarillo y luego el (S)-isómero correspondiente (0.271 g, 14%), también como un aceite amarillo. (S,R)-isómero: ^{1}HRMN (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 $(M+H)^+$; (S,S)-isómero: H^1RMN (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 se prepararon en una manera similar empleando la Extremo 1 en la síntesis del extremo-17.

Intermediario-17a		Diastereómero 1: ^{1}H RMN (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: Análisis calculado para: $C_{28}H_{30}N_2O_4$ 458.55; Encontrado: 459.44 $(M+H)^+$. Diastereómero 2: ^{1}H RMN (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: Análisis calculado para: $C_{28}H_{30}N_2O_4$ 458.55; Encontrado: 459.44 $(M+H)^+$.

Intermediario -17b		Diastereómero 1: TR = 11.76 min (Cond'n II); LCMS: Análisis calculado para: $C_{20}H_{22}N_2O_3$ 338.4 Encontrado: 339.39 $(M+H)^+$; Diastereómero 2: TR = 10.05 min (Cond'n II); LCMS: Análisis calculado 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: Análisis calculado para: $C_{21}H_{26}N_2O_2$ 338.44 Encontrado: 339.45 $(M+H)^+$; Diastereómero 2: T_R = 6.00 min (Cond'n I); LCMS: Análisis calculado para: $C_{21}H_{26}N_2O_2$ 338.44 Encontrado: 339.45 $(M+H)^+$.

Intermediario -17d		Diastereómero 1: TR = 7.19 min (Cond'n I); LCMS: Análisis calculado para: $C_{27}H_{29}NO_2$ 399.52 Encontrado: 400.48 $(M+H)^+$; Diastereómero 2: TR = 9.76 min (Cond'n I); LCMS: Análisis calculado para: $C_{27}H_{29}NO_2$ 399.52 Encontrado: 400.48 $(M+H)^+$.

Condiciones SFC quirales para determinar el tiempo de retención para los intermediarios 17b-17d

Condición 1

Columna: Chiralpak AD-H Columna, 4.6X250 mm, 5µm

Solventes: 90% CO2 - 10% metanol con 0.1%DEA

Temperatura: 35 °C

Presión: 150 bar

Relación de flujo: 2.0 mL/min.

Monitoreo UV @ 220 nm

Inyección: 1.0 mg/3mL metanol

Condición 2

Columna: Quiralcel OD-H Columna, 4.6X250 mm, 5µm

Solventes: 90% CO2 - 10% metanol con 0.1%DEA

Temperatura: 35 °C

Presión: 150 bar

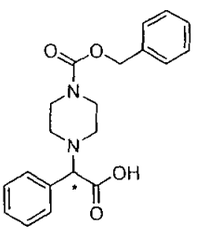
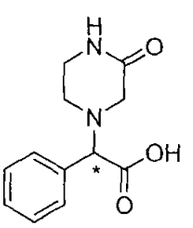
Relación de flujo: 2.0 mL/min.

Monitoreo UV @ 220 nm

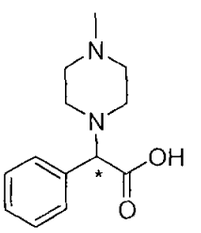
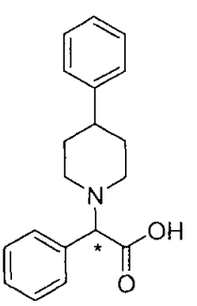
Inyección: 1.0 mg/mL metanol

Extremo 17, Extremo 2; ácido (R)-2-(4-Hidroxi-4-fenilpiperidin-1-il)-2-fenilacético: A una solución de (R)-2-(4-hidroxi-4-fenilpiperidin-1-il)-2-fenilacetato de (S)-1-feniletilo (0.350 g, 0.84 mmol) en diclorometano (5 mL) se agregó ácido trifluoroacético (1 mL) y la mezcla se agitó a temperatura ambiente durante 2 horas. Los volátiles se removieron subsecuentemente in vacuo y el residuo se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 20 x 100mm; CH_3CN-H_2O-0.1% 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 se prepararon en una manera similar:

Extremo 17a		TR = 2.21 (Cond'n II); ^{1}H RMN (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: Análisis calculado para: $C_{20}H_{22}N_2O_4$ 354.40; Encontrado: 355.38 $(M+H)^+$.
Extremo 17b		TR = 0.27 (Cond'n III); LCMS: Análisis calculado para: $C_{12}H_{14}N_2O_3$ 234.25; Encontrado: 235.22 $(M+H)^+$.

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Extremo 17c		TR = 0.48 (Cond'n II); LCMS: Análisis calculado para: $C_{13}H_{18}N_2O_2$ 234.29; Encontrado: 235.31 $(M+H)^+$.
Extremo 17d		TR = 2.21 (Cond'n I); LCMS: Análisis calculado para: $C_{19}H_{21}NO_2$ 295.38; Encontrado: 296.33 $(M+H)^+$.

Condiciones LCMS para determinar el tiempo de retención

Para los extremos 17a-17d

Condición 1

Columna: Phenomenex-Luna 4.6 X 50 mm S10

Inicio % B = 0

Final % B = 100

Tiempo de gradiente = 4 min

Relación de flujo = 4 mL/min

Longitud de onda = 220

Solvente A = 10% metanol - 90% H_2O - 0.1% TFA

Solvente B = 90% metanol - 10% H_2O - 0.1% TFA

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Condición 2

Columna: Waters-Sunfire 4.6 X 50 mm S5

Inicio % B = 0

Final % B = 100

Tiempo de gradiente = 2 min

Relación de flujo = 4 mL/min

Longitud de onda = 220

Solvente A = 10% metanol - 90% H_2O - 0.1% TFA

Solvente B = 90% metanol - 10% H_2O - 0.1% TFA

Condición 3

Columna: Phenomenex 10µ 3.0 X 50 mm

Inicio % B = 0

Final % B = 100

Tiempo de gradiente = 2 min

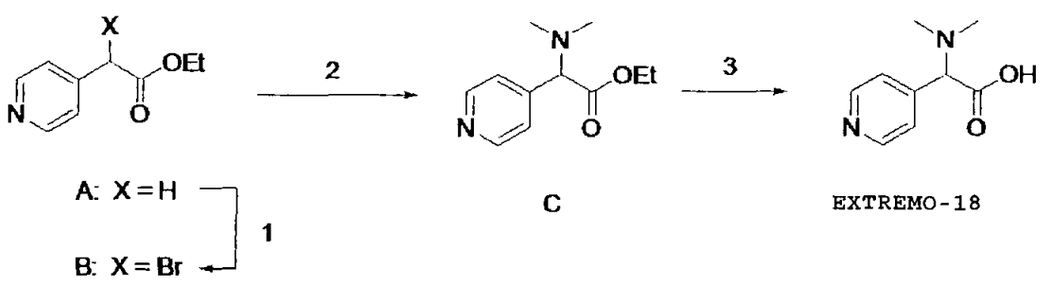
Relación de flujo = 4 mL/min

Longitud de onda = 220

Solvente A = 10% metanol - 90% H_2O - 0.1% TFA

Solvente B = 90% metanol - 10% H_2O - 0.1% TFA

Extremo 18



Extremo 1; 2-(4-piridil)-2-bromoacetato de (R,S)-Etilo: A una solución de 4-piridilacetato de etilo (1.00 g, 6.05 mmol) en THF seco (150 mL) a 0 °C bajo argón se agregó DBU (0.99 mL, 6.66 mmol). La mezcla de reacción se permitió calentar a temperatura ambiente durante 30 minutos y luego esto se enfrió a -78°C. A esta mezcla se agregó CBr_4 (2.21 g, 6.66 mmol) y se continuó agitando a -78°C durante 2 horas. La mezcla de reacción luego se apagó 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 in vacuo. El aceite amarillo resultante se purificó inmediatemente por cromatografía instantánea (SiO_2/ hexano-acetato de etilo, 1:1) para proporcionar el compuesto del título (1.40 g, 95%) como un aceite amarillo de alguna manera inestable. ^{1}HRMN (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: Análisis calculado para $C_9H_{10}BrNO_2$: 242, 244; encontrado: 243, 245 $(M+H)^+$.

Extremo 2; 2-(4-piridil)-2-(N,N-dimetilamino)acetato de (R,S)-Etilo: A una solución de 2-(4-piridil)-2-bromoacetato de (R,S)-etilo (1.40 g, 8.48 mmol) en DMF (10 mL) a temperatura ambiente se agregó dimetilamina (2M en THF, 8.5 mL, 17.0 mmol). Después de que se

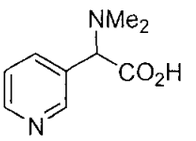
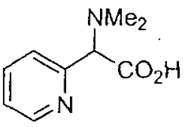
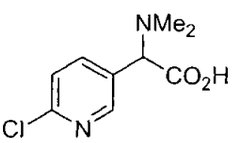
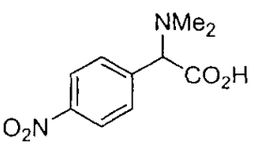
completa la reacción (como se juzga por tlc) los volátiles se removieron in vacuo y el residuo se purificó por cromatografía instantánea (Biotage, 40+M SiO_2 Columna; 50%-100% acetato de etilo-hexano) para proporcionar el compuesto del título (0.539 g, 31%) como un aceite amarillo ligero. ^{1}HRMN (400 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 $(M+H)^+$.

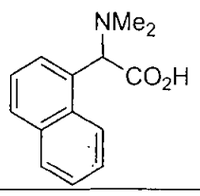
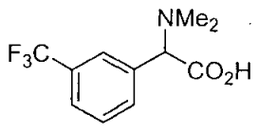
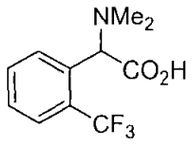
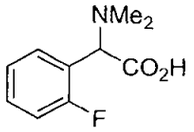
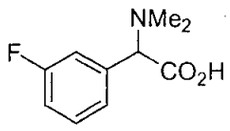
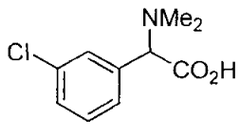
Extremo 3; ácido (R,S)-2-(4-Piridil)-2-(N,N-dimetilamino)acético: A una solución de 2-(4-piridil)-2-(N,N-dimetilamino)acetato de (R,S)-etilo (0.200 g, 0.960 mmol) en una mezcla de THF-metanol-H_2O (1:1:1, 6 mL) se agregó LiOH en polvo (0.120 g, 4.99 mmol) a temperatura ambiente. La solución se agitó durante 3 horas y luego esto se acidificó hasta pH 6 usando HCl 1N. La fase acuosa se lavó con acetato de etilo y luego esto se liofilizó para dar el diclorohidrato del compuesto del título como un sólido amarillo (que contiene LiCl). El producto se usó como tal en las Extremos posteriores.

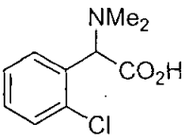
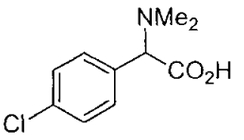
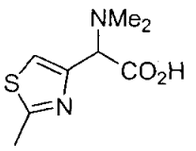
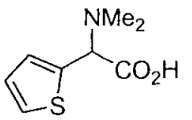
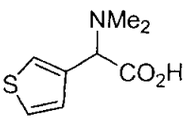
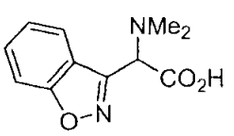
^{1}H RMN (400 MHz, DMSO-d_6) δ 8.49 (d, *J* = 5.7 Hz, 2H), 7.34 (d, *J* = 5.7 Hz, 2H), 3.56 (s, 1H), 2.21 (s, 6H).

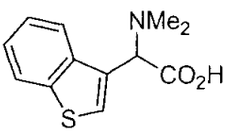
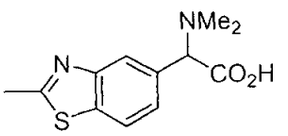
Los siguientes ejemplos se prepararon en una

manera similar usando el método descrito en el ejemplo 4;

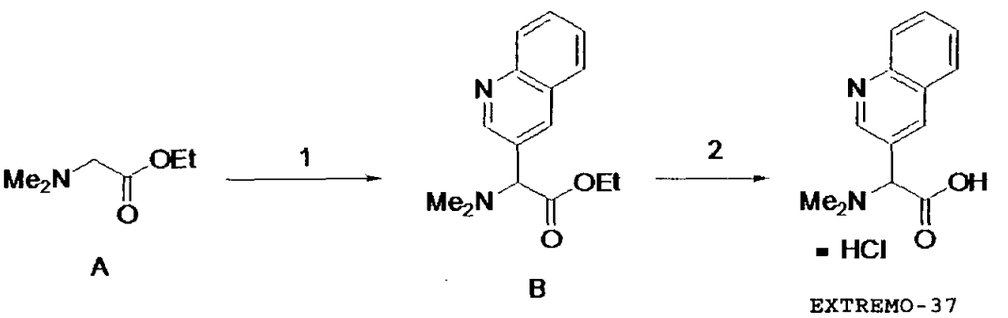
Extremo 19		LCMS: Análisis calculado para $C_9H_{12}N_2O_2$: 180; Encontrado: 181 $(M+H)^+$.
Extremo 20		LCMS: sin ionización. ^{1}HRMN (400 MHz, CD_3OD) δ 8.55 (d, J = 4.3 Hz, 1H), 7.84 (app t, J = 5.3 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.37 (app t, J = 5.3 Hz, 1H), 4.35 (s, 1H), 2.60 (s, 6H).
Extremo 21		LCMS: Análisis calculado para $C_9H_{11}ClN_2O_2$: 214, 216; Encontrado: 215, 217 $(M+H)^+$.
Extremo 22		LCMS: Análisis calculado para $C_{10}H_{12}N_2O_4$: 224; Encontrado: 225 $(M+H)^+$.

Extremo 23		LCMS: Análisis calculado para $C_{14}H_{15}NO_2$: 247; Encontrado: 248 $(M+H)^+$.
Extremo 24		LCMS: Análisis calculado para $C_{11}H_{12}F_3NO_2$: 247; Encontrado: 248 $(M+H)^+$.
Extremo 25		LCMS: Análisis calculado para $C_{11}H_{12}F_3NO_2$: 247; Encontrado: 248 $(M+H)^+$.
Extremo 26		LCMS: Análisis calculado para $C_{10}H_{12}FNO_2$: 247; Encontrado: 248 $(M+H)^+$.
Extremo 27		LCMS: Análisis calculado para $C_{10}H_{12}FNO_2$: 247; Encontrado: 248 $(M+H)^+$.
Extremo 28		LCMS: Análisis calculado para $C_{10}H_{12}ClNO_2$: 213, 215; Encontrado: 214, 217 $(M+H)^+$.

Extremo 29		LCMS: Análisis calculado para $C_{10}H_{12}ClNO_2$: 213, 215; Encontrado: 214, 217 $(M+H)^+$.
Extremo 30		LCMS: Análisis calculado para $C_{10}H_{12}ClNO_2$: 213, 215; Encontrado: 214, 217 $(M+H)^+$.
Extremo 31		LCMS: Análisis calculado para $C_8H_{11}N_2O_2S$: 200; Encontrado: 201 $(M+H)^+$.
Extremo 32		LCMS: Análisis calculado para $C_8H_{11}NO_2S$: 185; Encontrado: 186 $(M+H)^+$.
Extremo 33		LCMS: Análisis calculado para $C_8H_{11}NO_2S$: 185; Encontrado: 186 $(M+H)^+$.
Extremo 34		LCMS: Análisis calculado para $C_{11}H_{12}N_2O_3$: 220; Encontrado: 221 $(M+H)^+$.

Extremo 35		LCMS: Análisis calculado para $C_{12}H_{13}NO_2S$: 235; Encontrado: 236 $(M+H)^+$.
Extremo 36		LCMS: Análisis calculado para $C_{12}H_{14}N_2O_2S$: 250; Encontrado: 251 $(M+H)^+$.

Extremo 37

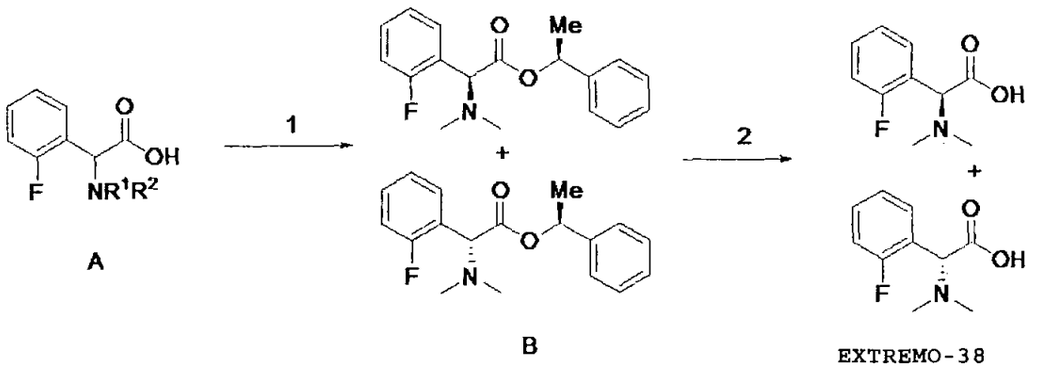


Extremo 1; 2-(quinolin-3-il)-2-(N,N-dimetilamino)-acetato de (R,S)-Etilo: Una mezcla de N,N-dimetilaminoacetato de etilo (0.462 g, 3.54 mmol), K_3PO_4 (1.90 g, 8.95 mmol), $Pd(t\text{-}Bu_3P)_2$ (0.090 g, 0.176 mmol) y tolueno (10 mL) se desgasificó con una corriente de burbujas de Ar durante 15 minutos. La mezcla de reacción luego se calentó a 100°C durante 12 horas, después de lo cual esto se enfrió a temperatura ambiente y se vació 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 in vacuo. El residuo se purificó primero por HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-5 mM NH_4OAc) y luego por cromatografía instantánea (SiO_2/ hexano-acetato de etilo, 1:1) para proporcionar el compuesto del título (0.128 g, 17%) como un aceite anaranjado. ^{1}HRMN (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 $(M+H)^+$.

Extremo 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 mmol) y 6M HCl (3 mL) se calentó a 100°C durante 12 horas. El solvente se removió in vacuo para proporcionar el diclorohidrato del compuesto del título (0.169 g, >100%) como una espuma amarilla ligera. El material no purificado se usó en las Extremos posteriores sin purificación adicional. LCMS: Análisis calculado para $C_{13}H_{14}N_2O_2$: 230; encontrado: 231 $(M+H)^+$.

Extremo 38



Extremo 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-fluorofenil)acético (2.60 g, 13.19 mmol), DMAP (0.209 g, 1.71 mmol) y (S)-1-feniletanol (2.09 g, 17.15 mmol) en CH_2Cl_2 (40 mL) se agregó EDCI (3.29 g, 17.15 mmol) y la mezcla se permitió agitar a temperatura ambiente durante 12 horas. El solvente luego se removió in vacuo 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 in vacuo. El residuo se purificó por cromatografía de gel de sílice (Biotage/ 0-50% dietil éter-hexano). La mezcla diastereómerica pura resultante luego se separó por HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0.1% TFA)

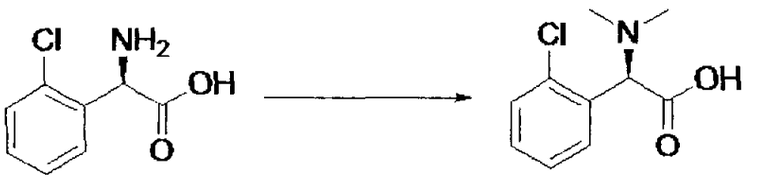
para dar primero (R)-2-(dimetilamino)-2-(2-fluorofenil)acetato de (S)-1-fenetilo (0.501 g, 13%) y luego (S)-2-(dimetilamino)-2-(2-fluorofenil)-acetato de (S)-1-fenetilo (0.727 g. 18%), ambos como sus sales TFA. (S,R)-isómero: ^{1}HRMN (400 MHz, CD_3OD) δ 7.65 - 7.70 (m, 1H), 7.55-7.60 (ddd, *J* = 9.4, 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 $(M+H)^+$; (S,S)-isómero: ^{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 $(M+H)^+$.

Extremo 2; ácido (R)-2-(dimetilamino)-2-(2-fluorofenil)acético: Una mezcla de la sal de TFA de 2-(dimetilamino)-2-(2-fluorofenil)acetato de (R)-((S)-1-feniletilo) (1.25 g, 3.01 mmol) y 20% $Pd(OH)_2/C$ (0.125 g) en etanol (30 mL) se hidrogenó a temperatura ambiente y presión atmosférica (H_2 globo) durante 4 horas. La solución luego se purgó con Ar, se filtró a través de tierra diatomácea (Celite®), y se concentró in vacuo. Esto dió el compuesto del título como un sólido incoloro (0.503 g, 98%). ^{1}H 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 puede obtenerse a partir de la sal TFA de 2-(dimetilamino)-2-(2-fluorofenil)acetato de (S)-((S)-1-feniletilo) en una manera similar.

Extremo 39

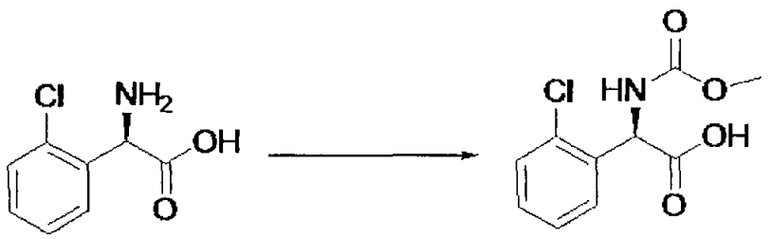


EXTREMO-39

Una mezcla de (R)-(2-clorofenil)glicina (0.300 g, 1.62 mmol), formaldehído (35% en solución acuosa, 0.80 mL, 3.23 mmol) y 20% $Pd(OH)_2/C$ (0.050 g) se hidrogenó a temperatura ambiente y presión atmosférica (H_2 globo) durante 4 horas. La solución luego se purgó con Ar, se filtró a través de tierra diatomácea (Celite®) y se concentró in vacuo. El residuo se purificó por HPLC preparativa de fase inversa (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0.1% 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 $(M+H)^+$.

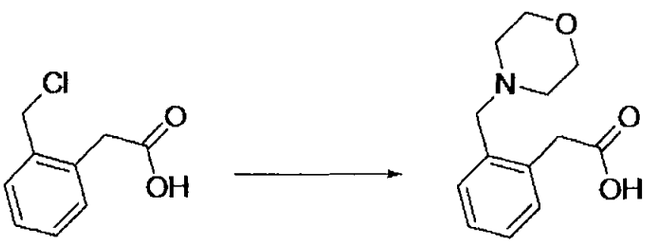
Extremo 40



EXTREMO-40

A una solución enfriada en hielo de (R)-(2-clorofenil)glicina (1.00 g, 5.38 mmol) y NaOH (0.862 g, 21.6 mmol) en H_2O (5.5 mL) se agregó cloroformiato de metilo (1.00 mL, 13.5 mmol) gota a gota. La mezcla se permitió agitar a 0°C durante 1 hora y luego esto se acidificó por 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 in vacuo para dar el compuesto del título ácido (R)-2-(metoxicarbonilamino)-2-(2-clorofenil)acético como una espuma anaranjada-amarilla (1.31 g, 96%). ^1H 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 $(M+H)^+$.

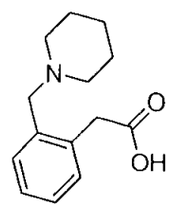
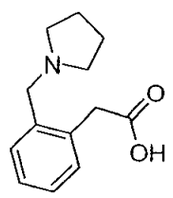
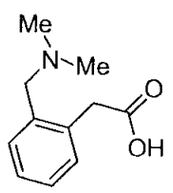
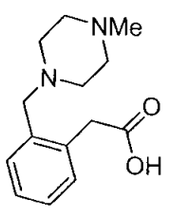
Extremo 41



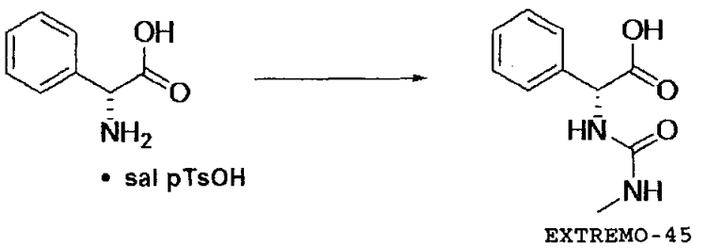
EXTREMO-41

A una suspensión de ácido 2-(2-(clorometil)fenil)acético (2.00 g, 10.8 mmol) en THF (20 mL) se agregó morfolina (1.89 g, 21.7 mmol) y la solución se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción luego se diluyó con acetato de etilo y se extrajo con H_2O (2x). La fase acuosa se liofilizó y el residuo se purificó por cromatografía de gel de sílice (Biotage/0-10% 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}HRMN (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 ejemplos se prepararon similarmente usando el método descrito para el extremo 41:

Extremo 42		LCMS: Análisis calculado para $C_{14}H_{19}NO_2$: 233; encontrado 234 $(M+H)^+$.
Extremo 43		LCMS: Análisis calculado para $C_{13}H_{17}NO_2$: 219; encontrado 220 $(M+H)^+$.
Extremo 44		LCMS: Análisis calculado para $C_{11}H_{15}NO_2$: 193; encontrado 194 $(M+H)^+$.
Extremo 45		LCMS: Análisis calculado para $C_{14}H_{20}N_2O_2$: 248; encontrado 249 $(M+H)^+$.

Extremo 45

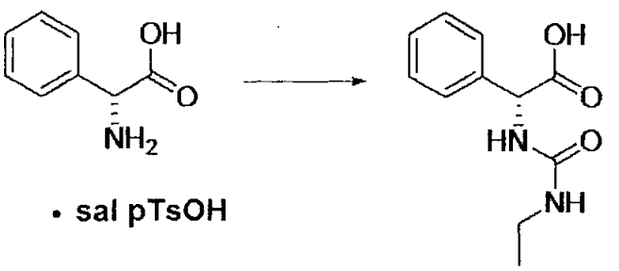


EXTREMO-45

El HMDS (1.85 mL, 8.77 mmol) se agregó a una suspensión de p-toluenosulfonato de ácido (R)-2-amino-2-fenilacético (2.83 g, 8.77 mmol) en CH_2Cl_2 (10 mL) y la mezcla se agitó a temperatura ambiente durante 30 minutos. El isocianato de metilo (0.5 g, 8.77 mmol) se agregó en una porción que se continuó agitando durante 30 minutos. La reacción se apagó por la adición de H_2O (5 mL) y el precipitado resultante se filtró, se lavó con H_2O y n-hexanos, y se secó bajo vacío. El ácido (R)-2-(3-metilureido)-2-fenilacético (1.5 g; 82 %) se recuperó como un sólido blanco y esto se usó sin purificación adicional. ^1H 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 × 46 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, TR = 1.38 min, 90% índice de

homogeneidad.

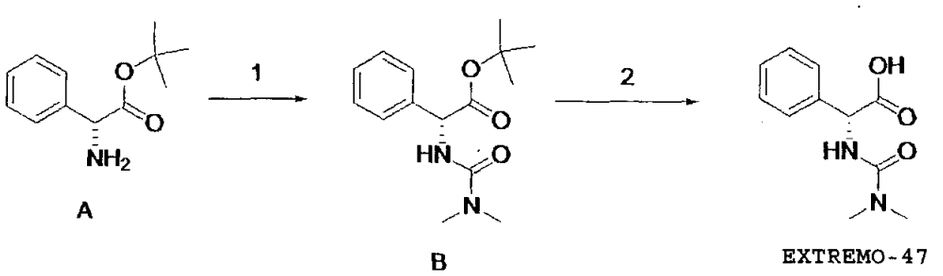
Extremo 46



EXTREMO-46

El producto deseado se preparó de conformidad al método descrito para el 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 × 506 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% H_3PO_4, B = 10% agua, 90% metanol, 0.2% H_3PO_4, TR = 0.87 min, 90% índice de homogeneidad.

Extremo 47



A

B

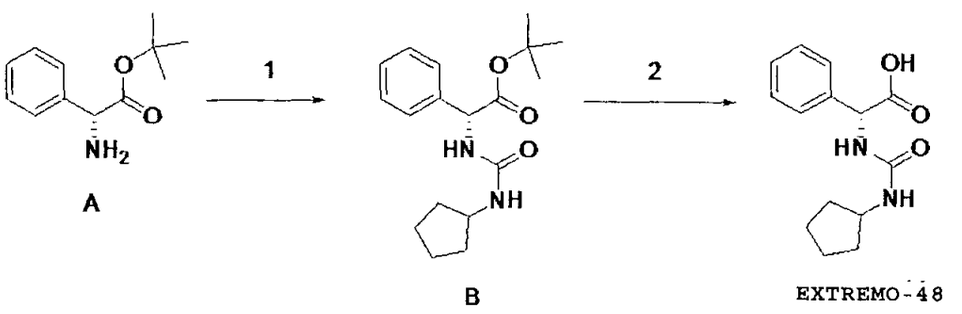
EXTREMO-47

Extremo 1; 2-(3,3-dimetilureido)-2-fenilacetato de (R)-tert-butilo: A una solución agitada de (R)-tert-butil-2-amino-2-fenilacetato (1.0 g, 4.10 mmol) y Base Hunig (1.79 mL, 10.25 mmol) en DMF (40 mL) se agregó cloruro de dimetilcarbamoilo (0.38 mL, 4.18 mmol) en porciones durante 10 minutos. Después de agitarse 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 1N aq. y salmuera, se secó ($MgSO_4$), se filtró y se concentró bajo presión reducida. El 2-(3,3-dimetilureido)-2-fenilacetato de (R)-tert-butilo se obtuvo como un sólido blanco (0.86 g; 75%) y se usó sin purificación adicional. ^1H 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 hasta 100% B sobre 4 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, TR = 2.26 min, 97% índice de homogeneidad.

Extremo 2; ácido (R)-2-(3,3-dimetilureido)-2-fenilacético: A una solución agitada de 2-(3,3-dimetilureido)-2-fenilacetato de ((R)-tert-butilo (0.86 g, 3.10 mmol) en CH_2Cl_2 (250 mL) se agregó TFA (15 mL)

gota a gota y la solución resultante se agitó a temperatura ambiente durante 3 h. El compuesto deseado luego se precipitó de la solución con una mezcla de EtOAC:Hexanos (5:20), se filtró completamente y se secó bajo presión reducida. El ácido (R)-2-(3,3-dimetilureido)-2-fenilacético se aisló como un sólido blanco (0.59g, 86%) y se usó sin purificación adicional. ^{1}H 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 hasta 100% B durante 2 minutos, 1 minutos tiempo de espera, A = 90% agua, 10% metanol, 0.2% H_3PO_4, B = 10% agua, 90% metanol, 0.2% H_3PO_4, TR = 0.75 min, 93% índice de homogeneidad.

Extremo 48



Extremo 1; 2-(3-ciclopentilureido)-2-fenilacetato de (R)-tert-butilo: A una solución agitada de clorohidrato de

ácido (R)-2-amino-2-fenilacético (1.0 g, 4.10 mmol) y Base Hunig (1.0 mL, 6.15 mmol) en DMF (15 mL) se agregó ciclopentil isocianato (0.46 mL, 4.10 mmol) gota a gota y durante 10 minutos. Después de agitarse a temperatura ambiente durante 3 horas, la reacción se concentró bajo presión reducida y el residuo resultante se tomó 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. El 2-(3-ciclopentilureido)-2-fenilacetato de (R)-tert-butilo se obtuvo 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: Análisis 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 hasta 100% B durante 4 minutos, 1 minutos tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, TR = 2.82 min, 96% índice de homogeneidad.

Extremo 2; ácido (R)-2-(3-ciclopentilureido)-2-fenilacético: A una solución agitada de 2-(3-ciclopentilureido)-2-fenilacetato de (R)-tert-butilo (1.31 g, 4.10 mmol) en CH_2Cl_2 (25 mL) se agregó TFA (4 mL) y trietilsilano (1.64 mL; 10.3 mmol) gota a gota, y la solución resultante se agitó a temperatura ambiente durante 6 horas. Los componentes volátiles se removieron bajo presión reducida

y el producto crudo se recristalizó en acetato de etilo/pentanos para proporcionar 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 hasta 100% B durante 2 minutos, 1 minutos tiempo de espera, A = 90% agua, 10% metanol, 0.2% H_3PO_4, B = 10% agua, 90% metanol, 0.2% H_3PO_4, TR = 1.24 min, 100% índice de homogeneidad.

Extremo 49

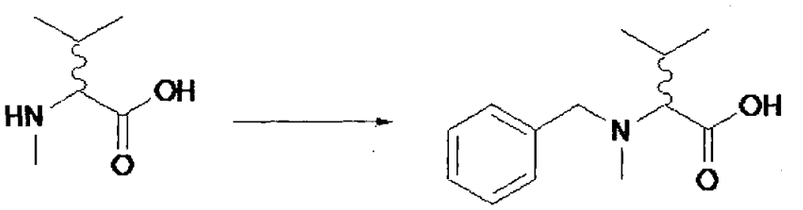


EXTREMO-49

A una solución agitada de ácido 2-(bencilamino)acético (2.0 g, 12.1 mmol) en ácido fórmico (91 mL) se agregó formaldehído (6.94 mL, 93.2 mmol). Después de cinco horas a 70°C, la mezcla de reacción se concentró bajo presión reducida hasta 20 mL y un precipitado sólido blanco. Siguiendo el filtrado, los licores madre se colectaron y además se concentraron bajo presión reducida proporcionando

el producto crudo. La purificación por HPLC preparativa de fase inversa (Xterra 30 X 100 mm, detección a 220 nm, relación de flujo 35 mL/min, 0 hasta 35% B durante 8 min; A = 90% agua, 10 % metanol, 0.1% TFA, B = 10% agua, 90 % metanol, 0.1% TFA) proporcionó el compuesto del título ácido 2-(bencilo(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

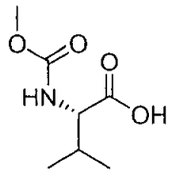


EXTREMO-50

A una solución agitada de ácido 3-metil-2-(metilamino)butanoico (0.50 g, 3.81 mmol) en agua (30 mL) se agregó K_2CO_3 (2.63 g, 19.1 mmol) y cloruro de bencilo (1.32 g, 11.4 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se extrajo con acetato de etilo (30 mL x 2) y la capa acuosa se concentró bajo presión reducida proporcionando el producto crudo el cual se purificó por HPLC preparativa de fase inversa (Xterra 30 x 100mm, detección a 220 nm, relación de

flujo 40 mL/min, 20 hasta 80% B durante 6 min; A = 90% agua, 10 % metanol, 0.1% TFA, B = 10% agua, 90 % metanol, 0.1% TFA) para proporcionar ácido 2-(bencilo(metil)amino)-3-metilbutanoico, Sal TFA (126 mg, 19%) como una cera 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

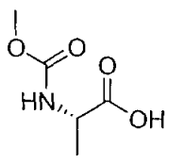


El Na_2CO_3 (1.83g, 17.2 mmol) se agregó a una solución en NaOH (33 mL de 1M/H_2O, 33 mmol) de L-valina (3.9 g, 33.29 mmol) y la solución resultante se enfrió con un baño de agua con hielo. Cloroformiato de metilo (2.8 mL, 36.1 mmol) se agregó en porciones durante 15 min, el baño frío se removió y la mezcla de reacción se agitó a temperatura ambiente durante 3.25 hr. La mezcla de reacción se lavó con éter (50 mL, 3x), y la fase acuosa se enfrió con baño de agua con hielo y se acidificó con HCl concentrado hasta un pH de la región de 1-2, y se

extrajo con CH_2Cl_2 (50 mL, 3x). La fase orgánica se secó ($MgSO_4$) y se evaporó in vacuo para proporcionar el extremo 51 como un sólido blanco (6 g). ^1H RMN para el rótamero 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

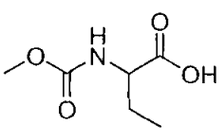
Extremo 52

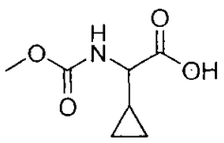
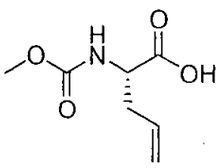


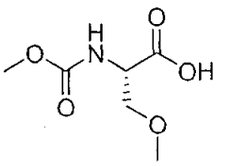
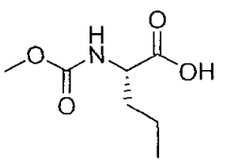
El extremo 52 se sintetizó a partir de L-Alanina de conformidad al procedimiento descrito para la síntesis del extremo 51. Para propósitos de caracterización, una porción del material crudo se purificó por HPLC de fase inversa (H_2O/MeOH/TFA) para proporcionar el extremo 52 como un aceite viscoso incoloro. ^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, 0.12H), 3.97 (m, 1H), 3.53 (s, 3H), 1.25 (d, J = 7.3, 3H).

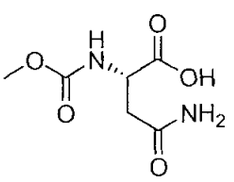
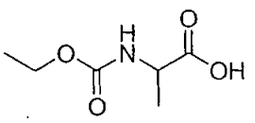
El extremo-53 hasta -64 se prepararon de materiales de partida apropiado de acuerdo al

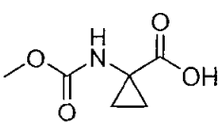
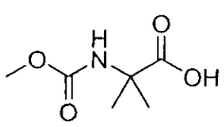
procedimiento descrito para la síntesis de extremo-51, con modificaciones anotadas si hay.

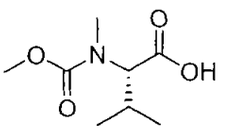
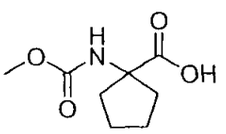
Extremo	Estructura	Datos
Extremo-53a: (R) *Extremo-53b*: (S)		^{1}H RMN (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.51 (br s, 1H), 7.4 (d, *J* = 7.9, 0.9H), 7.06 (app s, 0.1H), 3.86-3.82 (m, 1H), 3.53 (s, 3H), 1.75-1.67 (m, 1H), 1.62-1.54 (m, 1H), 0.88 (d, *J* = 7.3, 3H). TR = 0.77 minutos (Cond. 2); LC/MS: Análisis calculado para $[M+Na]^+$ $C_6H_{11}NNaO_4$: 184.06; encontrado 184.07. HRMS calculado para $[M+Na]^+$ $C_6H_{11}NNaO_4$: 184.0586; encontrado 184.0592.

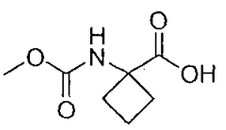
Extremo-54a: (R) *Extremo-54b*: (S)		^{1}H RMN (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.48 (s, 1H), 7.58 (d, *J* = 7.6, 0.9H), 7.25 (app s, 0.1H), 3.52 (s, 3H), 3.36-3.33 (m, 1H), 1.10-1.01 (m, 1H), 0.54-0.49 (m, 1H), 0.46-0.40 (m, 1H), 0.39-0.35 (m, 1H), 0.31-0.21 (m, 1H). HRMS calculado para $[M+H]^+$ $C_7H_{12}NO_4$: 174.0766; encontrado 174.0771
Extremo-55		^{1}H RMN (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 RMN (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 RMN (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). CL (Cond. 2): TR = 1.39 LC/MS: Análisis calculado para $[M+H]^+$ $C_7H_{14}NO_4$: 176.09; encontrado 176.06.

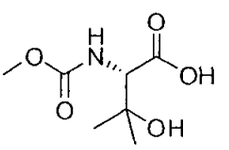
Extremo-58		^{1}H RMN (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.63 (bs, 1H), 7.35 (s,1H), 7.31 (d, *J* = 8.2, 1H), 6.92 (s, 1H), 4.33-4.29 (m, 1H), 3.54 (s, 3H), 2.54(dd, *J* = 15.5, 5.4, 1H), 2.43 (dd, *J* = 15.6, 8.0, 1H). TR = 0.16 min (Cond. 2); LC/MS: Análisis calculado para $[M+H]^+$ $C_6H_{11}N_2O_5$: 191.07; encontrado 191.14.
Extremo-59a: (R) *Extremo-59b*: (S)		^{1}H RMN (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: Análisis calculado 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 proporcionar un aceite viscoso incoloro que cristaliza a un sólido blanco hasta que se expone a alto vacío. ^{1}H RMN (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 (dos s, 3H), 1.30 (m, 2H), 0.98 (m, 2H). HRMS: Análisis calculado para $[M+H]^+$ $C_6H_{10}NO_4$: 160.0610; encontrado 160.0604.
Extremo-61		^{1}H RMN (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: Análisis calculado para $[M+H]^+$ $C_6H_{12}NO_4$: 162.0766; encontrado 162.0765.

Extremo-62		^{1}H RMN (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 singletes, 3H), 3.0 (s, 3H), 2.14-2.05 (m, 1H), 0.95 (d, *J* = 6.3, 3H), 0.81 (d, *J* = 6.6, 3H). LC/MS: Análisis calculado para $[M-H]^-$ $C_8H_{14}NO_4$: 188.09; encontrado 188.05.
Extremo-63		[Nota: la reacción se permitió correr por más de lo que se observa por el procedimiento general.] ^{1}H RMN (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: Análisis calculado para $[M+H]^+$ $C_8H_{14}NO_4$: 188.09; encontrado 188.19.

Extremo-64		[Nota: la reacción se permitió correr por más de lo que se observa por el procedimiento general.] ^{1}H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.35 (br s, 1H), 7.77 (s, 0.82H), 7.56/7.52 (traslapado 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).

Extremo-65

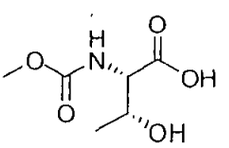


El cloroformiato de metilo (0.65 mL, 8.39 mmol) se agregó gota a gota durante 5 min a una mezcla enfriada (agua con hielo) de Na_2CO_3 (0.449 g, 4.23 mmol), NaOH (8.2 mL de 1M/H_2O, 8.2 mmol) y ácido (*S*)-3-hidroxi-2-(metoxicarbonilamino)-3-metilbutanoico (1.04 g, 7.81 mmol). La mezcla de reacción se agitó durante 45 min, y luego el baño de enfriamiento se removió y se continuó agitando durante unas 3.75 hr adicionales. La mezcla de reacción se lavó con CH_2Cl_2, y la fase acuosa se enfrió con un baño de

agua con hielo y se hizo ácida con HCl concentrado hasta una región pH de 1-2. El componente volátil se removió *in vacuo* y el residuo se tomó en una mezcla 2:1 de $MeOH/CH_2Cl_2$ (15 mL) y se filtra, y el filtrado se colocó en un rotoevaporador para proporcionar el 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).

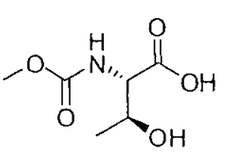
El extremo-66 y -67 se prepararon de materiales de partida apropiados comercialmente disponibles al emplear el procedimiento descrito para la síntesis de extremo-65.

Extremo-66



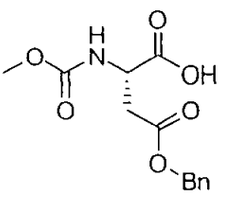
^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.58 (br s, 1H), 7.07 (d, J = 8.3, 0.13H), 6.81 (d, J = 8.8, 0.67H), 4.10-4.02 (m, 1.15H), 3.91 (dd, J = 9.1, 3.5, 0.85H), 3.56 (s, 3H), 1.09 (d, J = 6.2, 3H). [Nota: solamente las señales dominantes de NH se anotaron]

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: solamente las señales dominantes de NH se anotaron]

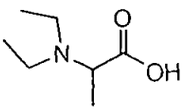
Extremo-68



El cloroformiato de metilo (0.38 ml, 4.9 mmol) se agregó gota a gota a una mezcla de 1N NaOH (aq) (9.0 ml, 9.0 mmol), 1M $NaHCO_3$ (ac) (9.0 ml, 9.0 mol), éster de β-bencilo del ácido L-aspártico (1.0 g, 4.5 mmol) y dioxano (9 ml). La mezcla de reacción se agitó a condiciones ambientales durante 3 hr, y luego se lava con acetato de etilo (50 ml, 3x). La capa acuosa se acidificó con 12N HCl hasta un pH ~ 1-2, y se extrae 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 *in vacuo* para proporcionar el extremo-68 como un aceite amarillo ligero (1.37g; la masa se proporciona teóricamente arriba, 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). CL (Cond. 2): TR = 1.90 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{13}H_{16}NO_6$: 282.10; encontrado 282.12.

Extremo-69a y -69b

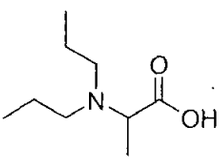


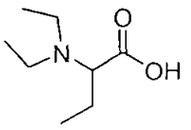
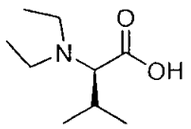
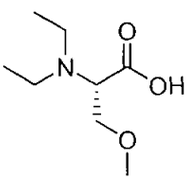
Extremo-69a: (R)-enantiómero
Extremo-69b: (S)-enantiómero

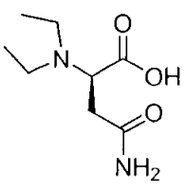
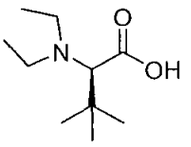
El $NaCNBH_3$ (2.416 g, 36.5 mmol) se agregó en lotes a una solución fría (~15 °C) agua (17 mL)/MeOH (10 mL) de alanina (1.338 g, 15.0 mmol). Unos pocos minutos después el acetaldehído (4.0 mL, 71.3 mmol) se agregó gota a gota durante 4 min, el baño de enfriamiento se removió, y la mezcla de reacción se agitó a temperatura ambiente durante 6 hr. Un acetaldehído adicional (4.0 mL) se agregó y la reacción se agitó durante 2 hr. El HCl concentrado se agregó lentamente a la mezcla de reacción hasta que el pH alcanza ~ 1.5, y la mezcla resultante se calentó durante 1 hr a 40°C. Más del componente volátil se removió *in vacuo* y el residuo se purificó con una resina de intercambio de iones Dowex ® 50WX8-

100 (la columna se lavó con agua, y el compuesto se eluyó con NH_4OH diluido, preparado al mezclar 18 ml de NH_4OH y 282 ml de agua) para proporcionar el extremo-69 (2.0 g) como un sólido higroscópico blanco opaco. ^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).

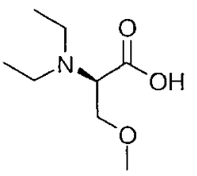
Los extremos-70 hasta -74 se prepararon de acuerdo al procedimiento descrito para la síntesis del extremo-69 al emplear materiales de partida apropiados.

Extremo-70a: (R) *Extremo-70b*: (S)		^1H RMN (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: Análisis calculado para $[M+H]^+$ $C_9H_{20}NO_2$: 174.15; encontrado 174.13.

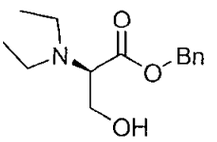
Extremo-71a: (R) *Extremo-71b*: (S)		^{1}H RMN (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 3.18-3.14 (m, 1H), 2.84-2.77 (m, 2H), 2.76-2.68 (m, 2H), 1.69-1.54 (m, 2H), 1.05 (t, *J* = 7.2, 6H), 0.91 (t, *J* = 7.3, 3H). LC/MS: Análisis calculado para $[M+H]^+$ $C_8H_{18}NO_2$: 160.13; encontrado 160.06.
Extremo-72		^{1}H RMN (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: Análisis calculado para $[M+H]^+$ $C_9H_{20}NO_2$: 174.15; encontrado 174.15.
Extremo-73		^{1}H RMN (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 RMN (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). TR = 0.125 minutos (Cond. 2); LC/MS: Análisis calculado para $[M+H]^+$ $C_8H_{17}N_2O_3$: 189.12; encontrado 189.13.
Extremo-74x		LC/MS: Análisis calculado para $[M+H]^+$ $C_{10}H_{22}NO_2$: 188.17; encontrado 188.21

Extremo-75



Extremo-75, Extremo a



El $NaBH_3CN$ (1.6 g, 25.5 mmol) se agregó a una solución fría (baño de hielo/agua) agua (25 ml)/metanol (15 ml) de H-D-Ser-OBzl HCl (2.0 g, 8.6 mmol). El acetaldehído (1.5 ml,

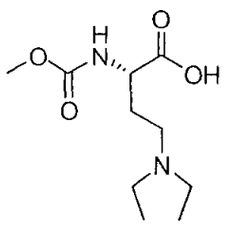
12.5 mmol) se agregó gota a gota durante 5 min, el baño de enfriamiento se removió, y la mezcla de reacción se agitó a temperatura ambiente durante 2 hr. La reacción se apagó cuidadosamente con 12N HCl y se concentra *in vacuo*. El residuo se disolvió en agua y se purifica con una HPLC de fase inversa (MeOH/H_2O/TFA) para proporcionar la sal TFA de 2-(dietilamino)-3-hidroxipropanoato de (R)-bencilo como un aceite viscoso incoloro (1.9g). ^{1}H 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): TR = 1.38 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{14}H_{22}NO_3$: 252.16; encontrado 252.19.

Extremo-75

El NaH (0.0727 g, 1.82 mmol, 60%) se agregó a una solución fría (hielo-agua) THF (3.0 mL) de la sal TFA 2-(dietilamino)-3-hidroxipropanoato de (R)-bencilo (0.3019 g, 0.8264 mmol) preparado arriba, y la mezcla se agitó durante 15 min. El yoduro de metilo (56 µL, 0.90 mmol) se agregó y se continuó agitando durante 18 hr mientras se permite el baño a una temperatura ambiente. La reacción se apagó con agua y se cargó en un cartucho MCX pre-condicionado MeOH (6 g), y se lava con metanol seguido por la elución del compuesto con 2N NH_3/Metanol. La remoción del componente volátil *in vacuo* proporciona el extremo-75, contaminada con ácido (R)-2-

(dietilamino)-3-hidroxipropanoico, como un semi-sólido amarillo (100 mg). El producto se usó como es sin purificación adicional.

Extremo-76

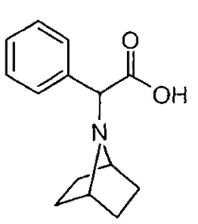


El $NaCNBH_3$ (1.60 g, 24.2 mmol) se agregó en lotes a una solución fría (~15 °C) agua/MeOH (12 mL cada uno) de ácido (*S*)-4-amino-2-(tert-butoxicarbonilamino)butanoico (2.17 g, 9.94 mmol). Unos pocos minutos después el acetaldehído (2.7 mL, 48.1 mmol) se agregó gota a gota durante 2 min, el baño de enfriamiento se removió, y la mezcla de reacción se agitó a temperatura ambiente durante 3.5 hr. Un acetaldehído adicional (2.7 mL, 48.1 mmol) se agregó y la reacción se agitó durante 20.5 hr. Más del componente MeOH se removió *in vacuo*, y la mezcla restante se trató con HCl concentrado hasta que el pH alcanza ~ 1.0 y luego se calienta durante 2 hr a 40°C. El componente volátil se removió *in vacuo*, y el residuo se trató con 4 M HCl/dioxano (20 mL) y se agita a temperatura ambiente durante 7.5 hr. El componente volátil se removió *in vacuo* y el residuo se purificó con resina de intercambio de iones Dowex ® 50WX8-100 (la columna se lavó con agua y el compuesto se eluyó con NH_4OH diluido, preparado

de 18 ml de NH_4OH y 282 ml de agua) para proporcionar el intermediario ácido (S)-2-amino-4-(dietilamino)butanoico como un sólido blanco opaco (1.73 g).

El cloroformiato de metilo (0.36 mL, 4.65 mmol) se agregó gota a gota durante 11 min a una mezcla fría (hielo-agua) de Na_2CO_3 (0.243 g, 2.29 mmol), NaOH (4.6 mL de 1M/H_2O, 4.6 mmol) y el producto anterior (802.4 mg). La mezcla de reacción se agitó durante 55 min, y luego el baño de enfriamiento se removió y se continuó agitando durante unoas 5.25 hr adicionales. La mezcla de reacción se diluyó con volumen igual de agua y se lava con CH_2Cl_2 (30 mL, 2x), y la fase acuosa se enfrió con un baño de agua con hielo y se hizo ácida con HCl concentrado hasta una región pH de 2. El componente volátil luego se removió *in vacuo* y el material crudo se hizo base libre con resina MCX (6.0g; la columna se lavó con agua, y la muestra se eluyó con 2.0 M NH_3/MeOH) para proporcionar el extremo-76 impura como un sólido blanco opaco (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.

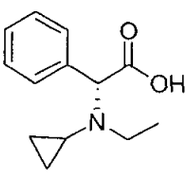
Extremo-77a y -77b



Extremo-77a: enantiómero-1
Extremo-77b: enantiómero-2

La síntesis del extremo-77 se condujo de acuerdo al procedimiento descrito para el extremo-7 al usar 7-azabiciclo[2.2.1]heptano para la Extremo de desplazamiento SN_2, y al efectuar la separación enantiomérica del intermediario 2-(7-azabiciclo[2.2.1]heptan-7-il)-2-fenilacetato de bencilo usando la siguiente afección: el intermediario (303.7 mg) se disolvió en etanol, y la solución resultante se inyectó en una columna HPLC quiral (columna Chiracel AD-H, 30 x 250 mm, 5 um) eluido con 90% CO_2-10% EtOH a 70 mL/min, y una temperatura de 35 °C para proporcionar 124.5 mg del enantiómero-1 y 133.8 mg del enantiómero-2. Estos ésteres de bencilo se hidrogenizaron de acuerdo a la preparación del extremo-7 para proporcionar el extremo-77: ^1H 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). CL (Cond. 1): TR = 0.67 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{14}H_{18}BrNO_2$: 232.13; encontrado 232.18. HRMS: Análisis calculado para $[M+H]^+$ $C_{14}H_{18}BrNO_2$: 232.1338; encontrado 232.1340.

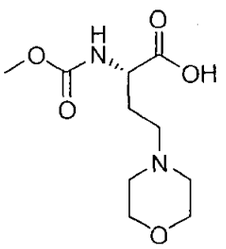
Extremo-78



El $NaCNBH_3$ (0.5828 g, 9.27 mmol) se agregó a una mezcla de la sal HCl del ácido (*R*)-2-(etilamino)-2-

fenilacético (un intermediario en la síntesis del extremo-3; 0.9923 mg, 4.60 mmol) y (1-etoxiciclopropoxi)trimetilsilano (1.640 g, 9.40 mmol) en MeOH (10 mL), y la mezcla semi-heterogénea se calentó a 50°C con un baño de aceite durante 20 hr. Más (1-etoxiciclopropoxi)trimetilsilano (150 mg, 0.86 mmol) y $NaCNBH_3$ (52 mg, 0.827 mmol) se agregaron y la mezcla de reacción se calentó durante unas 3.5 hr adicionales. Luego se permitió enfriar hasta temperatura ambiente y se hace ácida hasta una región ~ pH de 2 con HCl concentrado, y la mezcla se filtró y el filtrado se colocó en un rotoevaporador. El material crudo resultante se colocó en *i*-PrOH (6 mL) y se caliente para disolución de efecto, y la parte no disuelta se filtró completamente y el filtrado se concentra *in vacuo*. Alrededor de 1/3 del material crudo resultante se purificó con una HPLC de fase inversa (H_2O/MeOH/TFA) para proporcionar la sal TFA del extremo-78 como un aceite viscoso incoloro (353 mg). ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz; después intercambio de 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). CL (Cond. 1): TR = 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



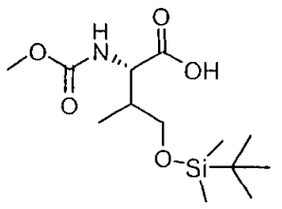
El ozono se burbujeó a través de una solución fría (-78 °C) CH_2Cl_2 (5.0 mL) extremo-55 (369 mg, 2.13 mmol) durante alrededor de 50 min hasta que la mezcla de reacción alcanza una tintura de color azul. El Me_2S (10 gotas de pipeta) se agregó, y la mezcla de reacción se agitó durante 35 min. el baño -78°C se reemplazó con un baño -10°C y se continua agitando durante unos 30 min adicionales, y luego el componente volátil se removió *in vacuo* para proporcionar un aceite viscoso incoloro.

$NaBH_3CN$ (149 mg, 2.25 mmol) se agregó a una solución MeOH (5.0 mL) del material crudo anterior y morfolina (500 µL, 5.72 mmol) y la mezcla se agitó a temperatura ambiente durante 4 hr. Se enfrió a temperatura de hielo-agua y se trata con HCl concentrado para llevar su pH hasta ~2.0, y luego se agita durante 2.5 hr. El componente volátil se removió *in vacuo*, y el residuo se purificó con una combinación de resina MCX (lavado MeOH; 2.0 N elusión NH_3/MeOH) y una HPLC de fase inversa (H_2O/MeOH/TFA) para proporcionar el extremo-79 que contiene cantidad desconocida

de morfolina.

Con objeto de consumir el contaminante de morfolina, el material anterior se disolvió en CH_2Cl_2 (1.5 mL) y se trata con Et_3N (0.27 mL, 1.94 mmol) seguido por anhídrido acético (0.10 mL, 1.06 mmol) y se agita a temperatura ambiente durante 18 hr. THF (1.0 mL) y H_2O (0.5 mL) se agregaron y se continuan agitando durante 1.5 hr. El componente volátil se removió *in vacuo*, y el residuo resultante se pasó a través de resina MCX (lavado MeOH; 2.0 N elusión NH_3/MeOH) para proporcionar el extremo-79 impura como un aceite viscoso café, el cual se usó para la siguiente Extremo sin purificación adicional.

Extremo-80a y -80b



Extremo-80a: S/S-diastereómero
Extremo-80b: S/R-diastereómero

El $SOCl_2$ (6.60 mL, 90.5 mmol) se agregó gota a gota durante 15 min a una mezcla fría (hielo-agua) de ácido (S)-3-amino-4-(benciloxi)-4-oxobutanoico (10.04g, 44.98 mmol) y MeOH (300 mL), el baño de enfriamiento se removió y la mezcla de reacción se agitó a temperatura ambiente durante 29 hr. Más del componente volátil se removió *in vacuo* y el residuo se dividió cuidadosamente entre EtOAc (150 mL) y solución

$NaHCO_3$ saturado. La fase acuosa se extrajo con EtOAc (150 mL, 2x), y la fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró *in vacuo* para proporcionar (S)-1-bencilo 4-metil 2-aminosuccinato como un aceite incoloro (9.706g). ^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). CL (Cond. 1): TR = 0.90 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{12}H_{16}NO_4$: 238.11; encontrado 238.22.

El $Pb(NO_3)_2$ (6.06 g, 18.3 mmol) se agregó durante 1 min a una solución CH_2Cl_2 (80 mL) de (S)-1-bencilo 4-metil 2-aminosuccinato (4.50 g, 19.0 mmol), 9-bromo-9-fenil-9*H*-fluoreno (6.44 g, 20.0 mmol) y Et_3N (3.0 mL, 21.5 mmol), y la mezcla heterogénea se agitó a temperatura ambiente durante 48 hr. La mezcla se filtró y el filtrado se trató con $MgSO_4$ y se filtra nuevamente, y el filtrado final se concentró. El material crudo resultante se sometió a una purificación Biotage (350 g gel de sílice, elusión CH_2Cl_2) para proporcionar (S)-1-bencilo 4-metil 2-(9-fenil-9H-fluoren-9-ilamino)succinato como 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). CL (Cond. 1): TR = 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 mmol) se agregó gota a gota durante 10 min a una solución fría (-78 °C) THF (50 mL) de (S)-1-bencilo 4-metil 2-(9-fenil-9H-fluoren-9-ilamino)succinato (3.907 g, 8.18 mmol) y se agita durante ~1 hr. El MeI (0.57 mL, 9.2 mmol) se agregó gota a gota durante 8 min a la mezcla, y se continuó agitando durante 16.5 hr mientras se permite el baño de enfriamiento se descongela a temperatura ambiente. Después de apagar con solución NH_4Cl saturado (5 mL), más del componente orgánico se removió *in vacuo* 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 *in vacuo*, y el material crudo resultante se purificó con un Biotage (350 g gel de sílice; 25% EtOAc/hexanos) para proporcionar 3.65 g de unas mezclas diastereoméricas 2S/3S y 2S/3R de 1-bencilo 4-metil 3-metil-2-(9-fenil-9H-fluoren-9-ilamino)succinato en relación ~1.0:0.65 (^{1}H RMN). La estereoquímica del isómero dominante no se determinó a esta unión, y la mezcla se sometió a la siguiente Extremo sin separación. Los datos ^{1}H RMN parciales (DMSO-d_6, δ = 2.5 ppm, 400 MHz): diastereómero mayor, δ 4.39 (d, J = 12.3, 1H de CH_2), 3.33 (s, 3H, traslape con señal 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). CL (Cond. 1): TR = 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 mmol) se agregó gota a gota durante 10 min hasta una slución fría (-78 °C) THF (120 mL) de (2S)-1-bencilo 4-metil 3-metil-2-(9-fenil-9H-fluoren-9-ilamino)succinato (3.37 g, 6.86 mmol) preparado arriba, y se agita a -78°C durante 20 hr. La mezcla de reacción se removió del baño de enfriamiento y se vacía 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 secó ($MgSO_4$), se filtró y se concentró *in vacuo*. Una malla de gel de sílice del material crudo se preparó y se sometió a cromatografía (25% EtOAc/hexanos; elusión de gravedad) para proporcionar 1.1g de (2S,3S)-bencilo 4-hidroxi-3-metil-2-(9-fenil-9*H*-fluoren-9-ilamino)butanoato, contaminada con alcohol bencílico, como un aceite viscoso incoloro y (2S,3R)-bencilo 4-hidroxi-3-metil-2-(9-fenil-9*H*-fluoren-9-ilamino)butanoato que contiene el estereoisómero (2S,3R) como una impureza. Después la muestra se volvió a someter a las mismas condiciones de purificación de cromatografía de columna para proporcionar 750 mg de material purificado como una espuma blanca. [Nota: el isómero (2S, 3S) eluido antes el isómero (2S,3R) bajo la afección anterior]. Isómero (2S, 3S): ^1H 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, traslape con la señal de solvente), 1.58 (m, 1H), 0.88 (d, J = 6.8, 3H). CL (Cond. 1): TR = 2.00 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{31}H_{30}NO_3$: 464.45; encontrado 464.22. isómero (2S, 3R): ^1H 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). CL (Cond. 1): TR = 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 DIBAL se hicieron basadas en estudios NOE conducidos a derivados de lactona preparados de cada isómero al emplear el siguiente protocolo: LiHMDS (50 µL de 1.0 M/THF, 0.05 mmol) se agregó a una solución fría (hielo-agua) THF (2.0 mL) de 4-hidroxi-3-metil-2-(9-fenil-9*H*-fluoren-9-ilamino)butanoato de (2S,3S)-bencilo (62.7 mg, 0.135 mmol), y la mezcla de reacción se agitó a temperatura similar durante ~2 hr. El componente volátil se removió *in vacuo* y el residuo se dividió entre CH_2Cl_2 (30 mL), agua (20 mL) y solución NH_4Cl acuoso saturado (1 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se concentró *in vacuo*, y el material crudo resultante se sometió a una purificación Biotage (40 g gel de sílice; 10-15% EtOAc/hexanos) para proporcionar (3S,4S)-4-metil-3-(9-

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fenil-9*H*-fluoren-9-ilamino)dihidrofuran-2(3*H*)-ona como una película incolora de sólido (28.1 mg). El 4-hidroxi-3-metil-2-(9-fenil-9*H*-fluoren-9-ilamino)butanoato de (2*S*,3R)-bencilo se elaboró similarmente a (3S,4R)-4-metil-3-(9-fenil-9*H*-fluoren-9-ilamino)dihidrofuran-2(3*H*)-ona. Isómero (3S,4S)-lactona: ^{1}H 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 (m, 1H), 0.27 (d, *J* = 6.6, 3H). CL (Cond. 1): TR = 1.98 min; LC/MS: Análisis calculado para $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378.15; encontrado 378.42. Isómero (3S,4R)-lactona: ^{1}H RMN (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). CL (Cond. 1): TR = 2.03 min; LC/MS: Análisis calculado para $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378.15; encontrado 378.49.

El TBDMS-Cl (48 mg, 0.312 mmol) seguido por imidazol (28.8 mg, 0.423 mmol) se agregaro a una solución CH_2Cl_2 (3 ml) de 4-hidroxi-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3S)-bencilo (119.5 mg, 0.258 mmol), y la mezcla se agitó a temperatura ambiente durante 14.25 hr. La mezcla de reacción luego se diluyó con CH_2Cl_2 (30 mL) y se lava con agua (15 mL), y la capa orgánica se secó ($MgSO_4$), se filtró y se concentró *in*

vacuo. El material crudo resultante se purificó con un Biotage (40 g gel de sílice; 5% EtOAc/hexanos) para proporcionar 4-(tert-butildimetilsililoxi)-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3S)-bencilo, contaminada con impurezas basadas en TBDMS, como un aceite viscoso incoloro (124.4 mg). El 4-hidroxi-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo se elaboró similarmente a 4-(tert-butildimetilsililoxi)-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo. Isómero de éster de (2S,3S)-sililo: ^{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, 16 H), 4.70 (d, J = 12.4, 1H), 4.42 (d, J = 12.3, 1H), 3.28-3.19 (m, 3H), 2.56 (dd, J = 10.1, 5.5, 1H), 1.61 (m, 1H), 0.90 (d, J = 6.8, 3H), 0.70 (s, 9H), -0.13 (s, 3H), -0.16 (s, 3H). CL (Cond. 1, donde el tiempo de corrida se extendió hasta 4 min): TR = 3.26 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{37}H_{44}NO_3Si$: 578.31; encontrado 578.40. Isómero de éter de (2S,3R)-sililo: ^{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 globo de hidrógeno se enlazó a una mezcla de 4-(tert-butildimetilsililoxi)-3-metil-2-(9-fenil-9*H*-fluoren-9-

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ilamino)butanoato de (2S,3S)-bencilo (836 mg, 1.447 mmol) y 10% Pd/C (213 mg) en EtOAc (16 mL) y la mezcla se agitó a temperatura ambiente durante ~ 21 hr, donde el globo se volvió a cargar con H_2 como sea necesario. La mezcla de reacción se diluyó con CH_2Cl_2 y se filtra 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 del material crudo resultante y se somete a una cromatografía instantánea (mezcla 8:2:1 de EtOAc/i-PrOH/H_2O) para proporcionar ácido (2S,3S)-2-amino-4-(tert-butildimetilsililoxi)-3-metilbutanoico como un sólido esponjoso blanco (325 mg). El 4-(tert-butildimetilsililoxi)-3-metil-2-(9-fenil-9H-fluoren-9-ilamino)butanoato de (2S,3R)-bencilo se elaboró similarmente al ácido (2S,3R)-2-amino-4-(tert-butildimetilsililoxi)-3-metilbutanoico. Isómero de aminoácido (2S,3S): ^{1}H 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 aminoácido (2S,3R): ^{1}H 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

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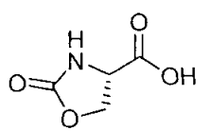
calculado para $[M+H]^+$ $C_{11}H_{26}NO_3Si$: 248.17; encontrado 248.44.

El agua (1 mL) y NaOH (0.18 mL de 1.0 M/H_2O, 0.18 mmol) se agregaron a una mezcla de ácido (2S,3S)-2-amino-4-(tert-butildimetilsililoxi)-3-metilbutanoico (41.9 mg, 0.169 mmol) y Na_2CO_3 (11.9 mg, 0.112 mmol), y se sonicaron durante alrededor de 1 min para efectuar la disolución de reactivos. La mezcla luego se enfrió con un baño de hielo-agua, cloroformiato de metilo (0.02 mL, 0.259 mmol) se agregó durante 30 s, y se continuó agitando vigorosamente a temperatura similar durante 40 min y luego a temperatura ambiente durante 2.7 hr. La mezcla de reacción se diluyó con agua (5 mL), se enfría con baño de hielo-agua y se trata gota a gota con solución acuosa HCl 1.0 N (~0.23 mL). La mezcla se diluyó además con agua (10 mL) y se extrae con CH_2Cl_2 (15 mL, 2x). La fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró *in vacuo* para proporcionar el extremo-80a como un sólido blanco opaco. El ácido (2S,3R)-2-amino-4-(tert-butildimetilsililoxi)-3-metilbutanoico se elaboró similarmente a el extremo-80b. Extremo-80a: ^1H 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 singletes, 3H), 3.48-3.40 (m, 2H), 2.22-2.10 (m, 1H), 0.85 (s, 9H), ~0.84 (d, 0.9H, traslape con señal t-Bu), 0.79 (d, J = 7, 2.1H), 0.02/0.01/0.00 (tres singletes traslapados, 6H).

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LC/MS: Análisis calculado para $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328.16; encontrado 328.46. Extremo-80b: ^1H 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.

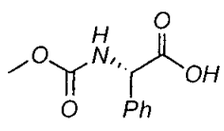
Extremo-81



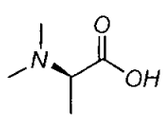
Preparado de acuerdo al protocolo descrito por Falb et al. *Synthetic Communications* 1993, *23*, 2839.

Extremo-82 hasta extremo-85

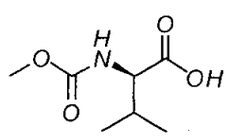
El extremo-82 hasta extremo-85 se sintetizaron de materiales de partida apropiados de acuerdo al procedimiento descrito para el extremo-51. Las muestras muestran perfiles de espectro similares como el de sus enantiómeros (esto es, extremo-4, extremo-13, extremo-51 y extremo-52, respectivamente)



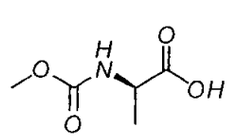
Extremo-82



Extremo-83

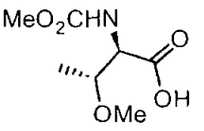


Extremo-84



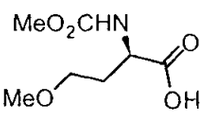
Extremo-85

Extremo-86



A una mezcla de O-metil-L-treonina (3.0 g, 22.55 mmol), NaOH (0.902 g, 22.55 mmol) en H_2O (15 mL) se agregó $ClCO_2Me$ (1.74 mL, 22.55 mmol) gota a gota a 0°C. La mezcla se permitió agitar durante 12 h y se hace ácida hasta pH 1 usando HCl 1N. La fase acuosa se extrajo con EtOAc y (2x250 mL) y 10% MeOH en CH_2Cl_2 (250 mL) y las fases orgánicas combinadas se concentraron bajo *in vacuo* para proporcionar un aceite incoloro (4.18 g, 97%) el cual fue de pureza suficiente para uso en las Extremos posteriores. ^{1}HRMN (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 $(M-H)^-$.

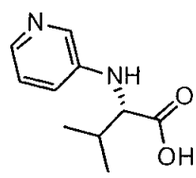
Extremo-87



A una mezcla de L-homoserina (2.0 g, 9.79 mmol), Na_2CO_3 (2.08 g, 19.59 mmol) en H_2O (15 mL) se agregó $ClCO_2Me$ (0.76 mL, 9.79 mmol) gota a gota a 0°C. La mezcla se permitió agitar durante 48 h y se hace ácida hasta pH 1 usando HCl 1N. La fase acuosa se extrajo con EtOAc y (2X250 mL) y las fases orgánicas

combinadas se concentraron bajo *in vacuo* para proporcionar un sólido incoloro (0.719 g, 28%) el cual fue de pureza suficiente para uso en las Extremos posteriores. ^{1}HRMN (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

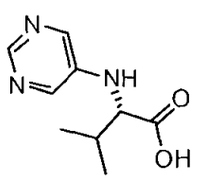


Una mezcla de L-valina (1.0 g, 8.54 mmol), 3-bromopiridina (1.8 mL, 18.7 mmol), K_2CO_3 (2.45 g, 17.7 mmol) y CuI (169 mg, 0.887 mmol) en DMSO (10 mL) se calentó a 100°C durante 12h. La mezcla de reacción se enfrió hasta temperatura ambiente, se vacía en H_2O (ca. 150 mL) y se lava con EtOAc (x2). Las capas orgánicas se extrajeron con una cantidad pequeña de H_2O y las fases acuosas combinadas se hicieron ácidas hasta ca. pH 2 con 6N HCl. El volumen se redujo hasta alrededor de un tercio y 20g de resina de intercambio de cationes (Strata) se agregó. La mezcla espesa se permitió reposar durante 20 min y se cargó en una almohadilla de resina de intercambio de cationes (Strata) (ca. 25g). La almohadilla se lavó con H_2O (200 mL), MeOH (200 mL), y luego NH_3 (3M en MeOH, 2X200 mL). Las fracciones

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apropiadas se concentraron *in vacuo* y el residuo (ca. 1.1 g) se disolvió en H_2O, congelado y liofilizado. El compuesto del título se obtuvo como una espuma (1.02 g, 62%). ^{1}HRMN (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: Análisis calculado para $C_{10}H_{14}N_2O_2$: 194; encontrado: 195 $(M+H)^+$.

Extremo-89

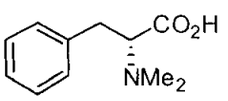


Una mezcla de L-valina (1.0 g, 8.54 mmol), 5-bromopirimidina (4.03 g, 17.0 mmol), K_2CO_3 (2.40 g, 17.4 mmol) y CuI (179 mg, 0.94 mmol) en DMSO (10 mL) se calentó a 100°C durante 12h. La mezcla de reacción se enfrió hasta temperatura ambiente, se vacía en H_2O (ca. 150 mL) y se lava con EtOAc (x2). Las capas orgánicas se extrajeron con una cantidad pequeña de H_2O y las fases acuosas combinadas se hicieron ácidas hasta ca. pH 2 con 6N HCl. El volumen se redujo hasta alrededor de un tercio y 20g de resina de intercambio de cationes (Strata) se agregó. La mezcla espesa se permitió reposar durante 20 min y se cargó en una almohadilla de resina de intercambio de cationes (Strata) (ca. 25g). La almohadilla se lavó con H_2O (200 mL), MeOH (200

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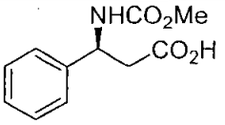
mL), y luego NH_3 (3M en MeOH, 2x200 mL). Las fracciones apropiadas se concentraron *in vacuo* y el residuo (ca. 1.1 g) se disolvió en H_2O, congelado y liofilizado. El compuesto del título se obtuvo como una espuma (1.02 g, 62%). ^{1}HRMN (400 MHz, CD_3OD) muestra la mezcla para contener valina y la pureza no puede estimarse. El material se usó como es en reacciones posteriores. LCMS: Análisis calculado para $C_9H_{13}N_3O_2$: 195; encontrado: 196 $(M+H)^+$.

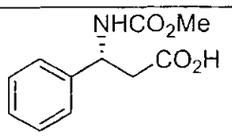
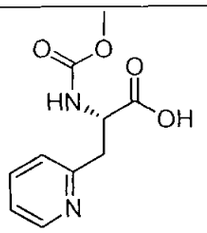
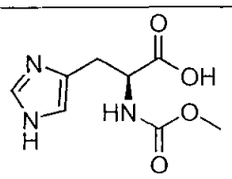
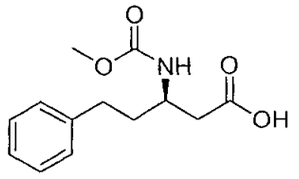
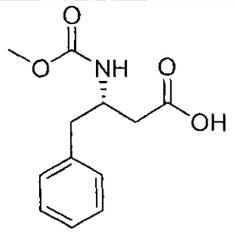
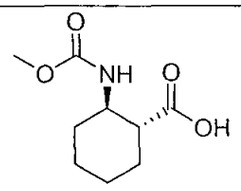
Extremo-90



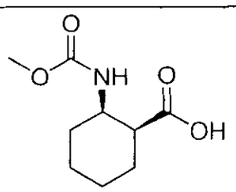
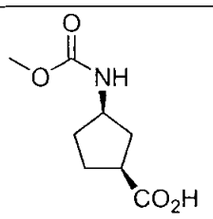
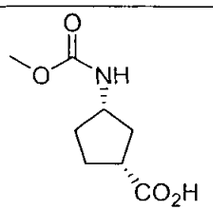
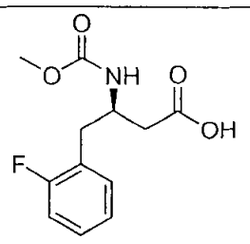
El extremo-90 se preparó de acuerdo al método descrito para la preparación del extremo-1. El material crudo se usó como es en Extremos posteriores. LCMS: Análisis calculado para $C_{11}H_{15}NO_2$: 193; encontrado: 192 $(M-H)^-$.

Las siguientes extremos se prepararon de acuerdo al método del 51:

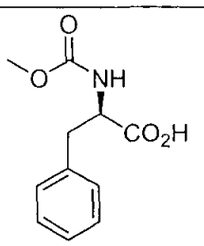
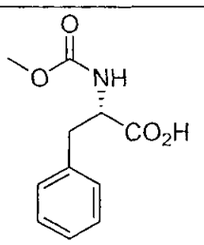
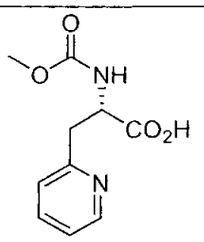
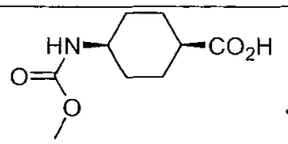
Extremo	Estructura	LCMS
Extremo-91		LCMS: Análisis calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$.

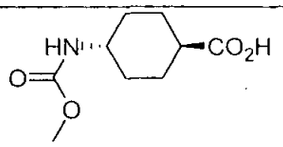
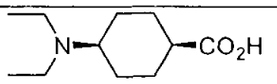
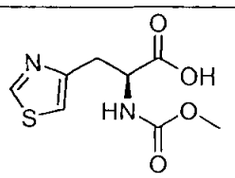
Extremo-92		LCMS: Análisis calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$.
Extremo-93		LCMS: Análisis calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.
Extremo-94		LCMS: Análisis calculado para $C_8H_{11}N_3O_4$: 213; encontrado: 214 $(M+H)^+$.
Extremo-95		LCMS: Análisis calculado para $C_{13}H_{17}NO_4$: 251; encontrado: 250 $(M-H)^-$.
Extremo-96		LCMS: Análisis calculado para $C_{12}H_{15}NO_4$: 237; encontrado: 236 $(M-H)^-$.
Extremo-97		LCMS: Análisis calculado para $C_9H_{15}NO_4$: 201; encontrado: 200 $(M-H)^-$.

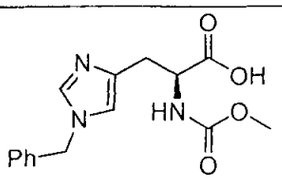
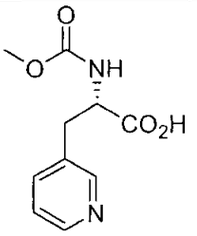
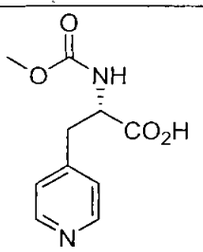
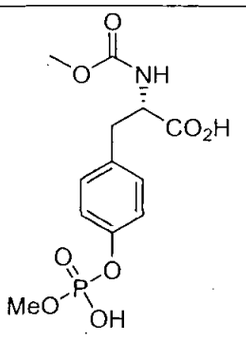
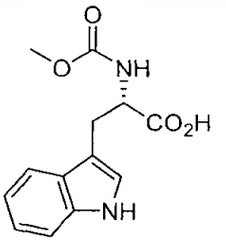
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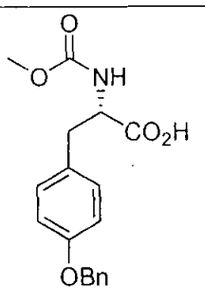
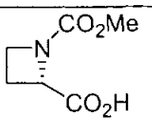
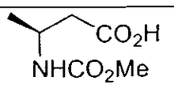
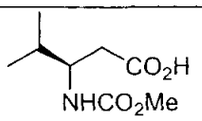
Extremo-98		LCMS: Análisis calculado para $C_9H_{15}NO_4$: 201; encontrado: 202 $(M+H)^+$.
Extremo-99		^{1}HRMN (400 MHz, CD_3OD) δ 3.88 - 3.94 (m, 1H), 3.60, 3.61 (s, 3H), 2.80 (m, 1H), 2.20 (m 1H), 1.82 - 1.94 (m, 3H), 1.45 - 1.71 (m, 2H).
Extremo-99a		^{1}HRMN (400 MHz, CD_3OD) δ 3.88 - 3.94 (m, 1H), 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: Análisis calculado para $C_{12}H_{14}NO_4F$: 255; encontrado: 256 $(M+H)^+$.

000903

Extremo-101		LCMS: Análisis calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$.
Extremo-102		LCMS: Análisis calculado para $C_{11}H_{13}NO_4$: 223; encontrado: 222 $(M-H)^-$
Extremo-103		LCMS: Análisis calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.
Extremo-104		^{1}HRMN (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).

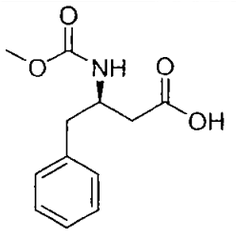
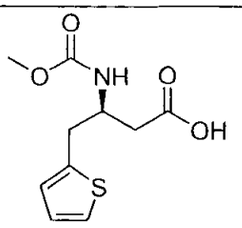
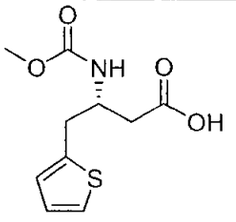
Extremo-105		^{1}HRMN (400 MHz, CD_3OD) δ 3.60 (s, 3H), 3.33 - 3.35 (m, 1H, parcialmente obscurecido por solvente), 2.37 - 2.41 y 2.16 - 2.23 (m, 1H), 1.94 - 2.01 (m, 4H), 1.43 - 1.53 (m, 2H), 1.17 - 1.29 (m, 2H).
Extremo-106		^{1}HRMN (400 MHz, CD_3OD) δ 3.16 (q, *J* = 7.3 Hz, 4H), 2.38 - 2.41 (m, 1H), 2.28 - 2.31 (m, 2H), 1.79 - 1.89 (m, 2H), 1.74 (app, ddd *J* = 3.5, 12.5, 15.9 Hz, 2H), 1.46 (app dt *J* = 4.0, 12.9 Hz, 2H), 1.26 (t, *J* = 7.3 Hz, 6H).
Extremo-107		LCMS: Análisis calculado para $C_8H_{10}N_2O_4S$: 230; encontrado: 231 $(M+H)^+$.

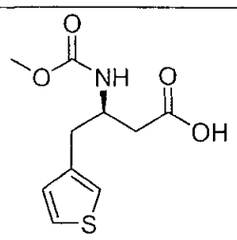
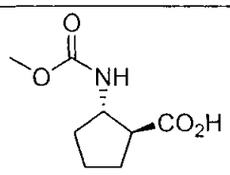
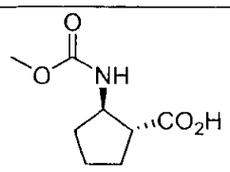
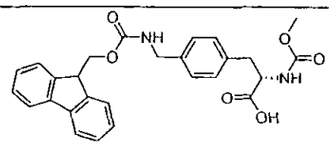
Extremo-108		LCMS: Análisis calculado para $C_{15}H_{17}N_3O_4$: 303; encontrado: 304 $(M+H)^+$.
Extremo-109		LCMS: Análisis calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.
Extremo-110		LCMS: Análisis calculado para $C_{10}H_{12}N_2O_4$: 224; encontrado: 225 $(M+H)^+$.
Extremo-111		LCMS: Análisis calculado para $C_{12}H_{16}NO_8P$: 333; encontrado: 334 $(M+H)^+$.
Extremo-112		LCMS: Análisis calculado para $C_{13}H_{14}N_2O_4$: 262; encontrado: 263 $(M+H)^+$.

Extremo-113		LCMS: Análisis calculado para $C_{18}H_{19}NO_5$: 329; encontrado: 330 $(M+H)^+$.
Extremo-114		^{1}HRMN (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}HRMN (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}HRMN (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).

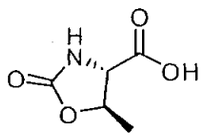
Extremo-117 hasta extremo-123

Para la preparación de los extremos -117 hasta extremo-123 los aminoácidos Boc fueron comercialmente disponibles y se desprotegieron por tratamiento con 25% TFA en CH_2Cl_2. Después de completar la reacción como se juzga por LCMS los solventes se removieron *in vacuo* y la sal TFA correspondiente del aminoácido se carbamoiló con cloroformiato de metilo de acuerdo al procedimiento para el extremo-51.

Extremo	Estructura	LCMS
Extremo-117		LCMS: Análisis calculado para $C_{12}H_{15}NO_4S$: 237; encontrado: 238 $(M+H)^+$.
Extremo-118		LCMS: Análisis calculado para $C_{10}H_{13}NO_4S$: 243; encontrado: 244 $(M+H)^+$.
Extremo-119		LCMS: Análisis calculado para $C_{10}H_{13}NO_4S$: 243; encontrado: 244 $(M+H)^+$.

Extremo-120		LCMS: Análisis calculado para $C_{10}H_{13}NO_4S$: 243; encontrado: 244 $(M+H)^+$.
Extremo-121		^{1}HRMN (400 MHz, $CDCl_3$) δ 4.06 - 4.16 (m, 1H), 3.63 (s, 3H), 3.43 (s, 1H), 2.82 y 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}HRMN (400 MHz, $CDCl_3$) δ 5.28 y 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: Análisis calculado para $C_{27}H_{26}N_2O_6$: 474; encontrado: 475 $(M+H)^+$.

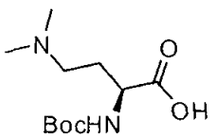
Preparación del extremo-124. Ácido (4S,5R)-5-metil-2-oxooxazolidin-4-carboxílico



Extremo-124

La sal de clorohidrato de éster de tert-butilo de L-treonina se carbamoiló de acuerdo al procedimiento para el extremo-51. La mezcla de reacción cruda se acidificó con 1N HCl hasta pH~1 y la mezcla se extrajo con EtOAc (2X50 mL). Las fases orgánicas combinadas se concentraron *in vacuo* para dar un incoloro el cual se solidifica al reposar. La capa acuosa se concentró *in vacuo* y la mezcla resultante del producto y sales inorgánicas se trituraron con EtOAc-CH_2Cl_2-MeOH (1:1:0.1) y luego la fase orgánica se concentra *in vacuo* para dar un aceite incoloro el cual se mostró por LCMS para ser el producto deseado. Ambas cosechas se combinaron para dar 0.52 g de un sólido. ^{1}HRMN (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 $(M+H)^+$.

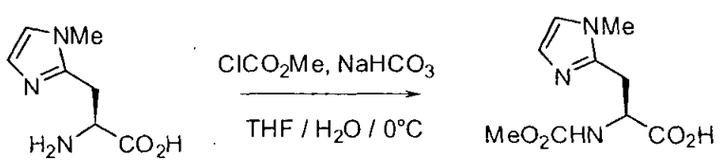
Preparación del extremo-125. Ácido (S)-2-(tert-butoxicarbonilamino)-4-(dimetilamino)butanoico.



Extremo-125

El extremo-125 se preparó de acuerdo al procedimiento para la preparación del extremo-1. El producto crudo se usó como es en reacciones posteriores. 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-*

Este procedimiento es una modificación de que se usa para preparar el extremo-51. A una suspensión de ácido (S)-2-amino-3-(1-metil-1H-imidazol-2-il)propanoico (0.80 g, 4.70 mmol) en THF (10mL) y H_2O (10 mL) a 0°C se agregó $NaHCO_3$ (0.88 g, 10.5 mmol). La mecla resultante se trató con $ClCO_2Me$ (0.40 mL, 5.20 mmol) y la mezcla se permite agitar a 0°C. Después de

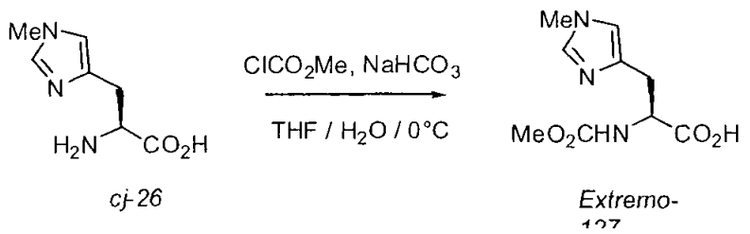
agitar durante ca. 2h LCMS no muestra material de partida restante. La reacción se hizo ácida hasta pH 2 con 6 N HCl.

Los solventes se removieron *in vacuo* y el residuo se suspendió en 20 mL de 20% MeOH en CH_2Cl_2. La mezcla se filtró y se concentra para dar una espuma amarillo ligero (1.21 g,). LCMS y ^1H RMN muestran el material para ser una mezcla 9:1 de éster de metilo y el producto deseado. Este material se colocó en THF (10mL) y H_2O (10mL), se enfría hasta 0°C y LiOH (249.1 mg, 10.4 mmol) se agregó. Después de agitar ca. 1h LCMS no muestra éster restante. Por lo tanto la mezcla se acidificó con 6N HCl y los solventes se removieron *in vacuo*. LCMS y ^1H RMN confirma 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 es en las Extremos posteriores sin purificación adicional.

^{1}HRMN (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 obscurecido por 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).



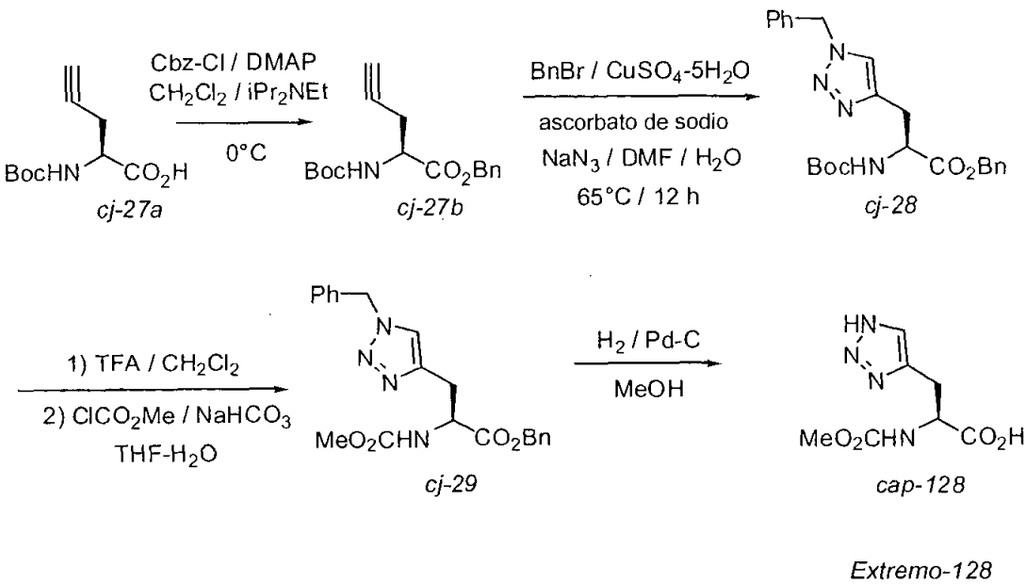
cj-26 *Extremo-127*

El extremo-127 se preparó de acuerdo al método para el extremo-126 anterior partiendo del ácido (S)-2-amino-3-(1-metil-1H-imidazol-4-il)propanoico (1.11 g, 6.56 mmol), $NaHCO_3$ (1.21 g, 14.4 mmol) y $ClCO_2Me$ (0.56 mL, 7.28 mmol). El compuesto del título se obtuvo como su sal HCl (1.79 g, >100%) contaminada con sales inorgánicas. LCMS y ^1H RMN muestran la presencia de ca. 5% del éster de metilo. La mezcla cruda se usó como es sin purificación adicional.

^{1}HRMN (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).

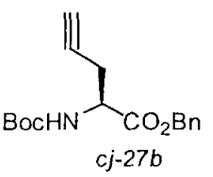
LCMS: Análisis calculado para $C_{17}H_{15}NO_2$: 392; encontrado: 393 $(M+H)^+$.

Preparación de ácido (S)-2-(metoxicarbonilamino)-3-(1H-1,2,3-triazol-4-il)propanoico (*Extremo*-128).



Extremo-128

Extremo 1. Preparación de 2-(tert-butoxicarbonilamino)pent-4-inoato de (S)-bencilo (cj-27b).

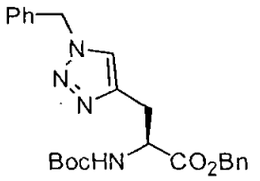


cj-27b

A una solución de cj-27a (1.01 g, 4.74 mmol), DMAP (58 mg, 0.475 mmol) y iPr_2NEt (1.7 mL, 9.8 mmol) en CH_2Cl_2 (100 mL) a 0°C se agregó Cbz-Cl (0.68 mL, 4.83 mmol). La solución se permitió agitar durante 4 h a 0°C, se lava (1N $KHSO_4$, salmuera), se seca (Na_2SO_4), se filtra y se concentra *in vacuo*. El residuo se purificó por cromatografía de columna instantánea (CCD 6:1 hex:EtOAc) para dar el compuesto del título (1.30 g,

91%) como un aceite incoloro. ^{1}HRMN (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 $(M+H)^+$.

Extremo 2. Preparación de 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(tert-butoxicarbonilamino)propanoato de (S)-bencilo (cj-28).



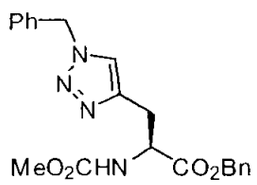
cj-28

A una mezcla de 2-(tert-butoxicarbonilamino)pent-4-inoato de (S)-bencilo (0.50 g, 1.65 mmol), ascorbato de sodio (0.036 g, 0.18 mmol), $CuSO_4$-$5H_2O$ (0.022 g, 0.09 mmol) y NaN_3 (0.13 g, 2.1 mmol) en DMF-H_2O (5 mL, 4:1) a temperatura ambiente se agregó BnBr (0.24 mL, 2.02 mmol) y la mezcla se calentó hasta 65°C. Después de 5h LCMS indica conversión inferior. Una porción adicional de NaN_3 (100 mg) se agregó y se continuó calentando durante 12h. La reacción se vació en EtOAc y H_2O y se agita. Las capas se separaron y la capa acuosa se extrajo 3x con EtOAc y las fases orgánicas combinadas se lavaron (H_2O x3, salmuera), se secaron (Na_2SO_4), se filtraron, y se concentraron. El residuo se purificó de forma instantánea (Biotage, 40+M 0-

5% MeOH en CH_2Cl_2; CCD 3% MeOH en CH_2Cl_2) para proporcionar un aceite amarillo ligero el cual se solifica al reposar (748.3 mg, 104%). La RMN fue consistente con el producto deseado pero sugiere la presencia de DMF. El material se usó como es sin purificación adicional. ^{1}HRMN (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 $(M+H)^+$.

Extremo 2. Preparación de 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(metoxicarbonilamino)propanoato de (S)-bencilo (cj-29).

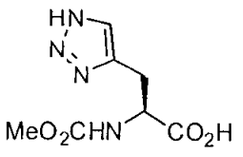


cj-29

Una solución de 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(tert-butoxicarbonilamino)propanoato de (S)-bencilo (0.52 g, 1.15 mmol) en CH_2Cl_2 se agregó TFA (4 mL). La mezcla se permitió agitar a temperatura ambiente durante 2h. La mezcla se concentró *in vacuo* para dar un aceite incoloro el cual se solidifica al reposar. Este material se disolvió en THF-H_2O y se enfría hasta 0°C. El $NaHCO_3$ sólido (0.25 g, 3.00 mmol) se agregó seguido por $ClCO_2Me$ (0.25 mL, 3.25

mmol). Después de agitar durante 1.5h la mezcla se hizo ácida hasta pH~2 con 6N HCl y luego se vacía 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 filtraron y se concentraron *in vacuo* para dar un aceite incoloro (505.8 mg, 111%, RMN sugiere la presencia de una impureza no identificada) el cual se solidifica mientras reposa en la bomba. El material se usó como es sin purificación adicional. ^{1}HRMN (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 $(M+H)^+$.

Extremo 3. Preparación de ácido (S)-2-(metoxicarbonilamino)-3-(1H-1,2,3-triazol-4-il)propanoico (*Extremo*-128).



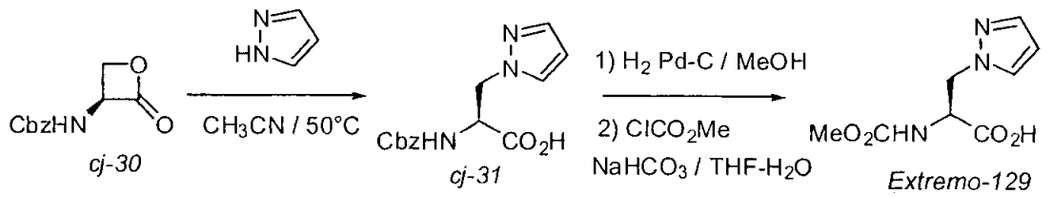
Extremo-128

El 3-(1-bencil-1H-1,2,3-triazol-4-il)-2-(metoxicarbonilamino)propanoato de (S)-bencilo (502 mg, 1.11 mmol) se hidrógeno en presencia de Pd-C (82 mg) en MeOH (5 mL) a presión atmosférica durante 12h. La mezcla se filtró a

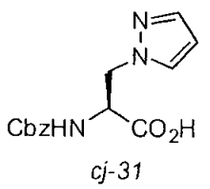
través de tierra diatomácea (Celite®) y se concentra *in vacuo*. El ácido (S)-2-(metoxicarbonilamino)-3-(1H-1,2,3-triazol-4-il)propanoico se obtuvo como una goma incolora (266 mg, 111%) la cual se contaminó con ca. 10% del éster de metilo. El material se usó como es sin purificación adicional.

^{1}HRMN (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).



Extremo 1. Preparación de ácido (S)-2-(benciloxicarbonilamino)-3-(1H-pirazol-1-il)propanoico (cj-31).



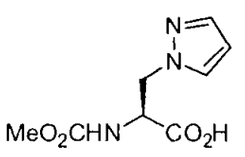
cj-31

Una suspensión de 2-oxooxetan-3-ilcarbamato de (S)-bencilo (0.67 g, 3.03 mmol), y pirazol (0.22 g, 3.29 mmol) en CH_3CN (12 mL) se calentó a 50°C durante 24h. La mezcla se enfrió hasta temperatura ambiente durante la noche y el sólido se filtra para proporcionar ácido (S)-2-(benciloxicarbonilamino)-3-(1H-pyrazol-1-il)propanoico (330.1 mg). El filtrado se concentró *in vacuo* y luego se tritura con una cantidad pequeña de CH_3CN (ca. 4 mL) para proporcionar una segunda 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}HRMN (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 $(M+H)^+$.

Extremo 2. Preparación de ácido (S)-2-(metoxicarbonilamino)-3-(1H-pirazol-1-il)propanoico (*Extremo*-129).



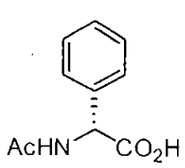
Extremo-129

El ácido (S)-2-(benciloxicarbonilamino)-3-(1H-pirazol-1-il)propanoico (0.20 g, 0.70 mmol) se hidrógeno en presencia de Pd-C (45 mg) en MeOH (5 mL) a presión atmosférica durante 2h. El producto aparente ser insoluble en MeOH, pr lo tanto

la mezcla rxn se diluyó con 5mL H_2O y unas pocas gotas de 6N HCl. La solución homogénea se filtró a través de tierra diatomácea (Celite®), y el MeOH se remueve *in vacuo*. La solución restante se congeló y se liotilizó para dar una espuma amarilla (188.9 mg). Este material se suspendió en THF-H_2O (1:1, 10mL) y luego se enfría hasta 0°C. A la mezcla fría se agregó $NaHCO_3$ (146.0 mg, 1.74 mmol) cuidadosamente (evolución de CO_2). Después la evolución de gas se cesó (ca. 15 min) $ClCO_2Me$ (0.06 mL, 0.78 mmol) se agregó gota a gota. La mezcla se permitió agitar durante 2h y se hizo ácida hasta pH~2 con 6N HCl y se vacía en EtOAc. Las capas se separaron y la fase acuosa se extrae 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%).

^{1}HRMN (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

El extremo-130 se preparó por acilación de (R)-fenilglicina comercialmente disponible análogo al procedimiento dado en: Calmes, M.; Daunis, J.; Jacquier, R.; Verducci, J. *Tetrahedron*, 1987, *43*(10), 2285.

EJEMPLOS

La presente descripción se describe en conexión con ciertas modalidades las cuales no intentan limitar su alcance. Por el contrario, la presente descripción cubre todas las alternativas, modificaciones y equivalentes como pueden incluirse dentro del alcance de las reivindicaciones. Así, los siguientes ejemplos, los cuales incluyen modalidades específicas, ilustrarán una práctica de la presente descripción, entendiéndose que los ejemplos son para los propósitos de ilustración de ciertas modalidades y se presentan para proporcionar lo que se cree que es la descripción más útil y fácil de entender de sus procedimientos y aspectos conceptuales.

Los porcentajes de la solución expresan una relación de peso a volumen y las relaciones de solución expresan una relación de volumen a volumen, al menos de que se indique de otra manera. El espectro de resonancia magnética nuclear (RMN) se registró ya sea en un espectrómetro Bruker 300, 400, o 500 MHz; los cambios químicos (δ) se reportaron en partes por millón. La cromatografía instantánea se llevó a cabo en gel de sílice (SiO_2) de conformidad a la técnica de

cromatografía instantánea de Still (*J. Org. Chem.* 1978, *43*, 2923).

El análisis de masas de baja resolución y la evaluación de pureza se llevaron a cabo en un sistema Shimadzu CL acoplado con el sistema Waters Micromass ZQ MS. Se deberá notar que el tiempo de retención puede variar ligeramente entre las máquinas. Las condiciones CL empleadas en determinar el tiempo de retención (TR) fueron:

Condición 1

Columna = Phenomenex-Luna 3.0X 50 mm S10

Inicio %B = 0

Final %B = 100

Tiempo de gradiente = 2 min

Tiempo de paro = 3 min

Relación de flujo = 4 mL/min

Longitud de onda = 220 nm

Solvente A = 0.1% TFA en 10% metanol/90%H_2O

Solvente B = 0.1% TFA en 90% metanol/10% H_2O

Condición 2

Columna = Phenomenex-Luna 4.6X50 mm S10

Inicio %B = 0

Final %B = 100

Tiempo de gradiente = 2 min

Tiempo de paro = 3 min

Relación de flujo = 5 mL/min

Longitud de onda = 220 nm

Solvente A = 0.1% TFA en 10% metanol/90%H_2O

Solvente B = 0.1% TFA en 90% metanol/10% H_2O

Condición 3

Columna = HPLC XTERRA C18 3.0 x 50mm S7

Inicio %B = 0

Final %B = 100

Tiempo de gradiente = 3 min

Tiempo de paro = 4 min

Relación de flujo = 4 mL/min

Longitud de onda = 220 nm

Solvente A = 0.1% TFA en 10% metanol/90%H_2O

Solvente B = 0.1% TFA en 90% metanol/10% H_2O

Método A: LCMS -Xterra MS C-18 3.0 x 50mm, 0 hasta 100% B durante 30.0 minutos de gradiente, 1 minuto tiempo de espera, A = 5% acetonitrilo, 95% agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% agua, 10mm acetato de amonio.

Método B: HPLC - X-Terra C-18 4.6 x 50mm, 0 hasta 100% B durante 10.0 minutos de gradiente, 1 minuto tiempo de espera, A = 10% metanol 90% agua 0.1% TFA, B = 90% metanol 10% agua 0.1% TFA.

Método C: HPLC - YMC C-18 4.6 x 50mm, 0 hasta 100% B durante 10.0 minutos de gradiente, 1 minuto tiempo de espera, A = 10% metanol 90% agua 0.2% H_3PO_4, B = 90% metanol 10% agua

0.2% H_3PO_4.

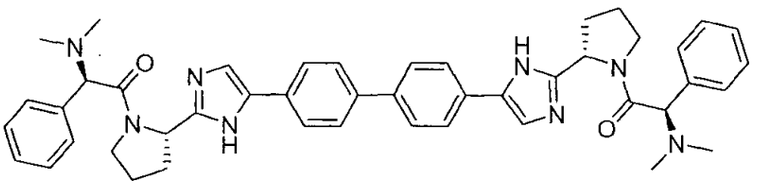
Método D: HPLC - Phenomenex C-18 4.6 x 150mm, 0 hasta 100% B durante 10.0 minutos de gradiente, 1 minuto tiempo de espera, A = 10% metanol 90% agua 0.2% H_3PO_4, B = 90% metanol 10% agua 0.2% H_3PO_4.

Método E: LCMS - Gemini C-18 4.6 x 50mm, 0 hasta 100% B durante 10.0 minutos de gradiente, 1 minuto tiempo de espera, A = 5% acetonitrilo, 95% agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% agua, 10mm acetato de amonio.

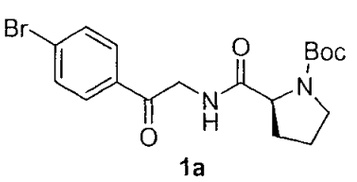
Método F: LCMS-Luna C-18 3.0 x 50mm, 0 hasta 100% B durante 7.0 minutos de gradiente, 1 minuto tiempo de espera, A = 5% acetonitrilo, 95% agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% agua, 10mm acetato de amonio.

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)



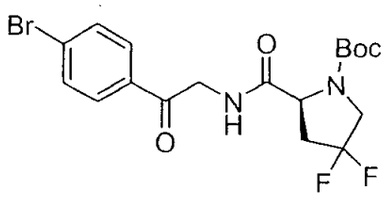
Ejemplo 1, Extremo a



1a

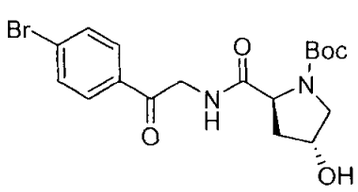
La *N,N*-Diisopropiletilamina (18 mL, 103.3 mmol) se agregó gota a gota, durante 15 minutos, a una mezcla heterogénea de *N*-Boc-L-prolina (7.139 g, 33.17 mmol), HATU (13.324 g, 35.04 mmol), la sal HCl de la 2-amino-1-(4-bromofenil)etanona (8.127 g, 32.44 mmol), y DMF (105 mL), y se agitó a condiciones ambientales durante 55 minutos. La mayoría del componente volátil se removió *in vacuo*, 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 *in vacuo*. Una malla de gel de sílice se preparó a partir del residuo y se sometió a cromatografía instantánea (gel de sílice; 50-60 % acetato de etilo/hexanos) para proporcionar la cetoamida 1a como un sólido blanco (12.8 g). ^{1}H 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). CL (Cond. I): TR = 1.70 min; LC/MS: Análisis calculado para $[M+Na]^+$ $C_{18}H_{23}BrN_2NaO_4$: 433.07; encontrado 433.09.

Los compuestos análogos tales como el intermediario 1-1a hasta 1-5a pueden prepararse por incorporar el aminoácido apropiadamente substituido y el isómero de bromuro de arilo.



1-1a

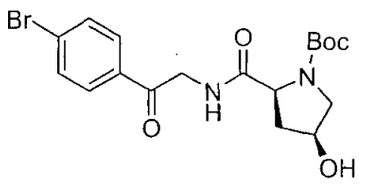
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.35/1.40 (dos br s, 9H), 2.27-2.42 (m, 1H), 2.73-2.95 (m, 1H), 3.62-3.89 (m, 2H), 4.36-4.50 (m, 1H), 4.51-4.60 (m, 1H), 4.62-4.73 (m, 1H), 7.75 (d, *J*=8.24 Hz, 2H), 7.92 (d, *J*=7.63 Hz, 2H), 8.31-8.49 (m, 1H). HPLC XTERRA C-18 4.6 x 30 mm, 0 hasta 100% B durante 4 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% H_3PO_4, B = 10% agua, 90% metanol, 0.2% H_3PO_4, TR = 1.59 minutos, 99% índice de homogeneidad. LCMS: Análisis calculado para $C_{18}H_{21}BrF_2N_2O_4$: 446.06; encontrado: 445.43 $(M-H)^+$.



1-2a

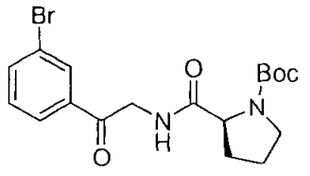
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm (8.25 1H, s), 7.91 (2H, d, *J*=8.24Hz), 7.75 (2H, d, *J*=8.24 Hz), 4.98 (1H, s), 4.59-4.63 (1H, m), 4.46-4.52 (1H, m), 4.23 (1H, m), 3.37 (1H, s), 3.23-3.28 (1H, m), 2.06 (1H, m), 1.88 (1H, s), 1.38 (3H, s), 1.33 (6H, s). LCMS - Phenomenex C-18 3.0 x 50mm, 0 hasta 100% B durante 4.0 minutos de gradiente, 1

minuto tiempo de espera, A = 10% metanol 90% agua 0.1% TFA, B = 90% metanol 10% agua 0.1% Fase móvil de TFA, TR = 3.34 minutos, Anal Calculado para $C_{18}H_{23}BrN_2O_5$ 427.30; encontrado 428.08 $(M+H)^+$.



1-3a

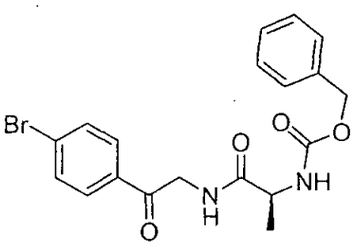
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.30 (1H, s) 7.93-7.96 (2H, m) 7.76 (2H d, *J*=8.24 Hz) 5.13 (1H, s) 4.66-4.71 (1H, m) 4.52-4.55 (1H, m) 4.17 (1H, m) 3.51 (1H, s) 3.16-3.19 (1H, m) 2.36 (1H, m) 1.78 (1H, s) 1.40 (s, 3H), 1.34 (s, 6H). LCMS - Phenomenex C-18 3.0 x 50mm, 0 hasta 100% B durante 4.0 minutos de gradiente, 1 minuto tiempo de espera, A = 10% metanol 90% agua 0.1% TFA, B = 90% metanol 10% agua 0.1% TFA, RT= 3.69 minutos, Anal Calculado para $C_{18}H_{23}BrN_2O_5$ 427.30; encontrado 428.16 $(M+H)^+$.



1-4a

^{1}H 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),

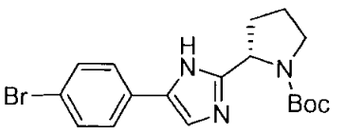
7.86 (dd, *J*=7.93, 1.22 Hz, 1H), 7.98 (d, *J*=7.63 Hz, 1H), 8.11 (s, 1H), 8.15-8.29 (m, 1H). LC/MS $(M+Na)^+$ = 433.12/435.12.



1-5a

Condiciones LCMS: Phenomenex LUNA C-18 4.6 x 50 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección. TR = 1.93 min; HRMS: Análisis calculado para $C_{19}H_{18}BrN_2O_4$ 418.05; encontrado: 419.07 $(M+H)^+$.

Ejemplo 1, Extremo b



1b

Una mezcla de cetoamida 1a (12.8 g, 31.12 mmol) y NH_4OAc (12.0 g, 155.7 mmol) en xilenos (155 mL) se calentó en un tubo sellado a 140°C durante 2 horas. El componente volátil se removió *in vacuo*, y el residuo se dividió cuidadosamente entre acetato de etilo y agua, por ello la solución de $NaHCO_3$ suficientemente saturada se agregó para hacer el pH de la fase acuosa ligeramente básica después de la agitación del sistema bifásico. Las capas se separaron, y la capa

acuosa se extrajo con un acetato de etilo adicional. La fase orgánica combinada se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró *in vacuo*. El material resultante se recristalizó a partir del acetato de etilo/hexanos para proporcionar dos cultivos de Imidazol 1b como un sólido denso amarillo ligero, que pesa 5.85 g. El licor madre se concentró *in vacuo* y se sometió a una cromatografía instantánea (gel de sílice; 30% acetato de etilo/hexanos) para proporcionar 2.23 g adicional 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). CL (Cond. Ib): TR = 1.71 min; >98% 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 de 1b se midió usando las condiciones HPLC quiral notadas a continuación (ee > 99% para los cultivos combinados; ee = 96.7% por la muestra de cromatografía instantánea):

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

Solvente: 2% etanol/heptano (isocrático)

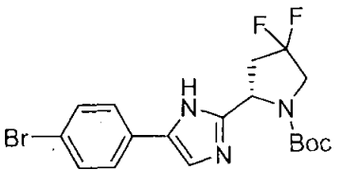
Relación de flujo: 1 mL/min

Longitud de onda: ya sea 220 ó 254 nm

Tiempo de retención relativa: 2.83 minutos (*R*), 5.34 minutos (*S*)

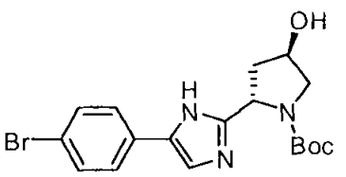
Los compuestos análogos tales como el intermediario 1-1b

hasta 1-4b pueden prepararse por incorporar la cetoamida apropiada:



1-1b

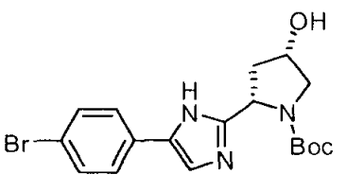
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.17/1.40 (dos br s, 9H), 2.50-2.74 (m, *J*=25.64 Hz, 1H), 2.84-3.07 (m, 1H), 3.88 (d, *J*=10.07 Hz, 2H), 5.03 (s, 1H), 7.50 (d, *J*=8.55 Hz, 2H), 7.60 (s, 1H), 7.70 (d, *J*=8.55 Hz, 2H), 12.10 (s, 1H). HPLC XTERRA C-18 4.6 × 30 mm, 0 hasta 100% B durante 4 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% H_3PO_4, B = 10% agua, 90% metanol, 0.2% H_3PO_4, TR = 1.59 minutos, 99% índice de homogeneidad; LCMS: Análisis calculado para $C_{18}H_{20}BrF_2N_3O_2$: 428.27; encontrado: 428.02 $(M)^+$.



1-2b

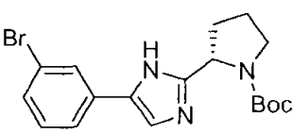
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 11.89-11.99 (1H, m), 7.68 (2H, d, *J*=8.54 Hz), 7.52-7.59 (1H, m), 7.48 (2H, d, *J*=8.54 Hz), 4.80 (1H, m), 4.33 (1H, s), 3.51-3.60 (1H, m), 3.34 (1H, d, *J*=10.99 Hz), 2.14 (1H, s), 1.97-2.05 (1H, m), 1.37 (3H, s), 1.10 (6H, s); LCMS - Phenomenex

C-18 3.0 x 50mm, 0 hasta 100% B durante 4.0 minutos de gradiente, 1 minuto tiempo de espera, A = 10% metanol 90% agua 0.1% TFA, B = 90% metanol 10% agua 0.1% TFA, (RT= 3.23 min) Anal 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 50mm, 0 hasta 100% B durante 4.0 minutos de gradiente, 1 minuto tiempo de espera, A = 10% metanol 90% agua 0.1% TFA, B = 90% metanol 10% agua 0.1% TFA, (RT= 3.41 min) Anal Calculado para $C_{18}H_{22}BrN_3O_3$ 408.30; encontrado 409.15 $(M+H)^+$.



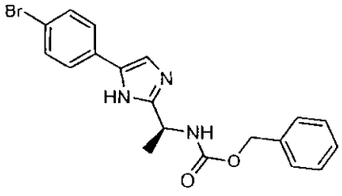
1-4b

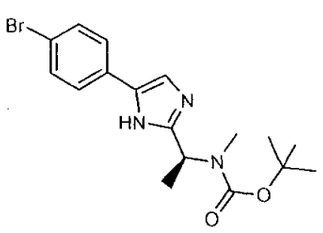
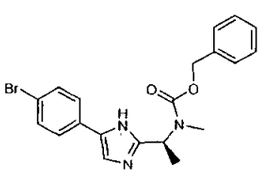
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 0.98-1.51 (m, 9H), 1.82-2.12 (m, 3H), 2.31-2.48 (m, 1H), 3.30-3.51 (m, 1H), 3.52-3.66 (m, 1H), 4.88-5.16 (m, 1H), 7.47 (t, *J*=7.93 Hz, 1H),

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.

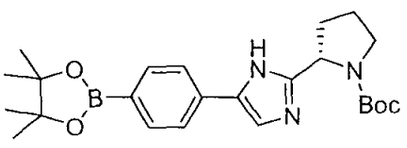
Los análogos de imidazol adicionales se hacen siguiendo los procedimientos similares a aquellos descritos arriba.

Condiciones CL: *Condición 1:* Phenomenex LUNA C-18 4.6 x 50 mm, 0 hasta 100% B durante 3 minutos, 1 minutos tiempo de espera, A = 90% de agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220 nm, 5 µL volumen de inyección. *Condición 2:* Phenomenex LUNA C-18 4.6 x 50 mm, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220 nm, 5 µL volumen de inyección.

Ejemplo	**Estructura**	**Dato**
1-5b		TR = 1.70 minutos (condición 2, 98%); HRMS: Análisis calculado para $C_{19}H_{18}BrN_3O_2$ 399.05; encontrado 400.08 $(M+H)^+$.

1-6b		TR = 1.64 minutos (condición 2, 98%); HRMS: Análisis calculado para $C_{17}H_{22}N_3O_2$ 379.09; encontrado 380.06 $(M+H)^+$.
1-7b		TR = 2.28 minutos (95%); LCMS: Análisis calculado para $C_{20}H_{21}BrN_3O_2$ 414.08; encontrado 414.08 $(M+H)^+$; HRMS: Análisis calculado para $C_{20}H_{21}BrN_3O_2$ 414.0817; encontrado 414.0798 $(M+H)^+$.

Ejemplo 1, Extremo c

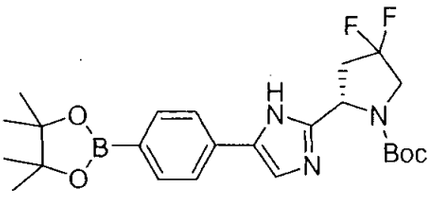


1c

El $Pd(Ph_3P)_4$ (469 mg, 0.406 mmol) se agregó a un tubo a presión que contiene una mezcla de bromuro 1b (4.008 g, 10.22 mmol), bis(pinacolato)diboro (5.422 g, 21.35 mmol), acetato de potasio (2.573g, 26.21 mmol) y 1,4-dioxano (80

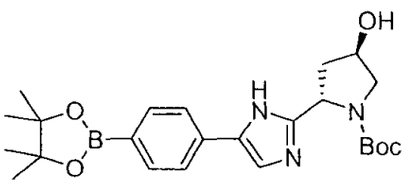
mL). El matraz de reacción se purgo con nitrógeno, se tapó y se calentó con un baño de aceite a 80°C durante 16.5 horas. La mezcla de reacción se filtró y el filtrado se concentró *in vacuo*. El material crudo se dividió cuidadosamente entre CH_2Cl_2 (150 mL) y un medio acuoso (50 mL agua + 10 mL solución de $NaHCO_3$ saturada). La capa acuosa se extrajo con CH_2Cl_2, y la fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró *in vacuo*. El material resultante se purificó con cromatografía instantánea (la muestra se cargó con solvente eluido; 20-35% acetato de etilo/CH_2Cl_2) para proporcionar el boronato 1c, contaminado con pinacol, como un sólido denso blanco opaco; el intervalo de mol relativo de 1c hasta pinacol fue alrededor de 10:1 (^1H RMN). La muestra pesa 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). CL (Cond. I): TR = 1.64 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{24}H_{35}BN_3O_4$: 440.27; encontrado 440.23.

Los compuestos análogos tales como el intermediario 1-1c hasta 1-4c pueden prepararse por incorporar el bromuro de arilo apropiado.



1-1c

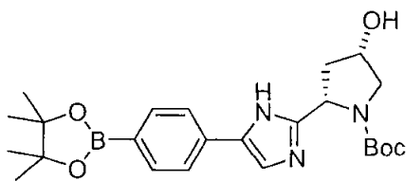
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.16 (s, 8H), 1.29 (s, 13H), 2.51-2.72 (m, 1H), 2.84-3.03 (m, 1H), 3.79-4.00 (m, 2H), 4.88-5.21 (m, 1H), 7.62 (d, *J*=7.93 Hz, 2H), 7.67 (s, 1H), 7.76 (d, *J*=7.93 Hz, 2H), 12.11/12.40 (dos br s, 1H). HPLC GEMINI C-18 4.6 x 50 mm, 0 hasta 100% B durante 4 minutos, 1 minuto tiempo de espera, A = 95% agua, 5% acetonitrilo, 0.1% NH_4OAc, B = 5% agua, 95% acetonitrilo, 0.1% NH_4OAc, TR = 1.62 minutos, 99% índice de homogeneidad. LCMS: Análisis calculado para $C_{34}H_{32}BF_2N_3O_4$: 475.34; encontrado: 474.78$(M-H)^+$.



1-2c

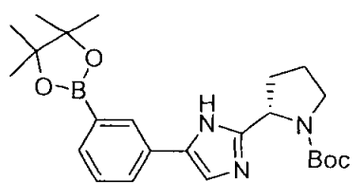
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 11.97 (1H, m), 7.62-7.75 (5H, m), 5.05 (1H d, *J*=3.36 Hz), 4.82 (m, 1H), 4.35 (m, 1H), 3.58 (1H, m), 2.389 (1H, s), 2.17 (1 H, m), 1.38 (3H, s), 1.30 (12H, s), 1.1 (6H, s); LCMS -

Phenomenex C-18 3.0 x 50mm, 0 hasta 100% B durante 4.0 minutos de gradiente, 1 minuto tiempo de espera, A = 5% acetonitrilo, 95% agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% agua, 10mm acetato de amonio, RT= 3.63 minutos, Análisis 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 50mm, 0 hasta 100% B durante 4.0 minutos de gradiente, 1 minuto tiempo de espera, A = 10% metanol 90% agua 0.1% TFA, B = 90% metanol 10% agua 0.1% TFA, RT= 3.64 minutos, Análisis calculado para $C_{24}H_{34}BN_3O_5$ 455.30; encontrado 456.30 $(M+H)^+$.



1-4c

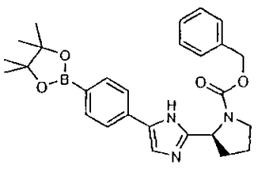
^1H RMN (500 MHz, DMSO-d_6) δ ppm 1.02-1.54 (m, 21H),

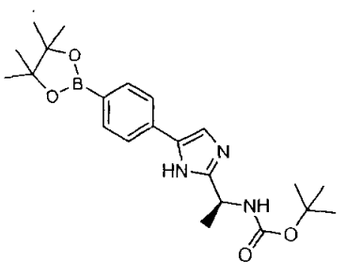
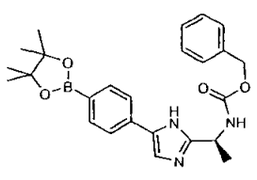
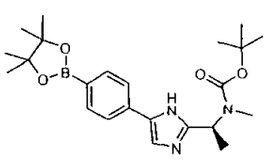
1.75-2.07 (m, 3H), 2.09-2.33 (m, 1H), 3.32-3.44 (m, 1H), 3.55 (s, 1H), 4.69-4.94 (m, 1H), 7.33 (t, *J*=7.32 Hz, 1H), 7.41-7.57 (m, 2H), 7.84 (d, *J*=7.32 Hz, 1H), 8.08 (s, 1H), 11.62-12.07 (m, 1H). LC/MS $(M+H)^+$ = 440.32.

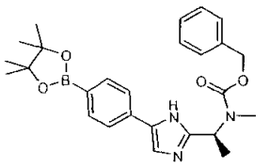
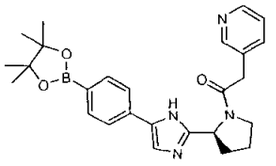
Esteres borónicos adicionales: Condiciones para 1-5c hasta 1-10c

Condiciones LCMS: Phenomenex LUNA C-18 4.6 x 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

Condiciones LCMS (Condición 2): Phenomenex LUNA C-18 4.6 x 50 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

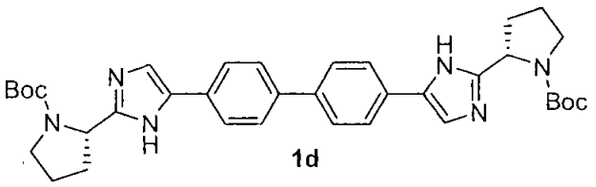
1-5c		TR = 1.84 minutos (condición 2); LCMS: Análisis calculado para $C_{27}H_{32}BN_3O_4$ 473; encontrado: 474 $(M+H)^+$.

1-6c		TR = 1.84 minutos (condición 2); LCMS: Análisis calculado para $C_{22}H_{32}BN_3O_4$ 413; encontrado: 414 $(M+H)^+$.
1-7c		TR = 1.85 minutos (condición 2); LCMS: Análisis calculado para $C_{25}H_{31}BN_3O_4$ 448; encontrado: 448 $(M+H)^+$.
1-8c		TR = 2.49 (76%, éster borónico) y 1.81 (21.4%, ácido borónico); LCMS: Análisis calculado para $C_{23}H_{35}N_3O_4B$ 428.27; encontrado: 428.27 $(M+H)^+$; HRMS: Análisis calculado para $C_{23}H_{35}N_3O_4B$ 428.2721; encontrado: 428.2716 $(M+H)^+$.

1-9c		TR = 2.54 (74.2%, éster borónico) y 1.93 (25.8%, ácido borónico); LCMS: Análisis calculado para $C_{26}H_{33}N_3O_4B$ 462.26; encontrado: 462.25 $(M+H)^+$; HRMS: Análisis calculado para $C_{26}H_{33}N_3O_4B$ 462.2564; encontrado: 462.2570 $(M+H)^+$.
1-10c		TR = 1.91 (64.5 %, éster borónico) y 1.02 (33.8 %, ácido borónico); LCMS: Análisis calculado para $C_{26}H_{32}N_4O_3{}^{10}B$ 458.26; encontrado: 458.28 $(M+H)^+$; HRMS: Análisis calculado para $C_{26}H_{32}N_4O_3{}^{10}B$ 458.2604; encontrado: 458.2617 $(M+H)^+$.

Ejemplo 1, Extremo d

(2S,2'S)-2,2'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil))di(1-pirrolidincarboxilato) de di-tert-butilo

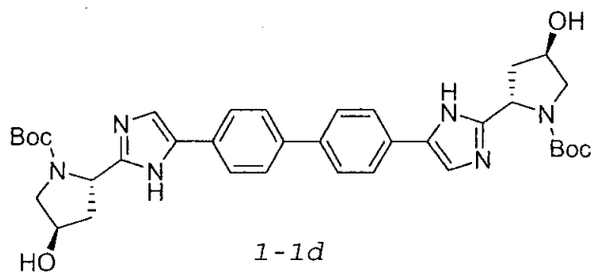


1d

El $Pd(Ph_3P)_4$ (59.9 mg, 0.0518 mmol) se agregó a una mezcla de bromuro 1b (576.1 mg, 1.469 mmol), boronato 1c (621.8 mg, 1.415 mmol), $NaHCO_3$ (400.4 mg, 4.766 mmol) en 1,2-dimetoxietano (12 mL) y agua (4 mL). La mezcla de reacción se mojó con nitrógeno, se calentó con un baño de aceite a 80°C durante 5.75 horas, y luego el componente volátil se removió *in vacuo*. El residuo se dividió entre 20% metanol/ $CHCl_3$ (60 mL) y agua (30 mL), y la fase acuosa se extrajo con 20% metanol/$CHCl_3$ (30 mL). La fase orgánica combinada se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró *in vacuo*. Una malla de gel de sílice se preparó a partir del material crudo resultante y se sometió a cromatografía instantánea (acetato de etilo) para proporcionar el dímero 1d, contaminado con Ph_3PO, como un sólido blanco opaco (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). CL (Cond. Ib): TR

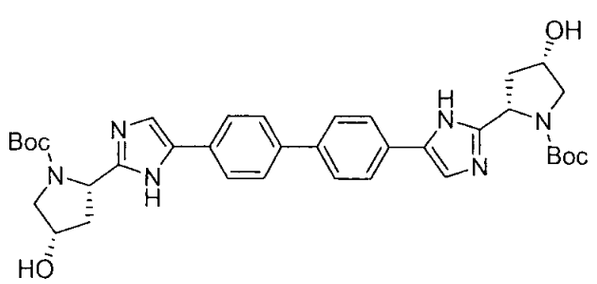
= 1.77 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{36}H_{45}BN_6O_4$: 625.35; encontrado 625.48.

Los análogos simétricos adicionales pueden prepararse en una manera similar.



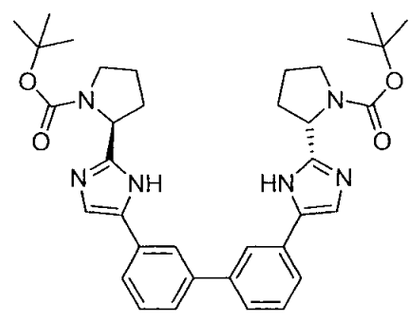
1-1d

El ejemplo 1-1d se preparó usando los intermediarios 1-2c y 1-2b. ^1H RMN (500 MHz, DMSO-d_6) δ ppm 11.94-12.22 (2H, m) 7.53-7.82 (10H, m) 4.82-4.92 (2 H, m) 4.34-4.43 (2 H, m) 3.55-3.64 (2 H, m) 3.36 (2 H, d, *J*=11.29 Hz) 2.12-2.22 (2 H, m) 2.02-2.11 (2 H, m) 1.40 (6 H, s) 1.14 (12 H, s); LCMS - Phenomenex C-18 3.0 x 50mm, 0 hasta 100% B durante 4.0 minutos de gradiente, 1 minuto tiempo de espera, A = 10% metanol 90% agua 0.1% TFA, B = 90% metanol 10% agua 0.1% TFA, RT= 3.32min, Análisis calculado para 656.79; encontrado 657.40 $(M+H)^+$. Nominal/HRMS - $(M+H)^+$-657.42, $(M-H)^-$-655.28.



1-2d

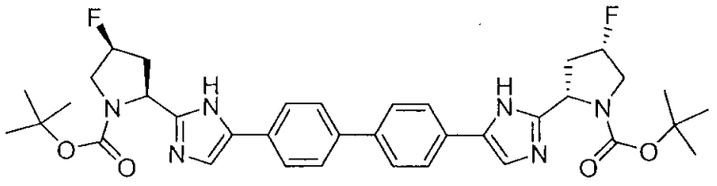
El ejemplo 1-2d se preparó usando los intermediarios 1-3b y 1-3c. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 12.00-12.20 (2H, m) 7.56-7.76 (10H, m) 4.90 (1H, s) 4.82 (1H, s) 4.25-4.34 (2H, m) 3.56 (2H, s) 3.34-3.47 (2H, m) 1.97-2.13 (4H, m) 1.39 (9H, m) 1.20 (9H, s); LCMS - Phenomenex C-18 3.0 x 50mm, 0 hasta 100% B durante 4.0 minutos de gradiente, 1 minuto tiempo de espera, A = 10% metanol 90% agua 0.1% TFA, B = 90% metanol 10% agua 0.1% TFA; TR = 3.35min, Análisis calculado para 656.79; encontrado 657.30 $(M+H)^+$.



1-2d-1

(2S)-2-(4-(3'-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-3-bifenilil)-1H-imidazol-2-il)-1-pirrolidincarboxilado de tert-butilo

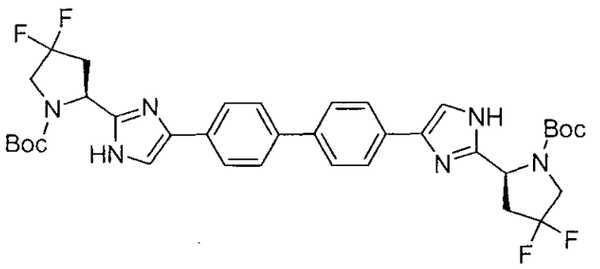
El ejemplo 1-2d-1 se preparó usando los intermediarios 1-4c y 1-4b. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.09-1.51 (m, 18H), 1.84-2.15 (m, 6H), 2.34-2.50 (m, 2H), 3.35-3.52 (m, 2H), 3.54-3.67 (m, 2H), 5.08 (d, *J*=5.49 Hz, 2H), 7.68 (t, *J*=7.78 Hz, 2H), 7.78-7.92 (m, 4H), 8.11-8.30 (m, 4H), 14.81 (s, 2H). LC/MS $(M+H)^+$ = 625.48.



1-2d-2

El diol 1-1d (0.15g, 0.23mmol) se agregó como un sólido a una solución de trifluoruro de bis(2-metoxietilo)aminoazufre (0.1mL, 0.51mmol) en 1.0mL de CH_2Cl_2 frío a -78°C. La reacción se agitó a -78°C durante dos horas y luego se calentó a temperatura ambiente y se agitó durante 2 horas. La reacción se vació en una solución de bicarbonato de sodio saturado y se agitó hasta que el burbujeo cesó. Las capas se separaron y la capa acuosa se extrajo una vez con CH_2Cl_2. Los orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron para dar un aceite amarillo. El aceite se trituró con CH_2Cl_2 y pentano para proporcionar el producto deseado como un sólido color canela (0.092g, 61%). ^1H RMN (500 MHz, DMSO-d_6) δ ppm 11.76-11.94 (2H, m), 7.77 - 7.85 (4 H, m), 7.66 - 7.72 (4 H, m), 7.60 - 7.66 (2 H, m, *J*=11.60 Hz), 5.39 (1 H, s), 5.28 (1 H, s), 5.03 (2 H, s), 3.66 - 3.79 (4 H, m), 2.61 - 2.70 (2 H, m), 2.28 - 2.38 (2 H, m), 1.42 (10 H, s), 1.24 (8 H, s). LCMS - Phenomenex C-18 3.0 x 50mm, 0 hasta 100% B durante 4.0 minutos de gradiente, 1 minuto tiempo de espera, A = 10% metanol 90% agua 0.1% TFA, B = 90% metanol 10% agua 0.1% TFA, (t_R= 3.58 min) Análisis calculado para $C_{36}H_{42}F_2N_6O_4$ 660.70;

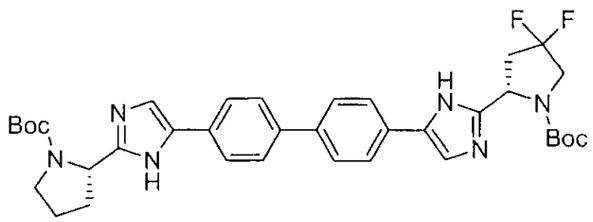
encontrado 661.68 $(M+H)^+$.



1-2d-3

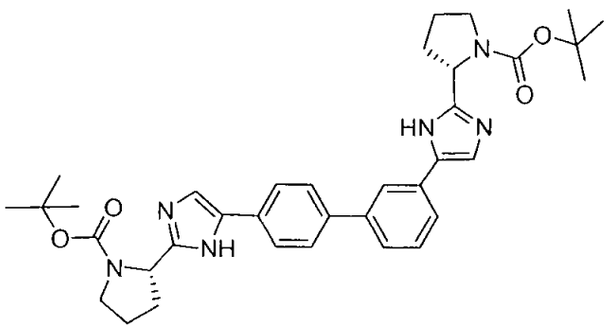
La preparación del 1-1b y 1-1c es en la misma manera como la preparación de 1d a partir de 1b y 1c. ^1H RMN (500 MHz, DMSO-d_6) δ ppm 1.18/1.40 (dos br. s., 18H), 2.53 - 2.75 (m, *J*=25.94 Hz, 2H), 2.86 - 3.06 (m, 2H), 3.78 - 4.02 (m, 4H), 5.04 (br s, 2H), 7.17 - 8.24 (m, 10H), 12.07/12.37 (dos br. s., 2H); HPLC XTERRA C-18 3.0 × 50 mm, 0 hasta 100% B durante 2 minutos, 1 minutos tiempo de espera, A = 90% agua, 10% metanol, 0.2% H_3PO_4, B = 10% agua, 90% metanol, 0.2% H_3PO_4, TR = 1.31 min, 99% índice de homogeneidad. LCMS: Análisis calculado para $C_{36}H_{40}F_4N_6O_4$: 696.73; encontrado: 967.64 $(M+H)^+$.

Los compuestos disimétricos tales como el intermediario 1-3d y 1-4d pueden prepararse por el mismo método. Por ejemplo, la reacción de 1-1c con 1b en la misma manera como se describe arriba para la preparación del 1d proporcionó el 1-3d. Similarmente, la reacción de 1-4c con 1b en la misma manera como se describe arriba para la preparación del 1d proporcionó el 1-4d.



1-3d

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.40/1.18 (dos br s, 18H), 1.90-2.02 (m, 2H), 2.02-2.12 (m, 1H), 2.28-2.46 (m, 2H), 2.68-2.87 (m, 1H), 3.35-3.49 (m, 1H), 3.53-3.62 (m, 1H), 3.82-4.10 (m, 2H), 4.92-5.11 (m, 1H), 5.28 (s, 1H), 7.79-8.00 (m, 8H), 8.03-8.25 (m, 2H), 13.77-15.16 (m, 2H); HPLC XTERRA C-18 3.0 x 50 mm, 0 hasta 100% B durante 4 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% H_3PO_4, B = 10% agua, 90% metanol, 0.2% H_3PO_4, TR = 1.22 minutos, 99% índice de homogeneidad. LCMS: Análisis calculado para $C_{36}H_{42}F_2N_6O_4$: 660.75; encontrado: 661.98 $(M+H)^+$.



1-4d

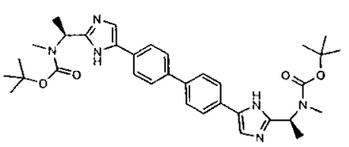
El ejemplo 1-4d se preparó a partir de 1-4c y 1b en una manera similar a la preparación de 1d a partir de 1b y 1c. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 0.99 -

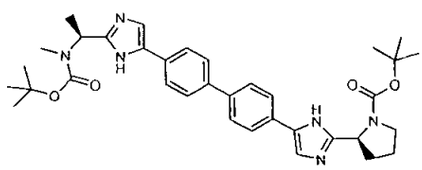
1.60 (m, 18 H) 1.75 - 2.11 (m, *J*=73.24 Hz, 6 H) 2.12 - 2.32 (m, 2 H) 3.32 - 3.41 (m, 2 H) 3.56 (s, 2 H) 4.63 - 5.02 (m, 2 H) 6.98 - 8.28 (m, 10 H) 11.67 - 12.33 (m, 2 H); condiciones CL: Phenomenex Luna 3.0 X 5.0mm S10, Solvente A - 0.1% TFA en 10% MeOH/90%H_2O, Solvente B - 0.1% TFA en 90% MeOH/10% H_2O, 0 hasta 100% B durante 2min, Tiempo de paro = 3min, Relación de flujo = 4ml/min, Longitud de onda = 220nm, LC/MS $(M+H)^+$ = 625.32. Tiempo de retención = 1.438 min

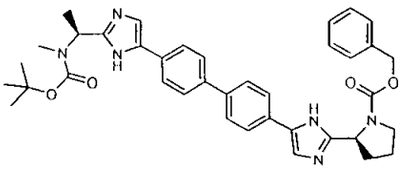
Los análogos de bifenilo adicionales se prepararon similarmente.

Condiciones CL para ejemplos 1-5d hasta 1-7d: *Condición 1*: Phenomenex LUNA C-18 4.6 x 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

Condición 2: Phenomenex LUNA C-18 4.6 x 50 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

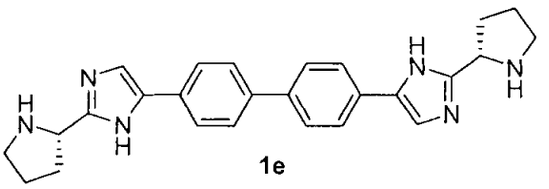
Ejemplo	*Nombre del compuesto*	*Estructura*	*Datos de caracterización*
1-5d	(4,4'-bifenildiilbis (1H-imidazol-5,2-diil(1S)-1,1-etandiil))bis (metilcarbamato) de di-tert-butilo	 Preparado a partir de **1-8c** y **1-6b**	TR = 1.64 minutos (>95%); LCMS: Análisis calculado $C_{34}H_{45}N_6O_4$ 601.35; encontrado: 601.48 $(M+H)^+$; HRMS: Análisis calculado para $C_{34}H_{44}N_6O_4$ 600.34; encontrado: 601.32 $(M+H)^+$.

1-6d	(2S)-2-(5-(4'-(2-((1S)-1-((tert-butoxicarbonil)(metil)amino)etil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidin carboxilato de tert-butilo	 Preparado a partir de **1-8c** y **1b**	TR = 1.63 minutos (>95%); LCMS: Análisis calculado $C_{35}H_{45}N_6O_4$ 613.34; encontrado: 613.56 $(M+H)^+$; HRMS: Análisis calculado para $C_{35}H_{44}N_6O_4$ 612.34; encontrado: 613.33 $(M+H)^+$.

1-7d	(2S)-2-(5-(4'-(2-((1S)-1-((tert-butoxicarbonil)(metil)amino)etil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidin carboxilato de bencilo	 Preparado a partir de **1-6b** y **1-5c**	TR = 1.65 minutos (>95%); LCMS: Análisis calculado $C_{38}H_{43}N_6O_4$ 647.33; encontrado: 647.44 $(M+H)^+$; HRMS: Análisis calculado para $C_{38}H_{42}N_6O_4$ 646.33; encontrado: 647.34 $(M+H)^+$.

Ejemplo 1, Extremo e

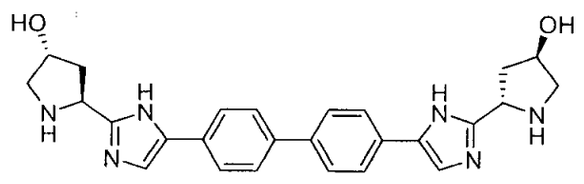
5,5'-(4,4'-bifenildiil)bis(2-((2S)-2-pirrolidinil)-1H-imidazol



1e

Una mezcla de carbamato 1d (560 mg) y 25% TFA/CH_2Cl_2 (9.0 mL) se agitó a condiciones ambientales durante 3.2 horas. El componente volátil se removió *in vacuo*, y el material resultante se congeló usando una columna MCX (lavado con metanol; 2.0 M NH_3/elución de metanol) para proporcionar pirrolidina 1e como un sólido amarillo opaco (340 mg). ^1H 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). CL (Cond. Ib): TR = 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

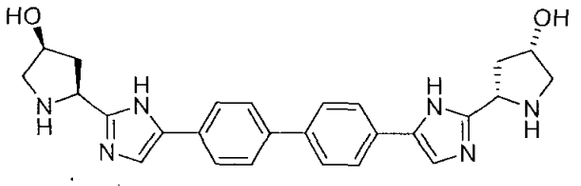
Los análogos adicionales tales como 1-1e hasta 1-4e pueden prepararse en una manera similar.



· 4 HCl

1-1e

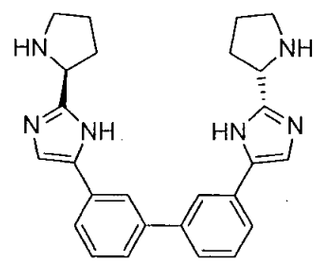
A una solución de 1-1d 5,5'-(5,5'-(bifenil-4,4'-diil)bis(1H-Imidazol-5,2-diil))bis(3-hidroxipirrolidina-1-carboxilato) de (3R,3'R,5S,5'S)-tert-butilo en 3mL dioxano se agregó 0.8mL de una solución 4.0 M de HCl en dioxano. La reacción se agitó durante 2 horas a temperatura ambiente y se concentró bajo presión reducida. El sólido color canela resultante se secó bajo vacío para dar 1-1e tetraclorohidrato de (3R,3'R,5S,5'S)-5,5'-(5,5'-(bifenil-4,4'-diil)bis(1H-Imidazol-5,2-diil))dipirrolidin-3-ol (0.55g, 100% de rendimiento). Se usó sin purificación adicional. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 10.33 (s, 2H), 9.85 (s, 2H), 8.09 (s, 2H), 8.01 (d, *J*=8.24 Hz, 4H), 7.88 (d, *J*=8.24 Hz, 4H), 5.14 (m, 2H), 4.62 (m, 2H), 3.61 (m, 2H), 3.23 (d, *J*=11.29 Hz, 2H), 2.64 (m, 2H), 2.44 (dd, *J*=13.43, 6.71 Hz, 2H); LCMS - Aguas-Sunfire C-18 4.6 x 50mm, 0 hasta 100% B durante 4.0 minutos de gradiente, 1 minuto tiempo de espera, A = 10% metanol 90% agua 0.1% TFA, B = 90% metanol 10% agua 0.1% TFA, TR = 1.35 minutos Análisis calculado para 456.30; encontrado 457.25 $(M+H)^+$; Nominal/HRMS - $(M+H)^+$ 457.35.



· 4 HCl

1-2e

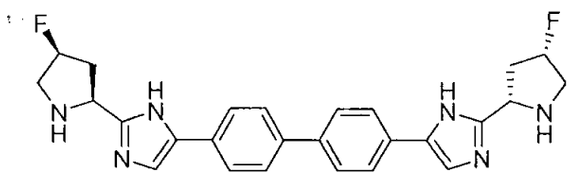
El ejemplo 1-2e se preparó en una manera similar al método descrito por la preparación del 1-1e. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 10.32 (1 H, s) 8.01 (2 H, s) 7.97 (4 H, d, *J*=8.24 Hz) 7.86 (4 H, d, *J*=8.24 Hz) 5.01-5.10 (2 H, m) 4.52-4.60 (2 H, m) 3.36-3.45 (2 H, m) 3.25 (2 H, s) 2.60-2.68 (2 H, m) 2.40-2.48 (2 H, m); LCMS - Phenomenex C-18 3.0 x 50mm, 0 hasta 100% B durante 4.0 minutos de gradiente, 1 minuto tiempo de espera, A = 10% metanol 90% agua 0.1% TFA, B = 90% metanol 10% agua 0.1% TFA, TR = 2.10min., Análisis calculado para 456.30; encontrado 457.22 $(M+H)^+$



1-2e-1

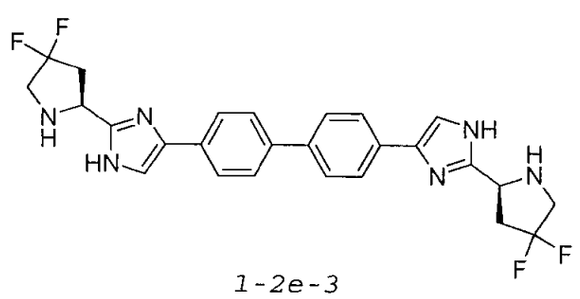
2-((2S)-2-pirrolidinil)-4-(3'-(2-((2S)-2-pirrolidinil)-1H-imidazol-5-il)-3-bifenilil)-1H-imidazol

El ejemplo 1-2e-1 se preparó a partir de 1-2d-1 en una manera similar descrita por la preparación de 1-1e. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.74-2.44 (m, 12H), 4.83 (s, 2H), 7.37-7.72 (m, 4H), 7.74-8.03 (m, 4H), 8.10 (s, 2H), 9.14 (s, 2H), 9.81 (s, 2H). LC/MS $(M+H)^+$ = 425.30.



1-2e-2

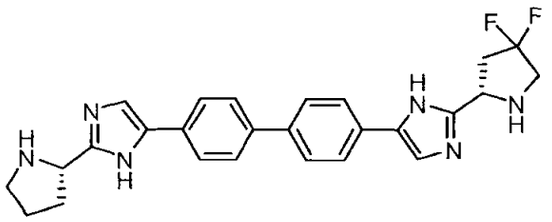
A una solución de 1-2d-2 (0.084g, 0.13mmol) en 1 mL de dioxano se agregó 0.5mL de una solución 4.0 M de HCl en dioxano. La reacción se agitó durante 2 horas a temperatura ambiente y se concentró bajo presión reducida. El sólido color canela resultante se secó bajo vacío para dar 1-2e-2 (0.077g, 100% de rendimiento). El compuesto se usó sin purificación adicional. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 8.00 (2H, s), 7.97 (4H, d, *J*=8.55 Hz), 7.85 (4H, d, *J*=8.24 Hz), 5.63 (1H, s), 5.52 (1H, s), 5.09 - 5.17 (2H, m), 3.67 - 3.74 (2H, m), 3.63 - 3.67 (2H, m), 3.07 - 3.14 (1H, m), 2.89 - 2.96 (1H, m), 2.81 - 2.87 (2H, m); LCMS - Phenomenex C-18 3.0 x 50mm, 0 hasta 100% B durante 4.0 minutos de gradiente, 1 minuto tiempo de espera, A = 10% metanol 90% agua 0.1% TFA, B = 90% metanol 10% agua 0.1% TFA, (t_R= 2.22 min) Análisis calculado para $C_{26}H_{26}F_2N_6$ 460.53; encontrado 461.37 $(M+H)^+$.



1-2e-3

La preparación del 1-2d-3 es en la misma manera como la preparación de 1-1e a partir de 1-1d. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 2.97 - 3.13 (m, 4H), 3.64 - 3.91 (m, 4H), 5.16 (d, *J*=6.41 Hz, 2H), 7.84 (d, *J*=7.93 Hz, 4H), 7.96 (d, *J*=7.93 Hz, 4H), 8.00 (s, 2H); HPLC XTERRA C-18 3.0 x 50 mm, 0 hasta 100% B durante 4 minutos, 1 minutos tiempo de espera, A = 90% agua, 10% metanol, 0.2% H_3PO_4, B = 10% agua, 90% metanol, 0.2% H_3PO_4, TR = 1.66 min, 92% índice de homogeneidad. LCMS: Análisis calculado para $C_{26}H_{24}F_4N_6$: 496.50; encontrado: 495.53 $(M-H)^-$.

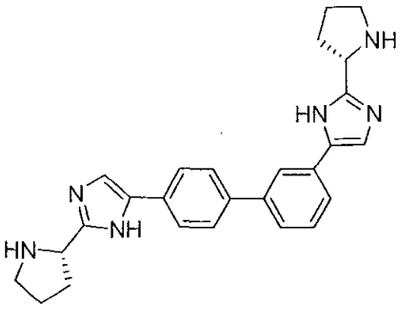
Los compuestos disimétricos análogos tales como los intermediarios 1-3e y 1-4e pueden prepararse por el mismo método.



1-3e

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.87-2.09 (m, 1H), 2.13-2.26 (m, 1H), 2.37-2.47 (m, 2H), 2.92-3.12 (m, 2H), 3.37 (s, 1H), 3.40-3.49 (m, 1H), 3.67-3.91 (m, 2H), 4.96-5.05 (m, 1H), 5.14 (t, *J*=8.70 Hz, 1H), 7.86 (t, *J*=9.00 Hz, 4H), 7.93-8.03 (m, 5H), 8.10 (s, 1H), 10.26/9.75 (dos br s., 2H); HPLC XTERRA C-18 3.0 x 50 mm, 0 hasta 100% B durante 4 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% H_3PO_4, B =

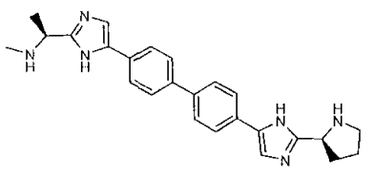
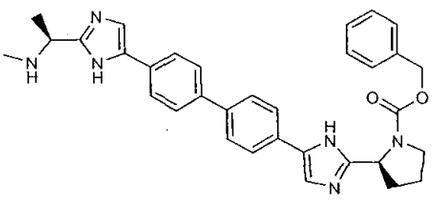
10% agua, 90% metanol, 0.2% H_3PO_4, TR = 0.8622 minutos, 99% índice de homogeneidad; LCMS: Análisis calculado para $C_{26}H_{26}F_2N_6$: 460.52; encontrado: 461.45 $(M+H)^+$.

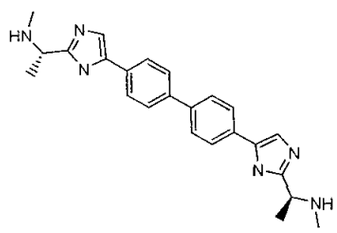


1-4e

El ejemplo 1-4e se preparó a partir de 1-4d en una manera similar a aquella descrita por la preparación de 1-1e a partir de 1-1d. ^1H RMN (500 MHz, DMSO-d_6) δ ppm 1.90 - 2.13 (m, 2 H) 2.12 - 2.31 (m, 2 H) 2.36 - 2.60 (m, 4 H) 3.29 - 3.55 (m, 4 H) 5.00 (s, 2 H) 7.35 - 8.50 (m, 10 H) 9.76 (s, 2 H) 10.12 - 10.45 (m, 2 H). Condiciones CL: Phenomenex Luna 3.0 X 5.0mm S10, Solvente A - 0.1% TFA en 10% MeOH/90%H_2O, Solvente B - 0.1% TFA en 90% MeOH/10% H_2O, 0 hasta 100% B over 2min, Tiempo de paro = 3min, Relación de flujo = 4ml/min, Longitud de onda = 220nm, LC/MS $(M+H)^+$ = 425.28. Tiempo de retención = 0.942 min

Los análogos adicionales se prepararon similarmente:

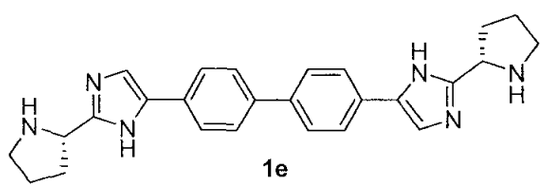
Ejemplo	*Nombre del compuesto*	*Estructura*	*Datos*
1-5e		 Preparado a partir de **1-6d**	TR = 1.37 min; LCMS: Análisis calculado para $C_{25}H_{28}N_6$ 412; encontrado: 413 $(M+H)^+$.
1-6e		 Preparado a partir de **1-7d**	TR = 1.43 min; LCMS: Análisis calculado para $C_{33}H_{35}N_6O_2$ 547; encontrado: 547 $(M+H)^+$.

1-7e		 Preparado a partir de **1-5d**	TR = 1.12 min; EMBR: Análisis calculado para $C_{24}H_{28}N_6$ 400.24; encontrado: 401.22 $(M+H)^+$.

Condiciones CL para 1-5e hasta 1-7e: Phenomenex LUNA C-18 4.6 x 50 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

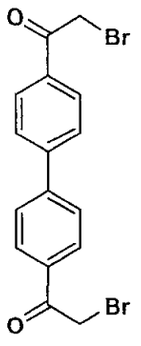
Síntesis Alternativa del Ejemplo 1, Extremo e

5,5'-(4,4'-bifenildiil)bis(2-((2S)-2-pirrolidinil)-1H-imidazol)



1e

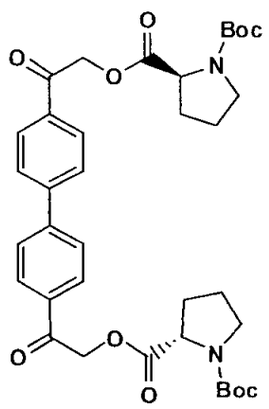
Ejemplo A-1e-1



Un matraz de fondo redondo de 3 cuellos, 1 L, equipado con una línea de nitrógeno, agitador de domo y termoacoplador se cargó con 20 g (83.9 mmol, 1 equiv) 1,1'-(bifenil-4,4'-diil)dietanona, 200 mL CH_2Cl_2 y 8.7 mL (27.1g, 169.3 mmol, 2.02 quiv) bromo. La mezcla se permitió agitar bajo nitrógeno durante alrededor de 20 h bajo condiciones de ambiente. La mezcla espesa resultante se cargó con 200 mL CH_2Cl_2 y se concentró bajo alrededor de 150 mL por medio de destilación al vacío. La mezcla espesa luego se intercambio en solvente en THF a un volúmen objetivo de 200 mL por medio de destilación al vacío. La mezcla espesa se enfrió a 20-25°C durante 1 h y se permitió agitar a 20-25°C durante una hora adicional. Los sólidos cristalinos blancos opacos se filtraron y lavados con 150 mL CH_2Cl_2. El producto se secó bajo vacío a 60°C para proporcionar 27.4 g (69.2 mmol, 82%) del producto deseado: ^{1}H RMN (400 MHz, $CDCl_3$) δ 7.95-7.85 (m, 4H), 7.60-7.50 (m, 4H), 4.26 (s, 4H); ^{13}C RMN (100 MHz, $CDCl_3$) δ 191.0, 145.1, 133.8, 129.9, 127.9, 30.8; IR (KBr, cm-1)

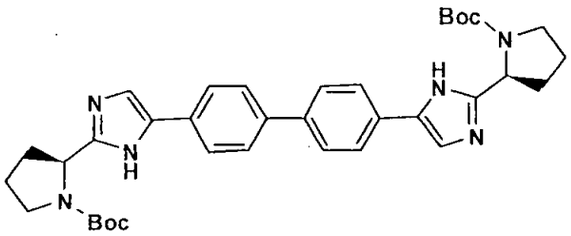
3007, 2950, 1691, 1599, 1199; Análisis calculado para $C_{16}H_{12}Br_2O_2$: C, 48.52; H, 3.05; Br, 40.34. Encontrado: C, 48.53; H, 3.03; Br, 40.53. HRMS calculado para $C_{16}H_{13}Br_2O_2$ (M + H; DCI$^+$): 394.9282. Encontrado: 394.9292. pf 224-226°C.

Ejemplo A-1e-2



Un matraz enchaquetado 500 mL, equipado con una línea de nitrógeno, termoacoplador y agitador de domo, se cargó con 20 g (50.5 mmol, 1 equiv) del Ejemplo A-1e-1, 22.8 g (105.9 moles, 2.10 equiv) 1-(*tert*-butoxicarbonil)-L-prolina, y 200 mL acetonitrilo. La mezcla espesa se enfrió a 20°C seguido por la adición de 18.2 mL (13.5 g, 104.4 mmol, 2.07 equiv) DIPEA. La mezcla espesa se entibió a 25°C y se permitió agitar durante 3 h. La solución orgánica, clara resultante se lavó con 3 x 100 mL 13% en peso NaCl acuoso. La solución rica en acetonitrilo se intercambió el solvente en tolueno (volumen objetivo = 215 mL) por destilación al vacío hasta que había menos de 0.5% vol acetonitrilo.

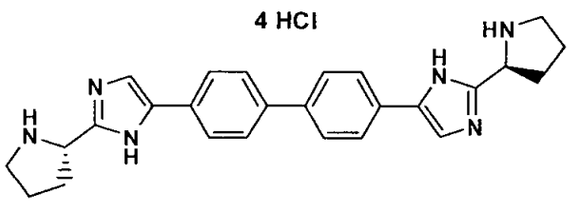
Ejemplo A-1e-3



La solución de tolueno anterior del Ejemplo A-1e-2 se cargó con 78 g (1.011 moles, 20 equiv) acetato de amonio y se calentó a 95-100°C. La mezcla se permitió agitar a 95-100°C durante 15 h. Después de que la reacción se completa, la mezcla se enfrió a 70-80°C y se cargó con 7 mL ácido acético, 40 mL n-butanol, y 80 mL de ácido acético acuoso 5% vol. La solución bifásica resultante se dividió mientras se mantiene una temperatura > 50°C. La fase orgánica rica se cargó con 80 mL de ácido acético acuoso 5% vol, 30 mL ácido acético y 20 mL n-butanol mientras se mantiene una temperatura >50°C. La solución bifásica resultante se dividió mientras se mantiene una temperatura > 50°C y la fase orgánica rica se lavó con un adicional 80 mL de ácido acético acuoso 5% vol. La fase orgánica rica luego se intercambio en solvente en tolueno a un volúmen objetivo de 215 mL por destilación al vacío. Mientras se mantiene una temperatura >60°C, 64 mL MeOH se cargó. La mezcla espesa resultante se calentó a 70-75°C y añejo durante 1 h. La mezcla espesa se enfrió a 20-25°C durante 1 h y se añejo a esa temperatura durante una hora adicional. La mezcla espesa se filtró y la torta se lavó con

200 mL 10:3 tolueno: MeOH. El producto se secó bajo vacío a 70°C, resultando en 19.8 g (31.7 mmol, 63%) del producto deseado: ^{1}H RMN (400 MHz, DMSO-d_6) δ 13.00-11.00 (s, 2H), 7.90-7.75 (m, 4H), 7.75-7.60 (m, 4H), 7.60-7.30 (s, 2H), 4.92-4.72 (m, 2H), 3.65-3.49 (m, 2H), 3.49-3.28 (m, 2H), 2.39-2.1 (m, 2H), 2.10-1.87 (m, 6H), 1.60-1.33 (s, 8H), 1.33-1.07 (s, 10H); ^{13}C RMN (100 MHz, DMSO-d_6) δ 154.1, 153.8, 137.5, 126.6, 125.0, 78.9, 78.5, 55.6, 55.0, 47.0, 46.7, 33.7, 32.2, 28.5, 28.2, 24.2, 23.5; IR (KBr, cm-1) 2975, 2876, 1663, 1407, 1156, 1125; HRMS calculado para $C_{36}H_{45}N_6O_4$ (M + H; ESI$^+$): 625.3502. Encontrado: 625.3502. pf 190-195°C (descompuesto).

Ejemplo A-1e-4

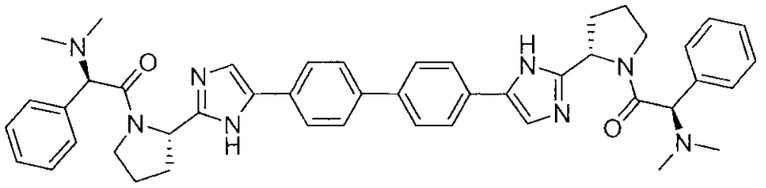


A un reactor 250 ml equipado con una línea de nitrógeno y agitador de domo, 25.0 g del Ejemplo A-1e-3 (40.01 mmol, 1 equiv) se cargó seguido por 250 mL metanol y 32.85 mL (400.1 mmol, 10 equiv) cloruro ácido acuoso 6M. La temperatura se incrementó a 50°C y se agitó a 50°C durante 5 h. La mezcla espesa resultante se enfrió a 20-25°C y se mantuvo con agitación por ca. 18 h. La filtración de la mezcla espesa proporcionó un sólido que se lavó sucesivamente con 100 ml

90% metanol/agua (p/p) y 2 x 100 ml de metanol. La torta húmeda se secó en un horno al vacío a 50°C durante la noche para dar 18.12 g (31.8 mmol, 79.4%) del producto deseado.

Recristalización del Ejemplo A-1e-4

A un reactor 250 ml equipado con una línea de nitrógeno y un agitador de domo, 17.8 g del Ejemplo A-1e-4 crudo se cargó seguido por 72 mL metanol. La mezcla espesa resultante se agitó a 50°C durante 4 h, se enfrió a 20-25°C y se mantuvo con agitación a 20-25°C durante 1 h. La filtración de la mezcla espesa proporcionó un sólido cristalino el cual se lavó con 60 ml metanol. La torta humeda resultante se secó en un horno al vacío a 50°C durante 4 días para proporcionar 14.7 g (25.7 mmol, 82.6%) del producto deseado: ^{1}H RMN (400 MHz, DMSO-d_6) δ 10.5-10.25 (br, 2H), 10.1-9.75 (br, 2H), 8.19 (s, 2H), 7.05 (d, J = 8.4, 4H), 7.92 (d, J = 8.5, 4H), 5.06 (m, 2H), 3.5-3.35 (m, 4H), 2.6-2.3 (m, 4H), 2.25-2.15 (m, 2H), 2.18-1.96 (m, 2H); ^{13}C RMN (100 MHz, DMSO- d_6) δ 156.6, 142.5, 139.3, 128.1, 127.5, 126.1, 116.9, 53.2, 45.8, 29.8, 24.3; IR (KBr, cm^{-1}) 3429, 2627, 1636, 1567, 1493, 1428, 1028. Análisis calculado para $C_{26}H_{32}N_6Cl_4$: C, 54.75; H, 5.65; Cl, 24.86; Ajustado para 1.9% de agua: C, 53.71; H, 5.76; N, 14.46; Cl, 24.39. Encontrado: C, 53.74; H, 5.72; N, 14.50; Cl, 24.49; KF = 1.9. pf 240°C (descompuesto)

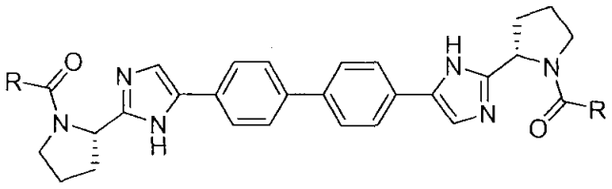


Ejemplo 1

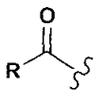
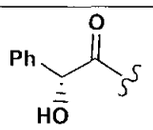
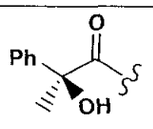
(1R,1'R)-2,2'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(N,N-dimetil-2-oxo-1-feniletanamina)

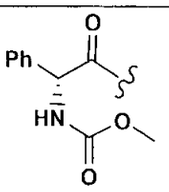
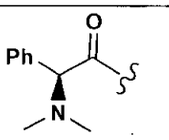
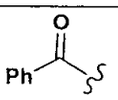
El HATU (44.6 mg, 0.117 mmol) se agregó a una mezcla de pirrolidina 1e (22.9 mg, 0.054 mmol), diisopropiletilamina (45 µL, 0.259 mmol) y Extremo 1 (28.1 mg, 0.13 mmol) en DMF (1.5 mL), y la mezcla resultante se agitó en el ambiente durante 90 minutos. El componente volátil se removió *in vacuo*, y el residuo se purificó primero por MCX (lavado con metanol; 2.0 M NH_3/elución de metanol) y luego por Sistema HPLC de fase inversa (H_2O/metanol/TFA) para proporcionar la sal TFA del ejemplo 1 como una espuma blanca opaca (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 NH imidazol fue muy amplia para generar un cambio químico]; CL (Cond.Ib): TR = 1.40 min; > 98% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{46}H_{51}N_8O_2$: 747.41; encontrado 747.58.

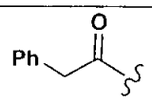
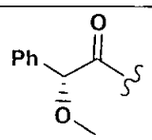
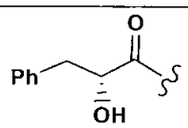
Ejemplos 2 hasta 24-4d

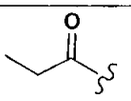
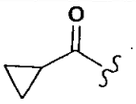
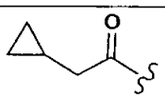


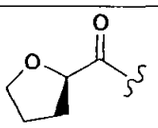
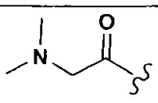
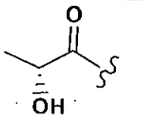
Los ejemplos 2 hasta 24-4h se prepararon como sales TFA sustituyendo los ácidos respectivos por el extremo 1 usando el mismo método descrito por el ejemplo 1. Las extremos en la siguiente tabla sin un número son comercialmente disponibles.

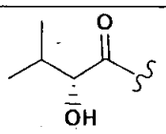
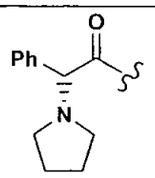
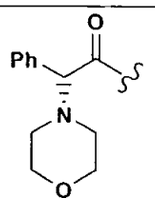
Ejemplo	*Nombre del Compuesto*		*TR (CL-Cond.); % índice de homogeneidad; Datos EM*
2	(1R,1'R)-2,2'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(2-oxo-1-feniletanol)		1.55 minutos (Cond. 1); >98%; LC/MS: Anal. Calculado para $[M+H]^+$ $C_{42}H_{41}N_6O_4$: 693.32; encontrado 693.46; HRMS: Anal. calculado para $[M+H]^+$ $C_{42}H_{41}N_6O_4$: 693.3189; encontrado 693.3182
3	(2S,2'S)-1,1'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(1-oxo-2-fenil-2-propanol)		1.77 minutos (Cond. 1); >98%; LC/MS: Anal. calculado para $[M+H]^+$ $C_{44}H_{45}N_6O_4$: 721.35; encontrado 721.52; HRMS: Anal. calculado para $[M+H]^+$ $C_{44}H_{45}N_6O_4$: 721.3502; encontrado 721.3515

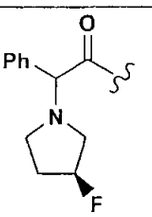
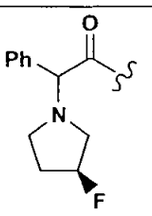
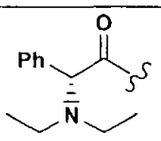
4	(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil))) biscarbamato de dimetilo	 *Extremo-4*	1.64 minutos (Cond. 1); >98%; LC/MS: Anal. calculado para $[M+H]^+$ $C_{46}H_{47}N_8O_6$: 807.36; encontrado 807.58
5	(1S,1'S)-2,2'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis (N,N-dimetil-2-oxo-1-feniletanamina)	 *Extremo-1*	1.33 minutos (Cond. 1); >98%; LC/MS: Anal. calculado para $[M+H]^+$ $C_{46}H_{51}N_8O_2$: 747.41; encontrado 747.64; HRMS: Anal. calculado para $[M+H]^+$ $C_{46}H_{51}N_8O_2$: 747.4135; encontrado 747.4103
6	5,5'-(4,4'-bifenildiil)bis(2-((2S)-1-benzoil-2-pirrolidinil)-1H-imidazol)		1.65 minutos (Cond. 1); >98%; LC/MS: Anal. calculado para $[M+H]^+$ $C_{40}H_{37}N_6O_2$: 633.30; encontrado 633.51

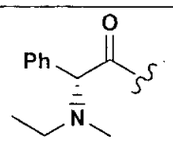
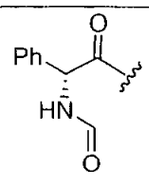
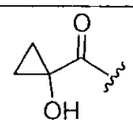
7	5,5'-(4,4'-bifenildiil)bis(2-((2S)-1-(fenilacetil)-2-pirrolidinil)-1H-imidazol)		1.71 minutos (Cond. 1); >98%; LC/MS: Anal. calculado para $[M+H]^+$ $C_{42}H_{41}N_6O_2$: 661.33; encontrado 661.53; HRMS: Anal. calculado para $[M+H]^+$ $C_{42}H_{41}N_6O_2$: 661.3291; encontrado 661.3300
8	5,5'-(4,4'-bifenildiil)bis(2-((2S)-1-((2R)-2-metoxi-2-fenilacetil)-2-pirrolidinil)-1H-imidazol)		1.63 minutos (Cond. 1); >98%; LC/MS: Anal. calculado para $[M+H]^+$ $C_{44}H_{45}N_6O_4$: 721.35; encontrado 721.59; HRMS: Anal. calculado para $[M+H]^+$ $C_{44}H_{45}N_6O_4$: 721.3502; encontrado 721.3536
9	(2R,2'R)-1,1'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(1-oxo-3-fenil-2-propanol)		1.71 minutos (Cond. 1); >98%; LC/MS: Anal. calculado para $[M+H]^+$ $C_{44}H_{45}N_6O_4$: 721.35; encontrado 721.58; HRMS: Anal. calculado para $[M+H]^+$ $C_{44}H_{45}N_6O_4$: 721.3502; encontrado 721.3497

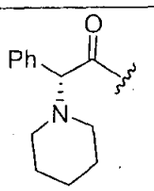
10	5,5'-(4,4'-bifenildiil)bis(2-((2S)-1-propionil-2-pirrolidinil)-1H-imidazol)		1.47 minutos (Cond. 1); >98%; LC/MS: Anal. calculado para $[M+H]^+$ $C_{32}H_{37}N_6O_2$: 537.30; encontrado 537.40; HRMS: Anal. calculado para $[M+H]^+$ $C_{32}H_{37}N_6O_2$: 537.2978; encontrado 537.2952
11	5,5'-(4,4'-bifenildiil)bis(2-((2S)-1-(ciclopropilcarbonil)-2-pirrolidinil)-1H-imidazol)		1.48 minutos (Cond. 1); >98%; LC/MS: Anal. calculado para $[M+H]^+$ $C_{34}H_{37}N_6O_2$: 561.30; encontrado 561.44
12	5,5'-(4,4'-bifenildiil)bis(2-((2S)-1-(ciclopropilacetil)-2-pirrolidinil)-1H-imidazol)		1.57 minutos (Cond. 1); >98%; LC/MS: Anal. calculado para $[M+H]^+$ $C_{36}H_{41}N_6O_2$: 589.33; encontrado 589.48; HRMS: Anal. calculado para $[M+H]^+$ $C_{36}H_{41}N_6O_2$: 589.3291; encontrado 589.3268

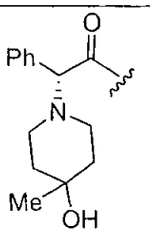
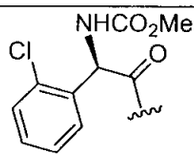
13	5,5'-(4,4'-bifenildiil)bis(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol)		1.44 minutos (Cond. 1); >98%; LC/MS: Anal. calculado para $[M+H]^+$ $C_{36}H_{41}N_6O_4$: 621.32; encontrado 621.52; HRMS: Anal. calculado para $[M+H]^+$ $C_{36}H_{41}N_6O_4$: 621.3189; encontrado 621.3191
14	2,2'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(N,N-dimetil-2-oxoetanamina)		1.27 minutos (Cond. 1); >98%; LC/MS: Anal. calculado para $[M+H]^+$ $C_{34}H_{43}N_8O_2$: 595.35; encontrado 595.54; HRMS: Anal. calculado para $[M+H]^+$ $C_{34}H_{43}N_8O_2$: 595.3509; encontrado 595.3503
15	(2R,2'R)-1,1'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(1-oxo-2-propanol)		1.36 minutos (Cond. 1); >98%; LC/MS: Anal. calculado para $[M+H]^+$ $C_{32}H_{37}N_6O_4$: 569.29; encontrado 569.44; HRMS: Anal. calculado para $[M+H]^+$ $C_{32}H_{37}N_6O_4$: 569.2876; encontrado 569.2872

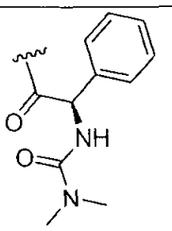
16	(2R,2'R)-1,1'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(3-metil-1-oxo-2-butanol)		1.51 minutos (Cond. 1); >98%; LC/MS: Anal. calculado para $[M+H]^+$ $C_{36}H_{45}N_6O_4$: 625.35; encontrado 625.50; HRMS: Anal. calculado para $[M+H]^+$ $C_{36}H_{45}N_6O_4$: 625.3502; encontrado 625.3517
17	5,5'-(4,4'-bifenildiil)bis(2-((2S)-1-((2R)-2-fenil-2-(1-pirrolidinil)acetil)-2-pirrolidinil)-1H-imidazol)	 *Extremo-5*	1.13 minutos (Cond. 1); >98%; LC/MS: Anal. calculado para $[M+H]^+$ $C_{50}H_{55}N_8O_2$: 799.45; encontrado 799.67
18	4,4'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil))) dimorfolina	 *Extremo-6*	1.11 minutos (Cond. 1); >98%; LC/MS: Anal. calculado para $[M+H]^+$ $C_{50}H_{55}N_8O_4$: 831.44; encontrado 831.71

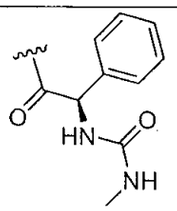
19	5,5'-(4,4'-bifenildiil)bis(2-((2S)-1-(((3S)-3-fluoro-1-pirrolidinil)(fenil)acetil)-2-pirrolidinil)-1H-imidazol)	 *Diaestereómero-1 Extremo-9a*	1.17 minutos (Cond. 1); 97%; LC/MS: Anal. calculado para $[M+H]^+$ $C_{50}H_{53}F_2N_8O_2$: 835.43; encontrado 835.51; HRMS: Anal. calculado para $[M+H]^+$ $C_{50}H_{53}F_2N_8O_2$: 835.4260; encontrado 835.4261
20	5,5'-(4,4'-bifenildiil)bis(2-((2S)-1-(((3S)-3-fluoro-1-pirrolidinil)(fenil)acetil)-2-pirrolidinil)-1H-imidazol)	 *Diaestereómero-2 Extremo-9b*	1.03 minutos (Cond. 1); >98%; LC/MS: Anal. calculado para $[M+H]^+$ $C_{50}H_{53}F_2N_8O_2$: 835.43; encontrado 835.51; HRMS: Anal. calculado para $[M+H]^+$ $C_{50}H_{53}F_2N_8O_2$: 835.4260; encontrado 835.4266
21	(1R,1'R)-2,2'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(N,N-dietil-2-oxo-1-feniletanamina)	 *Extremo-2*	1.13 minutos (Cond. 1); >98%; LC/MS: Anal. calculado para $[M+H]^+$ $C_{50}H_{59}N_8O_2$: 803.48; encontrado 803.56; HRMS: Anal. calculado para $[M+H]^+$ $C_{50}H_{59}N_8O_2$: 803.4761; encontrado 803.4728

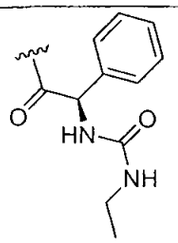
22	(1R,1'R)-2,2'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis (N-etil-N-metil-2-oxo-1-feniletanamina)	 *Extremo*-3	1.10 minutos (Cond. 1); >98%; LC/MS: Anal. calculado para $[M+H]^+$ $C_{48}H_{55}N_8O_2$: 775.45; encontrado 775.52; HRMS: Anal. calculado para $[M+H]^+$ $C_{50}H_{59}N_8O_2$: 775.4448; encontrado 775.4456
23	N,N'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil))) diformamida		1.22 minutos (Cond. 1); >98%; LC/MS: Anal. calculado para $[M+H]^+$ $C_{44}H_{43}N_8O_4$: 747.34; encontrado 747.38
24	1,1'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil carbonil)) diciclopropanol		1.77 minutos (Cond. 2); >98%; LC/MS: Anal. calculado para $[M+H]^+$ $C_{34}H_{37}N_6O_4$: 593.29; encontrado 593.16

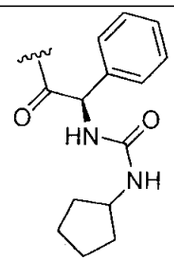
24-1	1,1'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil))) dipiperidina	 *Extremo-14*	^{1}HRMN (400 MHz, DMSO-d_6) δ 12.18 (m, 0.4H), 11.96 (m, 0.4H), 11.79 (m, 1.2H), 7.84-7.70 (m, 4H), 7.69-7.65 (m, 4H), 7.53-7.50 (m, 2H), 7.43-7.28 (m, 4H), 7.09-7.01 (m, 2H), 6.87-6.85 (m, 2H), 5.51-5.48 (m, 0.5H), 5.01-4.98 (m, 1.5H), 4.29 (m, 1.5H), 4.16 (m, 0.5H), 3.98 (m, 2H), 3.65-3.49 (m, 2H), 3.43-3.36 (m, 2H), 2.41-2.31 (m, 8H), 2.14-1.82 (m, 8H), 1.47-1.31 (m, 12H); LCMS: Anal. calculado para $C_{52}H_{58}N_8O_2$: 826; encontrado: 827 $(M+H)^+$.

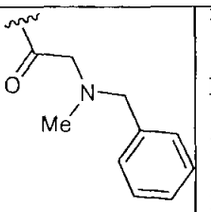
24-2	1,1'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))bis(4-metil-4-piperidinol)	 *Extremo-15*	^{1}HRMN (400 MHz, DMSO-d_6) δ 12.02 (br s, 1H), 11.82 (br s, 1H), 7.90-7.79 (m, 4H), 7.79-7.65 (m, 5H), 7.55 (br s, 2H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.39-7.25 (m, 3H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.04 (t, *J* = 7.6 Hz, 2H), 6.85 (d, *J* = 8.1 Hz, 2H), 5.15-4.96 (m, 2H), 4.31-3.96 (m, 6H), 2.35-2.20 (m, 2H), 2.05-1.94 (m, 4H), 1.94-1.81 (m, 4H), 1.50-1.35 (m, 9H), 1.35-1.20 (m, 5H), 1.09 (s, 2H), 1.05 (s, 4H); LCMS: Anal. calculado para $C_{54}H_{62}N_8O_4$: 886; encontrado: 887 $(M+H)^+$.
24-3	(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-1-(2-clorofenil)-2-oxo-2,1-etandiil))) biscarbamato de dimetilo		LCMS: Anal. calculado para $C_{46}H_{44}Cl_2N_8O_6$: 874; encontrado: 875 $(M+H)^+$.

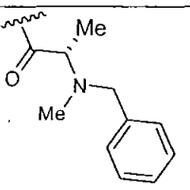
24-4a	N',N'''-(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))bis(1,1-dimetilurea)	 *Extremo-47*	^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.89-2.00 (m, *J*=17.09, 7.02 Hz, 4H), 2.06-2.13 (m, *J*=14.95, 3.97 Hz, 3H), 2.24-2.33 (m, *J*=8.70, 6.56 Hz, 2H), 2.79-2.84 (m, 12H), 3.29 (q, 2H), 3.95-4.03 (m, 3H), 5.26 (dd, *J*=8.55, 2.14 Hz, 3H), 5.52 (d, *J*=5.80 Hz, 3H), 6.72 (d, *J*=6.10 Hz, 3H), 7.02-7.07 (m, 1H), 7.29-7.36 (m, 3H), 7.39 (t, *J*=7.17 Hz, 4H), 7.46 (d, *J*=7.02 Hz, 3H), 7.92 (s, 8H), 8.12 (s, 2H); HPLC XTERRA C-18 4.6 × 30 mm, 0 hasta 100% B durante 4 minutos, 1 minuto tiempo de espera, A = 90% de agua, 10% metanol, 0.2% H_3PO_4, B = 10% de agua, 90% metanol, 0.2% H_3PO_4, TR = 2.13 minutos, 96% índice de homogeneidad; LCMS: Anal. calculado para $C_{48}H_{53}N_{10}O_4$: 832.42; encontrado: 833.43 $(M+H)^+$; HRMS: Anal. calculado para $C_{48}H_{54}N_{10}O_4$ 833.4251; encontrado: 833.4267 $(M+H)^+$.

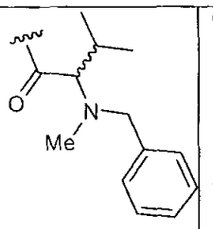
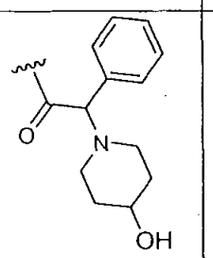
24-4b	N',N'''-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))bis(1-metilurea)	 *Extremo-45*	TR = 4.45 minutos (Gemini C-18 4.6 x 50mm, 0 hasta 100% B durante 10.0 minuto gradiente, 1 minuto tiempo de espera, A = 5% acetonitrilo, 95% de agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% de agua, 10mm acetato de amonio); LCMS: Anal. calculado para $C_{46}H_{48}N_{10}O_4$ 804.95; encontrado: 805.41 $(M+H)^+$; HRMS: Anal. calculado para $C_{46}H_{49}N_{10}O_4$ 805.3938; encontrado: 805.3929 $(M+H)^+$.

24-4c	N',N'''-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))bis(1-etilurea)	 *Extremo-46*	TR = 4.20 minutos (Gemini C-18 4.6 x 50mm, 0 hasta 100% B durante 10.0 minuto gradiente, 1 minuto tiempo de espera, A = 5% acetonitrilo, 95% de agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% de agua, 10mm acetato de amonio); LCMS: Anal. calculado para $C_{48}H_{52}N_{10}O_4$ 833.00; encontrado: 833.48 $(M+H)^+$.

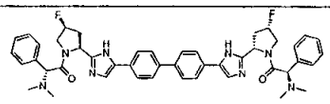
24-4d	N',N'''-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))bis(1-ciclopentilurea)	 *Extremo-48*	TR = 4.92 minutos (Gemini C-18 4.6 x 50mm, 0 hasta 100% B durante 10.0 minuto gradiente, 1 minuto tiempo de espera, A = 5% acetonitrilo, 95% de agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% de agua, 10mm acetato de amonio); LCMS: Anal. calculado para $C_{54}H_{60}N_{10}O_4$ 912.49; encontrado: 913.68 $(M+H)^+$; HRMS: Anal. calculado para $C_{54}H_{61}N_{10}O_4$ 913.4877; encontrado: 913.4899 $(M+H)^+$.

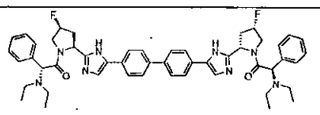
24-4e	2,2'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil)) bis (N-bencil-N-metil-2-oxoetanamina)	 *Extremo-49*	^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.97-2.43 (m, 8H), 2.64-2.91 (m, 6H), 3.45-3.63 (m, 2H), 3.62-3.76 (m, 2H), 4.14 (dd, 4H), 4.22-4.45 (m, 4H), 5.29 (s, 2H), 7.28-7.65 (m, 10H), 7.90 (s, 8H), 8.06 (s, 2H), 14.62 (s, 2H); HPLC Xterra 4.6 X 50 mm, 0 hasta 100% B durante 10 minutos, un minuto tiempo de espera, A = 90% de agua, 10% metanol, 0.2% ácido fosfórico, B = 10% de agua, 90% metanol, 0.2% ácido fosfórico. TR = 3.06 min; LCMS: Anal. calculado para: $C_{46}H_{50}N_8O_2$ 746.96; Encontrado: 747.41 $(M+H)^+$.

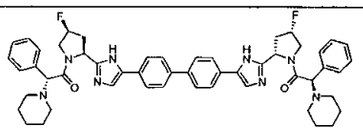
24-4f	(2S,2'S)-1,1'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil)) bis (N-bencil-N-metil-1-oxo-2-propanamina)		TR = 2.95 minutos (99%); HPLC Xterra 4.6 X 50 mm, 0 hasta 100% B durante 10 minutos, un minuto tiempo de espera, A = 90% de agua, 10% metanol, 0.2% ácido fosfórico, B = 10% de agua, 90% metanol, 0.2% ácido fosfórico; LCMS: Anal. calculado para: $C_{48}H_{54}N_8O_2$ 775.02; Encontrado: 775.45 $(M+H)^+$.

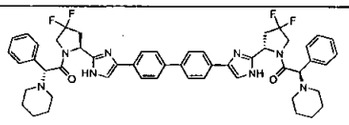
24-4g	1,1'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis (N-bencil-N,3-dimetil-1-oxo-2-butanamina)	 *Extremo-50*	TR = 3.86 minutos (100%); HPLC Xterra 4.6 X 50 mm, 0 hasta 100% B durante 10 minutos, un minuto tiempo de espera, A = 90% de agua, 10% metanol, 0.2% ácido fosfórico, B = 10% de agua, 90% metanol, 0.2% ácido fosfórico; LCMS: Anal. calculado para: $C_{52}H_{62}N_8O_2$ 831.13; Encontrado: 831.51 $(M+H)^+$.
24-4h	1,1'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil(2-oxo-1-fenil-2,1-etandiil)))di(4-piperidinol)	 *Extremo-8*	TR = 2.86 minutos (100%); HPLC Xterra 4.6 X 50 mm, 0 hasta 100% B durante 10 minutos, un minuto tiempo de espera, A = 90% de agua, 10% metanol, 0.2% ácido fosfórico, B = 10% de agua, 90% metanol, 0.2% ácido fosfórico; LCMS: Anal. calculado para: $C_{52}H_{58}N_8O_4$ 859.09; Encontrado: 859.45 $(M+H)^+$.

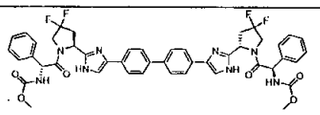
Ejemplos 24-5 hasta 24-18

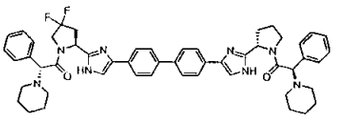
Ejemplo	*Nombre del Compuesto*	*Estructura*	*Datos*
24-5	1,1'-(4,4'-bifenildiilbis (1H-imidazol-5,2-diil((2S,4S)-4-fluoro-2,1-pirrolidindiil) ((1R)-2-oxo-1-fenil-2,1-etandiil))) dipiperidina	 de 1-2e-2 y *Extremo*-1	Gemini C-18 4.6 x 50mm, 0 hasta 100% B durante 10.0 minuto gradiente, 1 minuto tiempo de espera, A = 5% acetonitrilo, 95% de agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% de agua, 10mm acetato de amonio. (TR= 4.163 min); Nominal/EMBR - Calculado para $C_{46}H_{48}F_2N_8O_2$ 782.93; encontrado 783.40 $(M+H)^+$; Exacto/HRMS - Calculado para $C_{46}H_{49}F_2N_8O_2$ 783.3946; 783.3934 $(M+H)^+$.

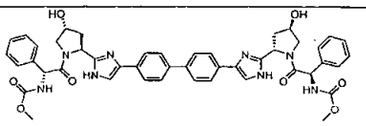
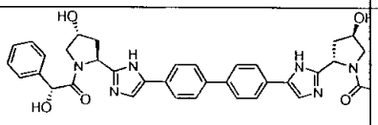
24-6	(1R,1'R)-2,2'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil((2S,4S)-4-fluoro-2,1-pirrolidindiil))bis(N,N-dietil-2-oxo-1-feniletanamina)	 de 1-2e-2 y *Extremo*-2	Gemini C-18 4.6 x 50mm, 0 hasta 100% B durante 10.0 minuto gradiente, 1 minuto tiempo de espera, A = 5% acetonitrilo, 95% de agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% de agua, 10mm acetato de amonio. (TR = 3.76 min); LCMS: Anal. calculado para $C_{50}H_{56}F_2N_8O_2$ 839.04; encontrado: 839.49 $(M+H)^+$; HRMS: Anal. calculado para $C_{50}H_{57}F_2N_8O_2$ 839.4572; encontrado: 839.4590 $(M+H)^+$.

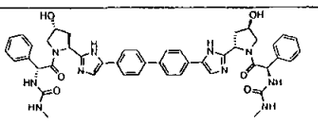
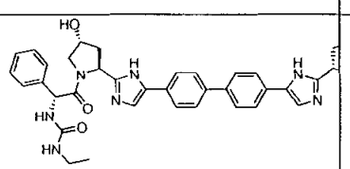
24-7	(1R,1'R)-2,2'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil((2S,4S)-4-fluoro-2,1-pirrolidindiil))bis(N,N-dimetil-2-oxo-1-feniletanamina)	 de 1-2e-2 y *Extremo*-14	Gemini C-18 4.6 x 50mm, 0 hasta 100% B durante 10.0 minuto gradiente, 1 minuto tiempo de espera, A = 5% acetonitrilo, 95% de agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% de agua, 10mm acetato de amonio. TR = 3.99 min; LCMS: Anal. calculado para $C_{52}H_{56}F_2N_8O_2$ 863.06; encontrado: 863.47 $(M+H)^+$; HRMS: Anal. calculado para $C_{52}H_{57}F_2N_8O_2$ 863.4572; encontrado: 863.4553 $(M+H)^+$.

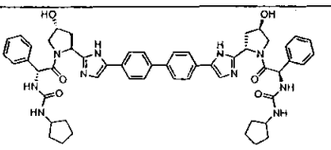
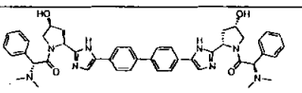
24-8	1,1'-(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((2S)-4,4-difluoro-2,1-pirrolidindiil)((1R)-2-oxo-1-fenil-2,1-etandiil))) dipiperidina	 de 1-2e-3 y *Extremo*-14	TR = 1.64 minutos, método B; LCMS: Anal. calculado para $C_{52}H_{54}F_4N_8O_6$: 898.43; encontrado: 899.46 $(M+H)^+$; HRMS: Anal. calculado para $C_{52}H_{55}F_4N_8O_6$ 899.4384; encontrado: 899.4380 $(M+H)^+$.

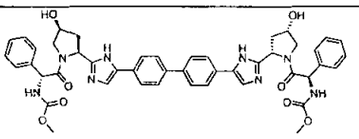
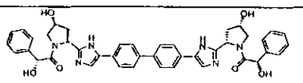
24-9	(4,4'-bifenildiilbis (1H-imidazol-4,2-diil((2S)-4,4-difluoro-2,1-pirrolidindiil) ((1R)-2-oxo-1-fenil-2,1-etandiil))) biscarbamato de dimetilo	 de 1-2e-3 y *Extremo*-4	TR = 2.62 minutos, método C; LCMS: Anal. calculado para $C_{46}H_{42}F_4N_8O_6$: 878.88; encontrado: 879.81 $(M+H)^+$; HRMS: Anal. calculado para $C_{46}H_{43}F_4N_8O_6$ 879.33242; encontrado: 879.3273 $(M+H)^+$.

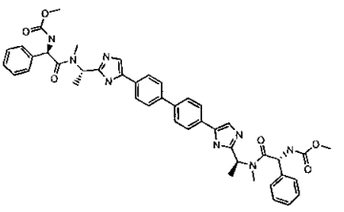
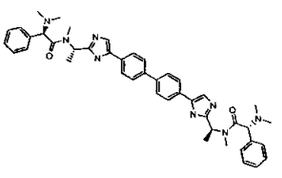
24-10	1-((1R)-2-((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2R)-2-fenil-2-(1-piperidinil) acetil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) piperidina	 de 1-3e y *Extremo*-14.	TR = 1.54 minutos, método B; LCMS: Anal. calculado para $C_{52}H_{56}F_2N_8O_6$: 862.45; encontrado: 863.46 $(M+H)^+$; HRMS: Anal. calculado para $C_{52}H_{57}F_2N_8O_6$ 863.4573; encontrado: 863.4572 $(M+H)^+$.

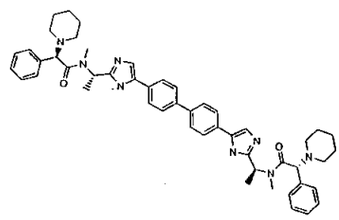
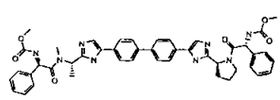
24-11	(4,4'-bifenildiilbis(1H-imidazol-5,2-diil((2S,4R)-4-hidroxi-2,1-pirrolidindiil)((1R)-2-oxo-1-fenil-2,1-etandiil))) biscarbamato de dimetilo	 de 1-1e y *Extremo*-4	TR = 8.54 minutos, método A; LCMS: Anal. calculado para $C_{46}H_{46}N_8O_8$ 838.93; encontrado: 839.41 $(M+H)^+$; HRMS: Anal. calculado para $C_{46}H_{47}N_8O_8$ 839.9300; encontrado: 839.3527 $(M+H)^+$.
24-12	(3R,5S,3'R,5'S)-5,5'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil))bis(1-((2R)-2-hidroxi-2-fenilacetil)-3-pirrolidinol)	 de 1-1e y ácido mandélico	TR = 6.92 minutos, método A; LCMS: Anal. calculado para $C_{42}H_{40}N_6O_6$ 724.81; encontrado: 725.43 $(M+H)^+$; HRMS: Anal. calculado para $C_{42}H_{41}N_6O_6$ 725.3087; encontrado: 725.3088 $(M+H)^+$.

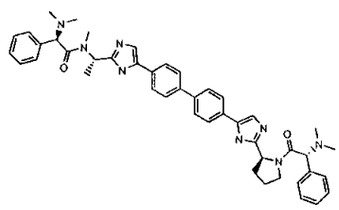
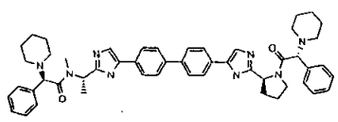
24-13	N,N''-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil((2S,4R)-4-hidroxi-2,1-pirrolidindiil)((1R)-2-oxo-1-fenil-2,1-etandiil)))bis(3-metilurea)	 Preparado de 1-1e y *Extremo*-45	TR = 3.80 minutos, método C; LCMS: Anal. calculado para $C_{46}H_{48}N_{10}O_6$ 836.95; encontrado: 837.52 $(M+H)^+$; HRMS: Anal. calculado para $C_{46}H_{49}N_{10}O_6$ 837.3836; encontrado: 837.3809 $(M+H)^+$.
24-14	N',N'''-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil((2S,4R)-4-hidroxi-2,1-pirrolidindiil)((1R)-2-oxo-1-fenil-2,1-etandiil)))bis(1-etilurea)	 Preparado de 1-1e y *Extremo*-46	TR = 4.39 minutos, método C; EMBR: Anal. calculado para $C_{48}H_{52}N_{10}O_6$ 865.003; encontrado: 865.56 $(M+H)^+$; HRMS: Anal. calculado para $C_{48}H_{53}N_{10}O_6$ 865.4149; encontrado: 865.4139 $(M+H)^+$.

24-15	N',N'''-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil((2S,4R)-4-hidroxi-2,1-pirrolidindiil)((1R)-2-oxo-1-fenil-2,1-etandiil)))bis(1-ciclopentil urea)	 Preparado de 1-1e y extremo-48	TR = 4.88 minutos, método B; EMBR: Anal. calculado para $C_{54}H_{60}N_{10}O_6$ 944.13; encontrado: 945.65 $(M+H)^+$; HRMS: Anal. calculado para $C_{54}H_{61}N_{10}O_6$ 945.4775; encontrado: 945.4769 $(M+H)^+$.
24-16	(3S,5S,3'S,5'S)-5,5'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil))bis(1-((2R)-2-(dimetilamino)-2-fenilacetil)-3-pirrolidinol)	 Preparado de 1-2e y extremo-1	TR = 3.66 minutos, método D; EMBR: Anal. calculado para $C_{46}H_{50}N_8O_4$ 778.39 encontrado: 779.39 $(M+H)^+$; HRMS: Anal. calculado para $C_{46}H_{51}N_8O_4$ 779.4033; encontrado: 779.4021 $(M+H)^+$.

24-17	(4,4'-bifenildiilbis(1H-imidazol-5,2-diil((2S,4S)-4-hidroxi-2,1-pirrolidindiil)((1R)-2-oxo-1-fenil-2,1-etandiil))) biscarbamato de dimetilo	 Preparado de 1-2e y *Extremo*-4	TR = 5.75 minutos, método C; EMBR: Anal. calculado para $C_{46}H_{46}N_8O_8$ 838.93; encontrado: 839.44 $(M+H)^+$; HRMS: Anal. calculado para $C_{46}H_{47}N_8O_8$ 839.3517 encontrado: 839.3519 $(M+H)^+$.
24-18	(3S,5S,3'S,5'S)-5,5'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil))bis(1-((2R)-2-hidroxi-2-fenilacetil)-3-pirrolidinol)	 de 1-2e y ácido mandélico	TR = 4.41 minutos, método D; EMBR: Anal. calculado para $C_{42}H_{40}N_6O_6$ 724.81; encontrado: 725.13 $(M+H)^+$.

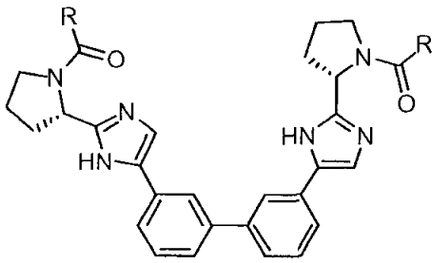
24-18-1	(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(1S)-1,1-etandiil(metilimino)((1R)-2-oxo-1-fenil-2,1-etandiil))) biscarbamato de dimetilo	 de 1-7e y *Extremo*-4	TR = 1.55 min[1]; EMBR: Anal. calculado para $C_{44}H_{46}N_8O_6$ 782.35; encontrado: 783.37 $(M+H)^+$; HRMS: Anal. calculado para $C_{44}H_{47}N_8O_6$ 783.3619 encontrado: 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	TR = 1.16 min[1]; EMBR: Anal. calculado para $C_{44}H_{50}N_8O_2$ 722.41; encontrado: 723.41 $(M+H)^+$; HRMS: Anal. calculado 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	TR = 1.28 min[1]; EMBR: Anal. calculado para $C_{50}H_{58}N_8O_2$ 802.47; encontrado: 803.50 $(M+H)^+$; HRMS: Anal. calculado 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-((metoxi carbonil)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	TR = 1.53 min[1]; EMBR: Anal. calculado para $C_{45}H_{46}N_8O_6$ 794.35; encontrado: 795.39 $(M+H)^+$; HRMS: Anal. calculado para $C_{45}H_{47}N_8O_6$ 795.3619 encontrado: 795.3616 $(M+H)^+$.

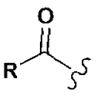
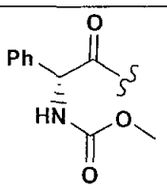
24-18-5	(2R)-2-(dimetilamino)-N-((1S)-1-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)etil)-N-metil-2-fenilacetamida	 Preparado de 1-5e y *Extremo*-1	TR = 1.21[1]; EMBR: Anal. calculado para $C_{45}H_{50}N_8O_2$ 734.41; encontrado: 735.46 $(M+H)^+$; HRMS: Anal. calculado para $C_{45}H_{51}N_8O_2$ 735.4135 encontrado: 735.4136 $(M+H)^+$.
24-18-6	(2R)-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)-2-(1-piperidinil) acetamida	 Preparado de 1-5e y *Extremo*-14	TR = 1.30[1]; EMBR: Anal. calculado para $C_{51}H_{58}N_8O_2$ 814.47; encontrado: 815.48 $(M+H)^+$; HRMS: Anal. calculado para $C_{51}H_{59}N_8O_2$ 815.4761 encontrado: 815.4744 $(M+H)^+$.

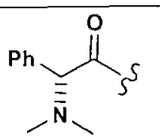
[1]Condiciones CL para 24-18-1 a través 24-18-6: Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% de agua, 10% metanol, 0.1% TFA, B = 10% de agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

Ejemplos 24-19 hasta 24-20



El Ejemplo 24-19 y 24-20 se prepararon como sales TFA de 1-2e-1 y los ácidos respectivos usando el mismo método descrito para el Ejemplo 1.

Ejemplo	*Nombre del compuesto*		*Datos*
24-19	((1*R*)-2-((2*S*)-2-(4-(3'-(2-((2*S*)-1-((2*R*)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1*H*-imidazol-5-il)-3-bifenilil)-1*H*-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 *Extremo-4*	^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.82-1.97 (m, 2H), 1.97-2.17 (m, 4H), 2.18-2.37 (m, 2H), 3.18 (d, *J*=9.77 Hz, 2H), 3.44-3.58 (m, 6H), 3.79-4.04 (m, 2H), 5.09-5.46 (m, 2H), 5.45-5.84 (m, 2H), 6.97-7.49 (m, 10H), 7.61-7.74 (m, 4H), 7.75-7.93 (m, 4H), 8.10-8.32 (m, 4H), 14.48 (app br s, 2H); TR = 1.34 min; LC/MS: Anal. calculado para $[M+H]^+$ $C_{46}H_{47}N_8O_6$: 807.36; encontrado 807.40

24-20	(1*R*)-2-((2*S*)-2-(4-(3'-(2-((2*S*)-1-((2*R*)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1*H*-imidazol-5-il)-3-bifenilil)-1*H*-imidazol-2-il)-1-pirrolidinil)-*N*,*N*-dimetil-2-oxo-1-feniletanamina	 *Extremo*-1	^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.71-2.32 (m, 8H), 3.33-3.68 (m, 2H), 3.89-4.16 (m, *J*=2.75 Hz, 2H), 4.96 (app br s, 12H), 5.26 (s, 2H), 5.45 (s, 2H), 7.03-7.78 (m, 12H), 7.84 (s, 4H), 8.07-8.43 (m, 4H), 9.90-10.87 (m, 2H); TR = 1.10 min; LC/MS: Anal. calculado para $[M+H]^+$ $C_{46}H_{51}N_8O_2$: 747.41; encontrado 747.45

Condiciones CL para 24-19 y 24-20:

Columna = Phenomenex-Luna 3.0X 50 mm S10

Inicio %B = 0

Final %B = 100

Tiempo de Gradiente = 2 min

Tiempo de paro = 3 min

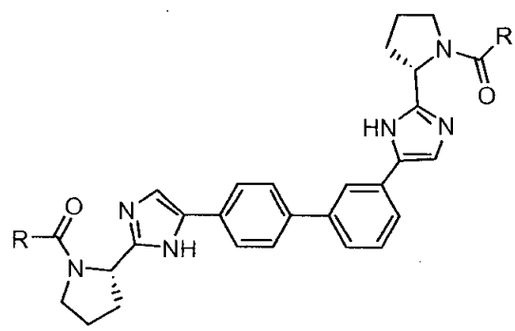
Relación de flujo = 4 mL/min

Longitud de onda = 220 nm

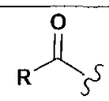
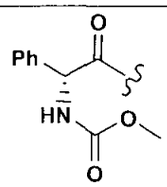
Solvente A = 0.1% TFA en 10% metanol/90%H_2O

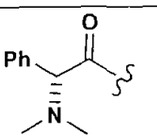
Solvent B = 0.1% TFA en 90% metanol/10% H_2O

Ejemplos 24-21 hasta 24-22



El Ejemplo 24-21 y 24-22 se prepararon como sales TFA de 1-4e y los ácidos carboxílicos respectivos usando el mismo método descrito para el Ejemplo 1.

Ejemplo	*Nombre del Compuento*		*Datos*
24-21	((1*R*)-2-((2*R*)-2-(4-(3'-(2-((2*S*)-1-((2*R*)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1*H*-imidazol-4-il)-4-bifenilil)-1*H*-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 *Extremo-4*	^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.73-2.37 (m, 8H), 3.13 (s, 2H), 3.36-4.29 (m, 8H), 5.26 (s, 2H), 5.53 (s, 2H), 6.99-8.61 (m, 22H), 14.51 (s, 2H); TR = 1.33 min; LC/MS: Anal. calculado para $[M+H]^+$ $C_{46}H_{47}N_8O_6$: 807.36; encontrado 807.58

24-22	(1*R*)-2-((2*R*)-2-(4-(3'-(2-((2*S*)-1-((2*R*)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1*H*-imidazol-4-il)-4-bifenilil)-1*H*-imidazol-2-il)-1-pirrolidinil)-*N*,*N*-dimetil-2-oxo-1-feniletanamina	 *Extremo*-1	^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.84-2.32 (m, 8H), 2.92-3.10 (m, 2H), 3.92-4.08 (m, 2H), 4.43 (app br s, 12H), 5.16-5.37 (m, 2H), 5.39-5.58 (m, 2H), 7.16-8.24 (m, 20H), 9.60-10.46 (m, 2H); TR = 1.08 min; LC/MS: Anal. calculado para $[M+H]^+$ $C_{46}H_{51}N_8O_2$: 747.41; encontrado 747.45

Condiciones CL para el 24-21 y 24-22:

Columna = Phenomenex-Luna 3.0X 50 mm S10

Inicio %B = 0

Final %B = 100

Tiempo de gradiente = 2 min

Tiempo de paro = 3 min

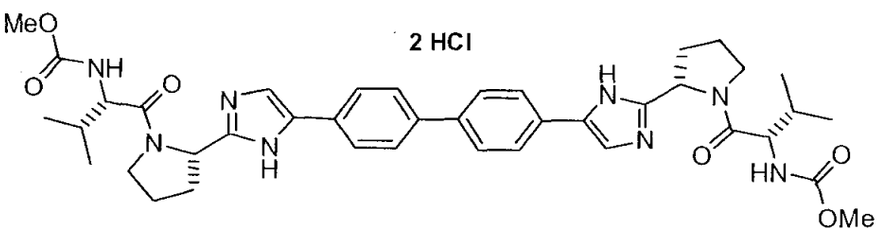
Relación de flujo = 4 mL/min

Longitud de onda = 220 nm

Solvente A = 0.1% TFA en 10% metanol/90%H_2O

Solvent B = 0.1% TFA en 90% metanol/10% H_2O

Ejemplo 24-23



((1S)-1-(((2S)-2-(5-(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

Un matraz de fondo redondo de 50 ml equipado con una línea de nitrógeno y una barra de agitación se cargó secuencialmente con 2.5 mL de acetonitrilo, 0.344 g (2.25 mmol, 2.5 equiv) hidrato de hidroxi benzotriazol, 0.374 g (2.13 mmol, 2.4 equiv) *N*-

(metoxicarbonil)-L-valina, 0.400 g (2.09 mmol, 2.4 equiv) clorohidrato de 1-(3-dimetiaminopropil)-3-etilcarbodiimida y 2.5mL adicionales de acetonitrilo. La solución resultante se agitó a 20°C durante 1 hora y se cargó con 0.501 g (0.88 mmol, 1 equiv) el Ejemplo A-1e-4. La mezcla espesa se enfrió a ca. 0°C y 0.45 g (3.48 mmol, 4 equiv) diisopropiletilamina se agregó durante 30 min mientras se mantiene una temperatura de bajo de 10°C. La solución se calentó lentamente a 15°C durante 3h y se mantuvo a 15°C durante 16h. La solución resultante se cargó con 3.3 g de NaCl acuoso al 13% en peso y se calentó a 50°C durante 1h. Después de enfriarse a 20°C, 2.5 mL de acetato de isopropilo se agregó. La fase orgánica rica se lavó con 2 x 6.9 mL de una solución 0.5 N NaOH que contiene 13 % en peso NaCl seguido por 3.3 g de NaCl acuoso al 13 % en peso. La mezcla luego se intercambió en el solvente en acetato de isopropilo por destilación al vacío a un volúmen objetivo de 10 mL. La solución turbia resultante se enfrió a 20°C y se filtró a través de un filtro 0.45 μm. La solución clara luego se intercambió en solvente en etanol por destilación al vacío con un volumen objetivo de 3 mL. Se agregó 1.67 mL (2.02 mmol, 2.3 equiv) de HCl 121 M

en etanol. La mezcla se agitó entonces a 25°C durante 15 horas. La mezcla espesa resultante se filtró y la torta filtro se lavó con 2.5 ml de 2:1 de acetona:etanol. Los sólidos se secaron en un horno al vacío a 50°C para dar 0.550 g (0.68 mmol, 77%) del producto deseado.

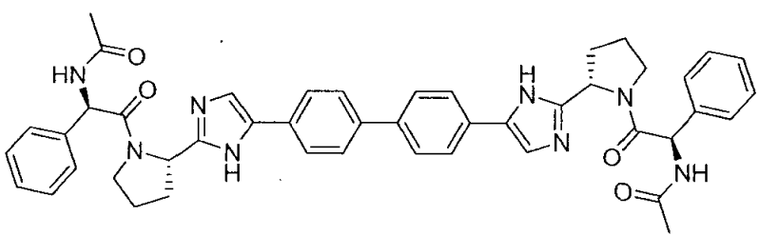
Recristalización del Ejemplo 24-23

Una solución del Ejemplo 24-23 preparada arriba se preparó al disolver 0.520 g del producto anterior en 3.65 mL de metanol. La solución se cargó entonces con 0.078 g de Carbono Cuno Zeta tipo 53SP y se permitió que se agitara durante 0.25 h. La mezcla se filtró entonces y se lavó con 6 ml de metanol. La solución rica en producto se concentró hasta 2.6 mL por destilación al vacío. Se agregó 7.8 mL de acetona y se permitió agitar a 25°C durante 15 h. Los sólidos se filtraron, se lavaron con 25 mL de 2:1 acetona: etanol y se secaron en un horno al vacío a 70 °C para dar 0.406 g (57.0%) del producto deseado como cristales blancos: ^{1}H RMN (400 MHz, DMSO-d_6, 80 °C): 8.02 (d, J=8.34 Hz, 4 H), 7.97 (s, 2 H), 7.86 (d, J=8.34 Hz, 4 H),
6.75 (s, 2 H), 5.27 (t, J=6.44 Hz, 2 H), 4.17 (t, J=6.95 Hz, 2 H), 3.97 - 4.11 (m, 2 H), 3.74 - 3.90 (m, 2 H), 3.57 (s, 6 H), 2.32 - 2.46 (m, 2 H), 2.09 -

2.31 (m, 6 H), 1.91 - 2.07 (m, 2 H), 0.88 (d, *J*=6.57 Hz, 6 H), 0.79 (d, *J*=6.32 Hz, 6 H); ^{13}C RMN (75 MHz, DMSO-d_6): δ 170.9, 156.9, 149.3, 139.1, 131.7, 127.1, 126.5, 125.9, 115.0, 57.9, 52.8, 51.5, 47.2, 31.1, 28.9, 24.9, 19.6, 17.7; IR (puro, cm^{-1}): 3385, 2971, 2873, 2669, 1731, 1650. Anal. Calculado para $C_{40}H_{52}N_8O_6Cl_2$: C, 59.18; H, 6.45; N, 13.80; Cl, 8.73. Encontrado C, 59.98; H, 6.80; N, 13.68; Cl, 8.77. pf 267 °C (descompuesto). Las posiciones pico de difracción características (grados 2θ ± 0.1) @ TA, se basan en un patrón de alta calidad colectado con un difractómetro (CuKα) con un hilado capilar con 2θ calibrado con un NIST, otros estándares apropiados son como sigue: 10.3, 12.4, 12.8, 13.3, 13.6, 15.5, 20.3, 21.2, 22.4, 22.7, 23.7.

Ejemplo 25

N,N'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))diacetamida

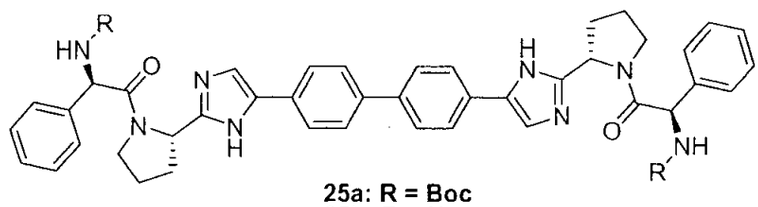


Ejemplo 25 Extremo a:

(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))biscarbamato de di-tert-butilo

y

Ejemplo 25 Extremo b:



25a: R = Boc
25b: R = H

El HATU (96.2 mg, 0.253 mmol) se agregó a una mezcla de pirrolidina 1e (52.6 mg, 0.124 mmol), diisopropiletilamina (100 µL, 0.57 mmol) y Boc-D-Phg-OH (69 mg, 0.275 mmol) en DMF (3.0 mL). La mezcla de reacción se agitó durante 25 minutos, y luego se diluyó con metanol y se purificó por sistema HPLC de fase inversa (H_2O/metanol/TFA). El HPLC eluido se neutralizó con exceso de 2.0 M/NH_3 en CH_3OH y el componente volátil se removió *in vacuo*. El residuo se dividió cuidadosamente entre CH_2Cl_2 y $NaHCO_3$ saturado. La fase acuosa se extrajo con más CH_2Cl_2 (2x). La fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró *in vacuo* para proporcionar 25a como una película del aceite semisólido (78.8 mg). CL (Cond. 1): TR = 1.99 min; >98% índice de

homogeneidad. LC/MS: Análisis calculado para $[M+H]^+$ $C_{52}H_{59}N_8O_6$: 891.46; encontrado 891.55.

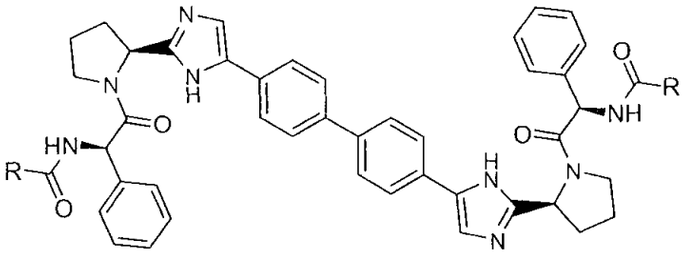
El carbamato 25a se convirtió a la amina 25b de conformidad al procedimiento descrito por la preparación del 1e. CL (Cond. 1): TR = 1.44 min; 97% índice de homogeneidad. LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{43}N_8O_2$: 691.35; encontrado 691.32

Ejemplo 25

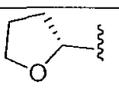
N,N'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))diacetamida

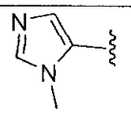
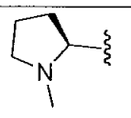
El anhídrido acético (20 µL, 0.21 mmol) se agregó a una solución DMF (1.5 mL) de amina 25b (29 mg, 0.042 mmol) y trietilamina (30 µL, 0.22 mmol) y se agitó durante 2.5 horas. La mezcla de reacción luego se trató con NH_3/metanol (1 mL de 2 M) y se agitó durante 1.5 horas adicionales. El componente volátil se removió *in vacuo* y el residuo se purificó por Sistema HPLC de fase inversa (H_2O/metanol/ TFA) para proporcionar la sal TFA del ejemplo 25 como una espuma blanca (28.1 mg). CL (Cond.Ib): TR = 1.61 min; >98% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{46}H_{47}N_8O_4$: 775.37; encontrado 775.40; HRMS: Análisis calculado para $[M+H]^+$ $C_{46}H_{47}N_8O_4$: 775.3720; encontrado 775.3723

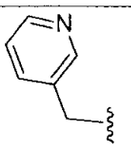
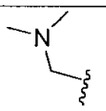
Ejemplo 25-1 hasta 25-5

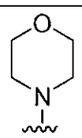


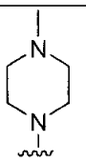
Los ejemplos 25-1 hasta 25-5 se prepararon a partir de 25b y el ácido carboxílico apropiado usando condiciones formados por amida estándar similares a aquellas descritas por la preparación del ejemplo 1 a partir de 1e. Los ejemplos 25-6 hasta 25-8 se prepararon a partir de 25b y el apropiado cloruro de carbamoilo o isocianato.

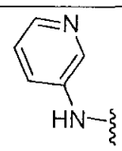
Número de ejemplo	Nombre del compuesto	R	TR (CL-Cond.); % de índice de homogeneidad; datos EM
25-1	(2R,2'R)-N,N'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))ditetrahidro-2-furancarboxamida		TR = 5.68 minutos; HPLC Xterra 4.6 X 50 mm, 0 hasta 100% B durante 10 minutos, un minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% ácido fosfórico, B = 10% agua, 90% metanol, 0.2% ácido fosfórico; LCMS: Análisis calculado para: $C_{52}H_{54}N_8O_6$: 887.06; Encontrado: 887.58 $(M+H)^+$

25-2	N,N'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))bis(1-metil-1H-imidazol-5-carboxamida)		TR = 3.54 minutos; HPLC Xterra 4.6 X 50 mm, 0 hasta 100% B durante 10 minutos, un minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% ácido fosfórico, B = 10% agua, 90% metanol, 0.2% ácido fosfórico; LCMS: Análisis calculado para: $C_{52}H_{50}N_{12}O_4$: 907.06; Encontrado: 907.42 $(M+H)^+$
25-3	(2S,2'S)-N,N'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))bis(1-metil-2-pirrolidincarboxamida)		TR= 3.1 minutos; HPLC Xterra 4.6 X 50 mm, 0 hasta 100% B durante 10 minutos, un minuto tiempo de espera , A = 90% agua, 10% metanol, 0.2% ácido fosfórico, B = 10% agua, 90% metanol, 0.2% ácido fosfórico; LCMS: Análisis calculado para: $C_{54}H_{60}N_{10}O_4$ 913.14; Encontrado: 913.54 $(M+H)^+$

25-4	N,N'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))bis(2-(3-piridinil)acetamida)		TR= 3.37 minutos; HPLC Xterra 4.6 X 50 mm, 0 hasta 100% B durante 10 minutos, un minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% ácido fosfórico, B = 10% agua, 90% metanol, 0.2% ácido fosfórico; LCMS: Análisis calculado para: $C_{56}H_{52}N_{10}O_4$ 929.10 Encontrado: 929.42 $(M+H)^+$
25-5	N,N'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))bis(2-(dimetilamino)acetamida) (nombre no preferido)		TR= 7.07 minutos; HPLC Xterra 4.6 X 50 mm, 0 hasta 100% B durante 10 minutos, un minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% ácido fosfórico, B = 10% agua, 90% metanol, 0.2% ácido fosfórico; LCMS: Análisis calculado para: $C_{50}H_{56}N_{10}O_4$ 861.07 Encontrado: 859.69 $(M+H)^+$

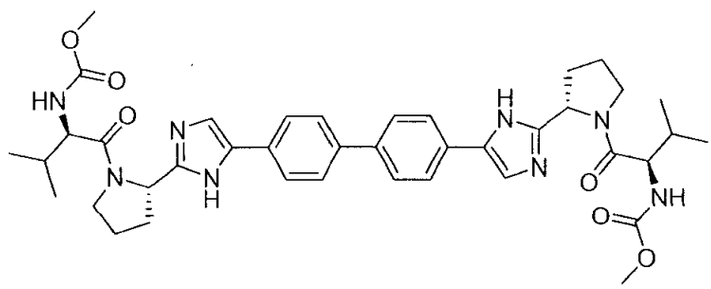
25-6	N,N'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))di(4-**morfolincarboxamida)**		^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.86-2.18 (m, 6H), 2.23-2.39 (m, 2H), 3.20-3.40 (m, 8H), 3.40-3.61 (m, 8H), 3.90-4.19 (m, 4H), 5.27 (dd, J=8.09, 3.51 Hz, 2H), 5.37-5.63 (m, 2H), 6.92-7.11 (m, 3H), 7.30-7.45 (m, 5H), 7.44-7.56 (m, 4H), 7.83-8.04 (m, 8H), 8.15 (s, 2H), 14.29 (s, 2H); HPLC Xterra 4.6 X 50 mm, 0 hasta 100% B durante 10 minutos, un minuto tiempo de espera , A = 90% agua, 10% metanol, 0.2% ácido fosfórico, B = 10% agua, 90% metanol, 0.2% ácido fosfórico, TR = 6.01 minutos; LCMS: Análisis calculado para: $C_{52}H_{56}N_{10}O_6$ 917.09; Encontrado: 917.72 $(M+H)^+$

25-7	N,N'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))bis(4-metil-1-piperazincarboxamida)		TR= 3.74 minutos; HPLC Xterra 4.6 X 50 mm, 0 hasta 100% B durante 10 minutos, un minuto tiempo de espera ., A = 90% agua, 10% metanol, 0.2% ácido fosfórico, B = 10% agua, 90% metanol, 0.2% ácido fosfórico; LCMS: Análisis calculado para: $C_{54}H_{62}N_{12}O_4$ 943.17; Encontrado: 943.84 $(M+H)^+$

25-8	N,N''-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))bis(3-(3-piridinil)urea)		^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.79-2.17 (m, 6H), 2.29 (d, J=9.77 Hz, 2H), 3.06-3.39 (m, 2H), 3.72-4.14 (m, 2H), 5.27 (dd, J=8.24, 2.75 Hz, 2H), 5.66 (d, J=7.02 Hz, 2H), 7.26-7.65 (m, 12H), 7.82-8.11 (m, 12H), 8.17 (s, 2H), 8.23-8.45 (m, 2H), 8.61-8.97 (m, 2H), 9.38 (s, 2H), 14.51 (s, 2H); HPLC Xterra 4.6 X 50 mm, 0 hasta 100% B durante 10 minutos, un minuto tiempo de espera , A = 90% agua, 10% metanol, 0.2% ácido fosfórico, B = 10% agua, 90% metanol, 0.2% ácido fosfórico, TR = 4.05 minutos; LCMS: Análisis calculado para: $C_{54}H_{50}N_{12}O_4$ 931.08; Encontrado: 931.78 $(M+H)^+$.

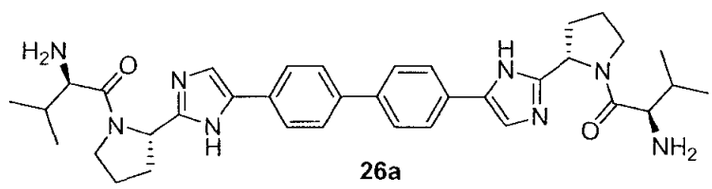
Ejemplo 26

((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-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 26, Extremo a

(2R,2'R)-1,1'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(3-metil-1-oxo-2-butanamina)



26a

La diamina 26a se preparó iniciando a partir de pirrolidina 1e y BOC-D-Val-OH de conformidad al procedimiento descrito para la síntesis de diamina 25b.

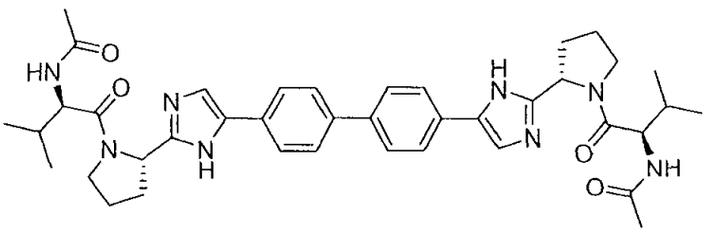
Ejemplo 26

((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-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

El cloroformiato de metilo (18 µL, 0.23 mmol) se agregó a una solución THF (1.5 mL) de diamina 26a (30 mg, 0.048 mmol) y trietilamina (30 µL, 0.22 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 3 horas. Los componentes volátiles se removieron *in vacuo*, y el residuo se trató con NH_3/metanol (2 mL de 2 M) y se agitó a condiciones ambientales durante 15 minutos. Todo el componente volátil se removió *in vacuo*, y el producto crudo se purificó por HPLC preparativa de fase inversa (H_2O/metanol/TFA) para proporcionar la sal TFA del ejemplo 26 como un sólido blanco (13.6 mg). CL (Cond.II): TR = 2.00 min; >98% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.39; encontrado 739.67; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.3932; encontrado 739.3966.

Ejemplo 27

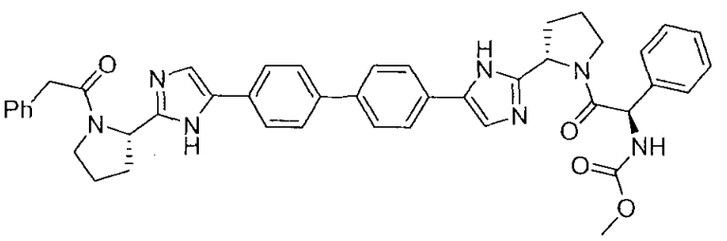
N-((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-acetamido-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)acetamida



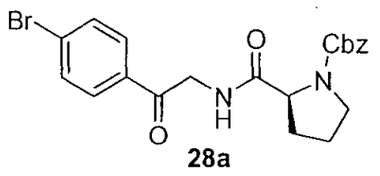
La diamina 26a se convirtió al ejemplo 27 (Sal TFA) de conformidad a un método descrito en la preparación del ejemplo 25. CL (Cond.II): TR = 1.93min; >98% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{51}N_8O_4$: 707.40; encontrado 707.59; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{51}N_8O_4$: 707.4033; encontrado 707.4054.

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



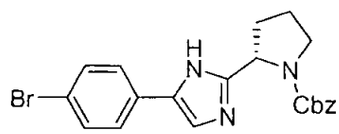
Ejemplo 28, Extremo a



28a

La HATU (19.868g, 52.25 mmol) se agregó a una mezcla heterogénea de *N*-Cbz-L-prolina (12.436 g, 49.89 mmol) y la sal HCl de la 2-amino-1-(4-bromofenil)etanona (12.157 g, 48.53 mmol) en DMF (156 mL). La mezcla se redujo en un baño de agua con hielo, e inmediatamente a continuación *N,N*-diisopropiletilamina (27 mL, 155 mmol) se agregó en porciones a esto durante 13 minutos. Después de que la adición base se completó, el baño frío se removió y la mezcla de reacción se agitó durante 50 minutos adicionales. El componente volátil se removió *in vacuo*; agua (125 mL) se agregó al sólido crudo resultante y se agitó durante alrededor de 1 hora. El sólido blanco opaco se filtró y se lavó con agua copiosa, y se secó *in vacuo* 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); CL (Cond. I): TR = 1.65 min; 98% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{21}H_{22}BrN_2O_4$: 445.08; encontrado 445.31.

Ejemplo 28, Extremo b



28b

La cetoamida 28a (10.723g, 24.08 mmol) se convirtió al 28b de conformidad al procedimiento descrito para la síntesis de carbamato 1b, con la excepción de que el material crudo se purificó por cromatografía instantánea (la muestra se cargó con solvente eluido; 50% acetato de etilo/hexanos). El bromuro 28b se recuperó como una espuma blanca opaca (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). CL (Cond.I): TR = 1.42 min; >95% 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 HPLC quiral, y un ee de 99% se observó.

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

Solvente: 20% etanol/heptano (isocrático)

Relación de flujo: 1 mL/min

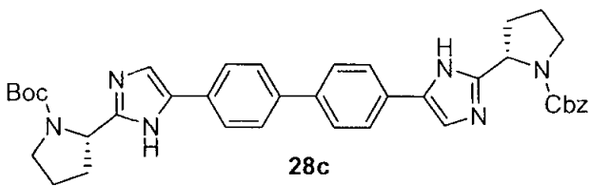
Longitud de onda: 254 nm

Tiempo de retención relativa: 1.82 minutos (*R*), 5.23

minutos (*S*)

Ejemplo 28, Extremo c

(2S,2'S)-2,2'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil))di(1-pirrolidincarboxilato) de bencil tert-butilo



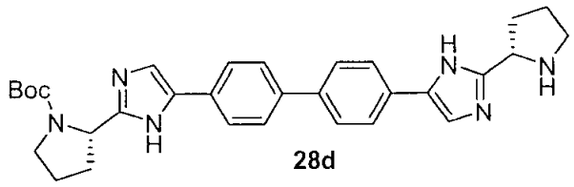
28c

El $Pd(Ph_3P)_4$ (711.4 mg, 0.616 mmol) se agregó a una mezcla de boronato éster 1c (7.582 g, ~ 17 mmol), bromuro 28b (7.62 g, 17.87 mmol), $NaHCO_3$ (4.779 g, 56.89 mmol) 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 luego el componente volátil se removió *in vacuo*. El residuo se dividió entre CH_2Cl_2 y agua, y la capa acuosa se extrajo con CH_2Cl_2. La fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró *in vacuo*. El material resultante se sometió a cromatografía instantánea (la muestra se cargó con una malla de gel de sílice; acetato de etilo se usó como eluyente) para proporcionar el bifenilo 28c como una espuma blanca opaca que contiene Ph_3PO impureza (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); CL (Cond.I): TR = 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, Extremo d

(2S)-2-(5-(4'-(2-((2S)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidincarboxilato de tert-butilo



28d

El K_2CO_3 (187.8 mg, 1.36 mmol) se agregó a una mezcla de catalizador (10% Pd/C; 205.3 mg), carbamato 28c (1.018 g, ~ 1.5 mmol), metanol (20 mL) y 3 gotas de agua con pipeta. Un globo de H_2 se colocó y la mezcla se agitó durante 6 horas. Luego, el catalizador adicional (10% Pd/C, 100.8 mg) y K_2CO_3 (101.8 mg, 0.738 mmol) se agregaron y se continuó agitando durante 3.5 horas. Durante el proceso de hidrogenación, el globo de H_2 se cargó a intervalos de tres tiempos. La mezcla de reacción se filtró a través de una almohadilla de tierra diatomácea (Celite® 521), y el filtrado se removió *in vacuo*. El material crudo resultante se sometió a cromatografía instantánea usando una columna corta (la

muestra se cargó con una malla de gel de sílice; 0-20% metanol/CH_2Cl_2 se usó como eluyente) para proporcionar el 28d como una espuma amarilla ligera (605.6 mg). ^{1}H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.18/11.89/11.82 (tres 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 (dos br s, 9H). Nota: la señal de NH pirrolidina parece que se sobrepone con las señales en la región 3.6-3.2 ppm; CL (Cond.I): TR = 1.21 min; >95% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{31}H_{37}N_6O_2$: 525.30; encontrado 525.40.

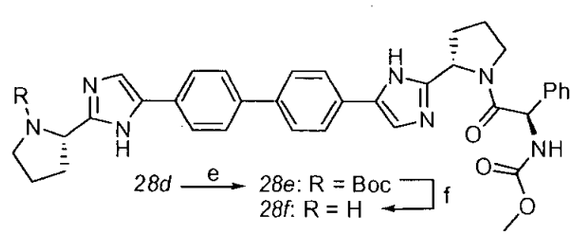
Ejemplo 28, Extremo e-f

Ejemplo 28 Extremo 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 tert-butilo

Ejemplo 28 Extremo 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

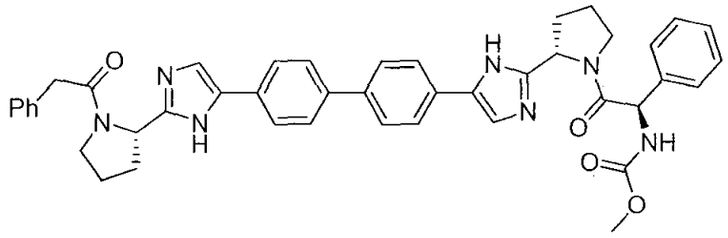


Extremo e: El HATU (316.6 mg, 0.833 mmol) se agregó a una solución DMF (7.0 mL) de pirrolidina 28d (427 mg, 0.813 mmol), Extremo-4 (177.6 mg, 0.849 mmol) y diisopropiletilamina (0.32 mL, 1.84 mmol), y la mezcla de reacción se agitó durante 45 minutos. El componente volátil se removió in vacuo, y el residuo se dividió entre CH_2Cl_2 (50 mL) y un medio acuoso (20 mL H_2O + 1 mL solución $NaHCO_3$ saturada). 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 in vacuo. El aceite amarillo resultante se purificó por cromatografía instantánea (gel de sílice; acetato de etilo) para proporcionar el 28e como una espuma amarilla (336 mg). CL (Cond. 1): TR = 1.68min; 91% de índice de homogeneidad; LC/MS: Anal. Calculado para $[M+H]^+$ $C_{41}H_{46}N_7O_5$: 716.35; encontrado 716.53.

Extremo f: El carbamato 28e se elavoró para la amina 28f al emplear el procedimiento descrito en la conversión de 1d to 1e. CL (Cond. 1): TR = 1.49min; >98% de índice de homogeneidad. LC/MS: Anal. Calculado para $[M+H]^+$ $C_{36}H_{38}N_7O_3$: 616.30; encontrado 616.37; HRMS: Anal. Calculado para $[M+H]^+$ $C_{36}H_{38}N_7O_3$: 616.3036; encontrado 616.3046.

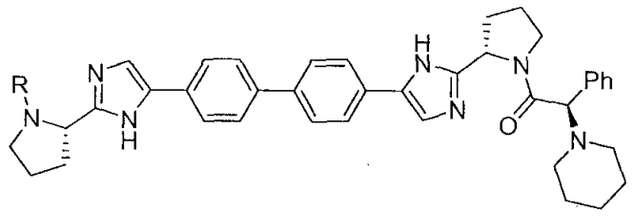
Ejemplo 28

((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 a la sal TFA del ejemplo 28 al emplear la última Extremo 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; incluye la señal de OCH_3 a 3.54 & 3.53), 2.45-1.72 (m, 8H). CL (Cond. Ib): TR = 1.66 minutos, >98% 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 28-1 hasta 28-4



Los ejemplos 28-1 hasta el 28-4 (Los grupos R se mostraron en la tabla a continuación) se prepararon en una

manera similar al ejemplo 28 por medio del intermedio del intermediario 28d.

Ejemplo 28-1

(1R)-N,N-dimetil-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etanamina

El extremo-1 se adjuntó, el carbamato Boc se removió con TFA or HCl, y Extremo-14 se adjuntó.

Ejemplo 28-2

1-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)piperidina

El ácido tetrahidrofuroico se adjuntó, el carbamato Boc se removió con TFA o HCl, y el extremo-14 se adjuntó.

Ejemplo 28-3

((1R)-1-(2-clorofenil)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)carbamato de metilo

El extremo-40 se adjuntó, el carbamato Boc se removió con TFA o HCl, y el extremo-14 se adjuntó.

Ejemplo 28-4

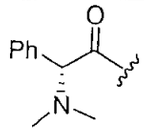
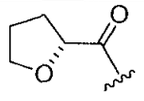
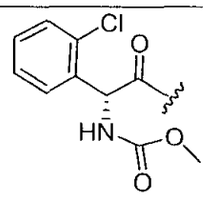
(1R)-1-(2-clorofenil)-N,N-dimetil-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etanamina

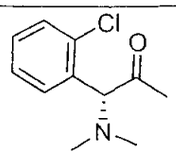
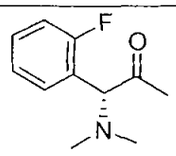
El extremo-39 se adjuntó, el carbamato Boc se removió con TFA o HCl, y el extremo-14 se adjuntó.

Ejemplo 28-5

(1R)-1-(2-fluorofenil)-N,N-dimetil-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etanamina

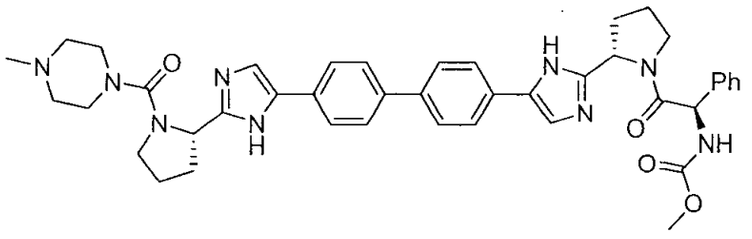
El extremo-38 se adjuntó, el carbamato Boc se removió con TFA o HCl, y el extremo-14 se adjuntó.

Ejemplo	Nombre del Compuesto	R	Datos
28-1	(1R)-N,N-dimetil-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etanamina		LCMS: Anal. Calculado para $C_{49}H_{54}N_8O_2$: 786; encontrado: 787 $(M+H)^+$.
28-2	1-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)piperidina		LCMS: Anal. Calculado para $C_{44}H_{49}N_7O_3$: 723; encontrado: 724 $(M+H)^+$.
28-3	((1R)-1-(2-clorofenil)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)carbamato de metilo		LCMS: Anal. Calculado para $C_{49}H_{51}ClN_8O_4$: 850; encontrado: 851 $(M+H)^+$.

28-4	(1R)-1-(2-clorofenil)-N,N-dimetil-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etanamina		LCMS: Anal. Calculado para $C_{49}H_{53}ClN_8O_2$: 820; encontrado: 821 $(M+H)^+$.
28-5	(1R)-1-(2-fluorofenil)-N,N-dimetil-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etanamina		LCMS: Anal. Calculado para $C_{49}H_{53}FN_8O_2$: 804; encontrado: 805 $(M+H)^+$.

Ejemplo 29

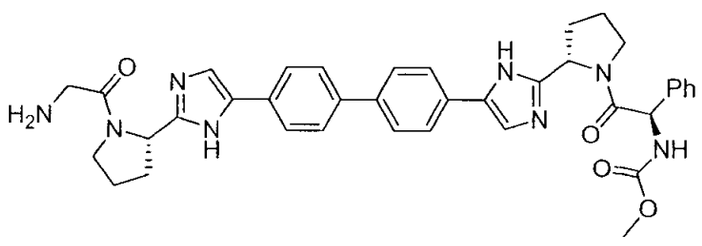
((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-metil-1-piperazinil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo



El cloruro de 4-Metilpiperazina-1-carbonilo/HCl (11.6 mg, 0.58 mmol) se agregó a una mezcla de 28f (30 mg, 0.049 mmol), trietilamina (15 µl, 0.11 mmol) y THF (1.0 mL), y se agitó a condiciones ambientales durante 1 hora. El componente volátil se removió *in vacuo*, y el residuo se purificó por HPLC de fase inversa (H_2O/metanol/TFA) para proporcionar la sal TFA del ejemplo 29 como una espuma amarilla ligera (29.3 mg). CL (Cond. 2): TR = 1.82 minutos, >98% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{48}N_9O_4$: 742.38; encontrado 742.49.

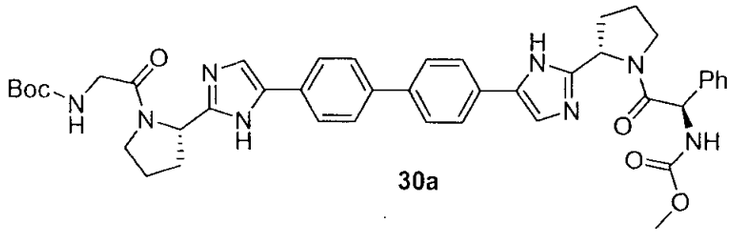
Ejemplo 30

((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-glicil-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo



Ejemplo 30, Extremo a

((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(tert-butoxicarbonil)glicil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo



30a

El carbamato 30a se preparó a partir de pirrolidina 28f y Boc-Glicina usando el procedimiento descrito por la preparación del 25a a partir de 1e. CL (Cond. 2): TR = 2.12 minutos, >98% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{49}N_8O_6$: 773.38; encontrado 773.46.

Ejemplo 30

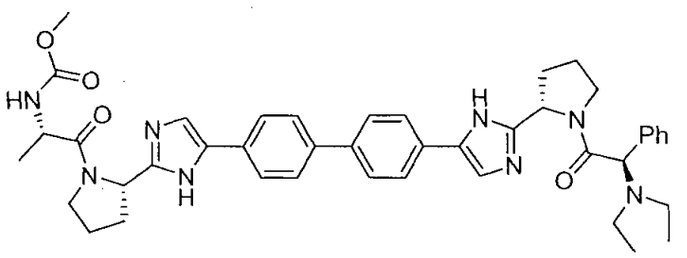
((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-glicil-2-pirrolidinil)-1H-

imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo

El carbamato 30a se convirtió al ejemplo 30 de conformidad al procedimiento descrito por la preparación del 1e a partir de 1d. CL (Cond. II): TR = 1.81 minutos, >98% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{41}N_8O_4$: 673.33; encontrado 673.43. HRMS: Análisis calculado para $[M+H]^+$ $C_{38}H_{41}N_8O_4$: 673.3251; encontrado 673.3262.

Ejemplo 30-1

((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo

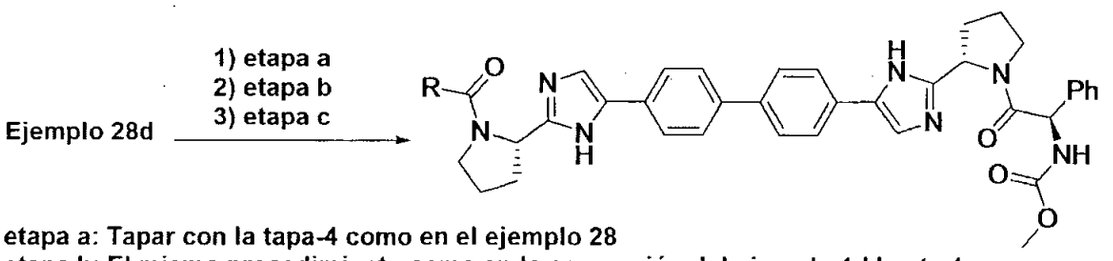


El ejemplo 30-1 se preparó en tres Extremos a partir del ejemplo 28d. Extremo uno: adjuntar el extremo 2 usando el procedimiento que describe la síntesis del 28e a partir del 28d. Extremo dos: Hidrolizar el carbamato Boc usando el procedimiento que describe la síntesis del

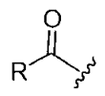
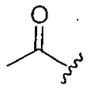
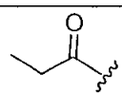
28f a partir del 28e. Extremo tres: Extremor el extremo 52 usando el procedimiento que describe la síntesis del 28e a partir del 28d. TR = 1.70 min (Cond. Ib); >95% índice de homogeneidad. LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.40; encontrado, 743.50. HRMS: Análisis calculado para $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.4033; encontrado, 743.4053.

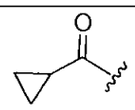
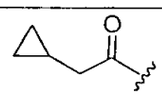
Substituyendo el cloruro de ácido apropiado o ácido carboxílico en el ejemplo 29 ó 30, los siguientes compuestos (Ejemplo 31-107) se prepararon como sales TFA.

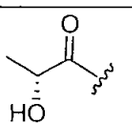
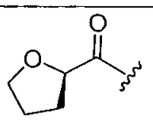
Ejemplo 31 hasta 84-88

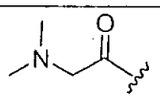
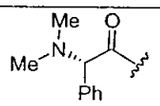


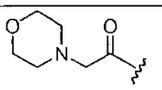
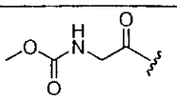
etapa a: Tapar con la tapa-4 como en el ejemplo 28
etapa b: El mismo procedimiento como en la conversión del ejemplo 1d hasta 1e
etapa c: Como en la última etapa del ejemplo 1 usando 1.1 equivalente del ácido carboxílico apropiado y HATU

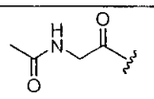
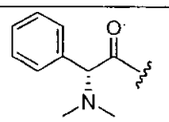
Ejemplo	Nombre del compuesto		Tiempo de retención (Condición-CL); Datos EM de índice de homogeneidad
31	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-acetil-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.54 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{40}N_7O_4$: 658.31; encontrado 658.42; HRMS: Análisis calculado para $[M+H]^+$ $C_{38}H_{40}N_7O_4$: 658.3142; encontrado 658.3135
32	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-propionil-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		1.57 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{39}H_{42}N_7O_4$: 672.33; encontrado 672.46; HRMS: Análisis calculado para $[M+H]^+$ $C_{39}H_{42}N_7O_4$: 672.3298; encontrado 672.3299

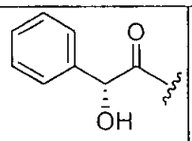
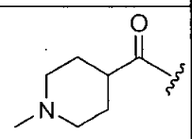
33	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(ciclopropilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.59 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{42}N_7O_4$: 684.33; encontrado 684.44; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{42}N_7O_4$: 684.3298; encontrado 684.3324
34	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(ciclopropilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.61 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{42}N_7O_4$: 698.35; encontrado 698.48; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{42}N_7O_4$: 698.3455; encontrado 698.3489

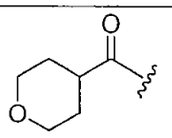
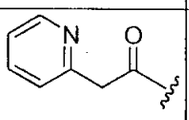
35	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hidroxipropanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.54 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{39}H_{42}N_7O_5$: 688.33; encontrado 688.47
36	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		1.59 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{44}N_7O_5$: 714.34; encontrado 714.49; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{44}N_7O_5$: 714.3404; encontrado 714.3430

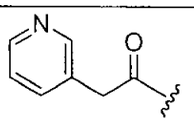
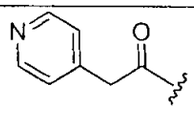
37	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dimetilglicil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.48 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{45}N_8O_4$: 701.36; encontrado 701.49; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{45}N_8O_4$: 701.3564; encontrado 701.3553
38	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-1	1.20 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{46}H_{49}N_8O_4$: 777.39; encontrado 777.61; HRMS: Análisis calculado para $[M+H]^+$ $C_{46}H_{49}N_8O_4$: 777.3877; encontrado 777.3909

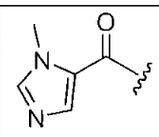
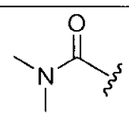
39	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morfolinilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.79 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{47}N_8O_5$: 743.37; encontrado 743.49; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{47}N_8O_5$: 743.3669; encontrado 743.3672
40	(2-((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-pirrolidinil)-2-oxoetil)carbamato de metilo		1.92 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{43}N_8O_6$: 731.33; encontrado 731.42; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{43}N_8O_6$: 731.3306; encontrado 731.3333

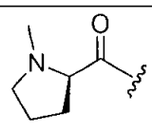
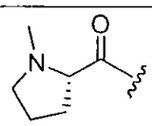
41	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-acetilglicil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.86 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{43}N_8O_5$: 715.34; encontrado 715.49; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{43}N_8O_5$: 715.3356; encontrado 715.3369
42	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.85 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{46}H_{49}N_8O_4$: 777.39; encontrado 777.56

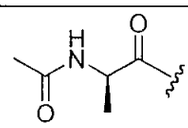
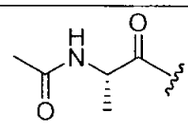
43	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hidroxi-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.96 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{44}N_7O_5$: 750.34; encontrado 750.51; HRMS: Análisis calculado para $[M+H]^+$ $C_{44}H_{44}N_7O_5$: 750.3404; encontrado 750.3437
44	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-metil-4-piperidinil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.78 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{49}N_8O_4$: 741.39; encontrado 741.55; HRMS: Análisis calculado para $[M+H]^+$ $C_{43}H_{49}N_8O_4$: 741.3877; encontrado 741.3893

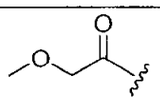
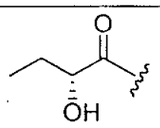
45	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(tetrahidro-2H-piran-4-ilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		1.87 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{46}N_7O_5$: 728.36; encontrado 728.52; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{46}N_7O_5$: 728.3560; encontrado 728.3587
46	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-piridinilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		1.80 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{43}N_8O_4$: 735.34; encontrado 735.51; HRMS: Análisis calculado para $[M+H]^+$ $C_{43}H_{43}N_8O_4$: 735.3407; encontrado 735.3416

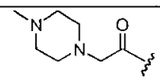
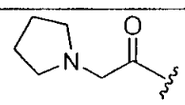
47	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-piridinilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		1.76 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{43}N_8O_4$: 735.34; encontrado 735.52
48	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-piridinilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		1.77 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{43}N_8O_4$: 735.34; encontrado 735.50; HRMS: Análisis calculado para $[M+H]^+$ $C_{43}H_{43}N_8O_4$: 735.3407; encontrado 735.3405

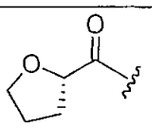
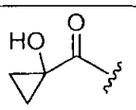
49	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-metil-1H-imidazol-5-il)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.77 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{42}N_9O_4$: 724.34; encontrado 724.51; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{42}N_9O_4$: 724.3360; encontrado 724.3380
50	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(dimetilcarbamoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.91 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{39}H_{43}N_8O_4$: 687.34; encontrado 687.49; HRMS: Análisis calculado para $[M+H]^+$ $C_{39}H_{43}N_8O_4$: 687.3407; encontrado 687.3414

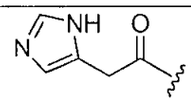
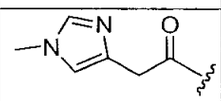
51	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-metil-D-prolil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-10	1.79 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.37; encontrado 727.34; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.3720; encontrado 727.3719
52	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-metil-L-prolil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 enantiómero de la Extremo-10	1.77 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.37; encontrado 727.33; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.3720; encontrado 727.3738

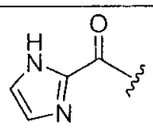
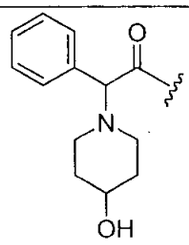
53	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-acetil-D-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.92 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{45}N_8O_5$: 729.35; encontrado 729.33; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{45}N_8O_5$: 729.3513; encontrado 729.3530
54	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-acetil-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.87 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{45}N_8O_5$: 729.35; encontrado 729.33

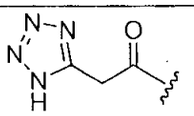
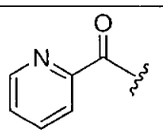
55	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(metoxiacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.89 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{39}H_{42}N_7O_5$: 688.32; encontrado 688.28; HRMS: Análisis calculado para $[M+H]^+$ $C_{39}H_{42}N_7O_5$: 688.3247; encontrado 688.3231
56	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hidroxibutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.91 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{44}N_7O_5$: 702.34; encontrado 702.30; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{44}N_7O_5$: 702.3404; encontrado 702.3393

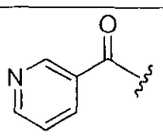
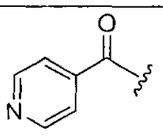
57	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-metil-1-piperazinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.80 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{50}N_9O_4$: 756.40; encontrado 756.36; HRMS: Análisis calculado para $[M+H]^+$ $C_{43}H_{50}N_9O_4$: 756.3986; encontrado 756.3965
58	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-pirrolidinilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		1.82 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.37; encontrado 727.33; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.3720; encontrado 727.3696

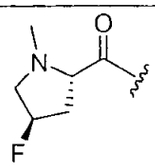
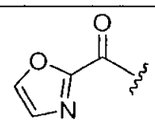
59	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		1.94 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{43}N_7O_5$: 714.34; encontrado 714.24
60	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-hidroxiciclopropil) carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.93 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{42}N_7O_5$: 700.32; encontrado 700.23; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{42}N_7O_5$: 700.3247; encontrado 700.3265

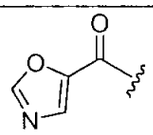
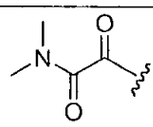
61	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-5-ilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.84 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{42}N_9O_4$: 724.34; encontrado 724.21; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{42}N_9O_4$: 724.3360; encontrado 724.3365
62	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-metil-1H-imidazol-4-il)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.85 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{44}N_9O_4$: 738.35; encontrado 738.22; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{44}N_9O_4$: 738.3516; encontrado 738.3539

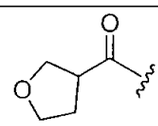
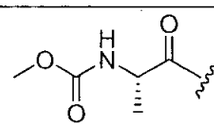
63	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-2-ilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.95 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{41}N_9O_4$: 710.32; encontrado 710.17
64	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-hidroxi-1-piperidinil)(fenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-8 Un diastereómero sencillo	1.92 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{49}H_{53}N_8O_5$: 833.41; encontrado 833.32; HRMS: Análisis calculado para $[M+H]^+$ $C_{49}H_{53}N_8O_5$: 833.4139; encontrado 833.4163

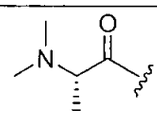
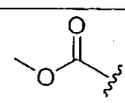
65	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-tetrazol-5-ilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		1.92 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{39}H_{40}N_{11}O_4$: 726.33; encontrado 726.22; HRMS: Análisis calculado para $[M+H]^+$ $C_{39}H_{40}N_{11}O_4$: 726.3265; encontrado 726.3290
67	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-piridinilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		2.03 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{41}N_8O_4$: 721.33; encontrado 721.31; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{41}N_8O_4$: 721.3251; encontrado 721.3247

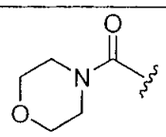
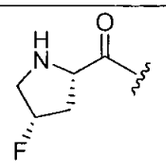
68	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-piridinilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		1.91 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{41}N_8O_4$: 721.33; encontrado 721.31; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{41}N_8O_4$: 721.3251; encontrado 721.3226
69	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-isonicotinoil-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.89 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{41}N_8O_4$: 721.33; encontrado 721.29; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{41}N_8O_4$: 721.3251; encontrado 721.3251

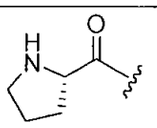
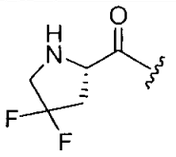
70	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4R)-4-fluoro-1-metil-L-prolil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-11	1.84 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{46}FN_8O_4$: 745.36; encontrado 745.27; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{46}FN_8O_4$: 745.3626; encontrado 745.3658
71	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-2-ilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.97 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{39}N_8O_5$: 711.30; encontrado 711.27

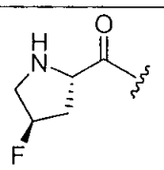
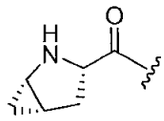
72	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-5-ilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.95 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{39}N_8O_5$: 711.30; encontrado 711.27; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{39}N_8O_5$: 711.3043; encontrado 711.3078
73	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimetilamino)(oxo)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.92 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{43}N_8O_5$: 715.34; encontrado 715.40

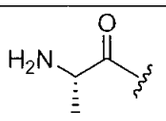
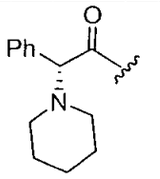
74	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(tetrahidro-3-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		1.91 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{44}N_7O_5$: 714.34; encontrado 714.39; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{44}N_7O_5$: 714.3404; encontrado 714.3433
75	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-12	1.94 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{45}N_8O_6$: 745.35 encontrado 745.34; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{45}N_8O_6$: 745.3462; encontrado 745.3486

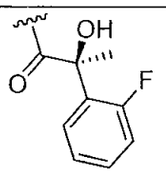
76	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dimetil-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.80 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{47}N_8O_4$ 715.37; encontrado 715.35 ; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{47}N_8O_4$ 715.3720; encontrado 715.3737
77	(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-pirrolidin carboxilato de metilo		1.97 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{40}N_7O_5$: 674.31; encontrado 674.66; HRMS: Análisis calculado para $[M+H]^+$ $C_{38}H_{40}N_7O_5$: 674.3091; encontrado 674.3110

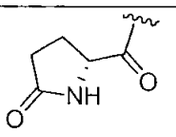
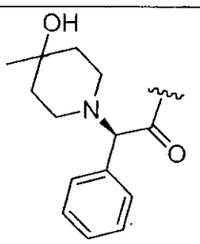
78	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morfolinilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.95 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{45}N_8O_5$: 729.35; encontrado 729.40; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{45}N_8O_5$: 729.3513; encontrado 729.3502
79	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4S)-4-fluoro-L-prolil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.80 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{44}FN_8O_4$: 731.84; encontrado 731.26

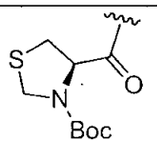
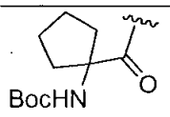
80	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-L-prolil-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		1.84 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{45}N_8O_4$: 713.36; encontrado 713.36; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{45}N_8O_4$: 713.3564; encontrado 713.3563
81	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4,4-difluoro-L-prolil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.88 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{43}F_2N_8O_4$: 749.34; encontrado 749.31; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{43}F_2N_8O_4$: 749.3375; encontrado 749.3390

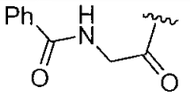
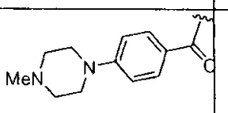
82	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4R)-4-fluoro-L-prolil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.83 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{44}FN_8O_4$: 731.35; encontrado 731.37; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{44}FN_8O_4$: 731.3470; encontrado 731.3502
83	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1S,3S,5S)-2-azabiciclo[3.1.0] hex-3-ilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.82 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{45}N_8O_4$: 725.36; encontrado 725.39; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{45}N_8O_4$: 725.3564; encontrado 725.3574

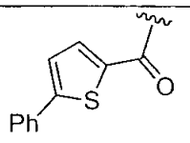
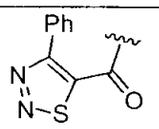
84	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-L-alanil-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.82 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{39}H_{43}N_8O_4$: 687.34; encontrado 687.32; HRMS: Análisis calculado para $[M+H]^+$ $C_{39}H_{43}N_8O_4$: 687.3407; encontrado 687.3435
84-1	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo	 Extremo-14	^{1}HRMN (400 MHz, CD_3OD) δ 7.90-7.85 (m, 9H), 7.81-7.79 (m, 1H), 7.63-7.57 (m, 5H), 7.45-7.32 (m, 6H), 5.51 (s, 1H), 5.45 (s, 1H), 5.33-5.29 (m, 2H), 4.06-4.01 (m, 2H), 3.63 (d, J = 4.04 Hz, 3H), 3.59-3.50 (m, 2H), 3.19-3.12 (m, 1H), 3.07-3.01 (m, 1H), 2.93-2.76 (m, 2H), 2.57-2.51 (m, 1H), 2.40-2.31 (m, 2H), 2.22-2.06 (m, 4H), 2.00-1.90 (m, 3H), 1.84-1.64 (m, 4H), 1.52-1.43 (m, 2H); LCMS: Análisis calculado para $C_{49}H_{52}N_8O_4$: 816; encontrado: 817 $(M+H)^+$.

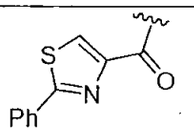
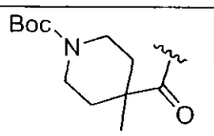
84-2	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(2-fluorofenil)-2-hidroxipropanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		^{1}HRMN (400 MHz, CD_3OD) δ 7.89-7.85 (m, 8H), 7.81-7.73 (2H), 7.67-7.65 (m, 1H), 7.45-7.26 (m, 7H), 7.13-7.08 (m, 1H), 6.94-6.89 (m, 0.5H), 6.72-6.67 (0.5H), 6.09-6.07 (m, 0.4H), 5.51 (s, 1H), 5.32-5.25 (m, 1.6H), 4.08-3.95 (m, 2H), 3.85-3.79 (1H), 3.64-3.63 (m, 3H), 3.56-3.49 (1H), 3.09-3.03 (m, 1H), 2.59-2.50 (m, 1H), 2.42-2.33 (m, 2H), 2.21-2.00 (m, 6H), 1.82-1.74 (m, 1H), 1.66 (d, J = 4.55 Hz, 3H); LCMS: Análisis calculado para $C_{45}H_{46}FN_7O_3$: 781; encontrado: 782 $(M+H)^+$.

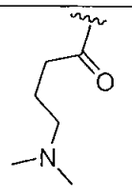
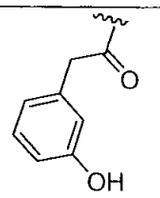
84-3	((1R)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(5-oxo-D-prolil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{41}H_{42}N_8O_5$: 726; encontrado: 727 $(M+H)^+$.
84-4	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(4-hidroxi-4-metil-1-piperidinil)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-15	LCMS: Análisis calculado para $C_{50}H_{54}N_8O_5$: 846; encontrado: 847 $(M+H)^+$.

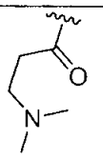
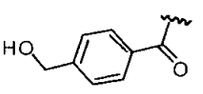
84-5	(4R)-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-1,3-tiazolidin-3-carboxilato de tert-butilo		LCMS: Análisis calculado para $C_{45}H_{50}N_8O_6S$: 830; encontrado: 831 $(M+H)^+$.
84-6	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-((tert-butoxicarbonil)amino)ciclopentil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{47}H_{54}FN_8O_6$: 826; encontrado: 827 $(M+H)^+$.

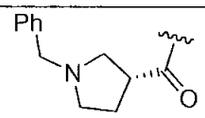
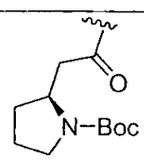
84-7	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-benzoilglicil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{45}H_{44}FN_8O_5$: 776; encontrado: 777 $(M+H)^+$.
84-8	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(4-metil-1-piperazinil)benzoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{48}H_{51}N_9O_4$: 817; encontrado: 818 $(M+H)^+$.

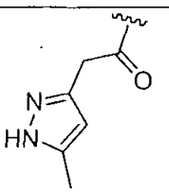
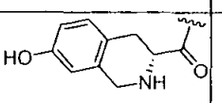
84-9	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-fenil-2-tienil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{47}H_{43}N_7O_4S$: 801; encontrado: 802 $(M+H)^+$.
84-10	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-fenil-1,2,3-tiadiazol-5-il)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{45}H_{41}N_9O_4S$: 803; encontrado: 804 $(M+H)^+$.

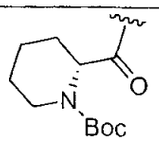
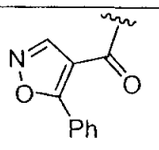
84-11	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-fenil-1,3-tiazol-4-il)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{46}H_{42}N_8O_4S$: 802; encontrado: 803 $(M+H)^+$.
84-12	4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((metoxicarbonil) amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-4-metil-1-piperidina carboxilato de tert-butilo		LCMS: Análisis calculado para $C_{48}H_{56}N_8O_6$: 840; encontrado: 841 $(M+H)^+$.

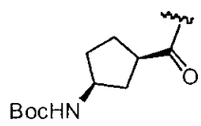
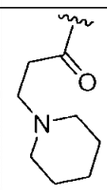
84-13	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(dimetilamino)butanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{42}H_{48}N_8O_4$: 728; encontrado: 729 $(M+H)^+$.
84-14	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-hidroxifenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{44}H_{43}N_7O_5$: 749; encontrado: 750 $(M+H)^+$.

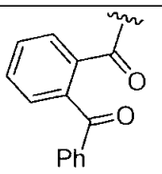
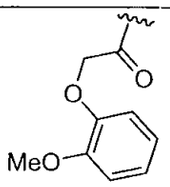
84-15	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dimetil-beta-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{41}H_{46}N_8O_4$: 714; encontrado: 715 $(M+H)^+$.
84-16	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(hidroximetil) benzoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{44}H_{43}N_7O_5$: 749; encontrado: 750 $(M+H)^+$.

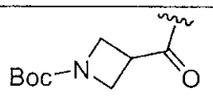
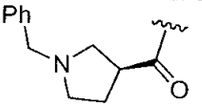
84-17	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3R)-1-bencil-3-pirrolidinil) carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{48}H_{50}N_8O_4$: 802; encontrado: 803 $(M+H)^+$.
84-18	(2S)-2-(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)-1-pirrolidin carboxilato de tert-butilo		LCMS: Análisis calculado para $C_{47}H_{54}N_8O_6$: 826; encontrado: 827 $(M+H)^+$.

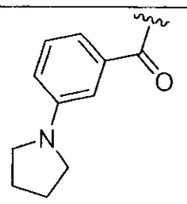
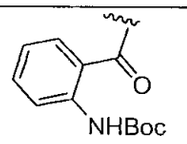
84-19	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-metil-1H-pirazol-3-il)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{42}H_{43}N_9O_4$: 737; encontrado: 738 $(M+H)^+$.
84-20	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3S)-7-hidroxi-1,2,3,4-tetrahidro-3-isoquinolinil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{46}H_{46}N_8O_5$: 790; encontrado: 791 $(M+H)^+$.

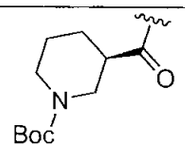
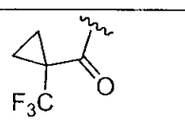
84-21	(2R)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-1-piperidina carboxilato de tert-butilo		LCMS: Análisis calculado para $C_{47}H_{54}N_8O_6$: 826; encontrado: 827 $(M+H)^+$.
84-22	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-fenil-4-isoxazolil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{46}H_{42}N_8O_5$: 786; encontrado: 787 $(M+H)^+$.

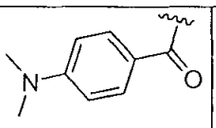
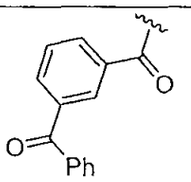
84-23	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1R,3S)-3-((tert-butoxicarbonil)amino)ciclopentil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{47}H_{54}N_8O_6$: 826; encontrado: 827 $(M+H)^+$.
84-24	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-piperidinil)propanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)carbamato de metilo		LCMS: Análisis calculado para $C_{44}H_{50}N_8O_4$: 754; encontrado: 755 $(M+H)^+$.

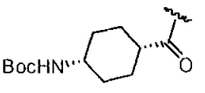
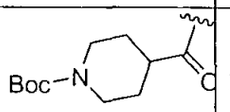
84-25	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-benzoilbenzoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{50}H_{45}N_7O_5$: 823; encontrado: 824 $(M+H)^+$.
84-26	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-metoxifenoxi)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{45}H_{45}N_7O_6$: 779; encontrado: 780 $(M+H)^+$.

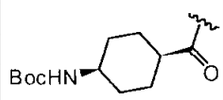
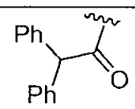
84-27	3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-1-azetidinacarboxilato de tert-butilo		LCMS: Análisis calculado para $C_{45}H_{50}N_8O_6$: 798; encontrado: 799 $(M+H)^+$.
84-28	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3S)-1-bencil-3-pirrolidinil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{48}H_{50}N_8O_4$: 802; encontrado: 803 $(M+H)^+$.

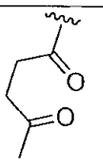
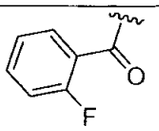
84-29	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-pirrolidinil)benzoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{47}H_{48}N_8O_4$: 788; encontrado: 789 $(M+H)^+$.
84-30	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-((tert-butoxicarbonil) amino)benzoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{48}H_{50}N_8O_6$: 834; encontrado: 835 $(M+H)^+$.

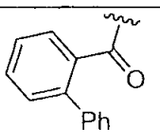
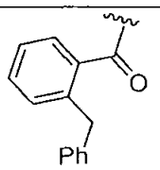
84-31	(3R)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((metoxicarbonil) amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-1-piperidina carboxilato de tert-butilo		LCMS: Análisis calculado para $C_{47}H_{54}N_8O_6$: 826; encontrado: 827 $(M+H)^+$.
84-32	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-(trifluorometil) ciclopropil) carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{41}H_{40}F_3N_7O_4$: 751; encontrado: 752 $(M+H)^+$.

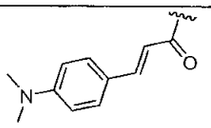
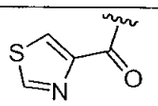
84-33	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(dimetilamino)benzoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{45}H_{46}N_8O_4$: 762; encontrado: 763 $(M+H)^+$.
84-34	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-benzoilbenzoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{50}H_{45}N_7O_5$: 823; encontrado: 824 $(M+H)^+$.

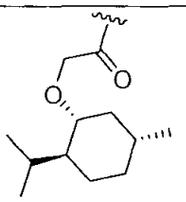
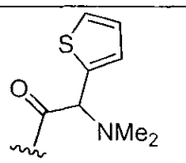
84-35	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-((tert-butoxicarbonil)amino)ciclohexil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{48}H_{56}N_8O_6$: 840; encontrado: 841 $(M+H)^+$.
84-36	4-(((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-pirrolidinil) carbonil)-1-piperidina carboxilato de tert-butilo		LCMS: Análisis calculado para $C_{47}H_{54}N_8O_6$: 826; encontrado: 827 $(M+H)^+$.

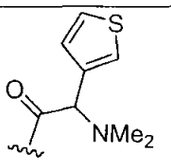
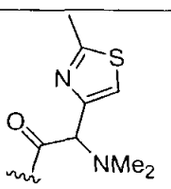
84-37	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-((tert-butoxicarbonil)amino)ciclohexil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{48}H_{56}N_8O_6$: 840; encontrado: 841 $(M+H)^+$.
84-38	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(difenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{50}H_{47}N_7O_4$: 809; encontrado: 810 $(M+H)^+$.

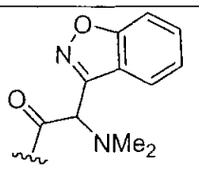
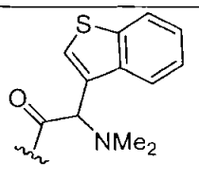
84-39	((1R)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-oxopentanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{41}H_{43}N_7O_5$: 713; encontrado: 714 $(M+H)^+$.
84-40	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-fluorobenzoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{43}H_{40}FN_7O_4$: 737; encontrado: 738 $(M+H)^+$.

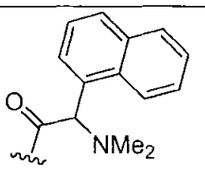
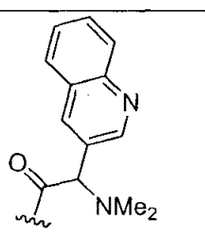
84-41	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-bifenililcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{49}H_{45}N_7O_4$: 795; encontrado: 796 $(M+H)^+$.
84-42	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-bencilbenzoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{50}H_{47}N_7O_4$: 809; encontrado: 810 $(M+H)^+$.

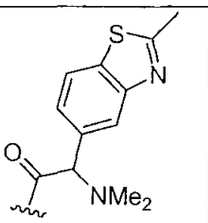
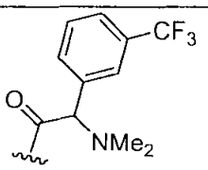
84-43	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2E)-3-(4-(dimetilamino)fenil)-2-propenoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{47}H_{48}N_8O_4$: 788; encontrado: 789 $(M+H)^+$.
84-44	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-tiazol-4-ilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{40}H_{38}N_8O_4S$: 726; encontrado: 727 $(M+H)^+$.

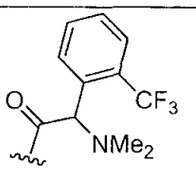
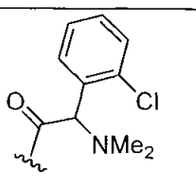
84-45	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((((1R,2S,5R)-2-isopropil-5-metilciclohexil)oxi)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{48}H_{57}N_7O_5$: 811; encontrado: 812 $(M+H)^+$.
84-46	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimetilamino)(2-tienil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-32	LCMS: Análisis calculado para $C_{44}H_{46}N_8O_4S$: 782; encontrado: 782 $(M+H)^+$.

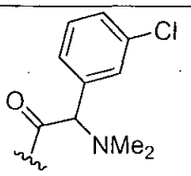
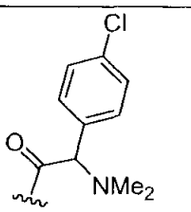
84-47	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimetilamino)(3-tienil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-33	LCMS: Análisis calculado para $C_{44}H_{46}N_8O_4S$: 782; encontrado: 782 $(M+H)^+$.
84-48	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimetilamino)(2-metil-1,3-tiazol-4-il)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-31	LCMS: Análisis calculado para $C_{44}H_{47}N_9O_4S$: 797; encontrado: 798 $(M+H)^+$.

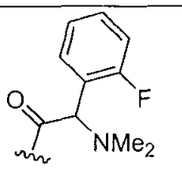
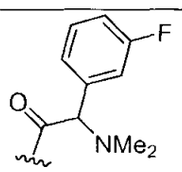
84-49	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,2-benzisoxazol-3-il(dimetilamino)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-34	LCMS: Análisis calculado para $C_{47}H_{47}N_9O_5$: 817; encontrado: 818 $(M+H)^+$.
84-50	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-benzotiofen-3-il(dimetilamino)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-35	LCMS: Análisis calculado para $C_{48}H_{48}N_8O_4S$: 832; encontrado: 833 $(M+H)^+$.

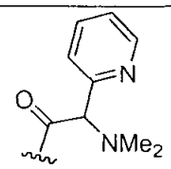
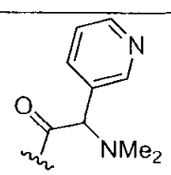
84-51	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimetilamino)(1-naftil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-23	LCMS: Análisis calculado para $C_{50}H_{50}N_8O_4$: 826; encontrado: 827 $(M+H)^+$.
84-52	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimetilamino)(3-quinolinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-37	LCMS: Análisis calculado para $C_{49}H_{49}N_9O_4$: 827; encontrado: 828 $(M+H)^+$.

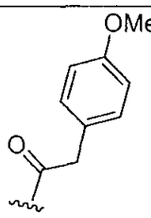
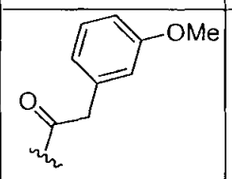
84-53	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimetilamino)(2-metil-1,3-benzotiazol-5-il)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-36	LCMS: Análisis calculado para $C_{48}H_{49}N_9O_4S$: 847; encontrado: 848 $(M+H)^+$.
84-54	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimetilamino)(3-(trifluorometil)fenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-24	LCMS: Análisis calculado para $C_{47}H_{47}F_3N_8O_4$: 844; encontrado: 845 $(M+H)^+$.

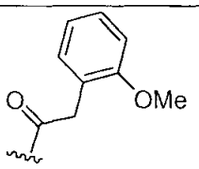
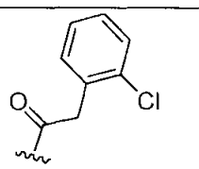
84-55	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimetilamino)(2-(trifluorometil)fenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-25	LCMS: Análisis calculado para $C_{47}H_{47}F_3N_8O_4$: 844; encontrado: 845 $(M+H)^+$.
84-56	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-chlorofenil)(dimetilamino)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-29	LCMS: Análisis calculado para $C_{46}H_{47}ClN_8O_4$: 810; encontrado: 811 $(M+H)^+$.

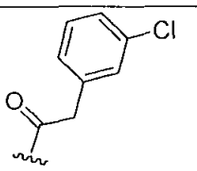
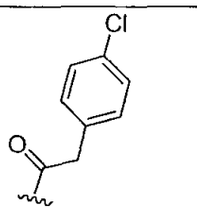
84-57	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-chlorofenil)(dimetilamino)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-28	LCMS: Análisis calculado para $C_{46}H_{47}ClN_8O_4$: 810; encontrado: 811 $(M+H)^+$.
84-58	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-clorofenil)(dimetilamino) acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-30	LCMS: Análisis calculado para $C_{46}H_{47}ClN_8O_4$: 810; encontrado: 811 $(M+H)^+$.

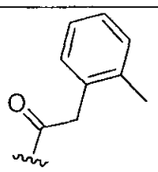
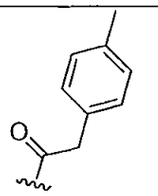
84-59	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimetilamino)(2-fluorofenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-26	LCMS: Análisis calculado para $C_{46}H_{47}FN_8O_4$: 794; encontrado: 795 $(M+H)^+$.
84-60	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimetilamino)(3-fluorofenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-27	LCMS: Análisis calculado para $C_{46}H_{47}FN_8O_4$: 794; encontrado: 795 $(M+H)^+$.

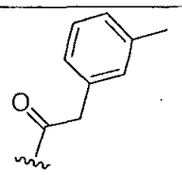
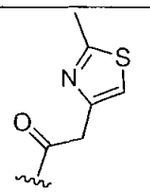
84-61	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((dimetilamino)(2-piridinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-20	LCMS: Análisis calculado para $C_{45}H_{47}N_9O_4$: 777; encontrado: 778 $(M+H)^+$.
84-62	((1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((dimetilamino)(3-piridinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-19	LCMS: Análisis calculado para $C_{45}H_{47}N_9O_4$: 777; encontrado: 778 $(M+H)^+$.

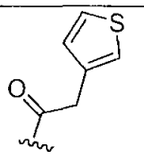
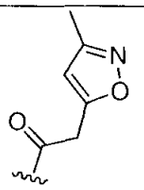
84-63	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-metoxifenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{45}H_{45}N_7O_5$: 763; encontrado: 764 $(M+H)^+$.
84-64	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-metoxifenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{45}H_{45}N_7O_5$: 763; encontrado: 764 $(M+H)^+$.

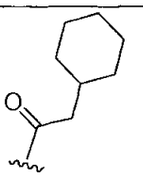
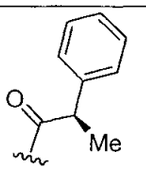
84-65	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-metoxifenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{45}H_{45}N_7O_5$: 763; encontrado: 764 $(M+H)^+$.
84-66	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-clorofenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{44}H_{42}ClN_7O_4$: 767; encontrado: 768 $(M+H)^+$.

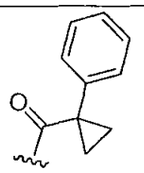
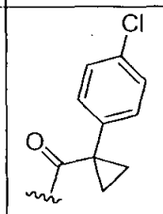
84-67	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-clorofenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{44}H_{42}ClN_7O_4$: 767; encontrado: 768 $(M+H)^+$.
84-68	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-clorofenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{44}H_{42}ClN_7O_4$: 767; encontrado: 768 $(M+H)^+$.

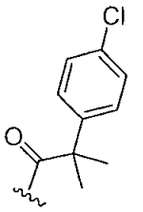
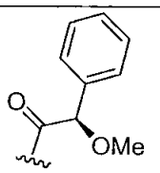
84-69	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-metilfenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{45}H_{45}N_7O_4$: 747; encontrado: 748 $(M+H)^+$.
84-70	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-metilfenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{45}H_{45}N_7O_4$: 747; encontrado: 748 $(M+H)^+$.

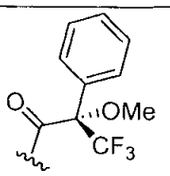
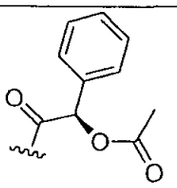
84-71	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-metilfenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{45}H_{45}N_7O_4$: 747; encontrado: 748 $(M+H)^+$.
84-72	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-metil-1,3-tiazol-4-il)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{42}H_{42}N_8O_4S$: 754; encontrado: 755 $(M+H)^+$.

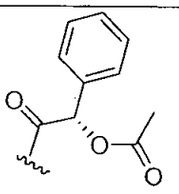
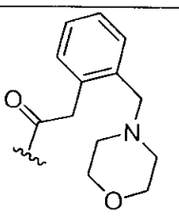
84-73	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-thienilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{42}H_{41}N_7O_4S$: 739; encontrado: 740 $(M+H)^+$.
84-74	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-metil-5-isoxazolil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{42}H_{42}N_8O_5$: 738; encontrado: 739 $(M+H)^+$.

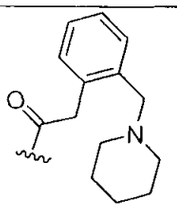
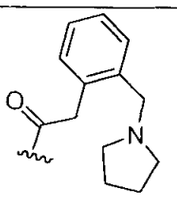
84-75	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(ciclohexilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{44}H_{49}N_7O_4$: 739; encontrado: 740 $(M+H)^+$.
84-76	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenilpropanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{45}H_{45}N_7O_4$: 747; encontrado: 748 $(M+H)^+$.

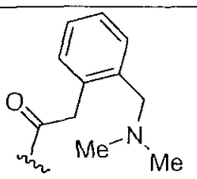
84-77	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-fenilciclopropil) carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{46}H_{45}N_7O_4$: 759; encontrado: 760 $(M+H)^+$.
84-78	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-(4-clorofenil) ciclopropil) carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{46}H_{44}ClN_7O_4$: 793; encontrado: 794 $(M+H)^+$.

84-79	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-(4-clorofenil)-2-metilpropanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{46}H_{46}ClN_7O_4$: 795; encontrado: 796 $(M+H)^+$.
84-80	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-metoxi-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		LCMS: Análisis calculado para $C_{45}H_{45}N_7O_5$: 763; encontrado: 764 $(M+H)^+$.

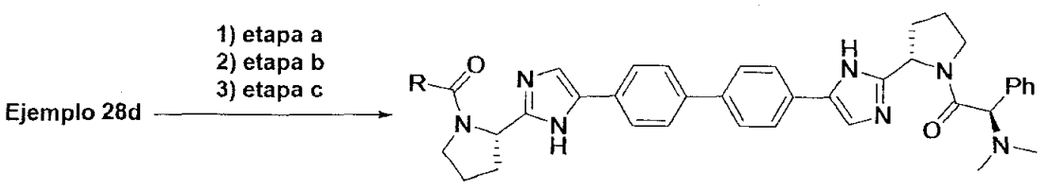
84-81	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3,3,3-trifluoro-2-metoxi-2-fenilpropanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{46}H_{44}F_3N_7O_5$: 831; encontrado: 832 $(M+H)^+$.
84-82	acetato de (1R)-2-((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-pirrolidinil)-2-oxo-1-feniletilo		LCMS: Análisis calculado para $C_{46}H_{45}N_7O_6$: 791; encontrado: 792 $(M+H)^+$.

84-83	Acetato de (1S)-2-((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-pirrolidinil)-2-oxo-1-feniletilo		LCMS: Análisis calculado para $C_{46}H_{45}N_7O_6$: 791; encontrado: 792 $(M+H)^+$.
84-84	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-(4-morfolinilmetil)fenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-41	LCMS: Análisis calculado para $C_{49}H_{52}N_8O_5$: 832; encontrado: 833 $(M+H)^+$.

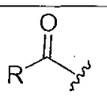
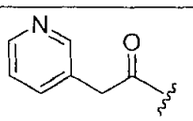
84-85	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-(1-piperidinilmetil)fenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo	 Extremo-42	LCMS: Análisis calculado para $C_{50}H_{54}N_8O_4$: 830; encontrado: 831 $(M+H)^+$.
84-86	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-(1-pirrolidinilmetil)fenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo	 Extremo-43	LCMS: Análisis calculado para $C_{49}H_{52}N_8O_4$: 816; encontrado: 816 $(M+H)^+$.

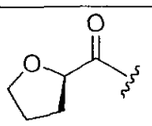
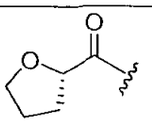
84-87	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-((dimetilamino)metil)fenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Extremo-44	LCMS: Análisis calculado para $C_{47}H_{50}N_8O_4$: 790; encontrado: 791 $(M+H)^+$.

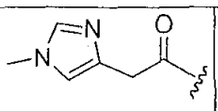
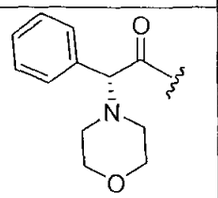
Ejemplos 85-94

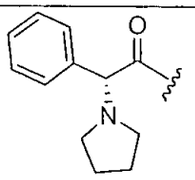
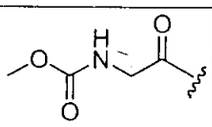


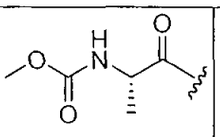
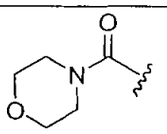
etapa a: Tapar con la tapa-1 como en el ejemplo 28
etapa b: El mismo procedimiento como en la conversión del ejemplo 1d hasta 1e
etapa c: Como en la última etapa del ejemplo 1 usando 1.1 equivalente del ácido carboxílico apropiado y HATU.

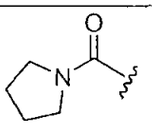
Ejemplo	Nombre del compuesto		Tiempo de retención (Condición-CL); Datos EM de índice de homogeneidad
85	(1R)-N,N-dimetil-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-piridinilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etanamina		1.64 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{45}N_8O_2$: 705.37; encontrado 705.43; HRMS: Análisis calculado para $[M+H]^+$ $C_{43}H_{45}N_8O_2$: 705.3665; encontrado 705.3675

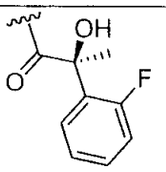
86	(1R)-N,N-dimetil-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etanamina		1.73 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{46}N_7O_3$: 684.37; encontrado 684.44; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{46}N_7O_3$: 684.3662; encontrado 684.3671
87	(1R)-N,N-dimetil-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etanamina		1.12 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{46}N_7O_3$: 684.37; encontrado 684.68; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{46}N_7O_3$: 684.3662; encontrado 684.3692

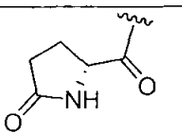
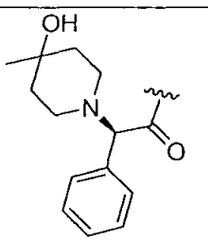
88	(1R)-N,N-dimetil-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-metil-1H-imidazol-4-il)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletanamina		1.66 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{46}N_9O_2$: 708.38; encontrado 708.36
89	(1R)-N,N-dimetil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(4-morfolinil)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletanamina	 Extremo-6	1.70 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{45}N_8O_4$: 701.36; encontrado 701.34; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{45}N_8O_4$: 701.3564; encontrado 701.3576

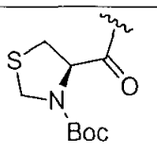
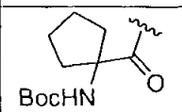
90	(1R)-N,N-dimetil-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-pirrolidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etanamina	 Extremo-5	1.80 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{48}H_{53}N_8O_2$: 773.43; encontrado 773.42; HRMS: Análisis calculado para $[M+H]^+$ $C_{48}H_{53}N_6O_2$: 773.4291; encontrado 773.4309
91	(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo		1.66 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{46}N_9O_2$: 708.38; encontrado 708.36; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{46}N_9O_2$: 708.3744; encontrado 708.3770

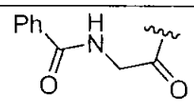
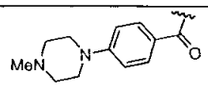
92	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	 Extremo-12	1.73 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{47}N_8O_4$: 715.37; encontrado 715.41; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{47}N_8O_4$: 715.3720; encontrado 715.3729
93	(1R)-N,N-dimetil-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morfolinilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletanamina		1.76 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{47}N_8O_3$: 699.38; encontrado 699.45; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{47}N_8O_3$: 699.3771; encontrado 699.3803

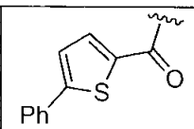
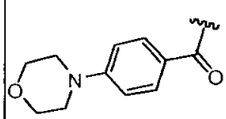
94	(1R)-N,N-dimetil-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-pirrolidinilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etanamina		1.86 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{47}N_8O_2$: 683.38; encontrado 683.46; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{47}N_8O_2$: 683.3822; encontrado 683.3835

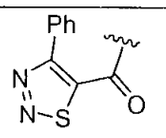
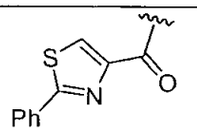
94-1	(2S)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-(2-fluorofenil)-1-oxo-2-propanol		^{1}HRMN (400 MHz, CD_3OD) δ 7.90-7.84 (m, 9H), 7.79-7.73 (m, 2H), 7.67-7.65 (m, 1H), 7.63-7.52 (m, 5H), 7.39-7.36 (m, 1H), 7.30-7.26 (m, 1H), 7.13-7.08 (m, 1H), 6.93-6.88 (m, 0.5H), 6.72-6.67 (m, 0.5H), 5.51 (s, 0.2H), 5.46 (s, 0.8H), 5.33-5.30 (m, 1H), 5.28-5.24 (m, 1H), 4.05-3.94 (m, 2H), 3.84-3.73 (m, 1H), 3.69-3.55 (m, 1H), 3.21-3.04 (m, 2H), 2.79 (br s, 6H), 2.39-2.33 (m, 2H), 2.21-1.93 (m, 5H), 1.65 (d, J = 4.55 Hz, 3H).; LCMS: Análisis calculado para $C_{45}H_{46}FN_7O_3$: 751; encontrado: 752 $(M+H)^+$.

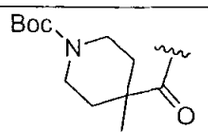
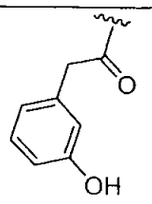
94-2	(5R)-5-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-pirrolidinona		LCMS: Análisis calculado para $C_{41}H_{44}N_8O_3$: 696; encontrado: 697 $(M+H)^+$.
94-3	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)-4-metil-4-piperidinol	 Extremo-15	LCMS: Análisis calculado para $C_{50}H_{56}N_8O_3$: 816; encontrado: 817 $(M+H)^+$.

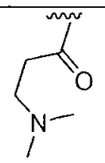
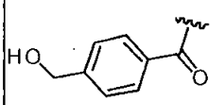
94-4	(4R)-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-1,3-tiazolidin-3-carboxilato de tert-butilo		LCMS: Análisis calculado para $C_{45}H_{52}N_8O_4S$: 800; encontrado: 801 $(M+H)^+$.
94-5	(1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)ciclopentil)carbamato de tert-butilo		LCMS: Análisis calculado para $C_{47}H_{56}FN_8O_4$: 796; encontrado: 797 $(M+H)^+$.

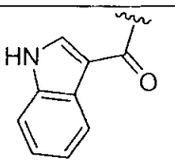
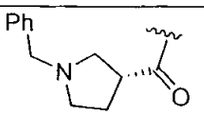
94-6	N-(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)benzamida		LCMS: Análisis calculado para $C_{45}H_{46}FN_8O_3$: 746; encontrado: 747 $(M+H)^+$.
94-7	(1R)-N,N-dimetil-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(4-metil-1-piperazinil)benzoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletanamina		LCMS: Análisis calculado para $C_{48}H_{53}N_9O_2$: 787; encontrado: 788 $(M+H)^+$.

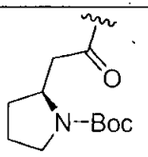
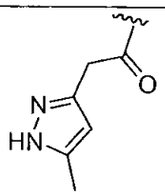
94-8	(1R)-N,N-dimetil-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-fenil-2-tienil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etanamina		LCMS: Análisis calculado para $C_{47}H_{45}N_7O_2S$: 771; encontrado: 772 $(M+H)^+$.
94-9	(1R)-N,N-dimetil-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(4-morfolinil)benzoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletanamina		LCMS: Análisis calculado para $C_{47}H_{50}N_8O_3$: 774; encontrado: 775 $(M+H)^+$.

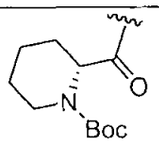
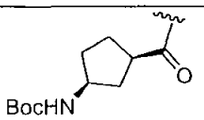
94-10	(1R)-N,N-dimetil-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-fenil-1,2,3-tiadiazol-5-il)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etanamina		LCMS: Análisis calculado para $C_{45}H_{43}N_9O_2S$: 773; encontrado: 774 $(M+H)^+$.
94-11	(1R)-N,N-dimetil-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-fenil-1,3-tiazol-4-il)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etanamina		LCMS: Análisis calculado para $C_{46}H_{44}N_8O_2S$: 772; encontrado: 773 $(M+H)^+$.

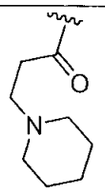
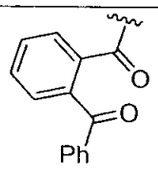
94-12	4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-4-metil-1-piperidinacarboxilato de tert-butilo		LCMS: Análisis calculado para $C_{48}H_{58}N_8O_4$: 810; encontrado: 811 $(M+H)^+$.
94-13	3-(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)fenol		LCMS: Análisis calculado para $C_{44}H_{45}N_7O_3$: 719; encontrado: 720 $(M+H)^+$.

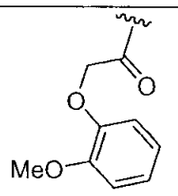
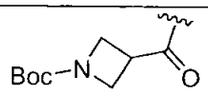
94-14	3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-3-oxo-1-propanamina		LCMS: Análisis calculado para $C_{41}H_{48}N_8O_2$: 684; encontrado: 685 $(M+H)^+$.
94-15	(4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)fenil)metanol		LCMS: Análisis calculado para $C_{44}H_{45}N_7O_3$: 719; encontrado: 720 $(M+H)^+$.

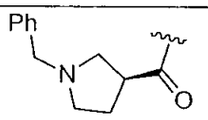
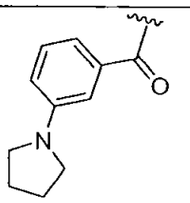
94-16	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-indol-3-ilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina		LCMS: Análisis calculado para $C_{45}H_{44}N_8O_2$: 728; encontrado: 729 $(M+H)^+$.
94-17	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3R)-1-bencil-3-pirrolidinil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina		LCMS: Análisis calculado para $C_{48}H_{52}N_8O_2$: 772; encontrado: 773 $(M+H)^+$.

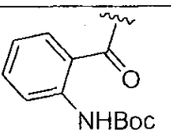
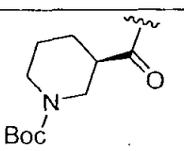
94-18	(2S)-2-(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)-1-pirrolidincarboxilato de tert-butilo		LCMS: Análisis calculado para $C_{47}H_{56}N_8O_4$: 796; encontrado: 797 $(M+H)^+$.
94-19	(1R)-N,N-dimetil-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-metil-1H-pirazol-3-il)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletanamina		LCMS: Análisis calculado para $C_{42}H_{45}N_9O_2$: 707; encontrado: 708 $(M+H)^+$.

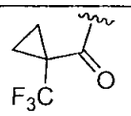
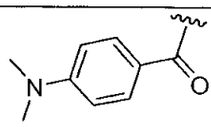
94-20	(2R)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-1-piperidinacarboxilato de tert-butilo		LCMS: Análisis calculado para $C_{47}H_{56}N_8O_4$: 796; encontrado: 797 $(M+H)^+$.
94-21	((1S,3R)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)ciclopentil)carbamato de tert-butilo		LCMS: Análisis calculado para $C_{47}H_{56}N_8O_4$: 796; encontrado: 797 $(M+H)^+$.

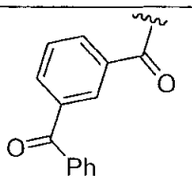
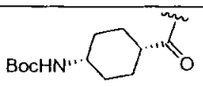
94-22	(1R)-N,N-dimetil-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-piperidinil)propanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etanamina		LCMS: Análisis calculado para $C_{44}H_{52}N_8O_2$: 724; encontrado: 725 $(M+H)^+$.
94-23	(2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)fenil)(fenil)metanona		LCMS: Análisis calculado para $C_{50}H_{47}N_7O_3$: 793; encontrado: 794 $(M+H)^+$.

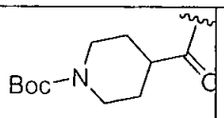
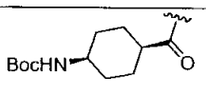
94-24	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-metoxifenoxi)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina		LCMS: Análisis calculado para $C_{45}H_{47}N_7O_4$: 749; encontrado: 750 $(M+H)^+$.
94-25	3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-1-azetidinacarboxilato de tert-butilo		LCMS: Análisis calculado para $C_{45}H_{52}N_8O_4$: 768; encontrado: 769 $(M+H)^+$.

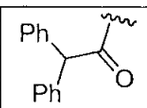
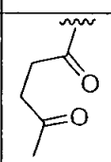
94-26	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3S)-1-bencil-3-pirrolidinil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina		LCMS: Análisis calculado para $C_{48}H_{52}N_8O_2$: 772; encontrado: 773 $(M+H)^+$.
94-27	(1R)-N,N-dimetil-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-(1-pirrolidinil)benzoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etanamina		LCMS: Análisis calculado para $C_{47}H_{50}N_8O_2$: 758; encontrado: 759 $(M+H)^+$.

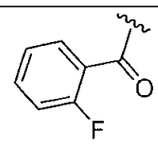
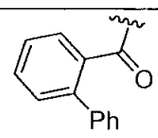
94-28	(2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)fenil)carbamato de tert-butilo		LCMS: Análisis calculado para $C_{48}H_{52}N_8O_4$: 804; encontrado: 805 $(M+H)^+$.
94-29	(3R)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-1-piperidinacarboxilato de tert-butilo		LCMS: Análisis calculado para $C_{47}H_{56}N_8O_4$: 796; encontrado: 797 $(M+H)^+$.

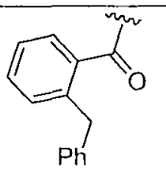
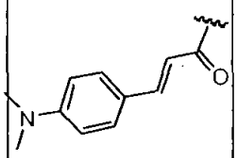
94-30	(1R)-N,N-dimetil-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-(trifluorometil)ciclopropil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etanamina		LCMS: Análisis calculado para $C_{41}H_{42}F_3N_7O_2$: 721; encontrado: 722 $(M+H)^+$.
94-31	4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-N,N-dimetilanilina		LCMS: Análisis calculado para $C_{45}H_{48}N_8O_2$: 732; encontrado: 733 $(M+H)^+$.

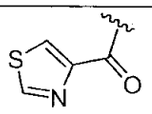
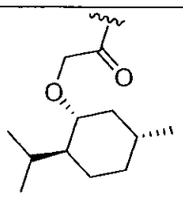
94-32	(3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)fenil)(fenil)metanona		LCMS: Análisis calculado para $C_{50}H_{47}N_7O_3$: 793; encontrado: 794 $(M+H)^+$.
94-33	(cis-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)ciclohexil)carbamato de tert-butilo		LCMS: Análisis calculado para $C_{48}H_{58}N_8O_4$: 810; encontrado: 811 $(M+H)^+$.

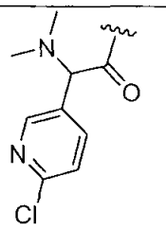
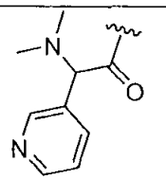
94-34	4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-1-piperidinacarboxilato de tert-butilo		LCMS: Análisis calculado para $C_{47}H_{56}N_8O_4$: 796; encontrado: 797 $(M+H)^+$.
94-35	(cis-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)ciclohexil)carbamato de tert-butilo		LCMS: Análisis calculado para $C_{48}H_{58}N_8O_4$: 810; encontrado: 811 $(M+H)^+$.

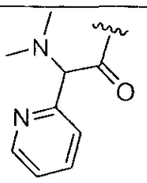
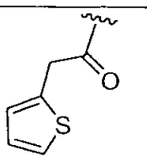
94-36	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(difenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina		LCMS: Análisis calculado para $C_{50}H_{49}N_7O_2$: 779; encontrado: 780 $(M+H)^+$.
94-37	5-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-5-oxo-2-pentanona		LCMS: Análisis calculado para $C_{41}H_{45}N_7O_3$: 683; encontrado: 684 $(M+H)^+$.

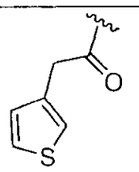
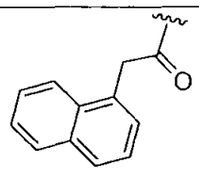
94-38	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-fluorobenzoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina		LCMS: Análisis calculado para $C_{43}H_{42}FN_7O_2$: 707; encontrado: 708 $(M+H)^+$.
94-39	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-bifenililcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina		LCMS: Análisis calculado para $C_{49}H_{47}N_7O_2$: 765; encontrado: 766 $(M+H)^+$.

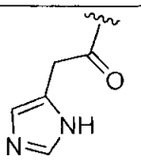
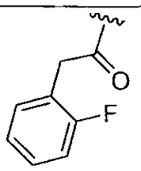
94-40	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-bencilbenzoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina		LCMS: Análisis calculado para $C_{50}H_{49}N_7O_2$: 779; encontrado: 780 $(M+H)^+$.
94-41	4-((1E)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-3-oxo-1-propen-1-il)-N,N-dimetilanilina		LCMS: Análisis calculado para $C_{47}H_{50}N_8O_2$: 758; encontrado: 759 $(M+H)^+$.

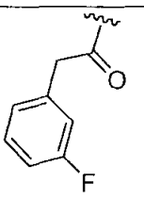
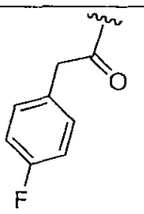
94-42	(1R)-N,N-dimetil-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-tiazol-4-ilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etanamina		LCMS: Análisis calculado para $C_{40}H_{40}N_8O_2S$: 696; encontrado: 697 $(M+H)^+$.
94-43	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1R,2S,5R)-2-isopropil-5-metilciclohexil)oxi)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina		LCMS: Análisis calculado para $C_{48}H_{59}N_7O_3$: 781; encontrado: 782 $(M+H)^+$.

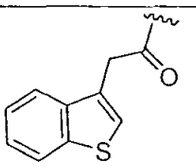
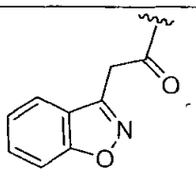
94-44	1-(6-cloro-3-piridinil)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxoetanamina	 Extremo-21	LCMS: Análisis calculado para $C_{45}H_{48}ClN_9O_2$: 781; encontrado: 782 $(M+H)^+$.
94-45	2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-(3-piridinil)etanamina	 Extremo-19	LCMS: Análisis calculado para $C_{45}H_{49}N_9O_2$: 747; encontrado: 748 $(M+H)^+$.

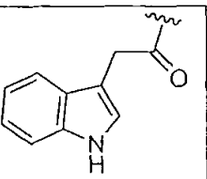
94-46	2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-(2-piridinil)etanamina	 Extremo-20	LCMS: Análisis calculado para $C_{45}H_{49}N_9O_2$: 747; encontrado: 748 $(M+H)^+$.
94-47	(1R)-N,N-dimetil-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-tienil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etanamina		LCMS: Análisis calculado para $C_{42}H_{43}N_7O_2S$: 709; encontrado: 710 $(M+H)^+$.

94-48	(1R)-N,N-dimetil-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-tienilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etanamina		LCMS: Análisis calculado para $C_{42}H_{43}N_7O_2S$: 709; encontrado: 710 $(M+H)^+$.
94-49	(1R)-N,N-dimetil-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-naftilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletanamina		LCMS: Análisis calculado para $C_{48}H_{47}N_7O_2$: 753; encontrado: 754 $(M+H)^+$.

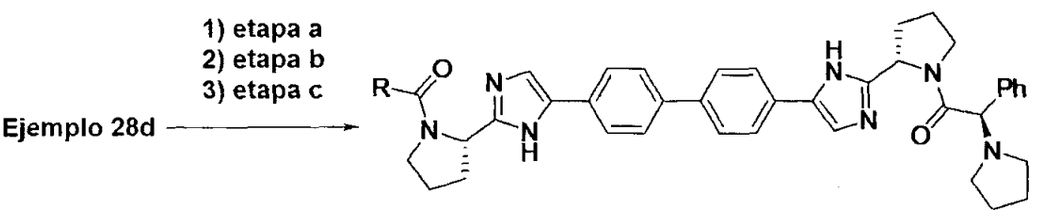
94-50	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-5-ilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina		LCMS: Análisis calculado para $C_{41}H_{43}N_9O_2$: 693; encontrado: 694 $(M+H)^+$.
94-51	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-fluorofenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina		LCMS: Análisis calculado para $C_{44}H_{44}FN_7O_2$: 721; encontrado: 722 $(M+H)^+$.

94-52	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-fluorofenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina		LCMS: Análisis calculado para $C_{44}H_{44}FN_7O_2$: 721; encontrado: 722 $(M+H)^+$.
94-53	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((4-fluorofenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina		LCMS: Análisis calculado para $C_{44}H_{44}FN_7O_2$: 721; encontrado: 722 $(M+H)^+$.

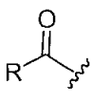
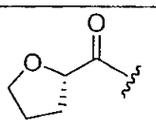
94-54	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1-benzotiofen-3-ilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina		LCMS: Análisis calculado para $C_{46}H_{45}N_7O_2S$: 759; encontrado: 760 $(M+H)^+$.
94-55	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,2-benzisoxazol-3-ilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina		LCMS: Análisis calculado para $C_{45}H_{44}N_8O_3$: 744; encontrado: 745 $(M+H)^+$.

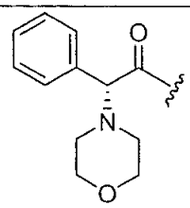
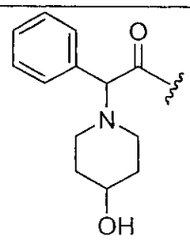
94-56	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-indol-3-ilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina		LCMS: Análisis calculado para $C_{46}H_{46}N_8O_2$: 742; encontrado: 743 $(M+H)^+$.

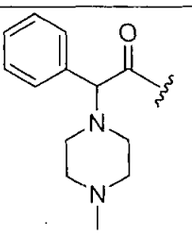
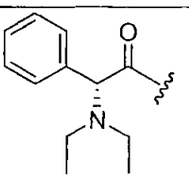
Ejemplos 95-103

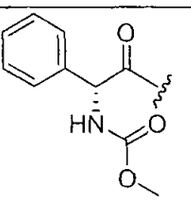
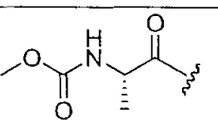


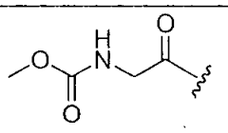
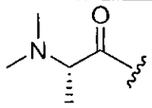
etapa a: Tapa w/ tapa-5 como en el ejemplo 28
etapa b: El mismo procedimiento como en la conversión del ejemplo 1d hastas 1e
etapa c: Como en la última etapa del ejemplo 1 usando 1.1 equivalente del ácido carboxílico apropiado y HATU

Ejemplo	Nombre del compuesto		Tiempo de retención (Condición-CL); Datos EM de índice de homogeneidad
95	2-((2S)-1-((2R)-2-fenil-2-(1-pirrolidinil)acetil)-2-pirrolidinil)-5-(4'-(2-((2S)-1-((2S)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol		1.16 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{48}N_7O_3$: 710.38; encontrado 710.60

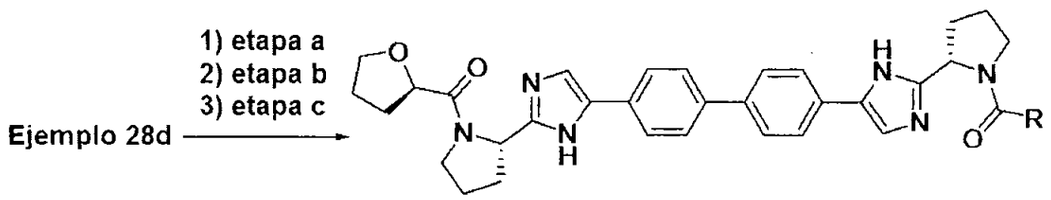
96	4-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-pirrolidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) morfolina	 Extremo-6	1.82 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{50}H_{55}N_8O_3$: 815.44; encontrado 815.45; HRMS: Análisis calculado para $[M+H]^+$ $C_{50}H_{55}N_8O_3$: 815.4397; encontrado 815.4395
97	1-(2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-pirrolidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)-4-piperidinol	 Un diastereómero sencillo Extremo-8	1.79 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{51}H_{57}N_8O_3$: 829.46; encontrado 829.43; HRMS: Análisis calculado para $[M+H]^+$ $C_{51}H_{57}N_8O_3$: 829.4554; encontrado 829.4585

98	1-metil-4-(2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-pirrolidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) piperazina	 Un diastereómero sencillo Extremo-17c	1.84 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{51}H_{58}N_9O_2$: 828.47; encontrado 828.45; HRMS: Análisis calculado para $[M+H]^+$ $C_{51}H_{58}N_9O_2$: 828.4713; encontrado 828.4722
99	(1R)-N,N-dietil-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-pirrolidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etanamina	 Extremo-2	1.86 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{50}H_{57}N_8O_2$: 801.46; encontrado 801.44; HRMS: Análisis calculado para $[M+H]^+$ $C_{50}H_{57}N_8O_2$: 801.4604; encontrado 801.4595

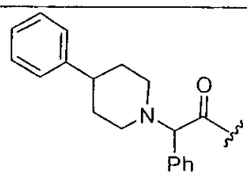
100	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-pirrolidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo	 Extremo-4	1.93 minutos (Cond. 2); LC/MS: Análisis calculado para $[M+H]^+$ $C_{48}H_{51}N_8O_4$: 803.40; encontrado 803.47 ; HRMS: Análisis calculado para $[M+H]^+$ $C_{48}H_{51}N_8O_4$: 803.4033; encontrado 803.4058
101	((1S)-1-metil-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-pirrolidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo	 Extremo-12	1.80 minutos (Cond. 2); LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{49}N_8O_4$: 741.39; encontrado 741.33; HRMS: Análisis calculado para $[M+H]^+$ $C_{43}H_{49}N_8O_4$: 741.3877; encontrado 741.3900

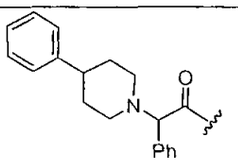
102	(2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-pirrolidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		1.80 minutos (Cond. 2); LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.37; encontrado 727.24; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.3720; encontrado 727.3743
103	(2S)-N,N-dimetil-1-oxo-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-pirrolidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-propanamina	 Extremo-13	1.69 minutos (Cond. 2); LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{51}N_8O_2$: 711.41; encontrado 711.37; HRMS: Análisis calculado para $[M+H]^+$ $C_{43}H_{51}N_8O_2$: 711.4135; encontrado 711.4154

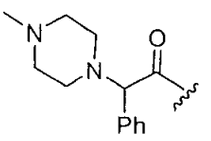
Ejemplos 103-1 hasta 103-12

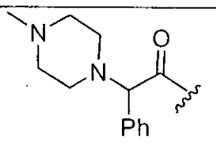


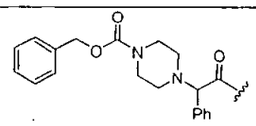
etapa a: Tapa con el ácido (R)-2-tetrahidrofúroico como en el ejemplo 28
etapa b: El mismo procedimiento como en la conversión del ejemplo 1a hasta 1e
etapa c: Como en la última etapa del ejemplo 1 usando 1.1 equivalente del ácido carboxílico apropiaco y HATU

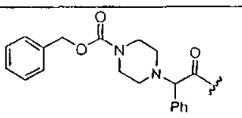
103-1	1-(2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)-4-fenilpiperidina	 Diastereómero 1 Extremo-17d	TR = 4.80 minutos; HPLC Xterra 4.6 X 50 mm, 0 hasta 100% B durante 10 minutos, un minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% ácido fosfórico, B = 10% agua, 90% metanol, 0.2% ácido fosfórico; LCMS: Análisis calculado para: $C_{50}H_{53}N_7O_3$ 800.03 Encontrado: 800.49 $(M+H)^+$

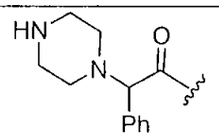
103-2	1-(2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)-4-fenilpiperidina	 Diastereómero 2 Extremo-17d	TR = 4.59 minutos; HPLC Xterra 4.6 X 50 mm, 0 hasta 100% B durante 10 minutos, un minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% ácido fosfórico, B = 10% agua, 90% metanol, 0.2% ácido fosfórico; LCMS: Análisis calculado para: $C_{50}H_{53}N_7O_3$ 800.03 Encontrado: 800.48 $(M+H)^+$

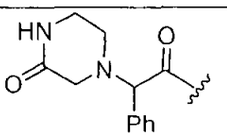
103-3	1-metil-4-(2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etil) piperazina	 Diastereómero 1 Extremo-17c	TR = 3.36; HPLC Xterra 4.6 X 50 mm, 0 hasta 100% B durante 10 minutos, un minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% ácido fosfórico, B = 10% agua, 90% metanol, 0.2% ácido fosfórico; LCMS: Análisis calculado para: $C_{44}H_{50}N_8O_3$ 738.94 Encontrado: 739.49 $(M+H)^+$

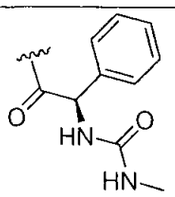
103-4	1-metil-4-(2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etil) piperazina	 Diastereómero 2 Extremo-17c	TR = 3.47 minutos; HPLC Xterra 4.6 X 50 mm, 0 hasta 100% B durante 10 minutos, un minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% ácido fosfórico, B = 10% agua, 90% metanol, 0.2% ácido fosfórico; LCMS: Análisis calculado para: $C_{44}H_{50}N_8O_3$ 738.94 Encontrado: 739.51 $(M+H)^+$

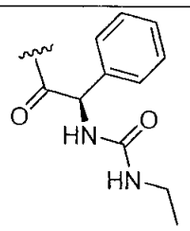
103-5	4-(2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)-1-piperazina carboxilato de bencilo	 Diastereómero 1 Extremo-17a	TR = 5.00 minutos; HPLC Xterra 4.6 X 50 mm, 0 hasta 100% B durante 10 minutos, un minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% ácido fosfórico, B = 10% agua, 90% metanol, 0.2% ácido fosfórico; LCMS: Análisis calculado para: $C_{51}H_{54}N_8O_5$ 859.05 Encontrado: 859.51 $(M+H)^+$

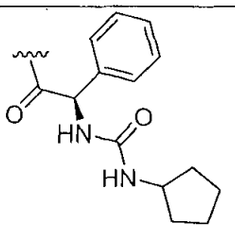
103-6	4-(2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etil)-1-piperazina carboxilato de bencilo	 Diastereómero 2 Extremo-17a	TR = 5.10 minutos; HPLC Xterra 4.6 X 50 mm, 0 hasta 100% B durante 10 minutos, un minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% ácido fosfórico, B = 10% agua, 90% metanol, 0.2% ácido fosfórico; LCMS: Análisis calculado para: $C_{51}H_{54}N_8O_5$ 859.05 Encontrado: 859.49 $(M+H)^+$

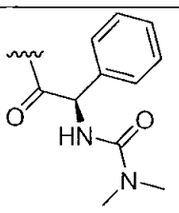
103-7	1-(2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etil)piperazina	 preparado por hidrogenolizar el 103-5	TR = 3.61 minutos; HPLC Xterra 4.6 X 50 mm, 0 hasta 100% B durante 10 minutos, un minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% ácido fosfórico, B = 10% agua, 90% metanol, 0.2% ácido fosfórico; LCMS: Análisis calculado para: $C_{43}H_{48}N_8O_3$ 724.91 Encontrado: 725.47 $(M+H)^+$

103-8	4-(2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etil)-2-piperazinona	 Extremo-17b	TR = 3.97; HPLC Xterra 4.6 X 50 mm, 0 hasta 100% B durante 10 minutos, un minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% ácido fosfórico, B = 10% agua, 90% metanol, 0.2% ácido fosfórico; LCMS: Análisis calculado para: $C_{43}H_{46}N_8O_4$ 738.90 Encontrado: 739.56 $(M+H)^+$

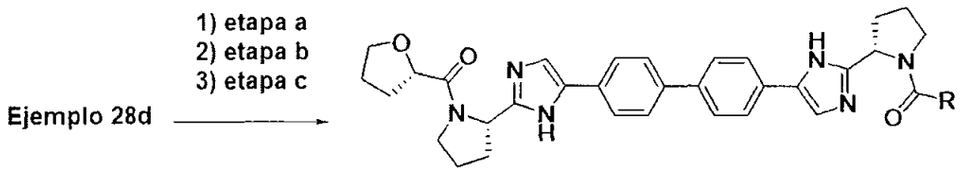
103-9	1-metil-3-((1R)-2-oxo-1-fenil-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) urea	 empleando Extremo-45	HPLC XTERRA C-18 4.6 × 30 mm, 0 hasta 100% B durante 4 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% H_3PO_4, B = 10% agua, 90% metanol, 0.2% H_3PO_4, TR = 1.81 minutos, 96% índice de homogeniedad.; LCMS: Análisis calculado para $C_{41}H_{44}N_8O_4$: 712.84; encontrado: 713.37 $(M+H)^+$; HRMS: Análisis calculado para $C_{41}H_{45}N_8O_4$ 713.3564; encontrado: 713.3564 $(M+H)^+$.

103-10	1-etil-3-((1R)-2-oxo-1-fenil-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) urea	 empleando Extremo-46	HPLC XTERRA C-18 4.6 × 30 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% H_3PO_4, B = 10% agua, 90% metanol, 0.2% H_3PO_4, TR = 1.88 minutos, 95% índice de homogeniedad; LCMS: Análisis calculado para $C_{42}H_{46}N_8O_4$: 726.87; encontrado: 727.71 $(M+H)^+$; HRMS: Análisis calculado para $C_{42}H_{47}N_8O_4$ 727.3720; encontrado: 727.3695 $(M+H)^+$.

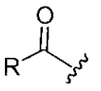
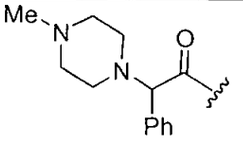
103-11	1-ciclopentil-3-((1R)-2-oxo-1-fenil-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) urea	 empleando Extremo-48	HPLC XTERRA C-18 4.6 × 30 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% H_3PO_4, B = 10% agua, 90% metanol, 0.2% H_3PO_4, TR = 2.11 minutos, 96% índice de homogeniedad; LCMS: Análisis calculado para $C_{45}H_{50}N_8O_4$: 766.93; encontrado: 767.45 $(M+H)^+$; HRMS: Análisis calculado para $C_{45}H_{51}N_8O_4$ 767.4033; encontrado: 767.4032 $(M+H)^+$.

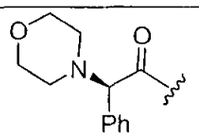
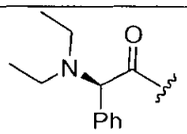
103-12	1,1-dimetil-3-((1R)-2-oxo-1-fenil-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) urea	 empleando Extremo-47	HPLC XTERRA C-18 4.6 × 30 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% H_3PO_4, B = 10% agua, 90% metanol, 0.2% H_3PO_4, TR = 1.87 minutos, 97% índice de homogeniedad; LCMS: Análisis calculado para $C_{42}H_{46}N_8O_4$: 726.87; encontrado: 727.38 $(M+H)^+$; HRMS: Análisis calculado para $C_{42}H_{47}N_8O_4$ 727.3720; encontrado: 727.3723 $(M+H)^+$.

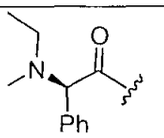
Ejemplos 104-107



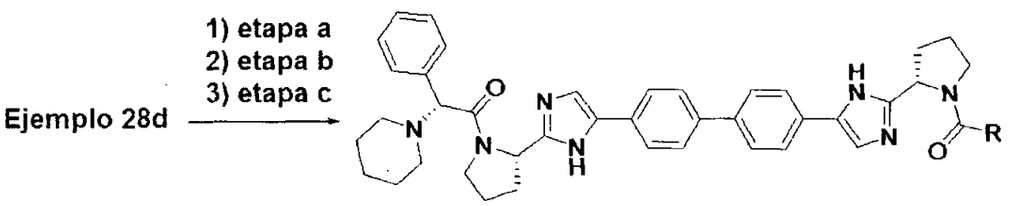
etapa a: Tapa con ácido (S)-2-tetrahidrofúroico como en el ejemplo 28
etapa b: El mismo procedimiento como en la conversión del ejemplo 1d hasta el ejemplo 1e
etapa c: Como en la última etapa del ejemplo 1 usando 1.1 equivalente del ácido carboxílico apropiado y HATU

Ejemplo	Nombre del compuesto		Tiempo de retención (Condición-CL); Datos EM de índice de homogeneidad
104	1-metil-4-(2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) piperazina	 Un diastereómero sencillo Extremo-17c	1.12 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{51}N_8O_3$: 739.41; encontrado 739.63; HRMS: Análisis calculado para $[M+H]^+$ $C_{44}H_{51}N_8O_3$: 739.4084; encontrado 739.4054

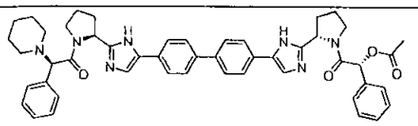
105	4-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) morfolina	 Extremo-6	1.13 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{48}N_7O_4$: 726.38; encontrado 726.63; HRMS: Análisis calculado para $[M+H]^+$ $C_{43}H_{48}N_7O_4$: 726.3768; encontrado 726.3803
106	(1R)-N,N-dietil-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etanamina	 Extremo-2	1.12 minutos (Cond. 1); 97%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{50}N_7O_3$: 712.40; encontrado 712.45; HRMS: Análisis calculado para $[M+H]^+$ $C_{43}H_{50}N_7O_3$: 712.3975; encontrado 712.3998

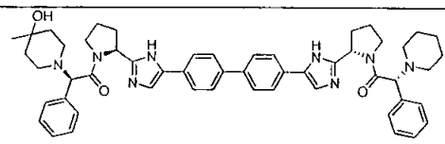
107	(1R)-N-etil-N-metil-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etanamina	 Extremo-3	1.10 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{48}N_7O_3$: 698.38; encontrado 698.45; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{48}N_7O_3$: 698.3819; 698.3823

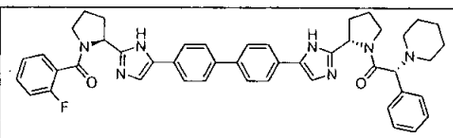
Ejemplos 107-1 hasta 107-30

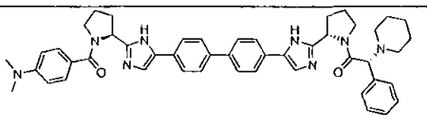
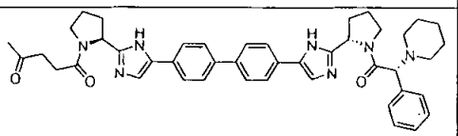


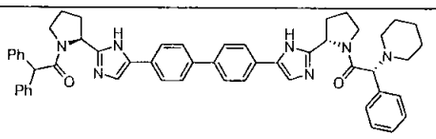
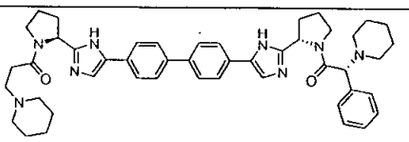
etapa a: Tapar con la tapa-14 como en el ejemplo 28
etapa b: El mismo procedimiento como en la conversión del ejemplo 1d hasta 1e
etapa c: Como en la última etapa del ejemplo 1 usando 1.1 equivalente del ácido carboxílico apropiado y HATU

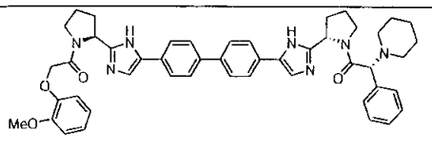
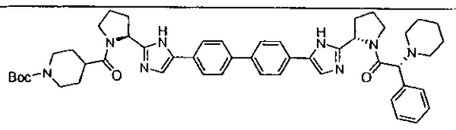
Número del ejemplo	Nombre del compuesto	Estructura	Datos
Ejemplo 107-1	acetato de (1S)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etilo		^{1}HRMN (400 MHz, $CDCl_3$) δ 7.63-7.85 (m, 8H), 7.48- 7.54 (m, 2H), 7.26- 7.46 (m, 7H), 6.94- 7.17 (m, 3H), 6.22 y 6.18 (s, 1H, rotámeros, 1:1), 5.99 y 5.68 (s, 1H, rotámeros, 1:1), 5.61 y 5.54 (d, J = 7.8 Hz, 1H, rotámeros, 1:1), 5.20- 5.23 y 5.10-5.13 (m, 1H, rotámeros, 1:1), 4.46 y 4.43 (s, 1H, rotámeros, 1:1), 3.97-4.06 (m, 1H), 3.89- 3.93 y 3.78-3.84 (m, 1H, rotámeros, 1:1), 3.63- 3.72 y 3.46-3.60 (m, 1H, rotámeros, 1:1), 3.23-3.32 (m, 2H), 2.41-2.59 (m, 4H), 2.13- 2.26 (m, 2H), 2.11 y 2.10 (s, 3H, rotámeros, 1:1), 2.05-2.09 (m, 2H), 1.97-1.98 (m, 1H), 1.82-1.90 (m, 1H), 1.58 (br s, 4H), 1.45 (br s, 2H); LCMS: Análisis calculado para $C_{49}H_{51}N_7O_4$: 801; encontrado: 802 $(M+H)^+$.

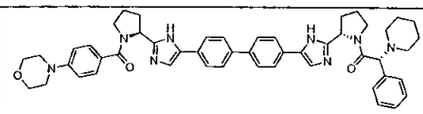
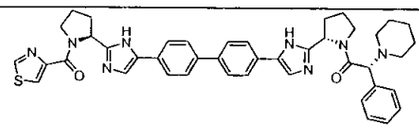
Ejemplo 107-2	4-metil-1-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil) acetil)-2-pirrolidinil) -1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etil)-4-piperidinol		LCMS: Análisis calculado para $C_{53}H_{60}N_8O_3$: 856; encontrado: 857 $(M+H)^+$.

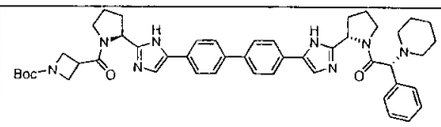
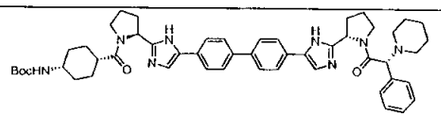
Ejemplo 107-3	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-fluorobenzoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) piperidina		LCMS: Análisis calculado para $C_{46}H_{56}FN_7O_2$: 747; encontrado: 748 $(M+H)^+$.

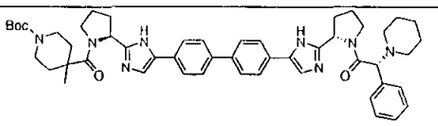
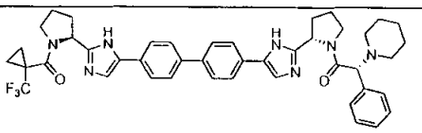
Ejemplo 107-4	N,N-dimetil-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)anilina		LCMS: Análisis calculado para $C_{48}H_{52}N_8O_2$: 772; encontrado: 773 $(M+H)^+$.
Ejemplo 107-5	5-oxo-5-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-pentanona		LCMS: Análisis calculado para $C_{44}H_{49}N_7O_3$: 723; encontrado: 724 $(M+H)^+$.

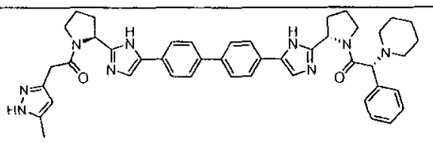
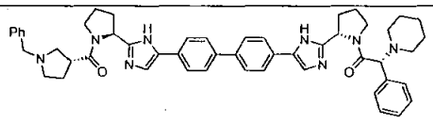
Ejemplo 107-6	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(difenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) piperidina		LCMS: Análisis calculado para $C_{53}H_{53}N_7O_2$: 819; encontrado: 820 $(M+H)^+$.
Ejemplo 107-7	1-(3-oxo-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) propil) piperidina		LCMS: Análisis calculado para $C_{47}H_{56}N_8O_2$: 764; encontrado: 765 $(M+H)^+$.

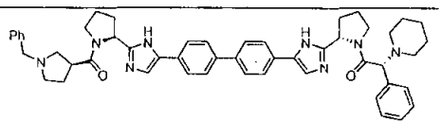
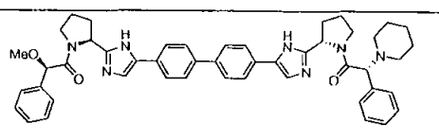
Ejemplo 107-8	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-metoxifenoxi)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) piperidina		LCMS: Análisis calculado para $C_{48}H_{51}N_7O_4$: 789; encontrado: 790 $(M+H)^+$.
Ejemplo 107-9	4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-1-piperidinacarboxilato de tert-butilo		LCMS: Análisis calculado para $C_{50}H_{60}N_8O_4$: 836; encontrado: 837 $(M+H)^+$.

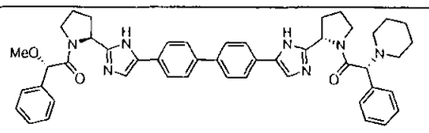
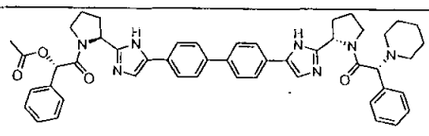
Ejemplo 107-10	4-(4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)fenil)morfolina		LCMS: Análisis calculado para $C_{50}H_{54}N_8O_3$: 814; encontrado: 815 $(M+H)^+$.
Ejemplo 107-11	1-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-tiazol-4-ilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) Piperidina		LCMS: Análisis calculado para $C_{43}H_{44}N_8O_2S$: 736; encontrado: 737 $(M+H)^+$.

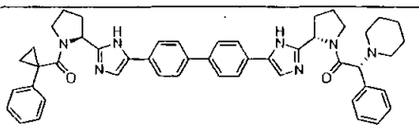
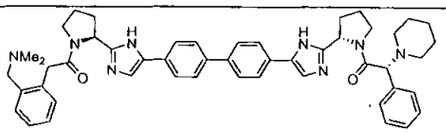
Ejemplo 107-12	3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-1-azetidinacarboxilato de tert-butilo		LCMS: Análisis calculado para $C_{48}H_{56}N_8O_4$: 808; encontrado: 809 $(M+H)^+$.
Ejemplo 107-13	(cis-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil) acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil) ciclohexil) carbamato de tert-butilo		LCMS: Análisis calculado para $C_{51}H_{62}N_8O_4$: 850; encontrado: 851 $(M+H)^+$.

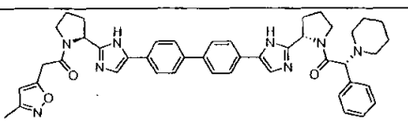
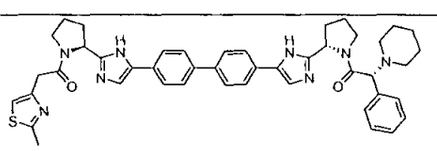
Ejemplo 107-14	4-metil-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-1-piperidinacarboxilato de tert-butilo		LCMS: Análisis calculado para $C_{51}H_{62}N_8O_4$: 850; encontrado: 851 $(M+H)^+$.
Ejemplo 107-15	1-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-(trifluorometil)ciclopropil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)piperidina		LCMS: Análisis calculado para $C_{44}H_{46}F_3N_7O_2$: 761; encontrado: 762 $(M+H)^+$.

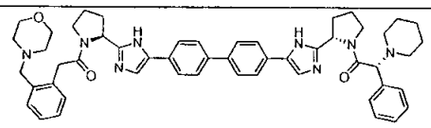
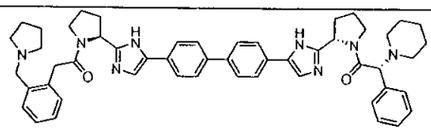
Ejemplo 107-16	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((5-metil-1H-pirazol-3-il)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) piperidina		LCMS: Análisis calculado para $C_{45}H_{49}N_9O_2$: 747; encontrado: 748 $(M+H)^+$.
Ejemplo 107-17	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3R)-1-bencil-3-pirrolidinil) carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) piperidina		LCMS: Análisis calculado para $C_{51}H_{56}N_8O_2$: 812; encontrado: 813 $(M+H)^+$.

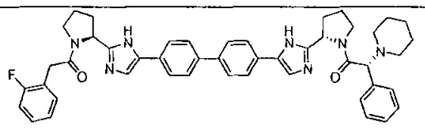
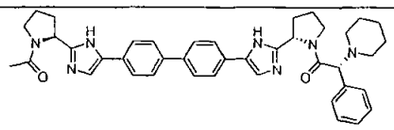
Ejemplo 107-18	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((3S)-1-bencil-3-pirrolidinil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) piperidina		LCMS: Análisis calculado para $C_{51}H_{56}N_8O_2$: 812; encontrado: 813 $(M+H)^+$.
Ejemplo 107-19	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-metoxi-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) piperidina		LCMS: Análisis calculado para $C_{48}H_{51}N_7O_3$: 773; encontrado: 774 $(M+H)^+$.

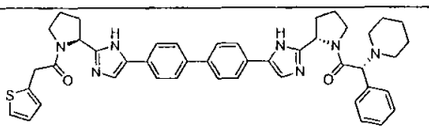
Ejemplo 107-20	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-metoxi-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) piperidina		LCMS: Análisis calculado para $C_{48}H_{51}N_7O_3$: 773; encontrado: 774 $(M+H)^+$.
Ejemplo 107-21	Acetato de (1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil) acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etilo		LCMS: Análisis calculado para $C_{49}H_{51}N_7O_4$: 801; encontrado: 802 $(M+H)^+$.

Ejemplo 107-22	1-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-fenil ciclopropil) carbonil)-2-pirrolidinil) -1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etil) piperidina		LCMS: Análisis calculado para $C_{49}H_{51}N_7O_2$: 769; encontrado: 770 $(M+H)^+$.
Ejemplo 107-23	N,N-dimetil-1-(2-(2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil) acetil)-2-pirrolidinil) -1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etil)fenil) metanamina		LCMS: Análisis calculado para $C_{50}H_{56}N_8O_2$: 800; encontrado: 801 $(M+H)^+$.

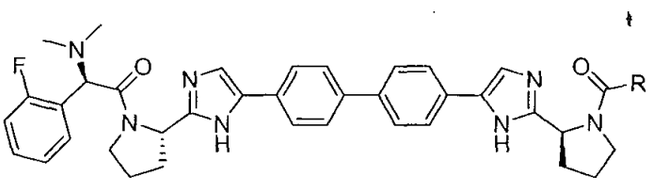
Ejemplo 107-24	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((3-metil-5-isoxazolil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) piperidina		LCMS: Análisis calculado para $C_{45}H_{48}N_8O_3$: 748; encontrado: 749 $(M+H)^+$.
Ejemplo 107-25	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-metil-1,3-tiazol-4-il)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) piperidina		LCMS: Análisis calculado para $C_{45}H_{48}N_8O_2S$: 764; encontrado: 765 $(M+H)^+$.

Ejemplo 107-26	4-(2-(2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil) acetil)-2-pirrolidinil) -1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etil)bencil) morfolina		LCMS: Análisis calculado para $C_{52}H_{58}N_8O_3$: 842; encontrado: 843 $(M+H)^+$.
Ejemplo 107-27	1-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-(1-pirrolidinil metil)fenil) acetil)-2-pirrolidinil) -1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etil) piperidina		LCMS: Análisis calculado para $C_{52}H_{58}N_8O_2$: 826; encontrado: 827 $(M+H)^+$.

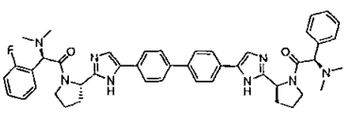
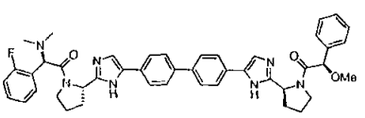
Ejemplo 107-28	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2-fluorofenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) piperidina		LCMS: Análisis calculado para $C_{47}H_{48}FN_7O_2$: 800; encontrado: 801 $(M+H)^+$.
Ejemplo 107-29	1-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-acetil-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) piperidina		LCMS: Análisis calculado para $C_{41}H_{45}FN_7O_2$: 667; encontrado: 668 $(M+H)^+$.

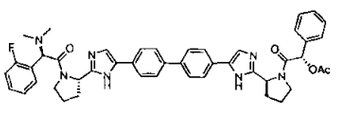
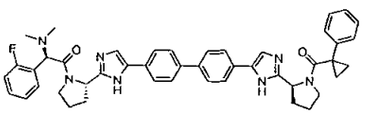
Ejemplo 107-30	1-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(2-tienilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etil) Piperidina		LCMS: Análisis calculado para $C_{45}H_{47}N_7O_2S$: 749; encontrado: 750 $(M+H)^+$.

Ejemplo 107-31 hasta 107-34

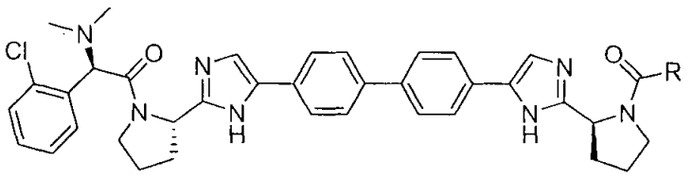


Los ejemplos 107-31 hasta 107-34 se prepararon en una manera similar al ejemplo 28. El extremo-38 se agregó al intermediario 28d, el carbamato Boc se removió con TFA o HCl y el ácido carboxílico apropiado se acopló.

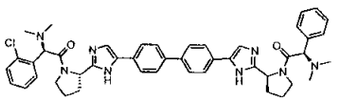
Ejemplo	Nombre del compuesto	Estructura	Datos
Ejemplo 107-31	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-(2-fluorofenil) acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina		LCMS: Análisis calculado para $C_{46}H_{49}FN_8O_2$: 764; encontrado: 765 $(M+H)^+$.
Ejemplo 107-32	(1R)-1-(2-fluorofenil)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-metoxi-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxoetanamina		LCMS: Análisis calculado para $C_{45}H_{46}FN_7O_3$: 751; encontrado: 752 $(M+H)^+$.

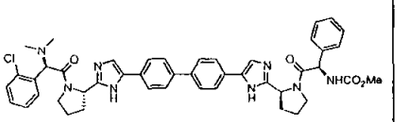
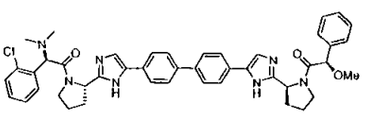
Ejemplo 107-33	Acetato de (1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-(2-fluorofenil) acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletilo		LCMS: Análisis calculado para $C_{46}H_{46}FN_7O_4$: 779; encontrado: 780 $(M+H)^+$.
Ejemplo 107-34	(1R)-1-(2-fluorofenil)-N,N-dimetil-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((1-fenil ciclopropil) carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etanamina		LCMS: Análisis calculado para $C_{46}H_{46}FN_7O_2$: 747; encontrado: 748 $(M+H)^+$.

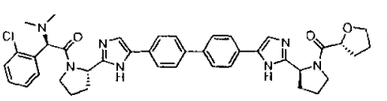
Ejemplo 107-35 hasta 107-38



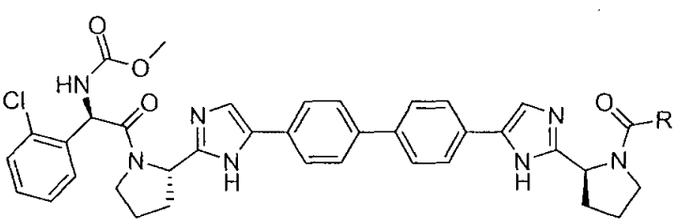
Los ejemplos 107-35 hasta 107-38 se prepararon en una manera similar al ejemplo 28. El extremo-39 se agregó al intermediario 28d, el carbamato Boc se removió con TFA o HCl y el ácido carboxílico apropiado se acopló.

Ejemplo	Nombre del compuesto	Estructura	Datos
Ejemplo 107-35	(1R)-1-(2-clorofenil)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxoetanamina		LCMS: Análisis calculado para $C_{46}H_{49}ClN_8O_2$: 780; encontrado: 781 $(M+H)^+$.

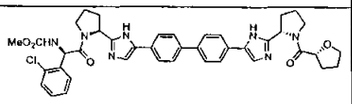
Ejemplo 107-36	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(2-clorofenil)-2-(dimetilamino) acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) carbamato de metilo		LCMS: Análisis calculado para $C_{46}H_{47}ClN_8O_4$: 810; encontrado: 811 $(M+H)^+$.
Ejemplo 107-37	(1R)-1-(2-clorofenil)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-metoxi-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxoetanamina		LCMS: Análisis calculado para $C_{45}H_{46}ClN_7O_3$: 767; encontrado: 768 $(M+H)^+$.

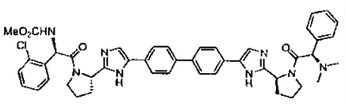
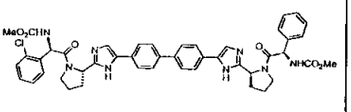
Ejemplo 107-38	(1R)-1-(2-clorofenil)-N,N-dimetil-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etanamina		LCMS: Análisis calculado para $C_{41}H_{44}ClN_7O_3$: 717; encontrado: 718 $(M+H)^+$.

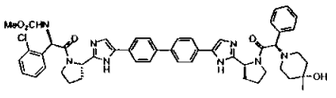
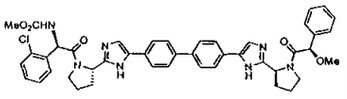
Ejemplo 107-39 hasta 107-43

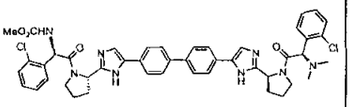


Los ejemplos 107-39 hasta 107-44 se prepararon en una manera similar al ejemplo 28. El extremo-40 se agregó al intermediario 28d, el carbamato Boc se removió con TFA o HCl y el ácido carboxílico apropiado se acopló.

Ejemplo	Nombre del compuesto	Estructura	Datos
Ejemplo 107-39	((1R)-1-(2-clorofenil)-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etil) carbamato de metilo		^{1}HRMN (400 MHz, CD_3OD) δ 7.58-7.77 (m, 8H), 7.42-7.55 (m, 2H), 7.19-7.39 (m, 4H), 5.94 y 5.89 (s, 1H, rotámeros, 1:1), 5.80 y 5.61 (s, 1H, rotámeros, 1:1), 5.43-5.47 y 5.35-5.38 (m, 1H, rotámeros, 1:1), 5.20-5.24 (m, 1H), 5.15- 5.18 (m, 1H), 4.67-4.70 y 4.39-4.42 (m, 1H, rotámeros, 1:1), 3.92-3.98 (m, 1H), 3.85-3.90 (m, 1H), 3.69-3.84 (m, 2H), 3.64 y 3.63 (s, 3H, rotámeros, 1:1), 3.53-3.59 (m, 1H), 2.35-2.46 (m, 1H), 2.21-2.29 (m, 2H), 2.06-2.17 (m, 3H), 1.84-2.01 (m, 4H), 1.66-1.76 y 1.41-1.47 (m, 1H, rotámeros, 1:1); LCMS: Análisis calculado para $C_{41}H_{42}ClN_7O_5$: 747; encontrado: 748 $(M+H)^+$.

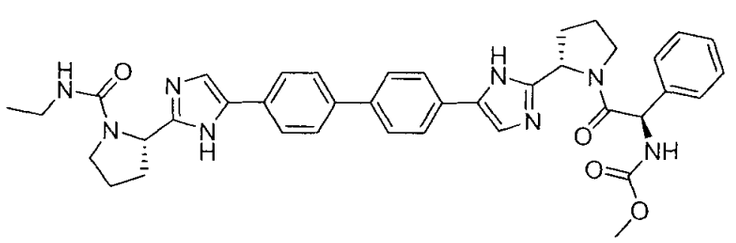
Ejemplo 107-40	((1R)-1-(2-clorofenil)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{46}H_{47}ClN_8O_4$: 810; encontrado: 811 $(M+H)^+$.
Ejemplo 107-41	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(2-clorofenil)-2-((metoxicarbonil)amino)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) carbamato de metilo		LCMS: Análisis calculado para $C_{46}H_{45}ClN_8O_6$: 840; encontrado: 841 $(M+H)^+$.

Ejemplo 107-42	((1R)-1-(2-clorofenil)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(4-hidroxi-4-metil-1-piperidinil)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{50}H_{53}ClN_8O_5$: 880; encontrado: 881 $(M+H)^+$.
Ejemplo 107-43	((1R)-1-(2-clorofenil)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-metoxi-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{45}H_{44}ClN_7O_5$: 797; encontrado: 798 $(M+H)^+$.

Ejemplo 107-44	((1R)-1-(2-clorofenil)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(2-clorofenil)-2-(dimetilamino)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{46}H_{46}Cl_2N_8O_4$: 844; encontrado: 845 $(M+H)^+$.

Ejemplo 108

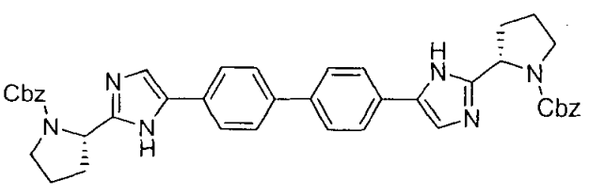
((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(etilcarbamoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo



El isocianato de etilo (5 µL, 0.063 mmol) se agregó a una solución de metanol (1.0 mL) de 28f (30 mg, 0.049 mmol) y se agitó a condiciones ambientales durante 1.8 horas. El residuo se trató con 2.0 M NH_3/metanol (2 mL) y se agitó durante 30 minutos adicionales, y todos los componentes volátiles se removieron *in vacuo*. El material resultante se purificó por HPLC de fase inversa (H_2O/metanol/TFA) para proporcionar la sal TFA del ejemplo 108 como una espuma amarilla ligera (16.7 mg) CL: 1.95 minutos (Cond. II); >98% índice de homogeneidad; LC/MS: Análisis calculado para [M+H]+ $C_{39}H_{43}N_8O_4$: 687.34; encontrado 687.53; HRMS: Análisis calculado para $[M+H]^+$ $C_{39}H_{43}N_8O_4$: 687.3407; encontrado 687.3417.

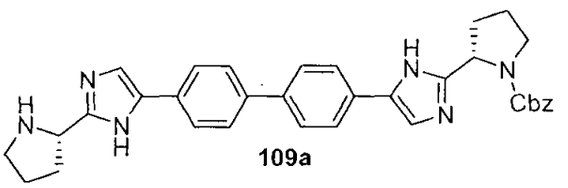
Ejemplo 109

(2S,2'S)-2,2'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil))di(1-pirrolidincarboxilato) de dibencilo



Ejemplo 109, Extremo a

(2S)-2-(5-(4'-(2-((2S)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidincarboxilato de bencilo

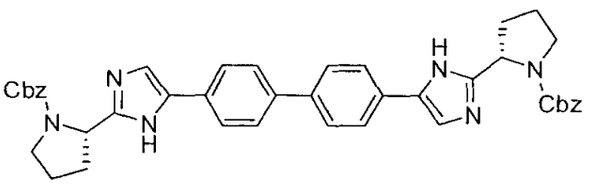


109a

La desprotección Boc del 28c usando el procedimiento descrito por la síntesis de pirrolidina 1e a partir del carbamato 1d proporcionó 109a. TR = 1.92 minutos (Cond II); > 98% índice de homogeneidad; LC/MS: Análisis calculado. $C_{34}H_{35}N_6O_2$: 559.28; encontrado 559.44.

Ejemplo 109

(2S,2'S)-2,2'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil))di(1-pirrolidincarboxilato) de dibencilo

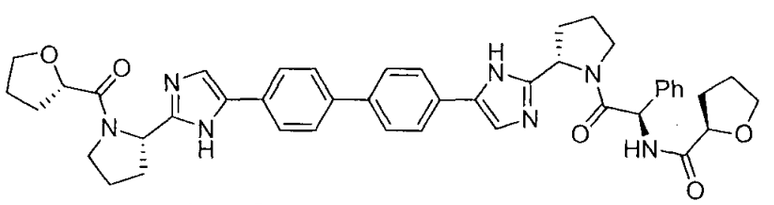


El cloroformiato de bencilo (10.5 µL, 0.0736 mmol) se agregó a una solución THF (2.0 mL) de 109a (37.1 mg, 0.664 mmol) y trietilamina (15 µl, 0.107 mmol), y se agitó bajo condiciones ambientales durante 6 horas. El componente volátil se removió *in vacuo*, y el residuo se trató con 2N

NH_3/metanol (2 mL) y se agitó durante 15 minutos. El componente volátil se removió *in vacuo*, y el residuo se purificó por HPLC de fase inversa (H_2O/metanol/TFA) para proporcionar la sal TFA del ejemplo 109 como una espuma blanca opaca (37.9 mg). CL (Cond. II): TR = 2.25 min; >98% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{41}N_6O_4$: 693.32; encontrado 693.59; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{41}N_6O_4$: 693.3189; encontrado 693.3220.

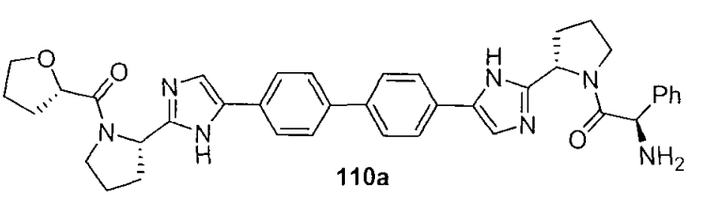
Ejemplo 110

(2R)-N-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)tetrahidro-2-furancarboxamida



Ejemplo 110, Extremo a

(1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etanamina



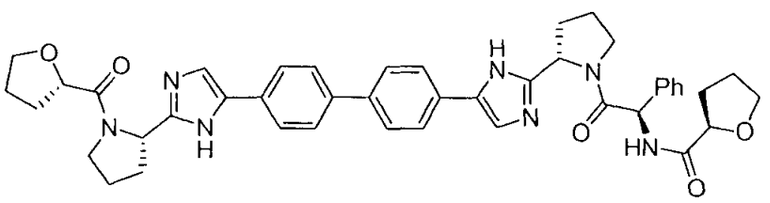
110a

La amina 110a se sintetizó partiendo del 28d y ácido (*S*)-

tetrahidrofuran-2-carboxílico al emplear secuencialmente los procedimientos descritos en la preparación del 28f (a partir de 28d) y 25b (a partir de 1e). CL (Cond. I): TR = 1.13 min; >98% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{39}H_{42}N_7O_3$: 656.34; encontrado 656.49; HRMS: Análisis calculado para $[M+H]^+$ $C_{39}H_{42}N_7O_3$: 656.3349; encontrado 656.3377.

Ejemplo 110

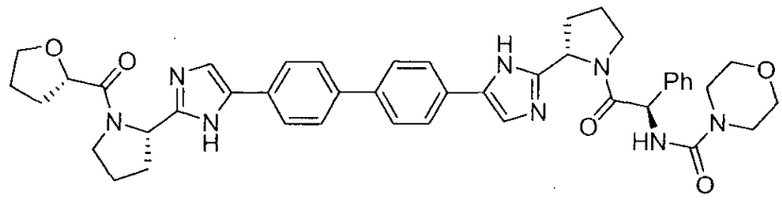
(2R)-N-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)tetrahidro-2-furancarboxamida



El ejemplo 110 (Sal TFA) se preparó a partir del ejemplo 110a y ácido (*S*)-tetrahidrofuran-2-carboxílico usando las condiciones descritas por la síntesis del Ejemplo 1 a partir de amina 1e. CL (Cond. I): TR = 1.28 min; >98% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.37; encontrado 754.60; HRMS: Análisis calculado para $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.3717; encontrado 754.3690.

Ejemplo 111

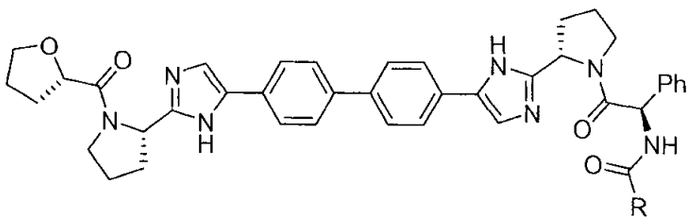
N-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)-4-morfolincarboxamida

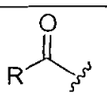
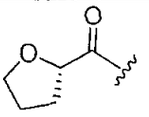


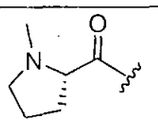
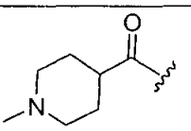
El ejemplo 111 (Sal TFA) se preparó a partir de amina 110a y cloruro de morfolin 4-carbonilo usando el procedimiento descrito por la síntesis del ejemplo 29 a partir de amina 28f. CL (Cond. I): TR = 1.28 min; >98% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{49}N_8O_5$: 769.38; encontrado 769.60.

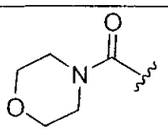
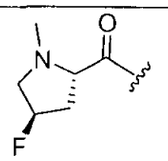
Usando los métodos similares descritos por la preparación del Ejemplo 111, los siguientes compuestos (Ejemplo 112-120) se sintetizaron como sales TFA.

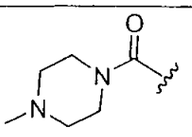
Ejemplo 112-117



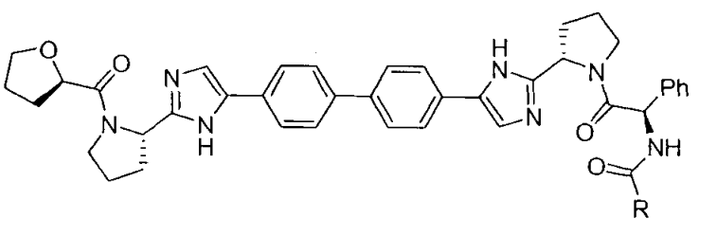
Ejemplo	*Nombre del compuesto*		*Tiempo de retención (Condición-LC); índice de homogeneidad Datos EM*
112	(2S)-N-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etil)tetrahidro-2-furancarboxamida		1.28 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.37; encontrado 754.59; HRMS: Análisis calculado para $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.3717; encontrado 754.3731

113	1-metil-N-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)-L-prolinamida		1.14 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{51}N_8O_4$: 767.40; encontrado 767.68; HRMS: Análisis calculado para $[M+H]^+$ $C_{44}H_{51}N_8O_4$: 767.4033; encontrado 767.4035
114	1-metil-N-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)-4-piperidin carboxamida		1.12 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{46}H_{53}N_8O_4$: 781.42; encontrado 781.67; HRMS: Análisis calculado para $[M+H]^+$ $C_{46}H_{53}N_8O_4$: 781.4190; encontrado 781.4195

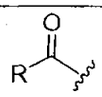
115	N-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etil)tetrahidro-2H-puran-4-carboxamida		1.24 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{45}H_{50}N_7O_5$: 768.39; encontrado 768.66; HRMS: Análisis calculado para $[M+H]^+$ $C_{45}H_{50}N_7O_5$: 768.3873; encontrado 768.3897
116	(4R)-4-fluoro-1-metil-N-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etil)-L-prolinamida	 *extremo*-11	1.16 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{45}H_{50}FN_8O_4$: 785.39; encontrado 785.63; HRMS: Análisis calculado para $[M+H]^+$ $C_{45}H_{50}FN_8O_4$: 785.3939; encontrado: 785.3940

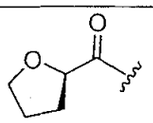
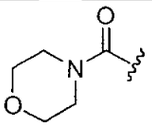
117	4-metil-N-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)-1-piperazin carboxamida		1.15 minutos (Cond. 1); 97.6%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{45}H_{52}N_9O_4$: 782.41; encontrado 782.64; HRMS: Análisis calculado para $[M+H]^+$ $C_{45}H_{52}N_9O_4$: 782.4142; encontrado 782.4161

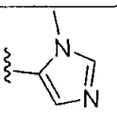
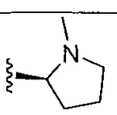
Ejemplos 118 hasta 120-9

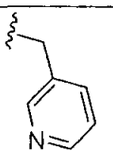


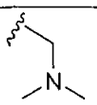
Los ejemplos 118 hasta 120-9 se prepararon como se describe en la preparación del Ejemplo 110a substituyendo ácido (R)-tetrahidrofuril carboxílico y el ácido carboxílico apropiado, cloruro ácido carboxílico, cloruro de carbamoilo, o isocianato.

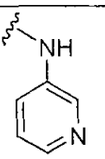
Ejemplo	*Nombre del compuesto*		*Tiempo de retención (CL-Afección); índice de homogeneidad; datos EM*
118	N-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) acetamida		1.89 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{44}N_7O_4$: 698.35; encontrado 698.25; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{44}N_7O_4$: 698.3455; encontrado 698.3474

119	(2R)-N-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) tetrahidro-2-furancarboxamida		1.99 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.37; encontrado 754.28; HRMS: Análisis calculado para $[M+H]^+$ $C_{44}H_{48}N_7O_5$: 754.3717; encontrado 754.3705
120	N-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) -4-morfolin carboxamida		2.00 minutos (Cond. 2); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{49}N_8O_5$: 769.38; encontrado 769.32

120-5	1-metil-N-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)-1H-imidazol-5-carboxamida		TR= 4.02 (97%); HPLC XTERRA C-18 4.6 × 30 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% H_3PO_4, B = 10% agua, 90% metanol, 0.2% H_3PO_4, TR = 1.87 minutos, 97% de índice de homogeneidad; LCMS: análisis calculado para: $C_{44}H_{45}N_9O_4$ 763.91; Encontrado: 764.52 $(M+H)^+$
120-6	1-metil-N-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)-L-prolinamida		TR= 3.68 (99%); HPLC XTERRA C-18 4.6 × 30 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% H_3PO_4, B = 10% agua, 90% metanol, 0.2% H_3PO_4, TR = 1.87 minutos, 97% de índice de homogeneidad; LCMS: análisis calculado para: $C_{45}H_{50}N_8O_4$ 766.95; Encontrado: 767.47 $(M+H)^+$

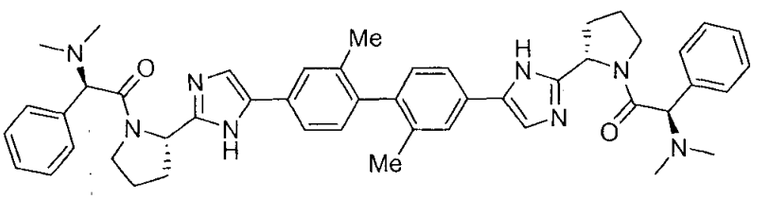
120-7	N-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)-2-(3-piridinil) acetamida		TR= 3.81 (99%); HPLC XTERRA C-18 4.6 × 30 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% H_3PO_4, B = 10% agua, 90% metanol, 0.2% H_3PO_4, TR = 1.87 minutos, 97% de índice de homogeneidad; LCMS: análisis calculado para: $C_{46}H_{46}N_8O_4$ 774.93; Encontrado: 775.47 $(M+H)^+$

120-8	N^2,N^2-dimetil-N-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) glicinamida		^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.71-2.44 (m, 12H), 2.65-2.89 (m, 6H), 3.04-3.21 (m, *J*=8.55 Hz, 1H), 3.46-3.68 (m, 1H), 3.64-4.07 (m, 6H), 4.64 (dd, *J*=8.09, 5.34 Hz, 1H), 5.09-5.30 (m, 2H), 5.66-5.86 (m, 1H), 7.32-7.49 (m, 4H), 7.82-8.22 (m, 10H), 9.15-9.38 (m, 1H), 9.68 (s, 1H), 14.60 (s, 2H); CLAr Xterra 4.6 X 50 mm, 0 hasta 100% B durante 10 minutos, uno minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% ácido fosfórico, B = 10% agua, 90% metanol, 0.2% ácido fosfórico, TR = 3.61 min; LCMS: análisis calculado para: $C_{52}H_{56}N_{10}O_6$ 740.91; Encontrado: 741.48 $(M+H)^+$.

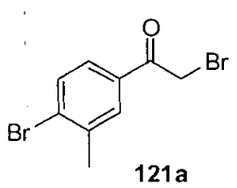
120-9	1-((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)-3-(3-piridinil)urea		^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.64-2.40 (m, 12H), 3.11-3.27 (m, 1H), 3.51-3.65 (m, 1H), 3.80 (dd, *J*=18.46, 6.87 Hz, 3H), 3.96-4.11 (m, 1H), 4.64 (dd, *J*=7.78, 5.34 Hz, 1H), 5.13-5.23 (m, 1H), 5.21-5.35 (m, 1H), 5.66 (d, *J*=7.02 Hz, 1H), 7.29-7.57 (m, 7H), 7.82-8.07 (m, 10H), 8.14 (s, 1H), 8.22 (d, *J*=4.58 Hz, 1H), 8.68 (s, 1H), 9.32 (s, 1H), 14.46 (s, 2H); HPLC Xterra 4.6 X 50 mm, 0 hasta 100% B durante 10 minutos, un minuto tiempo de espera, A = 90% agua, 10% metanol, 0.2% ácido fosfórico, B = 10% agua, 90% metanol, 0.2% ácido fosfórico, TR = 3.83 min; LCMS: análisis calculado para: $C_{45}H_{45}N_9O_4$ 775.92; Encontrado: 776.53 $(M+H)^+$.

Ejemplo 121

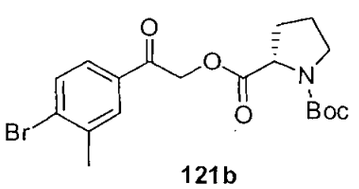
(1R,1'R)-2,2'-((2,2'-dimetil-4,4'-bifenildiil)bis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(N,N-dimetil-2-oxo-1-feniletanamina)



Ejemplo 121, Extremo a-b



121a



121b

El $PdCl_2(Ph_3P)_2$ (257 mg, 0.367 mmol) se agregó a una solución de dioxano (45 mL) de 1-bromo-4-yodo-2-metilbenceno (3.01 g, 10.13 mmol) y tri-*n*-butil(1-etoxivinil)estanano (3.826 g, 10.59 mmol) y se calienta a 80°C durante ~17 horas. La mezcla de reacción se trató con agua (15 mL), se enfría hasta ~0°C (hielo/agua), y luego NBS (1.839 g, 10.3 mmol) se agregó en lotes durante 7 minutos. Después de alrededor de 25 minutos de agitación, el componente volátil se removió *in vacuo*, 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 *in vacuo*. El material crudo resultante se purificó por una cromatografía de

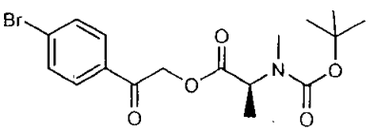
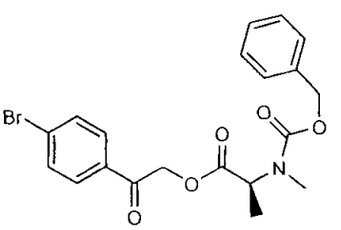
gravedad (gel de sílice; 4% acetato de etilo/hexanos)para proporcionar bromuro 121a como un sólido amarillo de tono café (2.699 g); la muesta es impura y contiene impurezas derivadas de estanano, entre otras. ^{1}H RMN ($CDCl_3$, δ = 7.24, 400 MHz): 7.83 (s, 1H), 7.63 (s, 2H), 4.30 (s, 2H), 2.46 (s, 3H).

Una solución de CH_3CN (15 mL) de 121a (2.69 g, < 9.21 mmol) se agregó en porciones durante 3 minutos a una solución de CH_3CN (30 mL) de (*S*)-Boc-prolina (2.215 g, 10.3 mmol) y trietilamina (1.40 mL, 10.04 mmol), y se agitó durante 90 minutos. El componente volátil se removió *in vacuo*, y el residuo se dividió entre agua y CH_2Cl_2, y la fase orgánica se secó ($MgSO_4$), se filtró y se concentró *in vacuo*. El material crudo resultante se purificó por una cromatografía instantánea (gel de sílice; 15-20% acetato de etilo/hexanos) para proporcionar 121b como un aceite viscoso incoloro (2.74g). ^{1}H 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); CL (Cond. I): TR = 1.91 min; >95% 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 en una forma análoga.

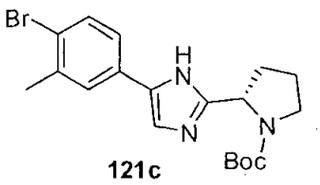
Condiciones CL: *Condición 1*: Phenomenex LUNA C-18 4.6 x 50

mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de sepra, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

Condición 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

Ejemplo	Estructura	Datos
121b-1		TR = 2.15 minutos (condición 2, 98%); EMBR: Análisis calculado para $C_{17}H_{22}NO_5$ 399.07; encontrado: 400.10 $(M+H)^+$.
121b-2		TR = 2.78 minutos (>90%); LCMS: Análisis calculado para $C_{20}H_{20}{}^{37}BrNO_5$ 435.05 encontrado: 458.02 $(M+Na)^+$.

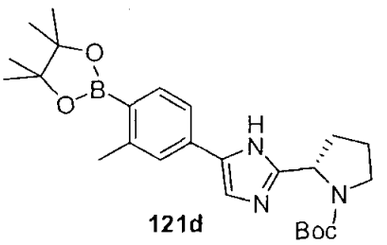
Ejemplo 121, Extremo c



121c

Una mezcla del cetoéster 121b (1.445 g, 3.39 mmol) y NH_4OAc (2.93 g, 38.0 mmol) en xilenos (18 mL) se calentó con un microondas a 140°C durante 80 minutos. El componente volátil se removió *in vacuo*, y el residuo se dividió cuidadosamente entre CH_2Cl_2 y agua, en donde suficiente solución $NaHCO_3$ saturado se agregó 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 *in vacuo*. El producto crudo se purificó por una cromatografía instantánea (gel de sílice, 40% acetato de etilo/hexanos) para proporcionar imidazol 121c como un sólido blanco opaco (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); CL (Cond. 1): TR = 1.91 min; >98% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{19}H_{25}BrN_3O_2$ 405.96; encontrado 406.11.

Ejemplo 121, Extremo d



121d

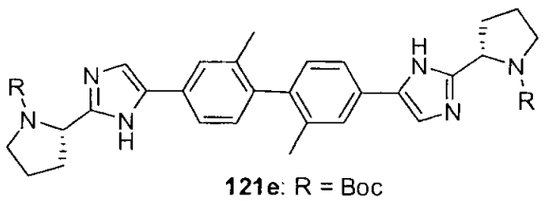
El $PdCl_2dppf{\cdot}CH_2Cl_2$ (50.1 mg, 0.061 mmol) se agregó a un tubo de presión que contiene una mezcla de bromuro 121c (538.3 mg, 1.325 mmol), bis(pinacolato)diboro (666.6 mg, 2.625 mmol), acetato de potasio (365.8 mg, 3.727 mmol) y DMF (10 mL). La mezcla de reacción se mojó con N_2 y se calienta a 80°C durante 24.5 horas. El componente volátil se removió *in vacuo* y el residuo se dividió entre CH_2Cl_2 y agua, en donde suficiente solución $NaHCO_3$ saturada se agregó para hacer el pH del medio acuoso neutral. La fase acuosa se extrajo con CH_2Cl_2, y la fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró *in vacuo*. El material resultante se purificó por un sistema Biotage (gel de sílice, 40-50% acetato de etilo/hexanos) para proporcionar boronato 121d como una espuma blanca (580 mg). De acuerdo a ^1H RMN la muestra contiene residuo de pinacol en una relación producto/pinacol de ~3. ^1H 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); CL (Cond. I): TR = 1.62 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{25}H_{37}BN_3O_4$ 454.29; encontrado 454.15

Ejemplo 121, Extremo e

y

ejemplo 121, Extremo f

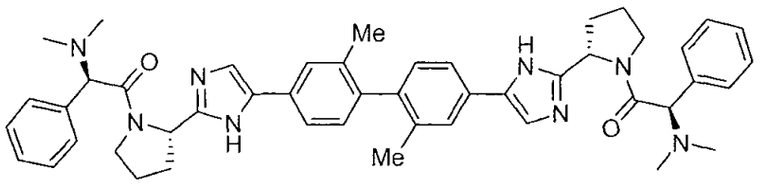


121e: R = Boc
121f: R = H

El carbamato 121e se preparó a partir de bromuro 121c y boronato 121d de acuerdo a la preparación del dímero 1d; CL (Cond. I): TR = 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 a la preparación de pirrolidina 1e, proporciona 121f como una espuma blanca opaca. ^1H 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 las señales amplias corresponden a la pirrolidina NH aparece en la región 2.8-3.2 ppm, el intervalo actual para su cambio

químico no puede determinarse. CL (Cond. 1): TR = 1.03 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{28}H_{33}N_6$ 453.28; encontrado 453.53



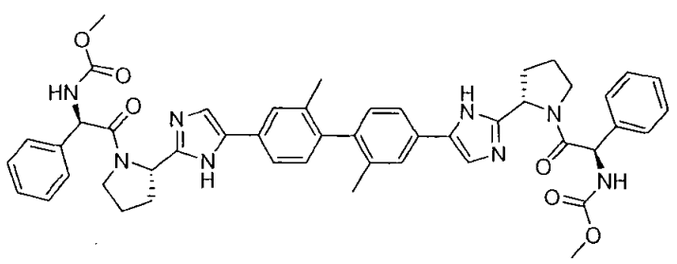
Ejemplo 121

(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 a la preparación del Ejemplo 1 de 1e; CL (Cond. I): TR = 1.14 min; >98% 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

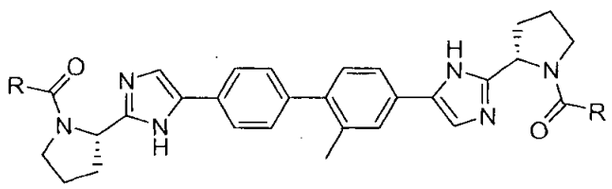
Ejemplo 122

((2,2'-dimetil-4,4'-bifenildiil)bis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))biscarbamato de dimetilo

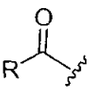
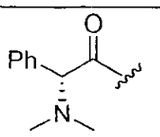


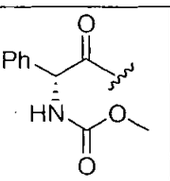
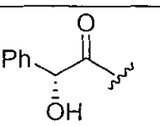
El ejemplo 122 (Sal TFA) se preparó a partir de pirrolidina 121f y Extremo 4 al usar el procedimiento descrito para la preparación del Ejemplo 1 de pirrolidina 1e. CL (Cond. I): TR = 1.35 min; >98% índice de homogeneidad; HRMS: Análisis calculado para $[M+H]^+$ $C_{48}H_{51}N_8O_6$ 835.3932; encontrado 835.3954

Ejemplo 123-125

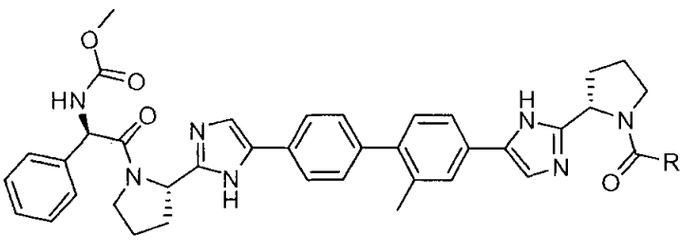


El ejemplo 123-125 se prepararon iniciando de boronato 1c y bromuro 121c al usar los métodos descritos en el Ejemplo 1, Extremo d, Ejemplo 1, Extremo e, y en la Extremo describe la preparación de Ejemplo 1.

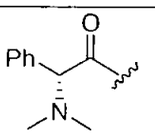
Ejemplo	*Nombre del compuesto*		*TR (CL-Cond.); % de índice de homogenedad; Datos EM*
123	(1R,1'R)-2,2'-((2-metil-4,4'-bifenildiil)bis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(N,N-dimetil-2-oxo-1-feniletanamina)	 *Extremo-1*	1.12 minutos (Cond. 1); >98%; LC/MS: análisis calculado para $[M+H]^+$ $C_{47}H_{53}N_8O_2$: 761.43; encontrado 761.49; HRMS: Análisis calculado para $[M+H]^+$ $C_{47}H_{53}N_8O_2$: 761.4291; encontrado 761.4311

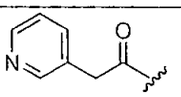
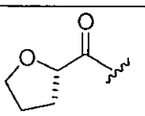
124	((2-metil-4,4'-bifenildiil)bis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))biscarbamato de dimetilo	 *Extremo-4*	1.34 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{47}H_{49}N_8O_6$: 821.38; encontrado 821.45; HRMS: Análisis calculado para $[M+H]^+$ $C_{47}H_{49}N_8O_6$: 821.3775; encontrado 821.3785
125	(1R,1'R)-2,2'-((2-metil-4,4'-bifenildiil)bis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(2-oxo-1-feniletanol)		1.23 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{43}N_6O_4$: 707.34; encontrado 707.38; HRMS: Análisis calculado para $[M+H]^+$ $C_{43}H_{43}N_6O_4$: 707.3346; encontrado 707.3356

Ejemplo 126-128



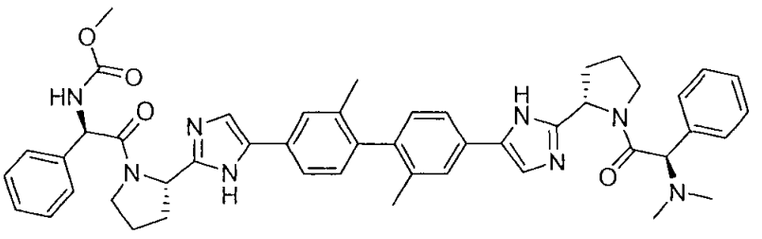
El ejemplo 126-128 se prepararon iniciando de bromuro 28b y boronato 121d al usar los métodos descritos en el Ejemplo 28 partiendo con la Extremo c.

Ejemplo	*Nombre del compuesto*		*TR (CL-Cond.); % de índice de homogeneidad; Datos EM*
126	((1R)-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: Análisis calculado para $[M+H]^+$ $C_{47}H_{51}N_8O_4$: 791.40; encontrado 791.70; HRMS: Análisis calculado para $[M+H]^+$ $C_{47}H_{51}N_8O_4$: 791.4033; encontrado 791.4061

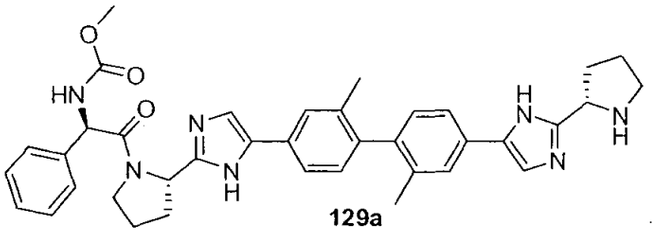
127	((1R)-2-((2S)-2-(5-(2'-metil-4'-(2-((2S)-1-(3-piridinilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.19 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{45}N_8O_4$: 749.36; encontrado 749.62; HRMS: Análisis calculado 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-furanilcarbonil)-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: Análisis calculado para $[M+H]^+$ $C_{42}H_{46}N_7O_5$: 728.36; encontrado 728.59; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{46}N_7O_5$: 728.3560; encontrado 728.3593

Ejemplo 129

((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-2,2'-dimetil-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo



Ejemplo 129, Extremo a

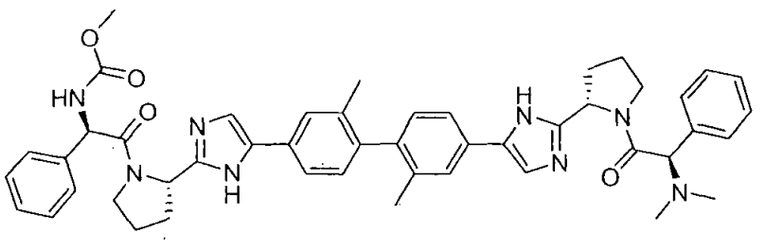


129a

HATU (104.3 mg, 0.274 mmol) se agregó a una mezcla de 121f, Extremo 4 (58.8 mg, 0.281 mmol) y diisopropiletilamina (110 µL, 0.631 mmol) en DMF (6.0 mL), y se agitó durante 90 minutos. El componente volátil se removió *in vacuo* y el material crudo resultante se purificó por HPLC de fase inversa (H_2O/metanol/TFA), y con base libre por Columna MCX (lavado de metanol; 2.0 M NH_3/metanol) para proporcionar 129a (89.9 mg). CL (Cond. 1): TR = 1.22 min; 95% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{42}N_7O_3$ 644.34; encontrado 644.55.

Ejemplo 129

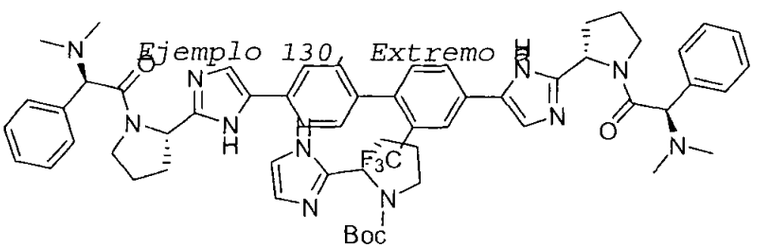
((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-2,2'-dimetil-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo



El ejemplo 129 (Sal TFA) se preparó a partir de 129a por el método usado para convertir el Ejemplo 1e hasta el Ejemplo 1. CL (Cond. 1): TR = 1.27 min; 97% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{48}H_{53}N_8O_4$ 805.42; encontrado 805.61.

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)



130a

El glioxal (2.0 mL de 40% en agua) se agregó en porciones durante 11 minutos a una solución en metanol de NH_4OH (32 mL) y (S)-Boc-prolinal (8.564 g, 42.98 mmol) y se agita a temperatura ambiente durante 19 horas. El componente volátil se removió *in vacuo* y el residuo se purificó por una cromatografía instantánea (gel de sílice, acetato de etilo) seguido por una recristalización (acetato de etilo, temperatura ambiente) para proporcionar Imidazol 130a como un sólido esponjoso blanco (4.43g). ^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). CL (Cond. 1): TR = 0.87 min; >95% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{12}H_{20}N_3O_2$ 238.16; encontrado 238.22. Imidazol 130a tiene un ee de 98.9% cuando se analiza bajo afección HPLC quiral anotada a continuación.

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

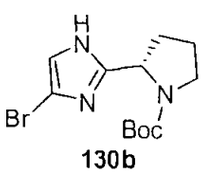
Solvente: 1.7% etanol/heptano (isocrático)

Relación de flujo: 1 mL/min

Longitud de onda: ya sea 220 ó 256 nm

Tiempo de retención relativa: 3.25min (*R*), 5.78 minutos (*S*)

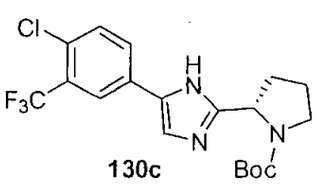
Ejemplo 130, Extremo b



130b

N-bromosuccinimida (838.4 mg, 4.71 mmol) se agregó en lotes, durante 15 minutos, a una solución enfriada (hielo/agua) CH_2Cl_2 (20 mL) de Imidazol 130a (1.0689 g, 4.504 mmol), y se agitó a temperatura similar durante 75 minutos. El componente volátil se removió *in vacuo*. El material crudo se purificó por sistema HPLC de fase inversa (H_2O/metanol/TFA) para separar bromuro 130b de su análogo dibromo y el material de partida no consumido. La HPLC eluida se neutralizó con exceso de NH_3/metanol y el componente volátil se removió *in vacuo*. 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 *in vacuo* 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). CL (Cond. I): TR = 1.10 min; >95% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{12}H_{19}BrN_3O_2$ 316.07; encontrado 316.10.

Ejemplo 130, Extremo c

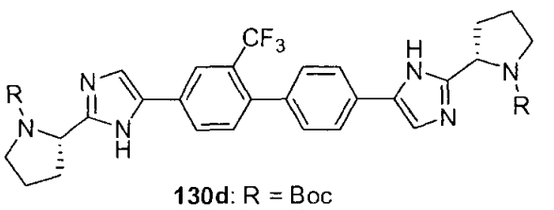


130c

$Pd(Ph_3P)_4$ (78.5 mg, 0.0679 mmol) se agregó a una mezcla

de bromuro 130b (545 mg, 1.724 mmol), 2-(4-cloro-3-(trifluorometil)fenil-4,4,5,5-tetrametil-1,3,2-dioxaborolano (542.8 mg, 1.771 mmol) (comercialmente disponible), $NaHCO_3$ (477 mg, 5.678 mmol) en 1,2-dimetoxietano (12.5 mL) y agua (4.2 mL). La mezcla de reacción se purgó con nitrógeno, se calienta con un baño de aceite a 80 °C durante 27 horas, y luego el componente volátil se removió *in vacuo*. El residuo se dividió entre CH_2Cl_2 y agua, y la capa orgánica se secó ($MgSO_4$), se filtró y se concentró *in vacuo*. El material crudo resultante se purificó por un sistema Biotage (gel de sílice, 40-50% acetato de etilo/hexanos) seguido por HPLC de fase inversa (agua/ metanol/TFA). La HPLC eluida se trató con 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 *in vacuo* 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). CL (Cond. I): TR = 1.52 min; >95% 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, Extremo d-e



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

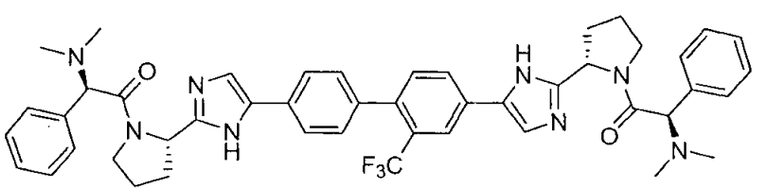
$Pd[P(t\text{-}Bu)_3]_2$ (48 mg, 0.094 mmol) se agregó a una mezcla de cloruro 130c (245 mg, 0.589 mmol), boronato 1c (277.1 mg, 0.631 mmol), KF (106.7 mg, 1.836 mmol) en DMF (6 mL), y se calienta a 110°C durante ~30 horas. El componente volátil se removió *in vacuo*, y el residuo se dividió entre CH_2Cl_2 (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 *in vacuo*. El material resultante se purificó por un sistema Biotage (gel de sílice, acetato de etilo) para proporcionar carbamato 130d como una espuma blanca opaca (297 mg). CL (Cond. I): TR = 1.44 min; >95% 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 lleva a cabo de conformidad a la preparación de pirrolidina 1e, proporcionando 130e como una espuma amarilla ligera. ^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 las señales amplias corresponden a la pirrolidina NH aparece en la región 2.8-3.2 ppm, el intervalo actual para su cambio químico no puede determinarse. CL (Cond. I): TR = 1.12 min; >95% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{27}H_{28}F_3N_6$ 493.23; encontrado 493.14.

Ejemplo 130

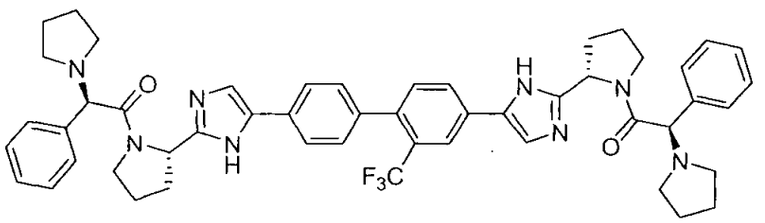
(1R,1'R)-2,2'-((2-(trifluorometil)-4,4'-bifenildiil)bis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(N,N-dimetil-2-oxo-1-feniletanamina)



Ejemplo 130 (Sal TFA) se preparó a partir de 130e de acuerdo a la preparación del Ejemplo 1 de pirrolidina 1e. CL (Cond. 1): TR = 1.17 min; >98% 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

5,5'-(2-(trifluorometil)-4,4'-bifenildiil)bis(2-((2S)-1-((2R)-2-fenil-2-(1-pirrolidinil)acetil)-2-pirrolidinil)-1H-imidazol)



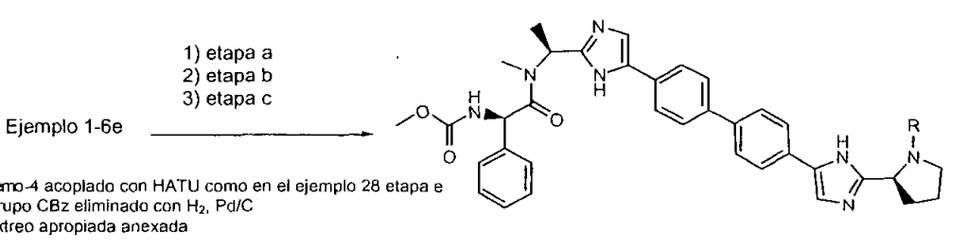
El ejemplo 131 (Sal TFA) se sintetizó a partir de 130e de acuerdo a la preparación del Ejemplo 130.

CL (Cond. 1): TR = 1.19 min; >98% índice de homogeneidad

LC/MS: Análisis calculado para $[M+H]^+$ $C_{51}H_{54}F_3N_8O_2$ 867.43; encontrado 867.51

HRMS: Análisis calculado para $[M+H]^+$ $C_{51}H_{54}F_3N_8O_2$ 867.4322; encontrado 867.4315

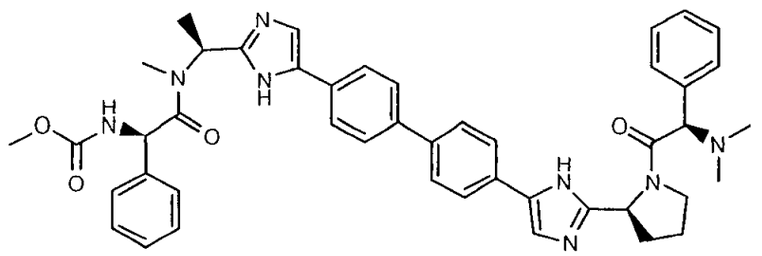
Ejemplo 131.1-1 hasta 131.1-2



Los ejemplos 131.1-1 a través de 131.1-2 se prepararon en una manera similar al ejemplo 28 por medio de intermediación del intermediario 1-6e después del extremo 4 anexa.

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 el carbamato CBz se removió de 1-6e con $Pd/C/H_2$.

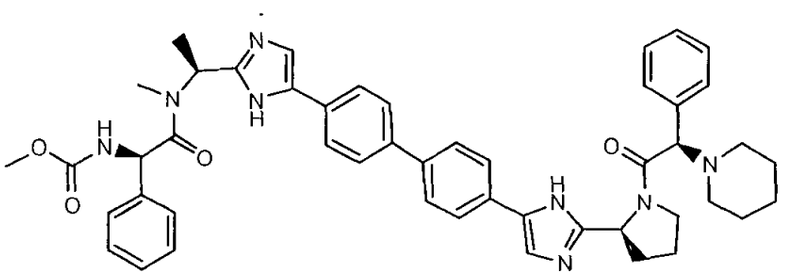
Condiciones LCMS: Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección. t_R = 1.42 min

EMBR: análisis calculado para $C_{45}H_{49}N_8O_4$ 765.39; encontrado: 765.38 $(M+H)^+$.

HRMS: análisis calculado para $C_{45}H_{49}N_8O_4$ Calcd 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



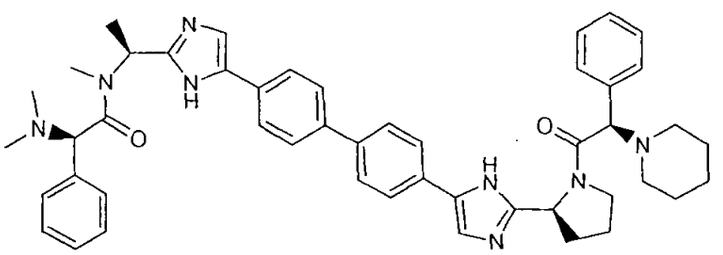
Extremo-14 se anexó después el carbamato CBz se removió de 1-6e con $Pd/C/H_2$.

Condiciones LCMS: Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección. t_R = 1.45 min (>95 %) EMBR: análisis calculado para $C_{48}H_{52}N_8O_4$ 805.42; encontrado: 805.41 $(M+H)^+$.

HRMS: análisis calculado $C_{48}H_{52}N_8O_4$ calculado 805.4190 encontrado: 805.4214 $(M+H)^+$.

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



Ejemplo 131. 2 se preparó en manera similar al ejemplo 131.1-1 y el ejemplo 131.1-2 por medior de la intermediación del intermediario 1-6e después del extremo-1 anexada.

El extremo-14 se anexó después el carbamato de CBz se removió con Pd/C/H_2.

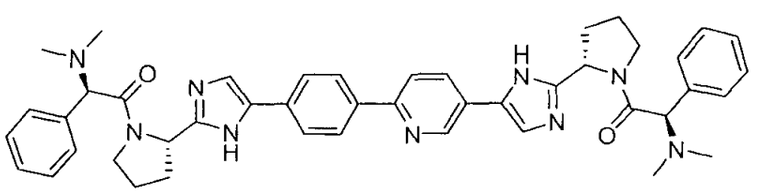
Condiciones LCMS: Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección. t_R = 1.28 min

EMBR: análisis calculado para $C_{48}H_{54}N_8O_2$ 775.44; encontrado: 775.45 $(M+H)^+$.

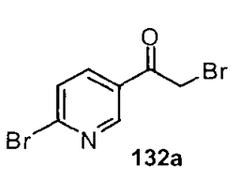
HRMS: análisis calculado $C_{48}H_{54}N_8O_2$ calculado 775.4448 encontrado: 775.4460 $(M+H)^+$.

Ejemplo 132

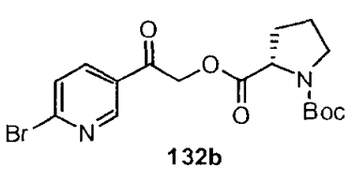
(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-3-piridinil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina



Ejemplo 132, Extremo a-b



132a



132b

Una solución CH_2Cl_2 (10 mL) de Br_2 (7.63 g, 47.74 mmol) se agregó gota a gota durante 5 min a una solución enfriada (hielo/agua) CH_2Cl_2 (105 mL) de 1-(6-bromopiridina-3-il)etanona (9.496 g, 47.47 mmol) y 48% HBr (0.4 mL). El baño frío se removió 40 min después, y se continuó agitando a temperatura ambiente durante alrededor de 66 hr. La torta del sólido que se formó se filtró, se lavó con CH_2Cl_2 y se secó in vacuo para proporcionar 132a impuro como un sólido blanco opaco (15.94 g).

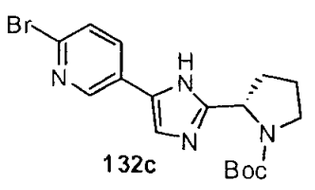
La Boc-L-prolina (9.70 g, 45.06 mmol) se agregó en un lote a una mezcla heterogénea de 132a crudo (15.4 g) y CH_3CN (150 mL), e inmediatamente Et_3N posterior (13.0 mL, 93.2 mmol) se agregó en porciones durante 6 min. La mezcla de reacción se agitó durante 50 min, el componente volátil se removió in vacuo y el residuo se dividió entre CH_2Cl_2 y agua. La capa CH_2Cl_2 se secó ($MgSO_4$) y se evaporó in vacuo, y el material resultante se purificó por cromatografía instantánea (gel de sílice; la muestra se cargó con solvente eluido; 25% EtOAc/hexanos) para proporcionar 132b como un aceite amarillo altamente viscoso (11.44g). ^1H RMN (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 (dos s, 9H).

CL (Cond. 1): TR = 2.01 min; >90% 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, Extremo c



132c

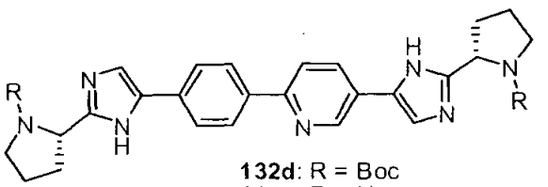
Una mezcla de cetoéster 132b (1.318 g, 3.19 mmol) y NH_4OAc (2.729 g, 35.4 mmol) en xilenos (18 mL) se calentó con un microondas a 140°C durante 90 min. El componente volátil se removió in vacuo y el residuo se dividió entre CH_2Cl_2 y agua, en donde suficiente solución $NaHCO_3$ saturada se agregó para neutralizar el medio acuoso. La fase acuosa se extrajo con CH_2Cl_2, y la fase orgánica combinada se secó ($MgSO_4$) y se evaporó in vacuo. El material crudo resultante se purificó por un sistema Biotage (gel de sílice; 50% EtOAc/hexanos) para proporcionar imidazol 132c como una espuma blanca opaca (1.025 g). ^1H RMN (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 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).

CL (Cond. 1): TR = 1.52 min; >98% 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, Extremo d-e



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

$Pd(Ph_3P)_4$ (115.1 mg, 0.10 mmol) se agregó a una mezcla de bromuro 132c (992mg, 2.52 mmol), boronato 1c (1.207 g, 2.747 mmol), $NaHCO_3$ (698.8 mg, 8.318 mmol) en 1,2-dimetoxietano (18 mL) y agua (4 mL). La mezcla de reacción se mojó con nitrógeno, se calienta con un baño de aceite a 90°C durante 37 hr y se permite enfriar hasta temperatura ambiente. La suspensión que se formó se filtró y se lavó con agua seguido por 1,2-dimetoxietano, y se secó in vacuo. Una malla de gel de sílice se preparó a partir del sólido crudo y se sometió una cromatografía instantánea (gel de sílice; EtOAc) para proporcionar carbamato 132d como un sólido blanco, el cual ligeramente amarillo se deja reposar a condiciones ambientales (1.124g). ^1H RMN indica que la muestra contiene residuo de MeOH en una relación de mol producto/MeOH de 1.3.

CL (Cond. 1): TR = 1.71 min; >98% 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

Carbamato 132d (217 mg) se trató con 25% TFA/CH_2Cl_2 (3.6 mL) y se agitó a condiciones ambientales durante 6 hr. El componente volátil se removió in vacuo, y el material resultante se hizo base libre por columna MCX (lavado MeOH; 2.0 M elución NH_3/MeOH) para proporcionar 132e como una espuma amarilla opaca que se solidifica gradualmente hasta el reposo (150.5 mg; masa se proporciona teóricamente arriba). ^1H RMN (DMSO, δ = 2.5 ppm; 400 MHz): 11.89 (muy amplio, 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 se observaron]

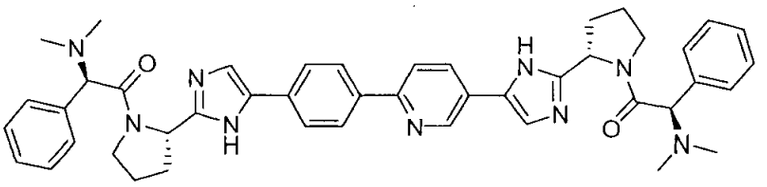
CL (Cond. 1): TR = 1.21min; >98% índice de homogeneidad

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 mmol) se agregó a una mezcla de pirrolidina 132e (23.1 mg, 0.054 mmol), (*i*-Pr)$_2$EtN (40 µL, 0.23 mmol) y Extremo 1 (25.3 mg, 0.117 mmol) en DMF (1.5 mL), y la mezcla se agitó a ambiente durante 1 hr. El componente volátil se removió in vacuo, y el residuo se purificó primero por MCX (lavado MeOH; 2.0 M elución NH_3/MeOH) y luego por HPLC de fase inversa (H_2O/MeOH/TFA) para proporcionar la sal TFA del Ejemplo 132 como una espuma amarilla (39.2 mg).

CL (Cond. 1): TR = 1.37min; >98% índice de homogeneidad

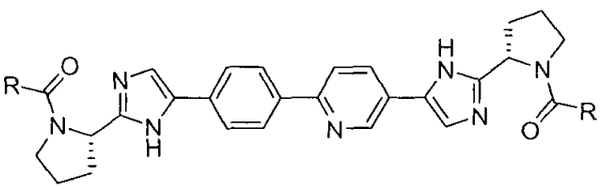
LC/MS: Análisis calculado para $[M+H]^+$ $C_{45}H_{50}N_9O_2$: 748.41; encontrado 748.53

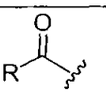
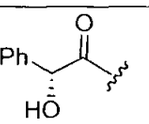
HRMS: Análisis calculado para $[M+H]^+$ $C_{45}H_{50}N_9O_2$: 748.4087; encontrado 748.4090

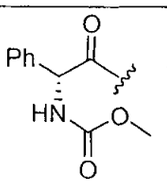
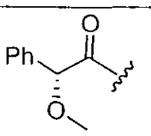
Los ejemplos 133-135 se prepararon como sales TFA de

132e al usar el mismo método de preparaciones como el Ejemplo 132 y reactivos apropiado.

Ejemplo 133-135

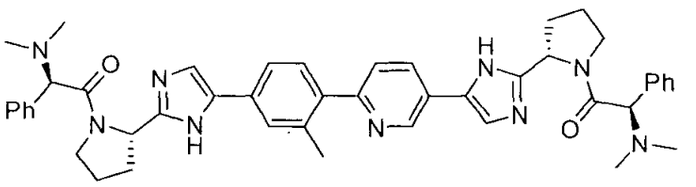


Ejemplo	*Nombre del compuesto*		*TR (CL-Cond.); % índice de homogeneidad; Datos EM*
133	(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-hidroxi-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-3-piridinil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletanol		1.49 min (Cond. 1); >98% LC/MS: análisis calculado para $[M+H]^+$ $C_{41}H_{40}N_7O_4$: 694.31; encontrado 694.42 HRMS: análisis calculado para $[M+H]^+$ $C_{41}H_{40}N_7O_4$: 694.3142, encontrado: 694.3164

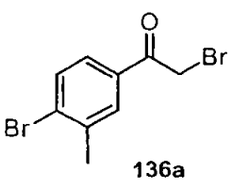
134	((1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-3-piridinil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 *extremo-4*	1.60 min (Cond. 1); >98% LC/MS: análisis calculado para $[M+H]^+$ $C_{45}H_{46}N_9O_6$: 808.36; encontrado 808.51 HRMS: análisis calculado para $[M+H]^+$ $C_{45}H_{46}N_9O_6$: 808.3571; encontrador 808.3576
135	5-(2-((2S)-1-((2R)-2-metoxi-2-fenilacetil)-2-pirrolidinil)-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: análisis calculado para $[M+H]^+$ $C_{43}H_{44}N_7O_4$: 722.35; encontrado 722.40 HRMS: análisis calculado para $[M+H]^+$ $C_{43}H_{44}N_7O_4$: 722.3455; encontrado722.3464

Ejemplo 136

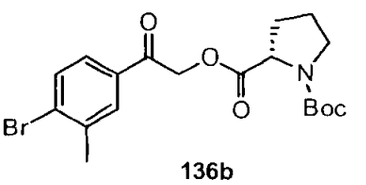
(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-metilfenil)-3-piridinil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina



Ejemplo 136, Extremo a y b



136a



136b

$PdCl_2(Ph_3P)_2$ (257 mg, 0.367 mmol) se agregó a una solución dioxano (45 mL) de 1-bromo-4-yodo-2-metilbenceno (3.01 g, 10.13 mmol) y tri-*n*-butil(1-etoxivinil)estanano (3.826 g, 10.59 mmol) y se calienta a 80°C durante ~17 hr. La mezcla de reacción se trató con agua (15 mL), se enfría hasta ~0°C (hielo/agua), y luego NBS (1.839 g, 10.3 mmol) se agregó en lotes durante 7 min. Alrededor de 25 min de agitación, el componente volátil se removió in vacuo, 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 ($MgSO_4$) y se

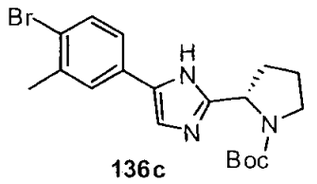
evaporó in vacuo. El material crudo resultante se purificó por una cromatografía de gravedad (gel de sílice; 4% EtOAc/hexanos)para proporcionar bromuro 136a como un sólido amarillo-de tono café (2.699 g); la muesta es impura y contiene impurezas derivadas de estanano, entre otras. ^{1}H RMN ($CDCl_3$, δ = 7.24, 400 MHz): 7.83 (s, 1H), 7.63 (s, 2H), 4.30 (s, 2H), 2.46 (s, 3H).

Una solución de CH_3CN (15 mL) de 136a (2.69 g, < 9.21 mmol) se agregó gota a gota durante 3 min a una solución de CH_3CN (30 mL) de (*S*)-Boc-prolina (2.215 g, 10.3 mmol) y Et_3N (1.40 mL, 10.04 mmol), y se agitó durante 90 min. El componente volátil se removió *in vacuo*, y el residuo se dividió entre agua y CH_2Cl_2, y la fase orgánica se secó ($MgSO_4$) y se evaporó in vacuo. El material crudo resultante se purificó por una cromatografía instantánea (gel de sílice; 15-20% EtOAc/hexanos) para proporcionar 136b como un aceite viscoso incoloro (2.74g). ^{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).

CL (Cond. 1): TR = 1.91 min; >95% índice de homogeneidad

LC/MS: Análisis calculado para $[M+Na]^+$ $C_{19}H_{24}BrNNaO_5$ 448.07; encontrado 448.10

Ejemplo 136, Extremo c



136c

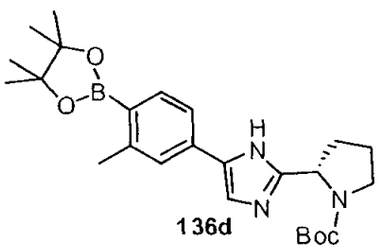
Una mezcla de cetoéster 136b (1.445 g, 3.39 mmol) y NH_4OAc (2.93 g, 38.0 mmol) en xilenos (18 mL) se calentó con un microondas a 140°C durante 80 min. El componente volátil se removió in vacuo, y el residuo se dividió cuidadosamente entre CH_2Cl_2 y agua, en donde suficiente solución $NaHCO_3$ saturada se agregó para neutralizar el medio acuoso. La fase acuosa se extrajo con CH_2Cl_2, y la fase orgánica combinada se secó ($MgSO_4$) y se evaporó in vacuo. El crudo se purificó por una cromatografía instantánea (gel de sílice, 40% EtOAc/hexanos) para proporcionar imidazol 136c como un sólido blanco opaco (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).

CL (Cond. 1): TR = 1.91 min; >98% índice de homogeneidad

LC/MS: Análisis calculado para $[M+H]^+$ $C_{19}H_{25}BrN_3O_2$ 405.96;

encontrado 406.11

Ejemplo 136, Extremo d



136d

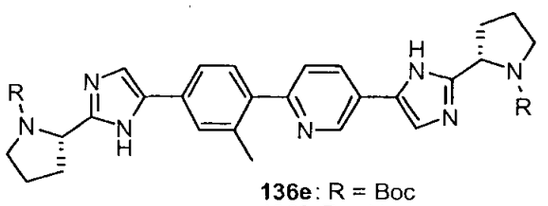
$PdCl_2dppf.CH_2Cl_2$ (50.1 mg, 0.061 mmol) se agregó a un tubo de presión que contiene una mezcla de bromuro 136c (538.3 mg, 1.325 mmol), bis(pinacolato)diboro (666.6 mg, 2.625 mmol), KOAc (365.8 mg, 3.727 mmol) y DMF (10 mL). La mezcla de reacción se mojó con N_2 y se calienta a 80°C durante 24.5 hr. El componente volátil se removió in vacuo y el residuo se dividió entre CH_2Cl_2 y água, en donde suficiente solución $NaHCO_3$ saturada se agregó para hacer el pH del medio acuoso neutral. La fase acuosa se extrajo con CH_2Cl_2, y la fase orgánica combinada se secó ($MgSO_4$) y se evaporó in vacuo. El material resultante se purificó por un sistema Biotage (gel de sílice, 40-50% EtOAc/hexanos) para proporcionar boronato 136d como una espuma blanca (580 mg). De acuerdo a ^1H RMN la muestra contiene residuo de pinacol en una relación 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).

CL (Cond. 1): TR = 1.62 min

LC/MS: Análisis calculado para $[M+H]^+$ $C_{25}H_{37}BN_3O_4$ 454.29; encontrado 454.15

Ejemplo 136, Extremo e-f



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

Biarilo 136e se preparó a partir de bromuro 132c y boronato 136d de acuerdo a la afección de acoplamiento descrita para la preparación de biarilo 132d.

CL (Cond. 1a): TR = 1.32 min; >90% índice de homogeneidad

LC/MS: Análisis calculado para $[M+H]^+$ $C_{36}H_{45}N_7O_4$ 640.36; encontrado 640.66

La desprotección de biarilo 136e se hizo de acuerdo a la preparación de pirrolidina 132e para proporcionar 136f como una espuma amarilla ligera. ^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

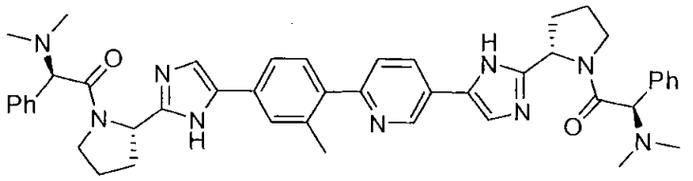
(s, 1H), 7.64-7.62 (m, 2H), 7.50 (d, J = 8.3, 1H), 7.46 (br s, 1H), 7.40 (d, J = 7.8, 1H), 4.21-4.14 (m, 2H), 3.00-2.93 (m, 2H), 2.90-2.82 (m, 2H), 2.40 (s, 3H), 2.11-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.82-1.66 (m, 4H). [Nota: la señal para la pirrolidina NH aparece en la región 3.22-2.80 y es demasiado amplia para hacer un cambio químico asignado.]

CL (Cond. 1): TR = 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



Ejemplo 136 (Sal TFA) se sintetizó a partir de 136f de acuerdo a la preparación del Ejemplo 132 de 132e.

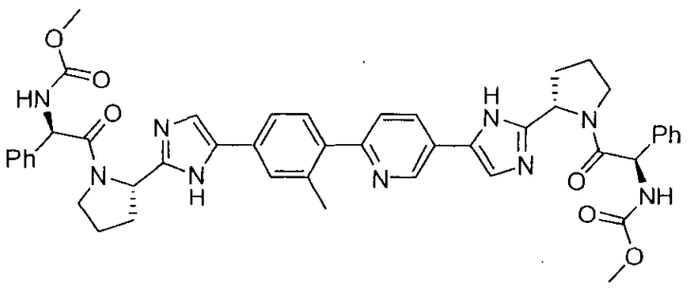
1.05 min (Cond. 1); >98%

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-5-il)-2-metilfenil)-3-piridinil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo

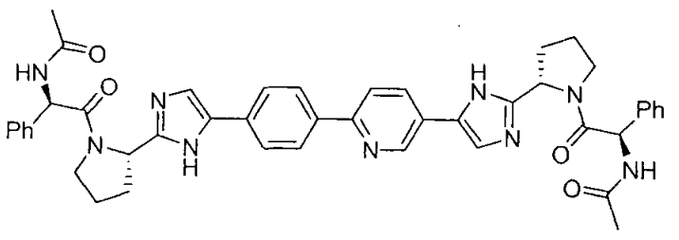


El ejemplo 138 fue preparado similarmente de la pirrolidina 136f y extremo-4. 1.60 min (Cond. Ia); >98%. LC/MS: Análisis calculado para $[M+H]^+$ $C_{46}H_{48}N_9O_6$: 822.37; encontrado 822.74

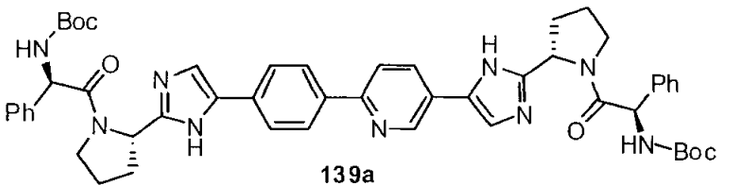
HRMS: Análisis calculado para $[M+H]^+$ $C_{46}H_{48}N_9O_6$: 822.3728; encontrado 822.3760

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, Extremo a



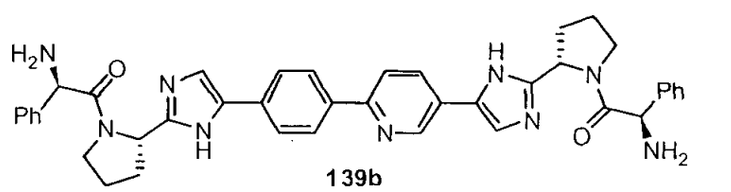
139a

HATU (99.8 mg, 0.262 mmol) se agregó a una mezcla de 132e (54.1 mg, 0.127 mmol), ácido (*R*)-2-(*t*-butoxicarbonilamino)-2-fenilacético (98.5 mg, 0.392 mmol) y *i*-Pr_2EtN (100 µL, 0.574 mol), y la mezcla de reacción se agitó durante 70 min. El componente volátil se removió in vacuo, y el residuo se purificó por HPLC de fase inversa (H_2O/MeOH/TFA), en donde la HPLC eluida se trató con exceso de 2.0 N NH_3/MeOH antes de la eliminación del componente volátil in vacuo. 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 ($MgSO_4$) y se evaporó in vacuo. El carbamato 139a se obtuvo es una película blanca de la espuma(82.3 mg).

CL (Cond. 1): TR = 1.97 min; >95% índice de homogeneidad.

LC/MS: Análisis calculado para $[M+H]^+$ $C_{51}H_{58}N_9O_6$: 892.45; encontrado 892.72

Ejemplo 139b, Extremo b



139b

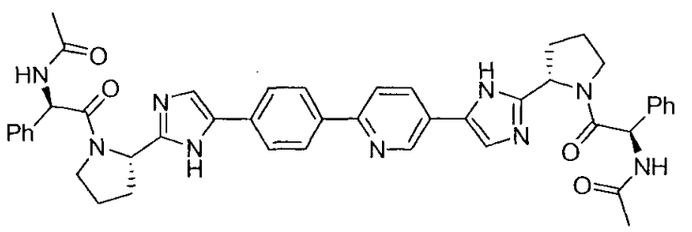
El carbamato 139a se desprotegió de la amina 139b al usar el procedimiento descrito para la preparación de pirrolidina 132e de 132d.

CL (Cond. 1): TR = 1.37 min; >95% 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



El anhídrido acético (20 µL, 0.212 mmol) se agregó a una solución DMF (1.5 mL) de 139b (31.2 mg, 0.045 mmol), y la mezcla de reacción se agitó durante 1 hr. NH_3/MeOH (1.0 mL de 2N) se agregó a la mezcla de reacción y se continuó agitando durante 100 min. El componente volátil se removió in vacuo y el material crudo resultante se purificó por HPLC de fase inversa (H_2O/MeOH/TFA) para proporcionar la sal TFA del Ejemplo 139 como un sólido amarillo ligero (24.1 mg).

CL (Cond. 1): TR = 1.53 min; >98% índice de homogeneidad

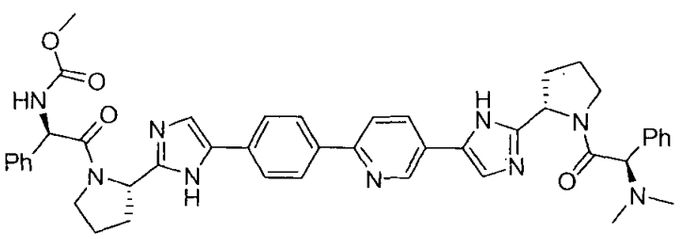
LC/MS: Análisis calculado para $[M+H]^+$ $C_{45}H_{46}N_9O_4$: 776.37;

encontrado 776.38

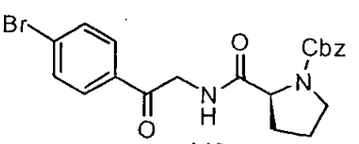
HRMS: Análisis calculado para $[M+H]^+$ $C_{45}H_{46}N_9O_4$: 776.3673; encontrado 776.3680

Ejemplo 140

((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-piridinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo



Ejemplo 140, Extremo a



140a

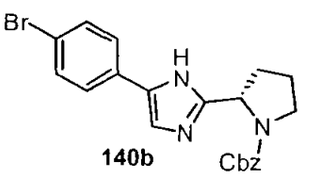
HATU (19.868g, 52.25 mmol) se agregó a una mezcla heterogénea de *N*-Cbz-L-prolina (12.436 g, 49.89 mmol) y la sal HCl de la 2-amino-1-(4-bromofenil)etanona (12.157 g, 48.53 mmol) en DMF (156 mL). La mezcla se disminuyó en un baño de agua con hielo, e inmediatamente *N,N*-diisopropiletilamina posterior (27 mL, 155 mmol) se agregó gota a gota a estos durante 13 min. Después la adición de la

base se completó, el baño frío se removió y la mezcla de reacción se agitó durante unos 50 min adicionales. El componente volátil se removió in vacuo; agua (125 mL) se agregó al sólido crudo resultante y se agitó durante alrededor de 1 hr. El sólido blanco opaco se filtró y se lavó con agua copiosa, y se secó in vacuo para proporcionar 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).

CL (Cond. 1): TR = 1.65 min; 98% índice de homogeneidad

LC/MS: Análisis calculado para $[M+H]^+$ $C_{21}H_{22}BrN_2O_4$: 445.08; encontrado 445.31

Ejemplo 140, Extremo b



140b

La cetoamida 140a (10.723g, 24.08 mmol) se convirtió a 140b de conformidad al procedimiento descrito para la síntesis de carbamato 132c, con la excepción de que el material crudo se purificó por cromatografía instantánea (gel de sílice; 50% EtOAc/hexanos). El bromuro 140b se recuperó como una espuma blanca opaca (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).

CL (Cond. 1): TR = 1.42 min; >95% 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 aseguró usando los siguientes métodos HPLC quirales, y un ee de 99% se observó.

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

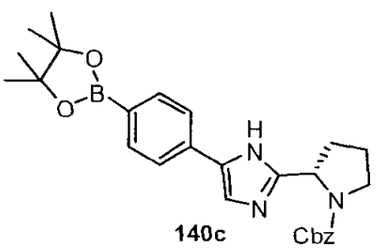
Solvente: 20% etanol/heptano (isocrático)

Relación de flujo: 1 ml/min

Longitud de onda: 254 nm

Tiempo de retención relativo: 1.82 min (*R*), 5.23 min (*S*)

Ejemplo 140, Extremo c



140c

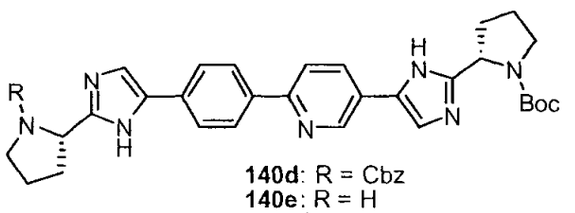
$Pd(Ph_3P)_4$ (208 mg, 0.180 mmol) se agregó a un tubo de presión que contiene una mezcla de bromuro 140b (1.80 g, 4.22 mmol), bis(pinacolato)diboro (2.146 g, 8.45 mmol), KOAc (1.8 g, 11.0 mmol) y 1,4-dioxano (34 mL). El matraz de reacción se purgó con nitrógeno, se tapó y se calienta con un baño de aceite a

80°C durante 23 hr. El componente volátil se removió in vacuo, y el residuo se dividió cuidadosamente entre CH_2Cl_2 (70 mL) y un medio acuoso (22 mL agua + 5 mL solución $NaHCO_3$ saturada). La capa acuosa se extrajo con CH_2Cl_2, y la fase orgánica combinada se secó ($MgSO_4$) y se evaporó in vacuo. El residuo aceitoso se cristalizó de EtOAc/hexanos para proporcionar dos cultivos de boronato 140c como un sólido amarillo (1.52 g). El licor madre se evaporó in vacuo y el material resultante se purificó por cromatografía instantánea (gel de sílice; 20-35% EtOAc/CH_2Cl_2) para proporcionar 140c adicional como un sólido blanco opaco, que contiene residuo de pinacol (772 mg).

CL (Cond. 1): TR = 1.95 min

LC/MS: Análisis calculado para $[M+H]^+$ $C_{27}H_{33}BN_3O_4$: 474.26; encontrado 474.31

Ejemplo 140, Extremo d-e



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

El arilbromuro 132c se acopló con boronato 140c para proporcionar 140d al usar el mismo procedimiento descrito por la síntesis de biarilo 132d. La muestra contiene la versión de desbromo de 132c como una impureza. Procede a la siguiente Extremo sin purificación adicional.

CL (Cond. 1): TR = 1.72 min; ~85% índice de homogeneidad

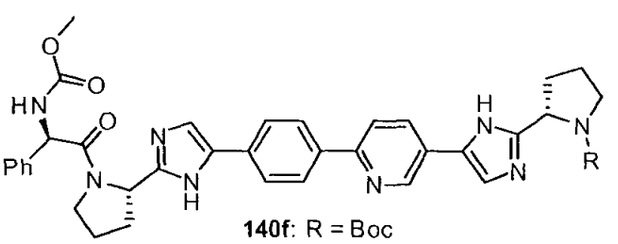
LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{42}N_7O_4$: 660.33; encontrado 660.30

Una mezcla de 10% Pd/C (226 mg), biarilo 140d (1.25 g) y MeOH (15 mL) se agitó bajo un globo de hidrógeno durante ~160 hr, en donde el suministro de hidrógeno se repusieron periodicamente como sea necesario. La mezcla de reacción se filtró a través de una almohadilla de tierra diatomácea (Celite®), y el filtrado se evaporó in vacuo para proporcionar 140e crudo como una espuma café-amarillenta (911 mg). Procede a la siguiente Extremo sin purificación adicional.

CL (Cond. 1): TR = 1.53 min

LC/MS: Análisis calculado para $[M+H]^+$ $C_{30}H_{36}N_7O_2$: 526.29; encontrado 526.23

Ejemplo 140, Extremo 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 la formación de amida y los protocolos de desprotección Boc usados en la síntesis del Ejemplo 132.

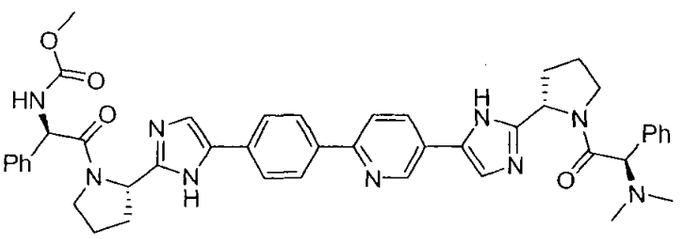
CL (Cond. 1): TR = 1.09 min; ~94% índice de homogeneidad

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 al usar el procedimiento descrito para la preparación del Ejemplo 132 del intermediario 132e.

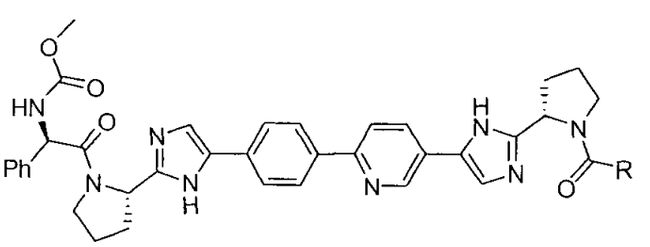
1.15 min (Cond. 1); >98% índice de homogeneidad

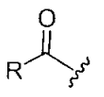
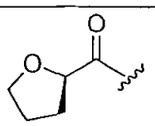
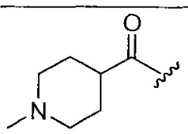
LC/MS: Análisis calculado para $[M+H]^+$ $C_{45}H_{40}N_7O_4$: 778.38; encontrado 778.48

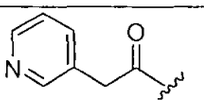
HRMS: Análisis calculado para $[M+H]^+$ $C_{45}H_{40}N_7O_4$: 778.3829; encontrado 778.3849

La sal TFA del Ejemplo 141-143 se sintetizaron del intermediario 140g y reactivos apropiados en una manera similar.

Ejemplo 141-143

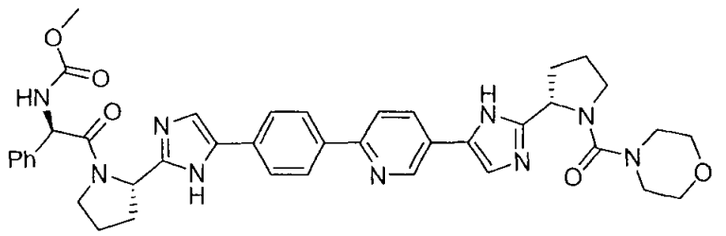


Ejemplo	*Nombre del compuesto*		*TR (CL-Cond.); % de índice de homogeneidad; Datos EM*
141	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-tetrahidro-2-furanilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-2-piridinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		1.15 min (Cond. 1); >98% LC/MS: análisis calculado para $[M+H]^+$ $C_{40}H_{43}N_8O_5$: 715.34; encontrado 715.44 HRMS: análisis calculado 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-5-il)-2-piridinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.07 min (Cond. 1); >98% LC/MS: análisis calculado para $[M+H]^+$ $C_{42}H_{48}N_9O_4$: 742.38; encontrado 742.48 HRMS: análisis calculado pára $[M+H]^+$ $C_{42}H_{48}N_9O_4$: 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: análisis calculado para $[M+H]^+$ $C_{42}H_{42}N_9O_4$: 736.34; encontrado 736.44 HRMS: análisis calculado 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 DMF (1.5 mL) de cloruro de morfolina-4-carbonilo (8.5 mg, 0.057 mmol) se agregó a una mezcla de *i*-Pr_2EtN (20 µL, 0.115 mmol) y 140g (27.3 mg, 0.044 mmol), y se agitó durante 100 min. El componente volátil se removió in vacuo y el residuo se purificó por HPLC de fase inversa (H_2O/MeOH/TFA) para proporcionar la sal TFA del Ejemplo 144 como una espuma amarilla (34.6 mg).

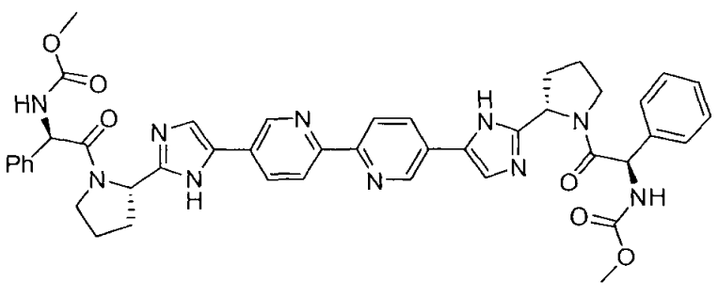
1.17 min (Cond. 1); >98%

LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{44}N_9O_5$: 730.35; encontrado 730.42

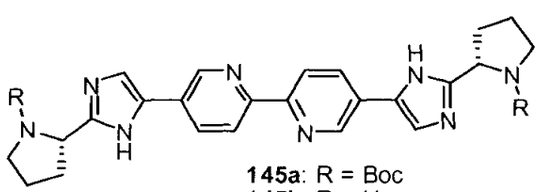
HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{44}N_9O_5$: 730.3465; encontrado 730.3477

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, Extremo a-b



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

$Pd(Ph_3P)_4$ (9.6 mg, 0.008 mmol) y LiCl (28 mg, 0.67 mmol) se agregaron a una mezcla de arilbromuro 132c (98.7 mg, 0.251 mmol) y hexametildiestaño (51.6 mg, 0.158 mmol), y se calienta a 80 °C durante ~ 3 días. El componente volátil se removió in vacuo y el material crudo resultante se purificó por cromatografía instantánea (gel de sílice; 0-10% MeOH/EtOAc) seguido por HPLC de fase inversa (H_2O/MeOH/TFA). La HPLC eluida se neutralizó con exceso de 2.0 N NH_3/MeOH, y el componente volátil se removió in vacuo. 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 ($MgSO_4$) y se evaporó in vacuo para proporcionar carbamato 145a como una película de aceite (8.7 mg).

CL (Cond. 1): TR = 1.68 min; >98% índice de homogeneidad

LC/MS: Análisis calculado para $[M+H]^+$ $C_{34}H_{43}N_8O_4$: 627.34; encontrado 627.47

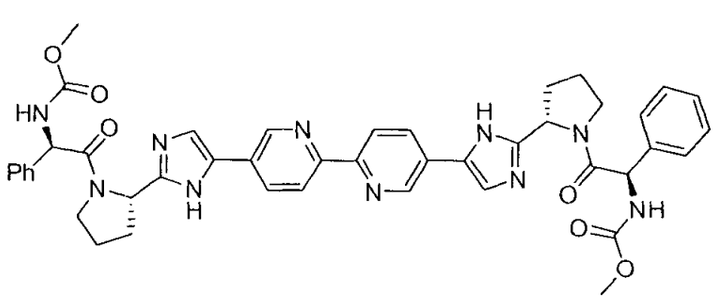
El carbamato 145a se elaboró a la pirrolidina 145b de acuerdo a la preparación de 132e a partir de 132d. ^1H RMN (DMSO, δ = 2.5 ppm; 400 MHz): 12.02 (señal br, 2H), 9.04 (d, J = 1.6, 2H), 8.34 (d, J = 8.3, 2H), 8.20 (dd, J = 8.3, 2.3, 2H), 7.67 (br s, 1H), 4.21 (m, 2H), 3.00-2.85 (m, 4H), 2.12-2.04 (m, 2H), 1.95-1.68 (m, 6H). [Nota: la señal de pirrolidina-NH no se observó].

CL (Cond. 1): TR = 1.17 min; >98% 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

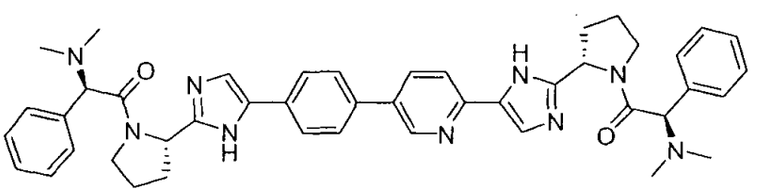


El ejemplo 145 (Sal TFA) se sintetizó a partir de 145b

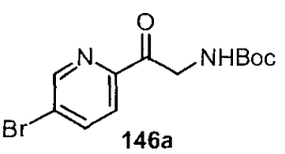
de acuerdo a la preparación del Ejemplo 132 a partir de 132e. CL (Cond. 1): TR = 1.63 min; 98% índice de homogeneidad LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{45}N_{10}O_6$: 809.35; encontrado 809.40

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



Ejemplo 146, Extremo a



146a

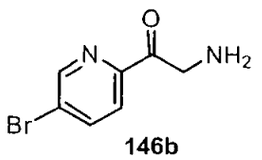
El *n*-BuLi (12.0 mL de 2.5M/hexanos, 30 mmol) se agregó en porciones durante 15 min a una semi-solución enfriada de (-78 °C) tolueno (300 mL) de 2,5-dibromopiridina (6.040 g, 25.5 mmol), y se agitó durante 2.5 hr. El 2-(metoxi(metil)amino)-2-oxoetilocarbamato de t-butilo (2.809 g, 12.87 mmol) se agregó en lotes durante 7 min, y se continuó agitando durante 1.5 hr a -78 °C. El baño a -78°C se reemplazó con baño a -60°C, el cual se permitió calentar

hasta -15°C durante 2.5 hr. La reacción se apagó con solución NH_4Cl saturada (20 mL), y la mezcla se permitió descongelar a temperatura ambiente y la capa orgánica se separó y se evaporó in vacuo. El material crudo resultante se purificó por cromatografía instantánea (gel de sílice; 15 % EtOAc/hexanos) para proporcionar un semisólido café rojizo, el cual se lavó con hexanos para remover el residuo colorado. La piridina 146a se recuperó como un sólido de color ceniza (842 mg). ^1H RMN (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 (dos app s, 7.83H + 1.17H).

CL (Cond. 1): TR = 2.00 min; >95% índice de homogeneidad

LC/MS: Análisis calculado para $[M+Na]^+$ $C_{12}H_{15}BrNaN_2O_3$: 337.02; encontrado 337.13

Ejemplo 146, Extremo b



146b

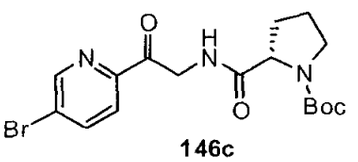
Se agregó 48% de HBr (1.0 mL) gota a gota a una solución en dioxano (5.0 mL) de carbamato 146a (840 mg, 2.66 mmol) durante 3 min, y la mezcla de reacción se agitó a temperatura ambiente durante 17.5 hr. El precipitado se filtró y se lavó con dioxano, y se secó in vacuo para proporcionar amina la sal HBr de 146b como un sólido blanco opaco (672.4 mg; el

equivalente molar exacto de la sal HBr no se determinó). ^{1}H RMN (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).

CL (Cond. 1): TR = 0.53 min

LC/MS: Análisis calculado para $[M+H]^+$ $C_7H_8BrN_2O$: 214.98; encontrado 215.00

Ejemplo 146, Extremo c



146c

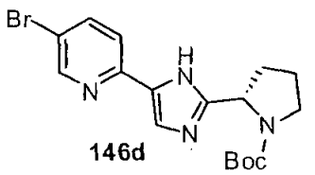
Se agregó *i*-Pr_2EtN (2.3 mL, 13.2 mmol) en porciones durante 15 min a una mezcla heterogénea de amina 146b (1.365g), (*S*)-Boc-prolina (0.957 g, 4.44 mmol) y HATU (1.70 g, 4.47 mmol) en DMF (13.5 mL), y se agita a temperatura ambiente durante 1 hr. El componente volátil se removió in vacuo y el residuo se dividió entre EtOAc (40 mL) y un medio acuoso (20 mL agua + 1 ml solución $NaHCO_3$ saturada). La capa acuosa se lavó con EtOAc (20 mL), y la fase orgánica combinada se secó ($MgSO_4$), se filtró y se evaporó in vacuo. El material crudo resultante se purificó por cromatografía instantánea (gel de sílice; 40-50% EtOAc/hexanos) para proporcionar cetoamida 146c como una espuma amarillo pálido (1.465g). ^{1}H RMN (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 (dos app s, 9H).

CL (Cond. 1): TR = 1.91 min

LC/MS: Análisis calculado para $[M+Na]^+$ $C_{17}H_{22}BrN_3NaO_4$: 434.07; encontrado 433.96.

Ejemplo 146, Extremo d



146d

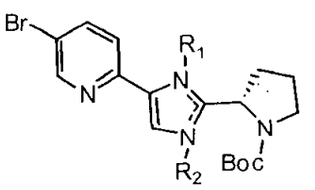
Una mezcla de cetoamida 146c (782.2 mg, 1.897 mmol) y NH_4OAc (800 mg, 10.4 mmol) en xilenos se calentó con un microondas (140°C) durante 90 min. El componente volátil se removió in vacuo y el residuo se dividió cuidadosamente entre CH_2Cl_2 y agua, en donde suficiente solución $NaHCO_3$ saturado se agregó para neutralizar esto. La fase acuosa se extrajo con CH_2Cl_2 (2x), y la fase orgánica combinada se secó ($MgSO_4$) y se evaporó in vacuo. El material crudo resultante se purificó por cromatografía instantánea (gel de sílice; 50% CH_2Cl_2/EtOAc) para proporcionar Imidazol 146d como un sólido blanco opaco (552.8 mg). ^1H RMN (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).

CL (Cond. 1): TR = 1.67 min; >95% índice de homogeneidad

LC/MS: Análisis calculado para $[M+Na]^+$ $C_{17}H_{21}BrN_4NaO_2$: 415.08; encontrado 415.12

Ejemplo 146, Extremo e



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

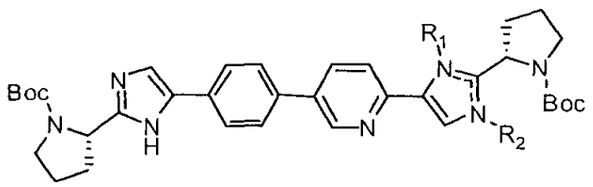
Se agregó NaH (60%; 11.6 mg, 0.29 mmol) en un lote a una mezcla heterogénea de Imidazol 146d (80 mg, 0.203 mmol) y DMF (1.5 mL), y se agitó a condiciones ambientales durante 30 min. SEM-Cl (40 µL, 0.226 mmol) se agregó en porciones durante 2 min a la mezcla de reacción anterior, y se continuó agitando durante 14 hr. El componente volátil se removió in vacuo 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 ($MgSO_4$) y se evaporó in vacuo. El material crudo se purificó por una cromatografía instantánea (gel de sílice; 20% EtOAc/hexanos) para proporcionar 146e como un aceite viscoso incoloro (87.5 mg). La regioquímica exacta de 146e no se determinó. ^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 + 4.7H), 0.97-0.81 (m, 2H), -0.03 (s, 9H).

CL (Cond. 1): TR = 2.1 min

LC/MS: Análisis calculado para $[M+H]^+$ $C_{23}H_{36}BrN_4O_3Si$: 523.17; encontrado 523.24

Ejemplo 146, Extremo f



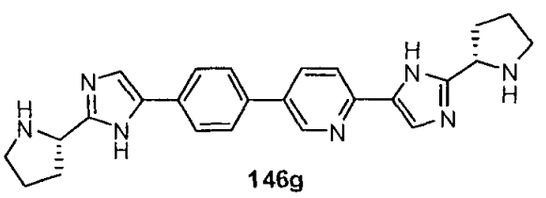
146f: (R_1 = H, R_2 = SEM) o (R_1 = SEM, R_2 = H)

$Pd(Ph_3P)_4$ (24.4 mg, 0.021 mmol) se agregó a una mezcla de Imidazol 146e (280 mg, 0.535 mmol), 1c (241.5 mg, 0.55 mmol) y $NaHCO_3$ (148.6 mg, 1.769 mmol) en 1,2-dimetoxietano (4.8 mL) y agua (1.6 mL). La mezcla de reacción se mojó con nitrógeno, se calienta con un baño de aceite a 80 °C durante ~24 hr y luego el componente volátil se removió in vacuo. El residuo se dividió entre CH_2Cl_2 y agua, y la fase orgánica se secó ($MgSO_4$) y se evaporó in vacuo. El material crudo se purificó por un sistema Biotage (gel de sílice; 75-100% EtOAc/hexanos) seguido por HPLC de fase inversa (H_2O/MeOH/TFA). La HPLC eluida se neutralizó con 2M NH_3/MeOH y se evaporó in vacuo, y el residuo se dividió entre agua y CH_2Cl_2. La capa orgánica se secó ($MgSO_4$) y se evaporó in vacuo para proporcionar 146f como una espuma blanca (162 mg).

CL (Cond. 1): TR = 2.1 min

LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{58}N_7O_5Si$: 756.43; encontrado 756.55

Ejemplo 146, Extremo g



146g

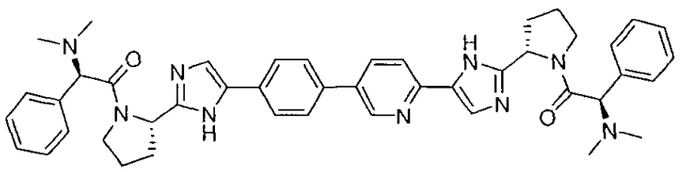
El carbamato 146f (208 mg, 0.275 mmol) se trató con 25% TFA/CH_2Cl_2 (4.0 mL) y se agita a temperatura ambiente durante 10 hr. El componente volátil se removió in vacuo y el residuo primero se hizo base libre por MCX (lavado MeOH; 2.0 M elución NH_3/MeOH) y luego se purifica por HPLC de fase inversa (H_2O/MeOH/TFA), y el material resultante se volvió hacer base libre (MCX) para proporcionar pirrolidina 146g como una película de aceite (53.7 mg). ^1H RMN (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).

CL (Cond. 1): TR = 0.95 min; >98% 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



Ejemplo 146 (Sal TFA) se sintetizó a partir de pirrolidina 146g de acuerdo a la preparación del Ejemplo 132 a partir del intermediario 132e.

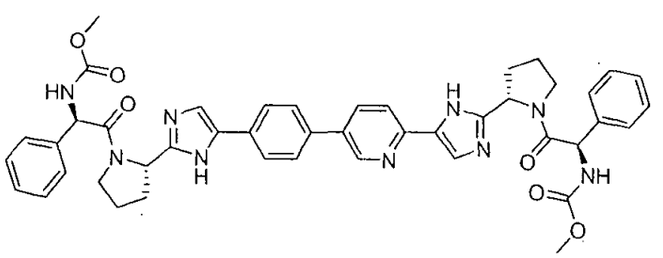
CL (Cond. 1): TR = 1.42 min; 96.5% índice de homogeneidad

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



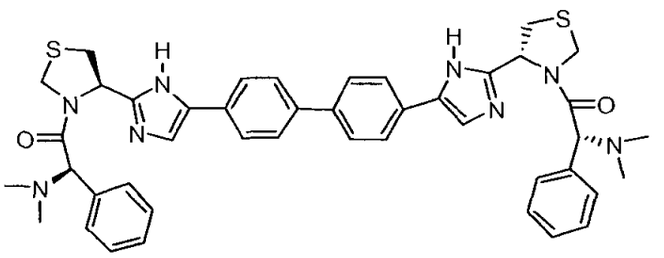
La sal TFA del ejemplo 147 se preparó similarmente del intermediario 146g al usar extremo-4.

CL (Cond. 1): TR = 1.66 min; 95% índice de homogeneidad

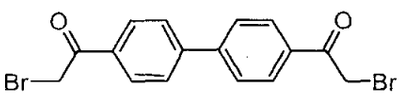
LC/MS: Análisis calculado para $[M+H]^+$ $C_{45}H_{46}N_9O_6$: 808.36; encontrado 808.55

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, Extremo a



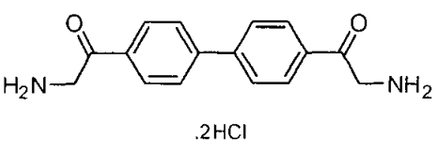
Una solución de bromo (1.3mL, 25.0mmol) en 15mL de ácido acético glacial se agregó gota a gota a una solución de 4-4'-diacetilbifenilo (3.0g, 12.5mmol) en 40 mL de ácido acético a 50°C. Hasta que se completa la adición de la mezcla se agitó a temperatura ambiente durante la noche. El producto precipitado se filtró completamente y se volvió a recristalizar de cloroformo para dar 1,1'-(bifenil-4,4'-

diil)bis(2-bromoetanona) (3.84g, 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/EMBR - Análisis calculado para 369.07 encontrado; $(M+H)^+$ - 397.33, $(M-H)^-$ - 395.14

Ejemplo 148, Extremo b



.2HCl

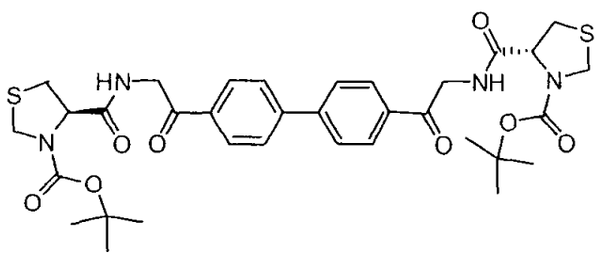
La diformilamida de sodio (3.66g, 38.5mmol) se agregó a una suspensión de 1,1'-(bifenil-4,4'-diil)bis(2-bromoetanona) (6.1g, 15.4mmol) en 85 mL de acetonitrilo. La mezcla se calentó a reflujo durante 4 horas y se concentró bajo presión reducida. El residuo se suspendió en 300mL 5% HCl en etanol y se calienta a reflujo durante 3.5 horas. La reacción se enfrió a temperatura ambiente y se coloca en el congelador durante 1 hora. El sólido precipitado se recolectó, se lavó con 200mL 1:1 etanol/éter seguido por 200mL pentano, y se secó bajo vacío para dar diclorohidrato de 1,1'-(bifenil-4,4'-diil)bis(2-aminoetanona) (4.85g, 92%). Se lleva a cabo sin purificación adicional.

^{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 50mm, 0 hasta 100% B durante 4.0

minutos de gradiente, 1 minuto tiempo de espera, A = 10% metanol 90% agua 0.1% TFA, B = 90% metanol 10% agua 0.1% TFA, t_R = 0.44 minutos, Análisis calculado para $C_{16}H_{16}N_2O_2$ 268.31 encontrado; 269.09 $(M+H)^+$.

Ejemplo 148, Extremo c



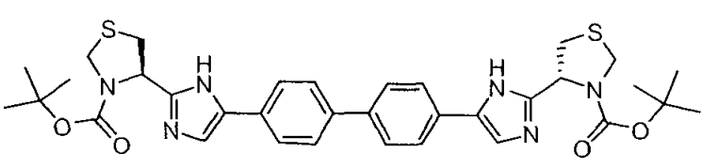
A una solución agitada de diclorohidrato de 1,1'-(bifenil-4,4'-diil)bis(2-aminoetanona) (0.7g, 2.1mmol), N-(tert-butoxi carbonil)-L-tioprolina (0.96g, 4.2mmol), y HATU (1.68g, 4.4mmol) en 14mL DMF se agregó diisopropiletilo amina (1.5mL, 8.4mmol) en porciones durante 5 minutos. La solución amarilla clara 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% metanol/cloroformo. Los orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), y se concentraron bajo presión reducida. El producto crudo se hizo por cromatografía en gel de sílice por elusión de gradiente con 10-50% acetato de etilo/CH_2Cl_2 para dar 4,4'-(2,2'-(bifenil-4,4'-diil)bis(2-

oxoetano-2,1-diil))bis(azanediil)bis(oxometilen)ditiazolidin-3-carboxilato de (4S,4'S)-tert-butilo (0.39g, 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 -Agua-Sunfire C-18 4.6 x 50mm, 0 hasta 100% B durante 4.0 minutos de gradiente, 1 minuto tiempo de espera, A = 10% metanol 90% agua 0.1% TFA, B = 90% metanol 10% agua 0.1% TFA, t_R = 3.69 min., Análisis calculado para $C_{34}H_{42}N_4O_8S_2$ 698.85 encontrado; 699.12 $(M+H)^+$.

Ejemplo 148, Extremo d



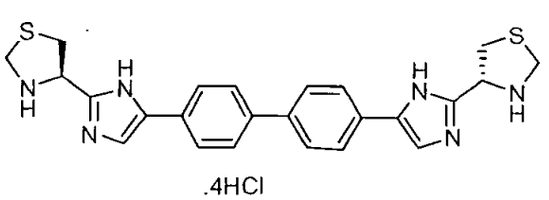
4,4'-(5,5'-(bifenil-4,4'-diil)bis(1H-Imidazol-5,2-diil))ditiazolidin-3-carboxilato de (4S,4'S)-tert-butilo (0.39g, 0.56 mmol) y acetato de amonio (0.43g, 5.6mmol) se suspendieron en 8mL oxileno en un recipiente de reacción de microondas. La mezcla se calentó bajo condiciones de microondas estándar a 140°C durante 70 minutos y se concentró bajo presión reducida. El residuo se disolvió en

30mL 20% metanol/cloroformo y se lavó con 10% $NaHCO_3$(aq). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), y se concentró bajo presión reducida. El producto crudo se hizo por cromatografía en gel de sílice por elución de gradiente con 1-6% 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)-tert-butilo (0.15g, 41%) como un sólido amarillo.

^{1}H 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 50mm, 0 hasta 100% B durante 3.0 minutos de gradiente, 1 minuto tiempo de espera, A = 5% acetonitrilo, 95% agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% agua, 10mm 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, Extremo 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)-tert-butilo en 1mL dioxano se agregó 0.3mL de

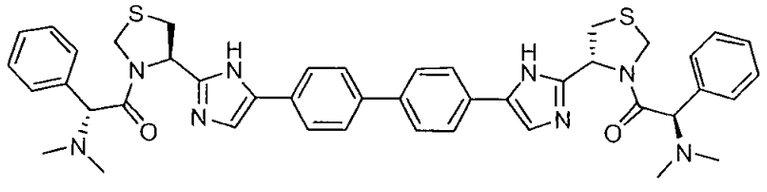
una solución 4.0M de HCl en dioxano. La reacción se agitó durante 3 horas a temperatura ambiente y se concentró bajo presión reducida. El sólido canela resultante se secó bajo vacío para dar tetraclorohidrato de 4,4'-bis(2-((S)-tiazolidin-4-il)-1H-imidazol-5-il)bifenil (0.12g, 100%) como un sólido amarillo.

^{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 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 hasta 100% B durante 4.0 minutos de gradiente, 1 minuto tiempo de espera, A = 5% acetonitrilo, 95% agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% agua, 10mm 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 tetraclorohidrato de (4,4'-bis(2-((S)-tiazolidin-4-il)-1H-imidazol-5-il)bifenilo (0.028g, 0.046mmol), ácido (R)-2-(dimetilamino)-2-fenilacético (Extremo 1, 0.017g, 0.0.10mmol), y HATU (0.039g, 0.10mmol) en 2mL de DMF se agregó diisopropiletil amina (0.05mL, 0.28mmol). La reacción se agitó a temperatura ambiente durante la noche (16 horas) y se concentró bajo presión reducida. El producto crudo se purificó por 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 (0.012g, 21%)

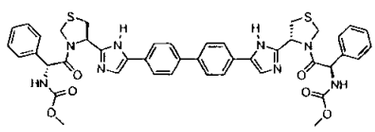
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 7.59 - 7.91 (20 H, m) 5.62 (2 H, dd, *J*=6.56, 2.59 Hz) 4.99 (2 H, d, *J*=8.85 Hz) 4.82/4.35 (2 H, s) 4.22 (2 H, s) 3.42 (2 H, s) 3.25 (2 H, s) 2.35-2.61 (12H, m)

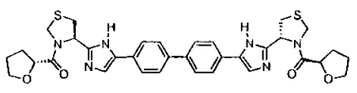
LCMS - Luna C-18 3.0 x 50mm, 0 hasta 100% B durante 7.0 minutos de gradiente, 1 minuto tiempo de espera, A = 5% acetonitrilo, 95% agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% agua, 10mm acetato de amonio fase móvil t_R = 3.128 min.

Nominal/EMBR - Calculado para $C_{44}H_{46}N_8O_2S_2$ 783.03; encontrado 783.28 $(M+H)^+$

Exacto/HRMS - Calculado para $C_{44}H_{47}N_8O_2S_2$ 783.3263; 783.3246 $(M+H)^+$

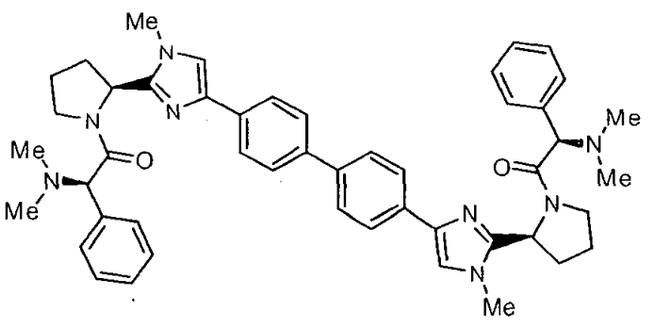
Ejemplos 149 y 150 se prepararon en una manera similar como se describe para la preparación del ejemplo 148.

Ejemplo	*Nombre del compuesto*	*estructura*	*Datos*
Ejemplo 149	(4,4'-bifenildiil bis(1H-imidazol-5,2-diil(4R)-1,3-tiazolidin-4,3-diil((1R)-2-oxo-1-fenil-2,1-etandiil)) biscarbamato de dimetilo	 de 148e y extremo-4	t_R = 3.36 min (LCMS - Luna C-18 3.0 x 50mm, 0 hasta 100% B durante 7.0 minuto de gradiente, 1 minuto tiempo de espera, A = 5% acetonitrilo, 95% agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% agua, 10mm acetato de amonio) EMBR: análisis calculado para $C_{44}H_{42}N_8O_6S_2$ 842.99 encontrado: 843.25 $(M+H)^+$ HRMS: análisis calculado para $C_{44}H_{43}N_8O_6S_2$ 843.2747 encontrado: 843.2724 $(M+H)^+$

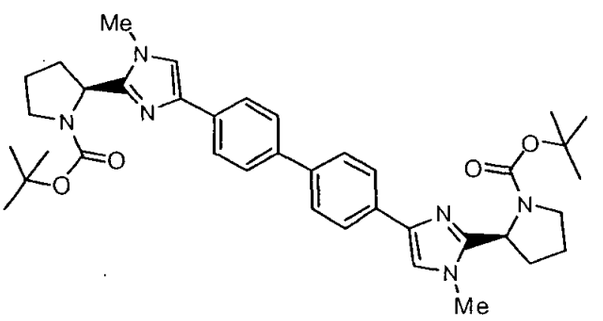
Ejemplo 150	(4R,4'R)-4,4'-(4,4'-bifenildiil bis(1H-imidazol-5,2-diil))bis(3-((2R)-tetrahidro-2-furanil carbonil)-1,3-tiazolidina)	 de 148e y ácido tetrahidrofuroico	t_R = 4.32 min (CLAr - X-Terra C-18 4.6 x 50mm, 0 hasta 100% B durante 10.0 minuto de gradiente, 1 minuto tiempo de espera, A = 10% metanol 90% agua 0.1% TFA, B = 90% metanol 10% agua 0.1% TFA) EMBR: análisis calculado para $C_{34}H_{36}N_6O_4S_2$ 656.83 encontrado: 657.32 $(M+H)^+$

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)



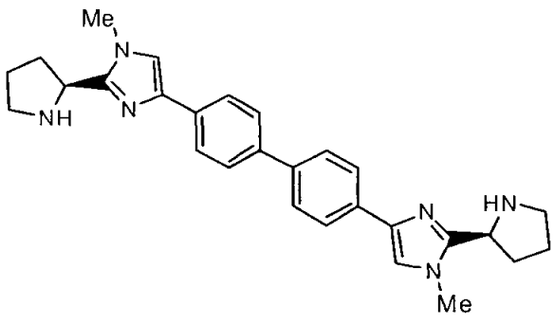
Ejemplo 151, Extremo a



A una solución agitada de 1d, 2,2'-(4,4'-(bifenil-4,4'-diil)bis(1H-Imidazol-4,2-diil))dipirrolidina-1-carboxilato de (2S,2'S)-tert-butilo (100 mg, 0.16 mmol) y yodometano (40 µL, 0.16 mmol) en CH_2Cl_2 (2 mL) se agregó hidruro de sodio (40%) (21.2 mg, 0.352 mmol). Después de cinco horas a temperatura ambiente, esto 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))dipirrolidina-1-carboxilato de (2S,2'S)-tert-butilo (~ 90 mg) se movió en la siguiente Extremo sin purificación adicional (pureza ~ 85%) LCMS: Análisis calculado para: $C_{38}H_{48}N_6O_4$ 652.83; Encontrado: 653.51 $(M+H)^+$. Se deberá reconocer que los isómeros de metilación múltiple son posibles en esta reacción y no se hizo ningún intento para asignarlos.

Ejemplo 151, Extremo b



151a, 2,2'-(4,4'-(bifenil-4,4'-diil)bis(1-metil-1H-Imidazol-4,2-diil))dipirrolidina-1-carboxilato de (2S,2'S)-tert-butilo (100 mg, 0.153 mmol) se trató con 4 M HCl/dioxano (20 mL). Después de tres horas a temperatura ambiente, esto se concentró bajo presión reducida. El producto de reacción crudo, 4,4'-bis(1-metil-2-((S)-pirrolidin-2-il)-1H-imidazol-4-il)bifenilo (~110 mg, sal HCl) se movió en la siguiente Extremo sin purificación adicional (pureza ~ 85%) LCMS: Análisis calculado para: $C_{28}H_{32}N_6$ 452.59; Encontrado: 453.38 $(M+H)^+$. Se presentan isómeros de imidazol múltiples y se llevan a cabo adelante.

Ejemplo 151

Se agregó HATU (58.9 mg, 0.150 mmol) 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 mmol), $(i\text{-Pr})_2$EtN (78 µL, 0.451 mmol) y Extremo 1, ácido (*R*)-2-(dimetilamino)-2-fenilacético (0.026 mg 0.150mmol) en DMF (1.0 mL). La mezcla resultante se agitó a temperatura ambiente hasta que el acoplamiento se completó como se determina por análisis LC/MS. La purificación se realizó por HPLC preparativa de fase inversa (Aguas-Sunfire 30 X 100mm S5, detección a 220 nm, relación de flujo 30 mL/min, 0 hasta 90% B durante 14 min; A = 90% agua, 10 % ACN, 0.1% TFA, B = 10% agua, 90 % ACN, 0.1% 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(pirrolidina-2,1-diil))bis(2-(dimetilamino)-2-feniletanona), Sales TFA.

Isómero 1 (8 mg, 8.6%) como una cera incolora.

^{1}H RMN (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 hasta 100% B durante 10 minutos, unos minutos tiempo de espera, A = 90% agua, 10% metanol, 0.2% ácido fosfórico, B = 10% agua, 90% metanol, 0.2% ácido fosfórico, TR = 2.74 min, 98%.

LCMS: Análisis calculado para: $C_{48}H_{54}N_8O_2$ 775.02; Encontrado: 775.50 $(M+H)^+$.

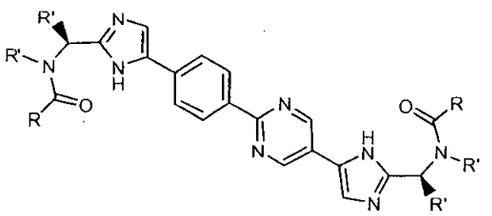
Isómero 2 (10.2 mg, 11%) como una cera incolora.

^{1}H RMN (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 hasta 100% B durante 10 minutos, unos minutos tiempo de espera, A = 90% agua, 10% metanol, 0.2% ácido fosfórico, B = 10% agua, 90% metanol, 0.2% ácido fosfórico, TR = 2.75 min, 90%.

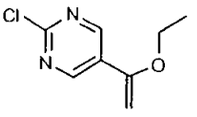
LCMS: Análisis calculado para: $C_{48}H_{54}N_8O_2$ 775.02; Encontrado: 775.52 $(M+H)^+$.

Ejemplo 152



Ejemplo 152a-1 Extremo a.

2-Cloro-5-(1-etoxivinil)pirimidina



A una solución de 5-bromo-2-cloropirimidina (12.5 g, 64.62 mmol) en DMF seco (175 mL) bajo N_2 se agregó tributil(1-etoxivinil)estanano (21.8 mL, 64.62 mmol) y diclorobis(trifenilfosfina)paladio (II) (2.27 g, 3.23 mmol). La mezcla se calentó a 100°C durante 3h

antes de permitirse agitar a temperatura ambiente durante 16 hr. La mezcla luego se diluyó con éter (200 mL) y se trató con solución de KF acuoso (55 g de fluoruro de potasio en 33 mL de agua). La mezcla de dos fases se agitó vigorosamente durante 1h a temperatura ambiente antes se filtró a través de tierra diatomácea (Celite®). El filtrado se lavó con solución de $NaHCO_3$ saturada y salmuera previo al secado (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 se combina la purificación por cromatografía instantánea Biotage™ en gel de sílice (elución de gradiente en una columna 65M usando 3% de acetato de etilo en hexanos hasta 25% acetato de etilo en hexanos con 3.0 L) proporcionando el compuesto del título como un sólido cristalino, blanco (18.2 g, 73%).

^{1}H RMN (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 x 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, TR = 2.53 min, 98.8% índice de

homogeneidad.

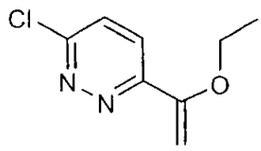
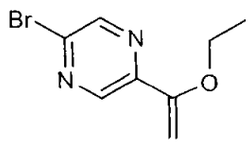
LCMS: Análisis calculado para $C_8H_{10}ClN_2O$ 185.05; encontrado: 185.04 $(M+H)^+$.

HRMS: Análisis calculado para $C_8H_{10}ClN_2O$ 185.0482; encontrado: 185.0490 $(M+H)^+$.

El mismo método se usó para la preparación de los Ejemplos 152a-2 & 152a-3:

Afección CL: *condición 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

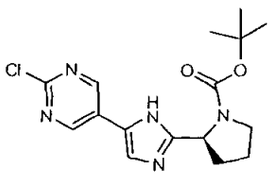
Condición 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

Ejemplo 152a-2	 de dicloropiridazina	t_R = 2.24 min 96.4%) LCMS: Análisis calculado para $C_8H_{10}ClN_2O$ 185.05; encontrado: 185.06 $(M+H)^+$. HRMS: Análisis calculado para $C_8H_{10}ClN_2O$ 185.0482; encontrado: 185.0476 $(M+H)^+$.
Ejemplo 152a-3	 de dibromopirazina	t_R = 2.82 min (52.7%, inseparable con 2,5-dibrompirazina (t_R =1.99 min, 43.2%)) LCMS: Análisis calculado para $C_8H_{10}BrN_2O$ 229.00; encontrado: 228.93 $(M+H)^+$.

Ejemplo 152d-1 hasta 152d-6

Ejemplo 152b-1, Extremo b.

2-(5-(2-cloropirimidin-5-il)-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-tert-butilo o éster de tert-butilo del ácido (S)-2-[5-(2-Cloro-pirimidin-5-il)-1H-imidazol-2-il]-pirrolidina-1-carboxílico



NBS (16.1 g, 90.7 mmol) se agregó en una porción a una solución agitada de 2-cloro-5-(1-etoxivinil)pirimidina (152a-1, 18.2 g, 98.6 mmol) en THF (267 mL) y H_2O (88 mL) a 0°C bajo N_2. La mezcla se agitó durante 1h a 0°C antes estos se diluyó con más H_2O y se extrajo con acetato de etilo (2x). Los extractos combinados se lavaron con solución de $NaHCO_3$ saturado y salmuera previo al secado (Na_2SO_4) y evaporación de solvente. LCMS Phenomenex LUNA C-18 4.6 x 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, TR = 1.52 min (pico no simétrico). LCMS: Análisis calculado para $C_6H_{14}BrClN_2O$ 235.92; encontrado: 236.85 $(M+H)^+$.

Ejemplo 152c-1, Extremo c.

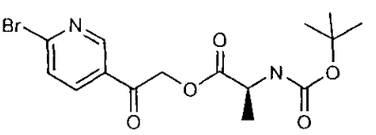
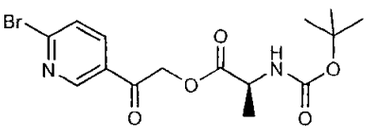
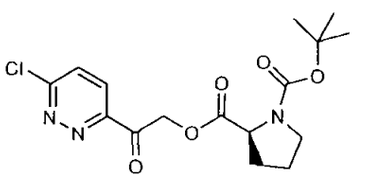
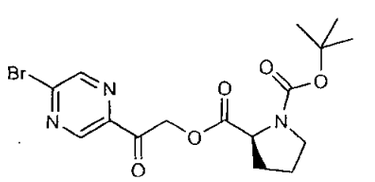
La mitad del residuo (2-bromo-1-(2-cloropirimidin-5-il)etanona, ~14.5g) crudo se disolvió en acetonitrilo anhidro (150 mL) y se trata directamente con N-Boc-L-prolina (9.76 g, 45.35 mmol) y diisopropiletilamina (7.9 mL, 45.35 mmol). Después se agitó durante 3h, el solvente se removió *in vacuo* y el residuo se dividió en acetato de etilo y agua. La fase orgánica se lavó con 0.1N ácido clorhídrico, solución de $NaHCO_3$ saturada y salmuera previo al secado (Na_2SO_4) y concentración. LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, TR = 2.66 min.

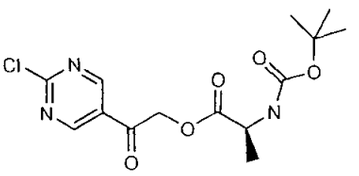
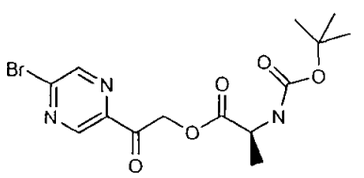
El mismo método se usó para preparar el ejemplo 152c a través de 152c-6.

Condiciones CL: *condición 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

Condición 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua,

90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

Ejemplo 152c-2		t_R = 1.81 min (condición 2, ~95 %) EMBR: Análisis calculado 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%) EMBR: Análisis calculado para $C_{15}H_{19}BrN_2O_5$ 386.05; encontrado: 387.07 $(M+H)^+$.
Ejemplo 152c-3a		t_R = 2.65 min LCMS: Análisis calculado 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: Análisis calculado para $C_{16}H_{21}BrN_3O_5$ 414.07 encontrado: 414.11 $(M+H)^+$.

Ejemplo 152c-5		t_R = 2.22 min LCMS: Análisis calculado para $C_{14}H_{18}ClN_3O_5$ 343.09 encontrado: indeterminado.
Ejemplo 152c-6		t_R = 2.41 min LCMS: Análisis calculado para $C_{14}H_{18}{}^{37}BrN_3O_5$ 389.04 encontrado: 412.03 $(M+Na)^+$.

Ejemplo 152d-1, Extremo d.

Este residuo (2-(2-(2-cloropirimidin-5-il)-2-oxoetilo) pirrolidina-1,2-dicarboxilato de (S)-1-tert-butilo) se tomó en xilenos (200 mL) y se trata para NH_4OAc (17.5 g, 0.23 mol). La mezcla se calentó a 140°C durante 2 hr en un matraz de extremo de rosca, de pared gruesa antes de que se enfriara a temperatura ambiente y se filtró por succión. El filtrado luego se concentró, se dividió en acetato de etilo y solución $NaHCO_3$ saturada y se lavó con salmuera previo al secado

(Na_2SO_4) y concentración. El precipitado original se dividió en solución $NaHCO_3$ acuosa y acetato de etilo y se sonica durante 2 min antes se filtró por succión. El filtrado se lavó con salmuera, se secó sobre (Na_2SO_4) y se evaporó completamente hasta secarse. La purificación de los residuos combinados por cromatografía instantánea Biotage™ en gel de sílice (65M Columna, preequilibración con 2%B para 900mL seguido por elución de gradiente con 2%B hasta 2%B para 450 ml seguido por 2%B hasta 40%B para 3000mL donde B=metanol y A=diclorometano) proporcionan el compuesto del título (7.0 g, 44% de rendimiento, 2 Extremos, fracción pura) como una espuma anaranjada amarillenta. Las fracciones mezcladas se sometieron a una segunda cromatografía Biotage™ en gel de sílice (40M Columna, preequilibración con 1%B para 600mL seguido por elución de gradiente con 1%B hasta 1%B para 150 ml seguido por 1%B hasta 10%B para 1500mL donde B=MeOH y A=CH_2Cl_2) proporcionan el compuesto del título adicional (2.8 g, 18%) como una espuma anaranjada-tono café. ^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 × 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, TR =

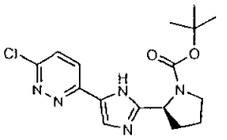
1.92 min, 94.7% índice de homogeneidad.

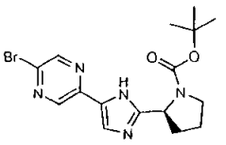
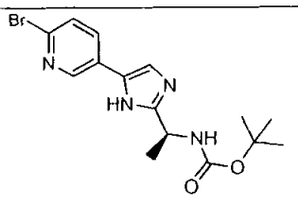
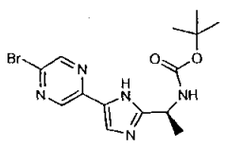
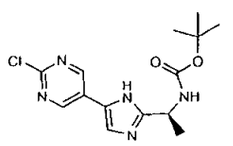
LCMS: Análisis calculado para $C_{16}H_{21}ClN_5O_2$ 350.14; encontrado: 350.23 $(M+H)^+$.

HRMS: Análisis calculado para $C_{16}H_{21}ClN_5O_2$ 350.1384; encontrado: 350.1398 $(M+H)^+$.

Condiciones CL: *Condición 1:* Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

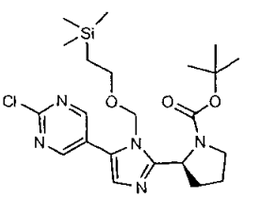
Condición 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

Ejemplo 152d-2	 de 152c-3a	t_R = 1.92 min (86.5%) LCMS: Análisis calculado para $C_{16}H_{21}ClN_5O_2$ 350.14; encontrado: 350.23 $(M+H)^+$. HRMS: Análisis calculado para $C_{16}H_{21}ClN_5O_2$ 350.1384; encontrado: 350.1393 $(M+H)^+$.

Ejemplo 152d-3	 de 152c-4	t_R = 1.90min (>95%) LCMS: Análisis calculado para $C_{16}H_{21}BrN_5O_2$ 394.09; encontrado: 393.82 $(M+H)^+$. HRMS: Análisis calculado para $C_{16}H_{21}BrN_5O_2$ 394.0879; encontrado: 394.0884 $(M+H)^+$.
Ejemplo 152d-4	 de 152c-3	t_R = 1.45 min (condición 2, 100%) EMBR: Análisis calculado para $C_{15}H_{19}BrN_4O_2$ 366.07 encontrado: 367.07 $(M+H)^+$.
Ejemplo 152d-5	 de 152c-6	t_R = 1.88 min (>95%) LCMS: Análisis calculado para $C_{14}H_{18}BrN_5O_2$ 367.06; encontrado: 368.10 $(M+H)^+$.
Ejemplo 152d-6	 de 152c-5	t_R = 1.66 min (85%) LCMS: Análisis calculado para $C_{14}H_{18}ClN_5O_2$ 323.11; encontrado: 324.15 $(M+H)^+$.

Ejemplo 152e-1, Extremo e.

Ejemplo 152e-1: 2-(5-(2-cloropirimidin-5-il)-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-tert-butilo



Hidruro de sodio (60% de dispersión en aceite mineral, 0.23 g, 5.72 mmol) se agregó en una porción a una solución agitada de 2-(5-(2-cloropirimidin-5-il)-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-tert-butilo (152d-1, 2.0 g, 5.72 mmol) en DMF seco (45 mL) a temperatura ambiente bajo N_2. La mezcla se agitó durante 5 min. Antes cloruro de SEM (1.01 mL, 5.72 mmol) se agregó en aproximadamente 0.1 mL de incrementos. La mezcla se agitó durante 3h antes se apagan con solución NH_4Cl saturado y se diluye con acetato de etilo. La fase orgánica se lavó con solución $NaHCO_3$ saturado y salmuera, se secó durante (Na_2SO_4), y se concentró. La fase acuosa original se extrajo dos veces más y el residuo combinado se purificó por cromatografía instantánea Biotage™ (40M Columna, 50 mL/min, preequilibración con 5%B para 750mL, seguido por Extremo de elución de gradiente con 5%B hasta 5%B para 150 mL, 5%B hasta 75%B para 1500 mL, luego 75%B hasta 100%B para 750 mL en donde el solvente B es acetato de etilo

y el solvente A es hexanos). La concentración del eluyente proporciona 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).

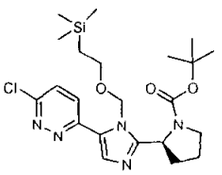
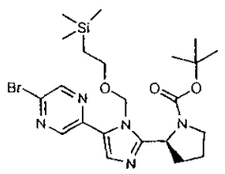
LCMS Phenomenex LUNA C-18 4.6 x 50 mm, 0 hasta 100% B durante 2 minutos, 2 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, TR = 2.38 min, 95% índice de homogeneidad.

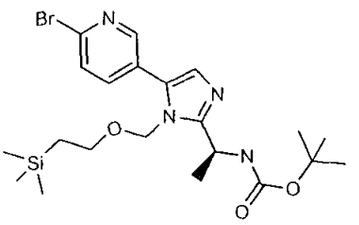
LCMS: Análisis calculado para $C_{22}H_{35}ClN_5O_3S_i$ 480.22; encontrado: 480.23 $(M+H)^+$.

HRMS: Análisis calculado para $C_{22}H_{35}ClN_5O_3S_i$ 480.2198; encontrado: 480.2194 $(M+H)^+$.

El mismo método se usó para preparar 152e- a través de 152e-4

Condiciones CL: *Condición 1:* Phenomenex LUNA C-18 4.6 x 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección. *Condición 2:* Phenomenex LUNA C-18 4.6 x 50 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

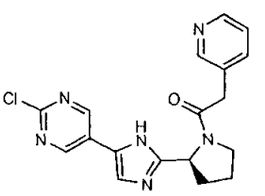
Ejemplo 152e-2	 de 152d-2	t_R = 2.34 min (85.7%) LCMS: Análisis calculado para $C_{22}H_{35}ClN_5O_3Si$ 480.22; encontrado: 480.22 $(M+H)^+$. HRMS: Análisis calculado para $C_{22}H_{35}ClN_5O_3Si$ 480.2198 encontrado: 480.2198 $(M+H)^+$.
Ejemplo 152e-3	 de 152d-3	t_R = 3.18 min (>95%) LCMS: Análisis calculado para $C_{22}H_{35}{}^{37}BrN_5O_3Si$ 526.17; encontrado: 525.99 $(M+H)^+$. HRMS: Análisis calculado 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%) EMBR: Análisis calculado para $C_{21}H_{33}BrN_4O_3Si$ 496.15 encontrado: 497.13 $(M+H)^+$.

Ejemplos 152f-1 hasta 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



Se agregó 4 *N* HCl frío (0°C) en dioxanos (5 mL) pr medio de jeringa a 2-(5-(2-cloropirimidin-5-il)-1*H*-imidazol-2-il)pirrolidina-1-carboxilato de (S)-tert-butilo (152d-1, 0.50 g, 1.43 mmol) en un matraz en forma de pera de 100 mL seguido por MeOH (1.0 mL). La suspensión se agitó a temperatura ambiente durante 4h antes se concentró completamente hasta secarse y se coloca bajo alto vacío durante 1h. También se

aisló el intermediario triclorohidrato de (S)-2-cloro-5-(2-(pirrolidin-2-il)-1*H*-imidazol-5-il)pirimidina como un sólido amarillo pálido (con un tinte anaranjado) el cual se usó sin purificación adicional. HATU (0.60 g, 1.57 mmol) se agregó en una porción a una solución agitada del intermediario triclorohidrato de (S)-2-cloro-5-(2-(pirrolidin-2-il)-1H-imidazol-5-il)pirimidina (0.46 g, 1.43 mmol, cantidad teórica), ácido 2-(piridin-3-il)acético (0.25 g, 1.43 mmol) y DIEA (1.0 mL, 5.72 mmol) en DMF anhidro (10 mL) a temperatura ambiente. La mezcla se agitó a temperatura ambiente durante 2h antes el DMF se removió *in vacuo*. El residuo se tomó en CH_2Cl_2 y se somete a cromatografía instantánea Biotage™ en gel de sílice (40M Columna, preequilibración con 0%B para 600mL seguido por Extremo de elución de gradiente con 0%B hasta 0%B para 150 mL seguido por 0%B hasta 15%B para 1500mL seguido por 15%B hasta 25% B para 999 mL en donde B= MeOH y A= CH_2Cl_2). Se aisló el compuesto del título (0.131 g, 25%, 2 Extremos) 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).

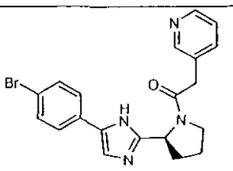
LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10%

metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, TR = 0.92 min, 95.1 % índice de homogeneidad.

LCMS: Análisis calculado para $C_{18}H_{18}ClN_6O$ 369.12; encontrado: 369.11 $(M+H)^+$.

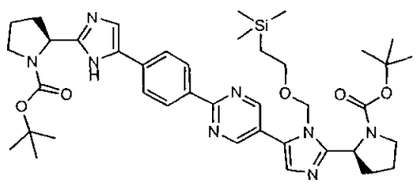
HRMS: Análisis calculado para $C_{18}H_{18}ClN_6O$ 369.1231; encontrado: 369.1246 $(M+H)^+$.

Ejemplo 152f Condiciones LCMS : Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

Ejemplo 152f-2	 preparado de 1b con el mismo procedimiento que describe la preparación de 152f-1 de 152d-1	t_R = 1.56min (>95%) LCMS: Análisis calculado para $C_{20}H_{20}BrN_4O$ 413.08; encontrado: 412.99 $(M+H)^+$.

Ejemplos 152g-1 hasta 152g-16

Ejemplo 152g-1 de 1c y 152e-1. Éster de tert-butilo del ácido (S)-2-[5-(2-{4-[2-((S)-1-tert-Butoxicarbonil-pirrolidin-2-il)-3H-imidazol-4-il]-fenil}-pirimidin-5-il)-1-(2-trimetilsilanil-etoximetil)-1H-imidazol-2-il]-pirrolidina-1-carboxílico



Pd $(Ph_3)_4$ (0.12 g, 0.103 mmol) se agregó 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)pirrolidina-1-carboxilato de (S)-tert-butilo (1c, 1.00 g, 2.27 mmol), 2-(5-(2-cloropirimidin-5-il)-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-tert-butilo (152c-1, 0.99 g, 2.06 mmol) y Na_2CO_2 (0.87 g, 10.3 mmol) 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 colocó en un baño de aceite precalentado (80°C) y se agita a 80°C durante 16h antes de que se agregue el catalizador adicional (0.12 g). Después de calentar la mezcla durante unas 12h adicionales a 80°C, la mezcla se enfrió a temperatura ambiente, se diluye con acetato de etilo y se lavó con solución $NaHCO_3$ saturado y salmuera previo al secado sobre sulfato de sodio anhidro y concentración

de solvente. La purificación del residuo por cromatografía instantánea Biotage™ en gel de sílice usando una Columna 40M (preequilibrada con 40% B seguido por la Extremo elución de gradiente con 40%B hasta 40%B para 150mL, 40%B hasta 100%B para 1500mL, 100%B hasta 100%B para 1000mL en donde B=acetato de etilo y A=hexanos) proporciona el compuesto del título como una espuma amarilla (1.533 g, 98%). Una cantidad pequeña de la espuma amarilla se purificó además para propósitos de caracterización por pHPLC (Phenomenex GEMINI, 30 x 100 mm, S10, 10 hasta 100% B durante 13 minutos, 3 minuto tiempo de espera, 40 mL/min, A = 95% agua, 5% acetonitrilo, 10mM NH_4OAc, B = 10% agua, 90% acetonitrilo, 10mM NH_4OAc) para proporcionar 95% puro el compuesto del título como un sólido blanco.

^1H RMN (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 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 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, TR = 2.91 min, 95% índice de homogeneidad.

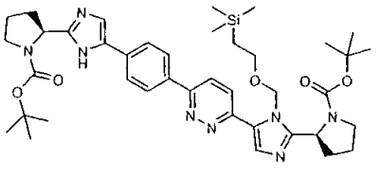
LCMS: Análisis calculado para $C_{40}H_{57}N_8O_5Si$ 757.42; encontrado: 757.42 $(M+H)^+$.

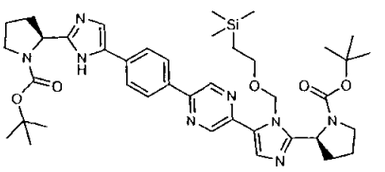
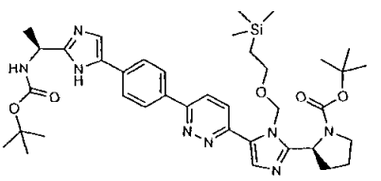
HRMS: Análisis calculado para $C_{40}H_{57}N_8O_5Si$ 757.4221;

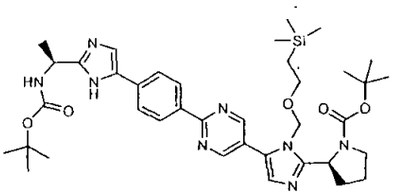
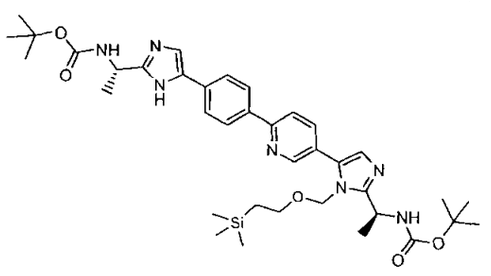
encontrado: 757.4191 $(M+H)^+$.

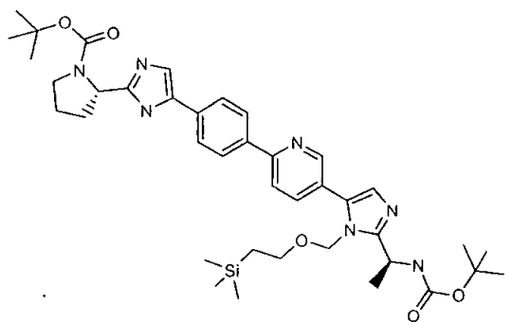
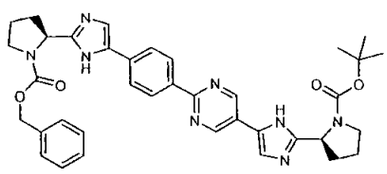
Se usó el mismo procedimiento para preparar los ejemplo 152g-2 al 152g-17

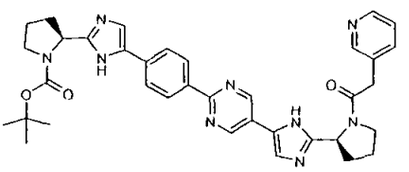
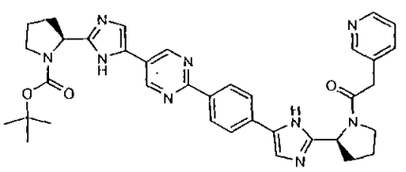
Condiciones CL: *Condición 1:* Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección. *Condición 2*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

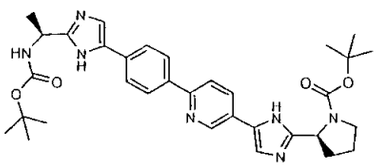
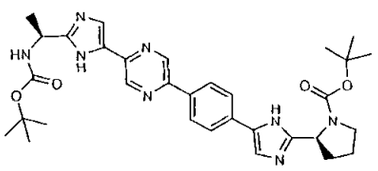
Ejemplo 152g-2	 Preparado de 1c y 152e-2	t_R = 2.81 min (79%) LCMS: Análisis calculado para $C_{40}H_{57}N_8O_5Si$ 757.42; encontrado: 758.05 $(M+H)^+$. HRMS: Análisis calculado para $C_{40}H_{57}N_8O_5Si$ 757.4221; encontrado: 757.4196 $(M+H)^+$.

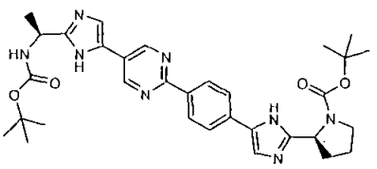
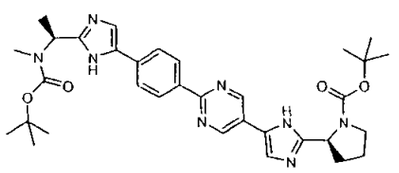
Ejemplo 152g-3	 Preparado de 1c y 152e-3	t_R = 2.89 min (>95%) LCMS: Análisis calculado para $C_{40}H_{57}N_8O_5Si$ 757.42; encontrado: 757.35 $(M+H)^+$. HRMS: Análisis calculado para $C_{40}H_{57}N_8O_5Si$ 757.4221; encontrado: 757.4191 $(M+H)^+$.
Ejemplo 152g-4	 Preparado de 1-6c y 152e-2	t_R = 2.87 min (97%) LCMS: Análisis calculado para $C_{38}H_{55}N_8O_5Si$ 731.41; encontrado: 731.26 $(M+H)^+$. HRMS: Análisis calculado para $C_{38}H_{55}N_8O_5Si$ 731.4065; encontrado: 731.4070 $(M+H)^+$.

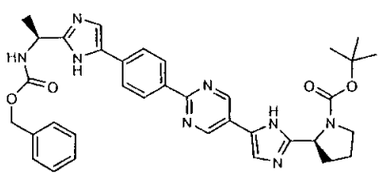
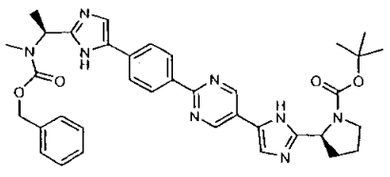
Ejemplo 152g-5	 Preparado de 1-6c y 152e-1	t_R = 2.94 min (>95%) LCMS: Análisis calculado para $C_{38}H_{55}N_8O_5Si$ 731.41; encontrado: 731.26 $(M+H)^+$. HRMS: Análisis calculado para $C_{38}H_{55}N_8O_5Si$ 731.4065; encontrado: 731.4046 $(M+H)^+$.
Ejemplo 152g-6	 Preparado de 1-6c y 152e-4	t_R = 1.99 min (condición 2, 96%) EMBR: Análisis calculado para $C_{37}H_{53}N_7O_2Si$ 703.39; encontrado: 704.34 $(M+H)^+$.

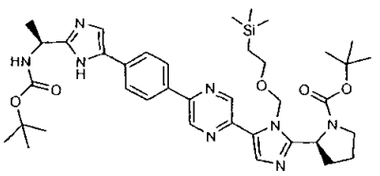
Ejemplo 152g-7	 Preparado de 1c y 152e-4	t_R = 1.99 min (condición 2, 96%) EMBR: Análisis calculado para $C_{39}H_{55}N_7O_5Si$ 729.40 encontrado: 730.42 $(M+H)^+$.
Ejemplo 152g-8	 Preparado de 1-5c y 152d-1	t_R = 2.15 min (>95%) LCMS: Análisis calculado para $C_{37}H_{41}N_8O_4$ 661.33; encontrado: 661.39 $(M+H)^+$. HRMS: Análisis calculado 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%) LCMS: Análisis calculado para $C_{36}H_{40}N_9O_3$ 646.76; encontrado: 646.47 $(M+H)^+$. HRMS: Análisis calculado para $C_{36}H_{40}N_9O_3$ no donado encontrado: no donado $(M+H)^+$.
Ejemplo 152g-10	 Preparado de 152d-1 y 1-10c	t_R = 1.71 min (>95%) LCMS: Análisis calculado para $C_{36}H_{40}N_9O_3$ 646.33; encontrado: 646.37 $(M+H)^+$. HRMS: Análisis calculado 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%) LCMS: Análisis calculado para $C_{33}H_{42}N_7O_4$ 600.33; encontrado: 600.11 $(M+H)^+$. HRMS: Análisis calculado 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%) LCMS: Análisis calculado para $C_{32}H_{41}N_8O_4$ 601.33; encontrado: 601.36 $(M+H)^+$. HRMS: Análisis calculado para $C_{32}H_{41}N_8O_4$ 601.3251; encontrado: 601.3253 $(M+H)^+$.

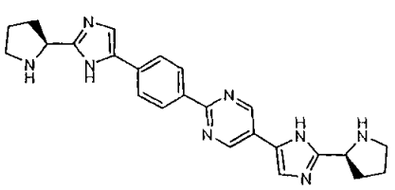
Ejemplo 152g-13	 Preparado de 1c y 152d-6	t_R = 2.11 min (98.5%) LCMS: Análisis calculado para $C_{32}H_{41}N_8O_4$ 601.33; encontrado: 601.36 $(M+H)^+$. HRMS: Análisis calculado para $C_{32}H_{41}N_8O_4$ 601.3251; encontrado: 601.3253 $(M+H)^+$.
Ejemplo 152g-14	 Preparado de 1-8c y 152d-1	t_R = 2.18 min (>95%) LCMS: Análisis calculado para $C_{33}H_{43}N_8O_4$ 615.34; encontrado: 615.38 $(M+H)^+$. HRMS: Análisis calculado 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%) LCMS: Análisis calculado para $C_{35}H_{39}N_8O_4$ 635.31; encontrado: 635.36 $(M+H)^+$. HRMS: Análisis calculado 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%) LCMS: Anal. Calcd $C_{36}H_{41}N_8O_4$ 649.33; encontrado: 649.39 $(M+H)^+$. HRMS: Análisis calculado 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%) LCMS: Análisis calculado para $C_{38}H_{54}N_8O_5Si$ 730.39; encontrado: 731.40 $(M+H)^+$. HRMS: Análisis calculado para $C_{38}H_{54}N_8O_5Si$ 731.4065; encontrado: 731.4045 $(M+H)^+$.

Ejemplo 152h-1-152h-7

Ejemplo 152h-1 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



Se agregó TFA (8 mL) en una porción a una solución agitada de éster de tert-butilo del ácido (S)-2-[5-(2-{4-[2-((S)-1-*tert*-butoxicarbonil-pirrolidin-2-il)-3*H*-imidazol-4-il]-fenil}-pirimidin-5-il)-1-(2-trimetilsilanil-etoximetil)-1*H*-imidazol-2-il]-pirrolidina-1-carboxílico (1.50 g, 1.98 mmol) en CH_2Cl_2 seco (30 mL) a temperatura ambiente. El matraz se selló y la mezcla se agitó a temperatura ambiente durante 16h antes de que los solvente(s) se removieran *in vacuo*. El residuo se tomó en metanol, se filtró a través de un filtro de jeringa PVDF (13mm x 0.45µm), distribuido a 8 viales pHPLC y se hace por cromatografía por HPLC (elución de gradiente de 10%B hasta 100%B durante 13 min en una columna Phenomenex C18, 30 x 100mm, 10µm, donde A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA). Después de la concentración de los tubos de ensayo seleccionados por evaporación de vacío rápido, el producto se disolvió en metanol y se neutraliza al pasar la solución a través de un cartucho de intercambio de aniones UCT CHQAX 110M75. Se aisló el compuesto del título como un sólido color amarillo mostaza (306.7 mg, 36% de rendimiento) hasta 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 × 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, TR = 1.33 min, >95% índice de homogeneidad.

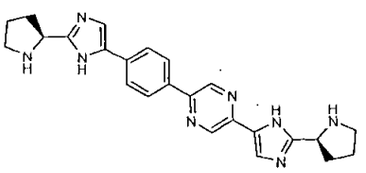
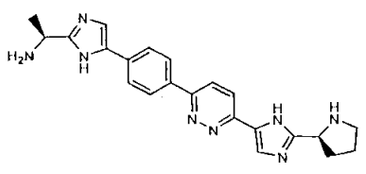
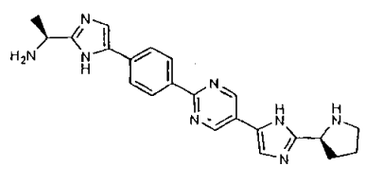
LCMS: Análisis calculado para $C_{24}H_{27}N_8$ 427.24; encontrado: 427.01 $(M+H)^+$.

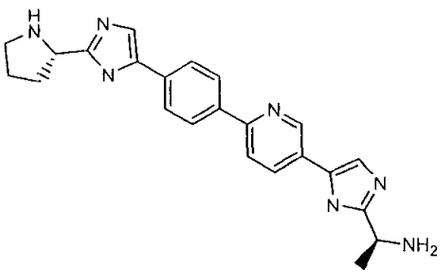
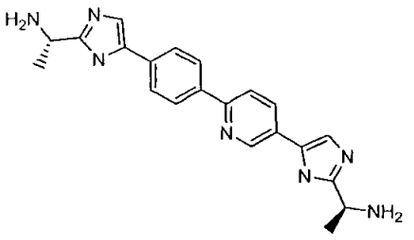
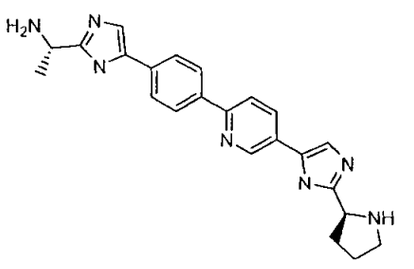
HRMS: Análisis calculado para $C_{24}H_{27}N_8$ 427.2359; encontrado: 427.2363 $(M+H)^+$.

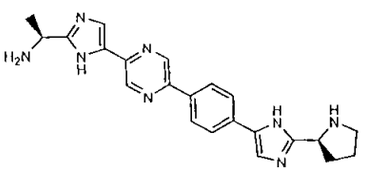
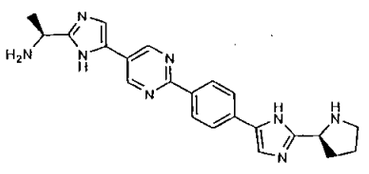
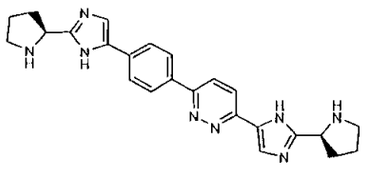
Las mismas condiciones se usaron para preparar los ejemplos 152h-2 hasta 152h-14.

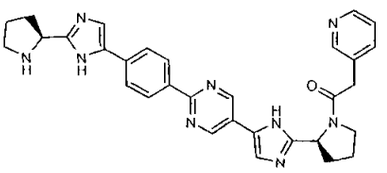
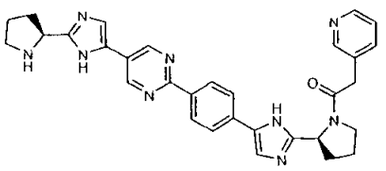
Condiciones CL: *Condición 1:* Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

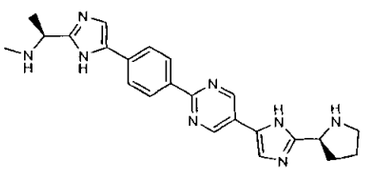
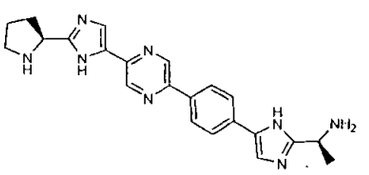
Condición 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

Ejemplo 152h-2	 Preparado de 152g-3	t_R = 1.36 min (98%) LCMS: Análisis calculado para $C_{24}H_{27}N_8$ 427.24; encontrado: 427.48 $(M+H)^+$. HRMS: Análisis calculado 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%) LCMS: Análisis calculado para $C_{22}H_{25}N_8$ 401.22; encontrado: 401.16 $(M+H)^+$. HRMS: Análisis calculado 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%) LCMS: Análisis calculado para $C_{22}H_{25}N_8$ 401.22; encontrado: 401.16 $(M+H)^+$. HRMS: Análisis calculado 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 LCMS: Análisis calculado para $C_{23}H_{25}N_7$ 399; encontrado: 400 $(M+H)^+$.
Ejemplo 152h-6	 Preparado de 152g-6	t_R = 0.81 min LCMS: Análisis calculado 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%) LCMS: Análisis calculado para $C_{23}H_{26}N_7$ 400.23; encontrado: 400.14 $(M+H)^+$. HRMS: Análisis calculado para $C_{23}H_{26}N_7$ 400.2250; encontrado: 400.2234 $(M+H)^+$.

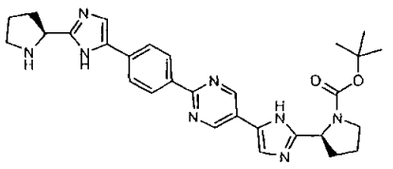
Ejemplo 152h-8	 Preparado de 152g-12	t_R = 1.29 min (>95%) LCMS: Análisis calculado para $C_{22}H_{25}N_8$ 401.22; encontrado: 401.21 $(M+H)^+$. HRMS: Análisis calculado para $C_{22}H_{25}N_8$ 401.2202; encontrado: 401.2204 $(M+H)^+$.
Ejemplo 152h-9	 Preparado de 152g-13	t_R = 1.29 min (97.6%) Condición 1 LCMS: Análisis calculado para $C_{22}H_{25}N_8$ 401.22; encontrado: 401.21 $(M+H)^+$. HRMS: Análisis calculado 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%) LCMS: Análisis calculado para $C_{24}H_{27}N_8$ 427.24; encontrado: 427.48 $(M+H)^+$. HRMS: Análisis calculado 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 LCMS: Análisis calculado para $C_{31}H_{32}N_9O$ 546.27; encontrado: 546.28 $(M+H)^+$. HRMS: Análisis calculado 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 LCMS: Análisis calculado para $C_{31}H_{32}N_9O$ 546.27; encontrado: 546.32 $(M+H)^+$. HRMS: Análisis calculado 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 LCMS: Análisis calculado para $C_{23}H_{26}N_8$ 414.24; encontrado: 415.27 $(M+H)^+$. HRMS: Análisis calculado 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 LCMS: Análisis calculado para $C_{22}H_{24}N_8$ 400.21; encontrado: 401.24 $(M+H)^+$. HRMS: Análisis calculado para $C_{22}H_{24}N_8$ 401.2202; encontrado: 401.2198 $(M+H)^+$.

Ejemplo 152i-1 hasta 152i-3

Ejemplo 152i-1 de 152g-8. éster de tert-butilo del ácido (S)-2-(5-{2-[4-((S)-2-Pirrolidin-2-il-3H-imidazol-4-il)-fenil]-pirimidin-5-il}-1H-imidazol-2-il)-pirrolidina-1-carboxílico.



Una solución de éster de tert-butilo del 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]-pirrolidina-1-carboxílico (317.1 mg, 0.48 mmol) en MeOH (1 mL) se agregó a una suspensión agitada de 10% paladio en carbono (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 evacuó tres veces con H_2 y se agitó durante 3h a presión de atmósfera. El catalizador adicional (20 mg) luego se agregó y la mezcla de reacción se agitó además durante 3h antes se filtró pr succión a través de Celite® y se concentró. El residuo se diluyó con MeOH, se filtró a través de un filtro de jeringa PVDF (13mm x 0.45µm), distribuido en 4 viales pHPLC y se hizo por cromatografía (elución de gradiente desde 20%B hasta

100%B durante 10 min en una Columna Phenomenex-Gemini C18 (30 x 100mm, 10µm) donde A = 95% agua, 5% acetonitrilo, 10mM NH_4OAc, B = 10% agua, 90% acetonitrilo, 10mM NH_4OAc). Después de la concentración de los tubos de ensayo seleccionados por evaporación de rápido vacío, 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*=8.3Hz, 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 de m, 6H), 1.41 y 1.17 (2s, 9H).

LCMS Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, TR = 1.77 min, >95 % índice de homogeneidad.

LCMS: Análisis calculado para $C_{29}H_{35}N_8O_2$ 527.29; encontrado: 527.34 $(M+H)^+$.

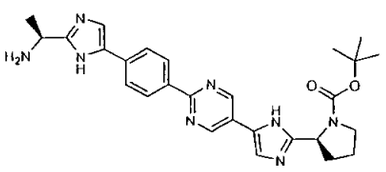
HRMS: Análisis calculado para $C_{29}H_{35}N_8O_2$ 527.2883; encontrado: 527.2874 $(M+H)^+$.

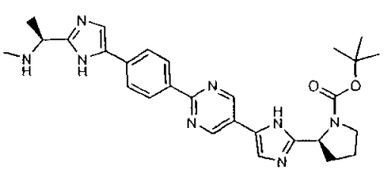
El mismo procedimiento se usó para preparar los ejemplos 152i-2 hasta 152i-3.

Condiciones CL: *Condición 1:* Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto

tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

Condición 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

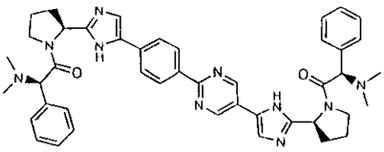
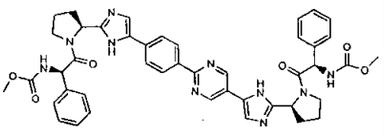
Ejemplo 152i-2	 Preparado de 152g-15	t_R = 1.70 min (95.7%) Condición 1 LCMS: Análisis calculado para $C_{27}H_{33}N_8O_2$ 501.27; encontrado: 501.35 $(M+H)^+$. HRMS: Análisis calculado para $C_{27}H_{33}N_8O_2$ 501.2726 encontrado: 501.2709 $(M+H)^+$.

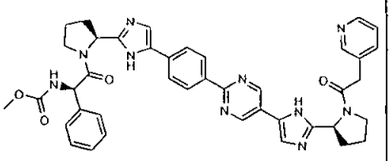
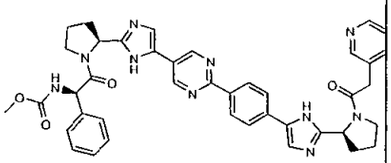
Ejemplo 152i-3	 Preparado de 152g-16	t_R = 1.77 min (>95%) Condición 1 LCMS: Análisis calculado para $C_{28}H_{35}N_8O_2$ 515.29; encontrado: 515.37 $(M+H)^+$. HRMS: Análisis calculado para $C_{28}H_{35}N_8O_2$ 515.2883 encontrado: 515.2869 $(M+H)^+$.

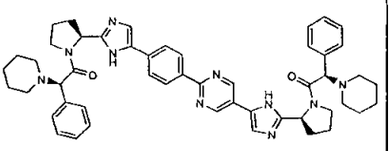
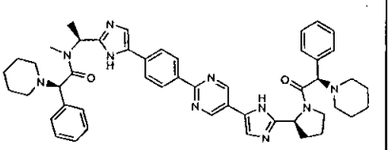
Ejemplos 152j-1 a 152j-28

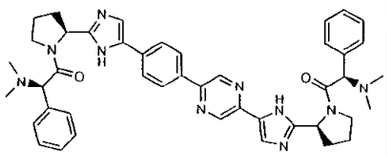
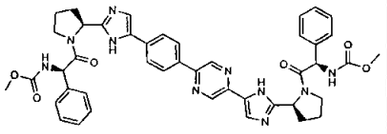
Los ejemplos 152j se aislaron como sales TFA o AcOH preparadas de acuerdo al método del ejemplo 148e hasta 148. Condiciones CL: Condición 1: Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección. Condición 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua,

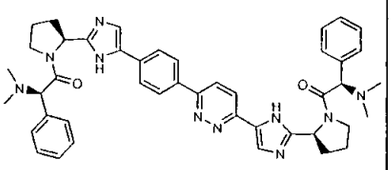
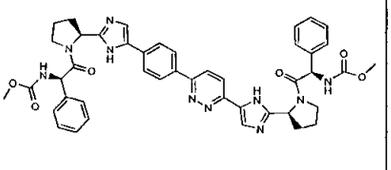
10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

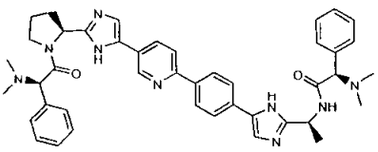
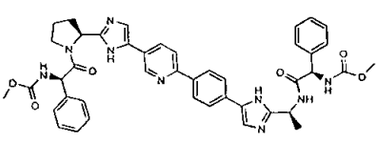
Ejemplo	Nombre del compuesto	Estructura	Datos
Ejemplo 152j-1	(1R)-2-((2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-5-pirimidinil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletananima	 Preparado de 152h-1 y extremo-1.	t_R = 1.61 min; (>95%); Condición 1 EMBR: Análisis Calculado para $C_{44}H_{49}N_{10}O_2$ 749.40 Encontrado: 749.32 $(M+H)^+$ HRMS: Análisis Calculado 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-pirimidinilo)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) carbamato de metilo	 Preparado de 152h-1 y extremo-4	t_R = 1.99 min (>95%); Condición 1 EMBR: Análisis Calculado para $C_{44}H_{45}N_{10}O_6$ 809.35 Encontrado: 809.17 $(M+H)^+$ HRMS: Análisis Calculado para $C_{44}H_{45}N_{10}O_6$ 809.3524 Encontrado: 809.3505 $(M+H)^+$

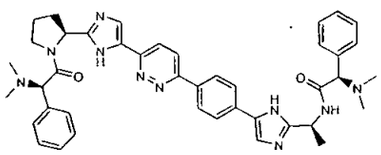
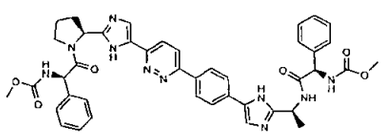
Ejemplo 152j-3	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4-(5-(2-((2S)-1-(3-piridinilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirimidinilo)fenil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo	 Preparado de 152h-11 y extremo-4	t_R = 1.65 min (92.3%); Condición 1 EMBR: Análisis Calculado para $C_{41}H_{41}N_{10}O_2$ 737.33 Encontrado: 737.49 $(M+H)^+$ HRMS: Análisis Calculado 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-pirimidinilo)-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 EMBR: Análisis Calculado para $C_{41}H_{41}N_{10}O_4$ 737.33 Encontrado: 737.75 $(M+H)^+$ HRMS: Análisis Calculado para$C_{41}H_{41}N_{10}O_4$ 737.3312 Encontrado: 737.3284 $(M+H)^+$

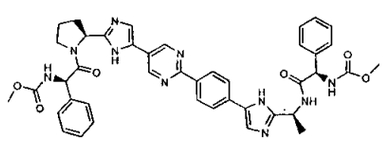
Ejemplo 152j-5	5-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-(4-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-4-il)fenil) pirimidina	 Preparado de 152h-1 y extremo-14	t_R = 1.70 min (>95%); Condición 1 EMBR: Análisis Calculado para $C_{50}H_{57}N_{10}O_2$ 829.47 Encontrado: 829.39 $(M+H)^+$ HRMS: Análisis Calculado 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-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirimidinilo)fenil)-1H-imidazol-2-il)etil)-2-(1-piperidinil) acetamida	 Preparado de 152h-13 y extremo-14	t_R = 1.66 min (>95%); Condición 1 EMBR: Análisis Calculado para$C_{49}H_{57}N_{10}O_2$ 817.47 Encontrado: 817.44 $(M+H)^+$ HRMS: Análisis Calculado para $C_{49}H_{57}N_{10}O_2$ 817.4666 Encontrado: 817.4673 $(M+H)^+$

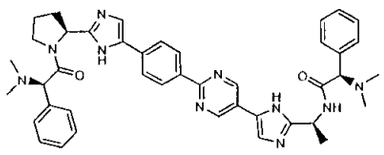
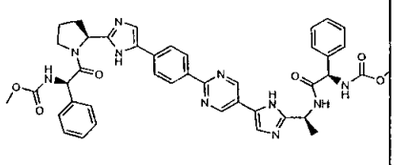
Ejemplo 152j-7	(1R)-2-((2S)-2-(5-(5-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-2-pirazinil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina	 Preparado de 152h-2 y extremo-1	t_R = 1.60 min (>95%); Condición 1 EMBR: Análisis Calculado para $C_{41}H_{49}N_{10}O_2$ 749.40 Encontrado: 749.31 $(M+H)^+$ HRMS: Análisis Calculado 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 EMBR: Análisis Calculado para$C_{44}H_{45}N_{10}O_6$ 809.35 Encontrado: 809.24 $(M+H)^+$ HRMS: Análisis Calculado para $C_{44}H_{45}N_{10}O_6$ 809.3523 Encontrado: 809.3493 $(M+H)^+$

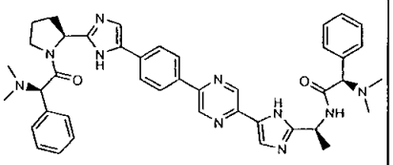
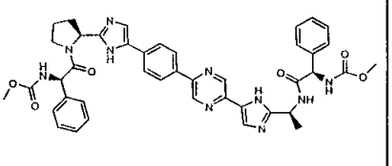
Ejemplo 152j-9	(1R)-2-((2S)-2-(5-(6-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-3-piridazinil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina	 Preparado de 152h-10 y extremo-1	t_R = 1.76 min (>95%); Condición 1 EMBR: Análisis Calculado para $C_{44}H_{49}N_{10}O_2$ 749.40 Encontrado: no observado $(M+H)^+$ HRMS: Análisis Calculado 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 EMBR: Análisis Calculado para $C_{44}H_{45}N_{10}O_6$ 809.35 Encontrado: 809.59 $(M+H)^+$ HRMS: Análisis Calculado para $C_{44}H_{45}N_{10}O_6$ 809.3524 Encontrado: 809.3499 $(M+H)^+$

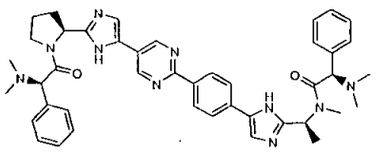
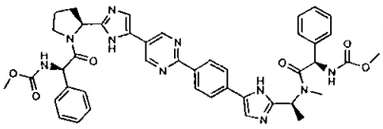
Ejemplo 152j-11	(2R)-2-(dimetilamino)-N-((1S)-1-(5-(4-(5-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-piridazinil)fenil)-1H-imidazol-2-il)etil)-2-fenil acetamida	 Preparado de 152h-7 y extremo-1	t_R = 1.56 min (>95%); Condición 1 EMBR: Análisis Calculado para $C_{43}H_{48}N_9O_2$ 722.39 Encontrado: 722.89 $(M+H)^+$ HRMS: Análisis Calculado 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-piridazinil)-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 EMBR: Análisis Calculado para $C_{43}H_{44}N_9O_6$ 782.34 Encontrado: 782.93 $(M+H)^+$ HRMS: Análisis Calculado para $C_{43}H_{44}N_9O_6$ 782.3415 Encontrado: 782.3398 $(M+H)^+$

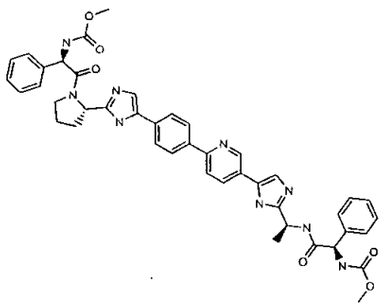
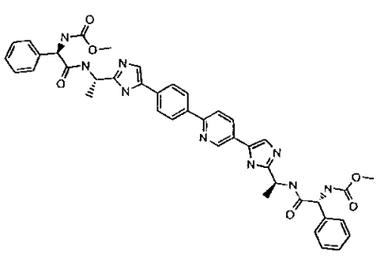
Ejemplo 152j-13	(2R)-2-(dimetilamino)-N-((1S)-1-(5-(4-(6-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-3-piridazinil)fenil)-1H-imidazol-2-il)etil)-2-fenil acetamida	 Preparado de 152h-3 y extremo-1	t_R = 1.55 min (>95%); Condición 1 EMBR: Análisis Calculado para $C_{42}H_{47}N_{10}O_2$ 723.39 Encontrado: 723.88 $(M+H)^+$ HRMS: Análisis Calculado 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)amino)etil)-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 EMBR: Análisis Calculado para $C_{42}H_{43}N_{10}O_6$ 783.34 Encontrado: 783.95 $(M+H)^+$ HRMS: Análisis Calculado para $C_{42}H_{43}N_{10}O_6$ 783.3367 Encontrado: 783.3337 $(M+H)^+$

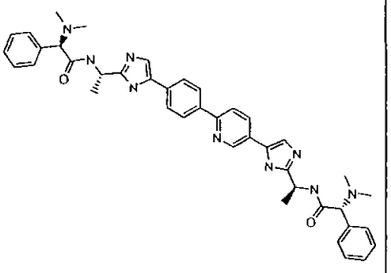
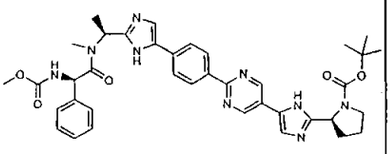
Ejemplo 152j-15	((1R)-2-((2S)-2-(5-(2-(4-(2-((1S)-1-(((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)amino)etil)-1H-imidazol-5-il)fenil)-5-pirimidinilo)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) carbamato de metilo	 Preparado de 152h-4 y extremo-4	t_R = 1.97 min (>95%); Condición 1 EMBR: Análisis Calculado para $C_{42}H_{43}N_{10}O_6$ 783.34 Encontrado: 783.97 $(M+H)^+$ HRMS: Análisis Calculado para $C_{42}H_{43}N_{10}O_6$ 783.3367 Encontrado: 783.3357 $(M+H)^+$

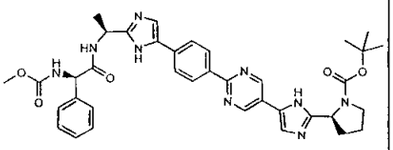
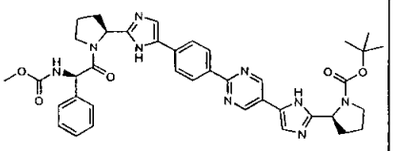
Ejemplo 152j-16	(2R)-2-(dimetilamino)-N-((1S)-1-(5-(2-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-5-pirimidinilo)-1H-imidazol-2-il)etil)-2-fenil acetamida	 Preparado de 152h-9 y extremo-1	t_R = 1.61 min (>95%); Condición 1 EMBR: Análisis Calculado para $C_{42}H_{47}N_{10}O_2$ 723.39 Encontrado: 723.52 $(M+H)^+$ HRMS: Análisis Calculado 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)amino)etil)-1H-imidazol-5-il)-2-pirimidinilo)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 EMBR: Análisis Calculado para$C_{42}H_{43}N_{10}O_6$ 783.34 Encontrado: 783.44 $(M+H)^+$ HRMS: Análisis Calculado para$C_{42}H_{43}N_{10}O_6$ 783.3367 Encontrado: 783.3328 $(M+H)^+$

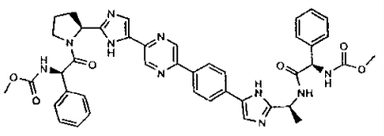
Ejemplo 152j-18	(2R)-2-(dimetilamino)-N-((1S)-1-(5-(5-(4-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-2-pirazinil)-1H-imidazol-2-il)etil)-2-fenilacetamida	 Preparado de 152h-8 y extremo-1	t_R = 1.60 min (>95%); Condición 1 EMBR: Análisis Calculado para $C_{42}H_{47}N_{10}O_2$ 723.39 Encontrado: 723.47 $(M+H)^+$ HRMS: Análisis Calculado 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 EMBR: Análisis Calculado para $C_{42}H_{43}N_{10}O_6$ 783.34 Encontrado: 783.69 $(M+H)^+$ HRMS: Análisis Calculado 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-pirimidinilo)fenil)-1H-imidazol-2-il)etil)-N-metil-2-fenil acetamida	 Preparado de 152h-13 y extremo-1	t_R = 1.54 min (>95%); Condición 1 EMBR: Análisis Calculado para $C_{43}H_{49}N_{10}O_2$ 737.40 Encontrado: 737.54 $(M+H)^+$ HRMS: Análisis Calculado 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-pirimidinilo)-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 EMBR: Análisis Calculado para $C_{43}H_{45}N_{10}O_6$ 797.35 Encontrado: 797.38 $(M+H)^+$ HRMS: Análisis Calculado 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-piridazinil)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%) EMBR: Análisis Calculado para $C_{43}H_{43}N_9O_6$ 781.33; Encontrado: 782.34 $(M+H)^+$. HRMS: Análisis Calculado 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-piridazinil)-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%) EMBR: Análisis Calculado para $C_{41}H_{41}N_9O_6$ 755.32; Encontrado: 756.35 $(M+H)^+$. HRMS: Análisis Calculado para $C_{41}H_{42}N_9O_6$ 756.3258 Encontrado: 756.3239 $(M+H)^+$.

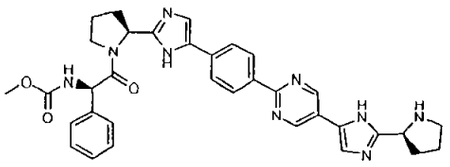
Ejemplo 152j-24	(2R)-2-(dimetilamino)-N-((1S)-1-(5-(6-(4-(2-((1S)-1-(((2R)-2-(dimetilamino)-2-fenilacetil)amino)etil)-1H-imidazol-5-il)fenil)-3-piridazinil)-1H-imidazol-2-il)etil)-2-fenilacetamida	 Preparado de 152h-6 y extremo 1	t_R = 1.18 min (Condición 2, 91%) EMBR: Análisis Calculado para $C_{41}H_{45}N_9O_2$ 695.37; Encontrado: 696.37 $(M+H)^+$. HRMS: Análisis Calculado 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 EMBR: Análisis Calculado para$C_{38}H_{44}N_9O_5$ 706.35; Encontrado: 706.53 $(M+H)^+$. HRMS: Análisis Calculado 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 EMBR: Análisis Calculado para $C_{37}H_{42}N_9O_5$ 692.33; Encontrado: 692.49 $(M+H)^+$. HRMS: Análisis Calculado 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 EMBR: Análisis Calculado para $C_{39}H_{44}N_9O_5$ 718.35; Encontrado: 718.49 $(M+H)^+$. HRMS: Análisis Calculado 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 EMBR: Análisis Calculado para $C_{42}H_{43}N_{10}O_6$ 783.34 Encontrado: 783.96 $(M+H)^+$ HRMS: Análisis Calculado para $C_{42}H_{43}N_{10}O_6$ 783.3367 Encontrado: 783.3375 $(M+H)^+$

Ejemplos 152k-1 hasta 152k-

Ejemplo 152k-1 de 152j-27. Éster de metilo del 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]-etilo}-carbámico



Se agregó HCl 4N frío (0°C) en dioxanos (4 mL) se agregó por medio de jeringa a éster de tert-butilo del 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}-pirrolidina-1-carboxílico (104.6 mg, 0.146 mmol) 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 min antes un precipitado se observó. Después de agitar además durante 1.75h, la suspensión se diluyó con éter y hexanos. La filtración por succión de una porción pequeña de la suspensión proporciona el compuesto del título como un sólido amarillo el cual se usó para propósitos de caracterización. El balance de la suspensión se concentró completamente hasta secarse y se coloca bajo alto vacío durante 16h. Se aisló el resto del compuesto del título también como un sólido amarillo (137.7 mg, 123%) el cual 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 × 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, TR = 1.79 min, >95 % índice de homogeneidad.

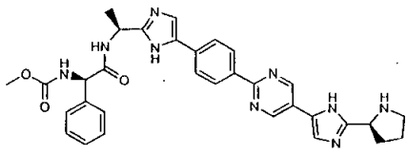
LCMS: Análisis calculado para $C_{34}H_{36}N_9O_3$ 618.29; encontrado: 618.42 $(M+H)^+$.

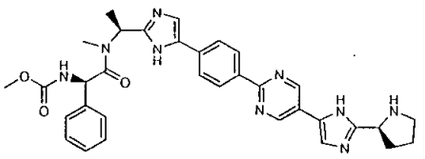
HRMS: Análisis calculado para $C_{34}H_{36}N_9O_3$ 618.2921; encontrado: 618.2958 $(M+H)^+$.

El mismo procedimiento se usó para preparar los ejemplos 152k-2 hasta 152k-3.

Condiciones CL: Condición 1: Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

Condición 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

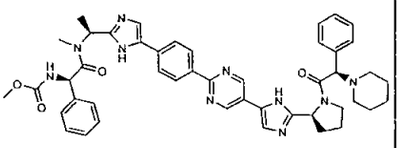
Ejemplo	Nombre del compuesto	Estructura	Datos
Ejemplo 152k-2		 Preparado de 152j-26	t_R = 1.74 min (>95 %); Condición 1 EMBR: Análisis calculado para $C_{32}H_{34}N_9O_3$ 592.28; encontrado: 592.41 $(M+H)^+$. HRMS: Análisis calculado para $C_{32}H_{34}N_9O_3$ 592.2785; encontrado: 592.2775 $(M+H)^+$.

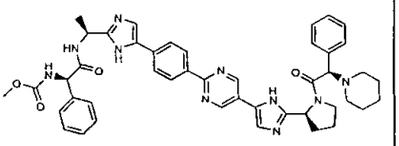
Ejemplo 152k-3		 Preparado de 152j-25	t_R = 1.79 min (>95 %); Condición 1 EMBR: Análisis calculado para $C_{33}H_{36}N_9O_3$ 606.29; encontrado: 606.43 $(M+H)^+$. HRMS: Análisis calculado para $C_{33}H_{36}N_9O_3$ 606.2941; encontrado: 606.2925 $(M+H)^+$.

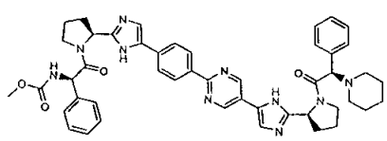
Ejemplos 1521-1 hasta 1521-

Los ejemplos 1521-1 hasta 1521-3 se aislaron como sales TFA o AcOH preparadas usando el mismo procedimiento para convertir el ejemplo 148e hasta 148. Condiciones CL: Condición 1: Phenomenex LUNA C-18 4.6 x 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

Condición 2: Phenomenex LUNA C-18 4.6 x 50 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

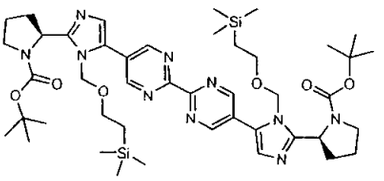
Ejemplo	Nombre del compuesto	Estructura	Datos
Ejemplo 152l-1	((1R)-2-(metil((1S)-1-(4-(4-(5-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirimidinil)fenil)-1H-imidazol-2-il)etil)amino)-2-oxo-1-feniletil) carbamato de metilo	 Preparado de 152k-3 y Extremo-14	t_R = 1.87 min (>95%); Condición 1 EMBR: Análisis calculado para $C_{46}H_{51}N_{10}O_4$ 807.41 encontrado 807.57 $(M+H)^+$ HRMS: Análisis calculado para $C_{46}H_{51}N_{10}O_4$ 807.4095 encontrado 807.4128 $(M+H)^+$

Ejemplo 1521-2	((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 EMBR: Análisis calculado para $C_{45}H_{49}N_{10}O_4$ 793.39 encontrado 793.52 $(M+H)^+$ HRMS: Análisis calculado para $C_{45}H_{49}N_{10}O_4$ 793.3938 encontrado 793.3934 $(M+H)^+$

Ejemplo 1521-3	((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 EMBR: Análisis calculado para $C_{47}H_{51}N_{10}O_4$ 819.41 encontrado 819.50 $(M+H)^+$ HRMS: Análisis calculado para $C_{47}H_{51}N_{10}O_4$ 819.4095 encontrado 819.4127 $(M+H)^+$

Ejemplo 153a-1 de 153a-4.

Ejemplo 153a-1 preparado de 152e-1. Éster de tert-butilo del ácido (S)-2-[5-{5'-[2-((S)-1-tert-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]-pirrolidina-1-carboxílico



A una solución agitada de 2-(5-(2-cloropirimidin-5-il)-1-((2-(trimetilsilil)etoxi)metil)-1H-imidazol-2-il)pirrolidina-1-carboxilato de (S)-tert-butilo (1.0 g, 2.08 mmol) y diclorobis(benzonitrilo)paladio (40 mg, 0.104 mmol) en DMF seco (10 mL) a temperatura ambiente bajo argón se agregó tetraquis(dimetilamino)etileno puro (1.0 mL, 4.16 mmol). La mezcla se calentó hasta 60°C durante 15h antes se diluyó con acetato de etilo y se filtró por succión a través de Celite. El filtrado se lavó con solución $NaHCO_3$ saturado y salmuera previo al secado durante Na_2SO_4 y evaporación de solvente. La purificación del residuo por cromatografía instantánea Biotage™ en gel de sílice (Extremo elución de gradiente con 15%B hasta 15%B para 150 mL, 15%B hasta 75%B para 1500 mL, 75%B hasta 100%B para 1000 mL, 100%B hasta 100%B para 1000 mL donde B=acetato de etilo y A=hexano seguido por una segunda elución de gradiente

con 10%B hasta 100%B para 700 mL donde B=metanol y A=acetato de etilo) proporciona 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 × 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, TR = 3.37min, >95% índice de homogeneidad.

LCMS: Análisis calculado para $C_{44}H_{69}N_{10}O_6Si_2$ 889.49; encontrado: 889.57 $(M+H)^+$.

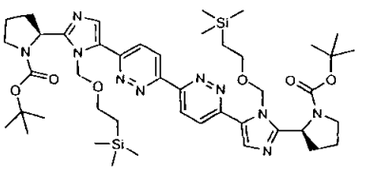
HRMS: Análisis calculado para $C_{44}H_{69}N_{10}O_6Si_2$ 889.4940; encontrado: 889.4920 $(M+H)^+$.

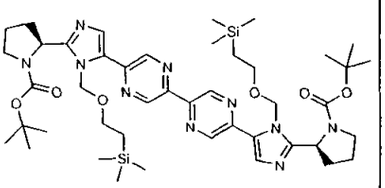
El mismo procedimiento se usó para preparar los Ejemplos 153a-2 a través de 153a-4.

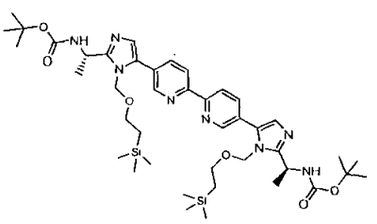
Condiciones CL: Condición 1. Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

Condición 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA,

220nm, 5 µL 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 EMBR: Análisis calculado para $C_{44}H_{69}N_{10}O_6Si_2$ 889.49; encontrado 889.56 $(M+H)^+$. HRMS: Análisis calculado 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 EMBR: Análisis calculado para $C_{44}H_{69}N_{10}O_6Si_2$ 889.49; encontrado 889.51 $(M+H)^+$. HRMS: Análisis calculado 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) EMBR: Análisis calculado para $C_{42}H_{66}N_8Si_2$ 834; encontrado 835 $(M+H)^+$.

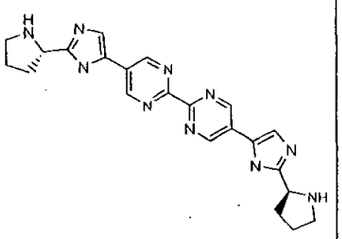
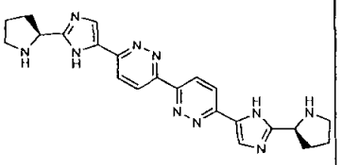
Ejemplo 153b-2-153b-3

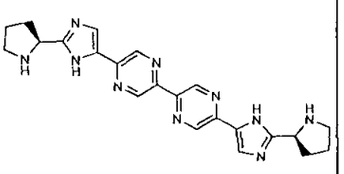
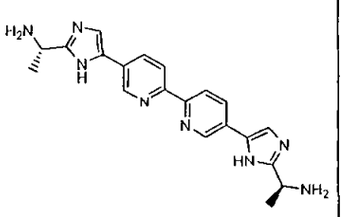
Las reacciones de hidrólisis se llevaron a cabo como arriba por el ejemplo 152h.

Condiciones CL: Condición 1: Phenomenex LUNA C-18 4.6 x 50 mm, 0 hasta 100% B durante 3 minutos, 1 minutos de tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220 nm, 5 µl de volumen de inyección.

Condición 2: Phenomenex LUNA C-18 4.6 x 50 mm, 0 hasta 100% B durante 2 minutos, 1 minutos de tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B =

10% agua, 90% metanol, 0.1% 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 EMBR: Análisis calculado para $C_{22}H_{25}N_{10}$ 429.23; encontrado 429.01 $(M+H)^+$. HRMS: Análisis calculado 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 EMBR: Análisis calculado para $C_{41}H_{41}N_{10}O_2$ 737.33 encontrado 737.49 $(M+H)^+$ HRMS: Análisis calculado para $C_{41}H_{41}N_{10}O_4$ 737.3312 encontrado 737.3342 $(M+H)^+$

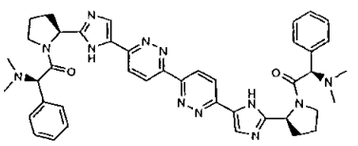
Ejemplo 153b-3		 Preparado de 153a-3	t_R = 1.40 min (>95%); Condición 1 EMBR: Análisis calculado para $C_{22}H_{25}N_{10}$ 429.23; encontrado 429.20 $(M+H)^+$. HRMS: Análisis calculado para $C_{22}H_{25}N_{10}$: 429.2264; Encontrado 429.2254 $(M+H)^+$
Ejemplo 153b-4		 Preparado de 153a-4	t_R = 0.85 min (condición 1) LCMS: Análisis calculado para $C_{20}H_{22}N_8$ 374; encontrado 375 $(M+H)^+$.

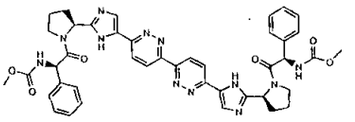
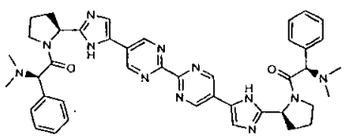
Ejemplos 153c-1 hasta 153c-7

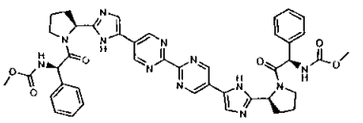
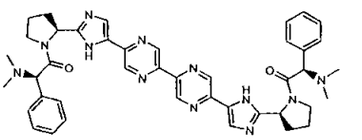
Los ejemplos 153c-1 hasta 153c-7 se aislaron como sales TFA o AcOH usando el procedimiento usado para convertir el ejemplo 148e a 184.

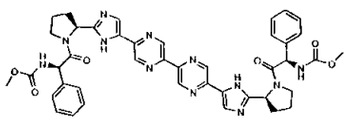
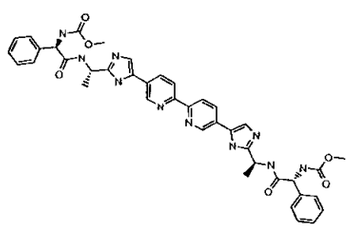
Condiciones CL: Condición 1: Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 3 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

Condición 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 hasta 100% B durante 2 minutos, 1 minuto tiempo de espera, A = 90% agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, 220nm, 5 µL volumen de inyección.

Ejemplo	Nombre del compuesto	Estructura	Datos
Ejemplo 153c-1	(1R,1'R)-2,2'-(3,3'-bipiridazina-6,6'-diilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidinadiil))bis(N,N-dimetil-2-oxo-1-fenil etanamina)	 Preparado de 153b-2 y Extremo-1	t_R = 1.55 min (>95%); Condición 1 EMBR: Análisis calculado para $C_{42}H_{47}N_{12}O_2$ 751.39 encontrado 751.64 $(M+H)^+$ HRMS: Análisis calculado para $C_{42}H_{47}N_{12}O_2$ 751.3945 encontrado 751.3936 $(M+H)^+$

Ejemplo 153c-2	(3,3'-bipiridazina-6,6'-diilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidinadiil((1R)-2-oxo-1-fenil-2,1-etanediil))) biscarbamato de dimetilo	 Preparado de 153b-2 y Extremo-4	t_R = 1.95 min (>95%); Condición 1 EMBR: Análisis calculado para $C_{42}H_{43}N_{12}O_6$ 811.34 encontrado 811.22 $(M+H)^+$ HRMS: Análisis calculado 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'-bipirimidina-5,5'-diilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidinadiil))bis(N,N-dimetil-2-oxo-1-fenil etanamina)	 Preparado de 153b-1 y Extremo-1	t_R = 1.51 min (>90%*); Condición 1 EMBR: Análisis calculado para $C_{42}H_{47}N_{12}O_2$ 751.39 encontrado 751.21 $(M+H)^+$ HRMS: Análisis calculado para $C_{42}H_{47}N_{12}O_2$ 751.3945 encontrado 751.3921 $(M+H)^+$

Ejemplo 153c-4	(2,2'-bipirimidina-5,5'-diilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidinadiil((1R)-2-oxo-1-fenil-2,1-etanediil))) Biscarbamato de dimetilo	 Preparado de 153b-1 y Extremo-4	t_R = 1.88 min (>95%); Condición 1 EMBR: Análisis calculado para $C_{42}H_{43}N_{12}O_6$ 811.34 encontrado 811.10 $(M+H)^+$ HRMS: Análisis calculado 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'-bipirazina-5,5'-diilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidinadiil)) bis(N,N-dimetil-2-oxo-1-feniletanamina)	 Preparado de 153b-3 y Extremo-1	t_R = 1.61 min (>95%); Condición 1 EMBR: Análisis calculado para $C_{42}H_{47}N_{12}O_2$ 751.39 encontrado 751.30 $(M+H)^+$ HRMS: Análisis calculado para $C_{42}H_{47}N_{12}O_2$ 751.3945 encontrado 751.3943 $(M+H)^+$

Ejemplo 153c-6	(2,2'-bipirazina-5,5'-diilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidinadiil((1R)-2-oxo-1-fenil-2,1-etanediil)))biscarbamato de dimetilo	 Preparado de 153b-3 y Extremo-4	t_R = 2.00 min (>95%); Condición 1 EMBR: Análisis calculado para $C_{42}H_{43}N_{12}O_6$ 811.34 encontrado 811.23 $(M+H)^+$ HRMS: Análisis calculado para $C_{42}H_{43}N_{12}O_6$ 811.3429 encontrado 811.3407 $(M+H)^+$
Ejemplo 153c-7	(2,2'-bipiridina-5,5'-diilbis(1H-imidazol-5,2-diil(1S)-1,1-etanediilimino((1R)-2-oxo-1-fenil-2,1-etanediil)))biscarbamato de dimetilo	 Preparado de 153b-4 y Extremo-4	t_R = 1.42 min (condición 2, 94%) EMBR: Análisis calculado para $C_{40}H_{40}N_{10}O_6$ 756.31; encontrado 757.34 $(M+H)^+$. HRMS: Análisis calculado para $C_{40}H_{41}N_{10}O_6$ 757.3211 encontrado 757.3180 $(M+H)^+$.

Sección LS de Condiciones CL:

Condición 1: Solvente A: 10% metanol/90% agua/0.1% TFA; Solvente B: 90% metanol/10% agua/0.1% TFA; Columna: Phenomenex-Luna 3.0 x 5.0mm S10; Longitud de onda: 220nM; Relación de flujo: 4 mL/min; 0% B hasta 100% B durante 4 min con 1 min de tiempo de espera.

Condición 2: Solvente A: 10% metanol/90% agua/0.1% TFA; Solvente B: 90% metanol/10% agua/0.1% TFA; Columna: Phenomenex 10u C18 3.0 x 5.0mm; Longitud de onda: 220nM; Relación de flujo: 4 mL/min; 0% B hasta 100% B durante 4 min con 1 min de tiempo de espera.

Condición 3: Solvente A: 5% acetonitrilo/95% agua/10 mmol acetato de amonio; Solvente B: 95% acetonitrilo/5% agua/10 mmol acetato de amonio; Columna: Phenomenex 10u C18 4.6 x 5.0mm; Longitud de onda: 220nM; Relación de flujo: 4 mL/min; 0% B hasta 100% B durante 4 min con 1 min de tiempo de espera.

Condición 4: Solvente A: 5% acetonitrilo/95% agua/10 mmol acetato de amonio; Solvente B: 95% acetonitrilo/5% agua/10 mmol acetato de amonio; Columna: Luna 4.6 x 50mm S10; Longitud de onda: 220nM; Relación de flujo: 4 mL/min; 0% B hasta 100% B durante 3 min con 1 min de tiempo de espera.

Condición 5: Solvente A: 10% metanol/90% agua/0.1% TFA; Solvente B: 90% metanol/10% agua/0.1% TFA; Columna: Phenomenex 10u C18 3.0 x 5.0mm; Longitud de onda: 220nM;

Relación de flujo: 4 mL/min; 0%B hasta 100% B durante 3 min con 1 min de tiempo de espera.

Condición 6: Solvente A: 5% acetonitrilo/95% agua/10 mmol acetato de amonio; Solvente B: 95% acetonitrilo/5% agua/10 mmol acetato de amonio; Columna: Phenomenex-Luna 3.0 x 50mm S10; Longitud de onda: 220 nM; Relación de flujo: 4 mL/min; 0%B hasta 100% B durante 8 min con 2 min de tiempo de espera.

Condición 7: Solvente A: 10% metanol/90% agua/0.1% TFA; Solvente B: 90% metanol/10% agua/0.1% TFA; Columna: Phenomenex-Luna 3.0 x 5.0mm S10; Longitud de onda: 220nM; Relación de flujo: 4 mL/min; 0% B hasta 100% B durante 3 min con 1 min de tiempo de espera.

Condición 8: Solvente A: 10% metanol/90% agua/0.2% H_3PO_4; Solvente B: 90% metanol/10% agua/0.2% H_3PO_4; Columna: YMC ODS-A 4.6 x 50mm S5; Longitud de onda: 220nM; Relación de flujo: 4 mL/min; 0% B hasta 100% B durante 4 min con un 1 min de tiempo de espera.

Condición 9: Solvente A: 10% metanol/90% agua/0.2% H_3PO_4; Solvente B: 90% metanol/10% agua/0.2% H_3PO_4; Columna: YMC ODS-A 4.6 x 50mm S5; Longitud de onda: 220 nM; Relación de flujo: 2.5 mL/min; 0% B hasta 50% B durante 8 min con 3 min de tiempo de espera.

Condición 10: Xbridge C18, 150 x4.6 mm I.D. S-3.5um; Fase Móvil A: 95% Agua-5% Acetonitrilo con 10 mM acetato de amonio (pH=5); Fase Móvil B: 95% Acetonitrilo-5% agua con 10 mM

acetato de amonio (pH=5); Isocrático 30% B durante 20 min; Relación de flujo: 1 mL/min; detección UV: 220 nm

Condición 11: Solvente A: 10% metanol/90% agua/0.1% TFA; Solvente B: 90% metanol/10% agua/0.1% TFA; Columna: Phenomenex 10u C18 3.0 x 5.0mm; Longitud de onda: 220nM; Relación de flujo: 4 mL/min; 30% B hasta 100% B durante 4 min con 1 min de tiempo de espera.

Condición 12: Solvente A: 10% metanol/90% agua/0.1% TFA; Solvente B: 90% metanol/10% agua/0.1% TFA; Columna: Phenomenex 10u C18 3.0 x 5.0mm; Longitud de onda: 220nM; Relación de flujo: 4 mL/min; 20% B hasta 100% B durante 4 min con 1 min de tiempo de espera.

Condición 13: Solvente A: 10% metanol/90% agua/0.2% H_3PO_4; Solvente B: 90% metanol/10% agua/0.2% H_3PO_4; Columna: YMC ODS-A 4.6 x 50mm S5; Longitud de onda: 220 nM; Relación de flujo: 2.5 mL/min; 0% B hasta 100% B durante 8 min con 3 min de tiempo de espera.

Sección LS de Condiciones HPLC Preparativas:

Condición 1: Solvente A: 10% metanol/90% agua/0.1% TFA; Solvente B: 90% metanol/10% agua/0.1% TFA; Columna: Phenomenex-Luna 30 x 100mm S10; Longitud de onda: 220nM; Relación de flujo: 30mL/min; 0% B hasta 100% B durante 10 min con 2 min de tiempo de espera.

Condición 2: Solvente A: 10% metanol/90% agua/0.1% TFA; Solvente B: 90% metanol/10% agua/0.1% TFA; Columna: Xterra

Prep EM C18 30 x 50mm 5u; Longitud de onda: 220nM; Relación de flujo: 30 mL/min; 0% B hasta 100% B durante 8 min con 3 min de tiempo de espera.

Condición 3: Solvente A: 10% metanol/90% agua/0.1% TFA; Solvente B: 90% metanol/10% agua/0.1% TFA; Columna: Xterra Prep EM C18 30 x 50mm 5u; Longitud de onda: 220nM; Relación de flujo: 25 mL/min; 10% B hasta 100% B durante 8 min con 2 min de tiempo de espera.

Condición 4: Solvente A: 10% metanol/90% agua/0.1% TFA; Solvente B: 90% metanol/10% agua/0.1% TFA; Columna: Xterra 19 x 100mm S5; Longitud de onda: 220 nM; Relación de flujo: 20 mL/min; 30% B hasta 100% B durante 5 min con 3 min de tiempo de espera.

Condición 5: Solvente A: 10% metanol/90% agua/0.1% TFA; Solvente B: 90% metanol/10% agua/0.1% TFA; Columna: Phenomenex-Luna 30 x 100mm S10; Longitud de onda: 220nM; Relación de flujo: 30 mL/min; 10% B hasta 100% B durante 8 min con 2 min de tiempo de espera

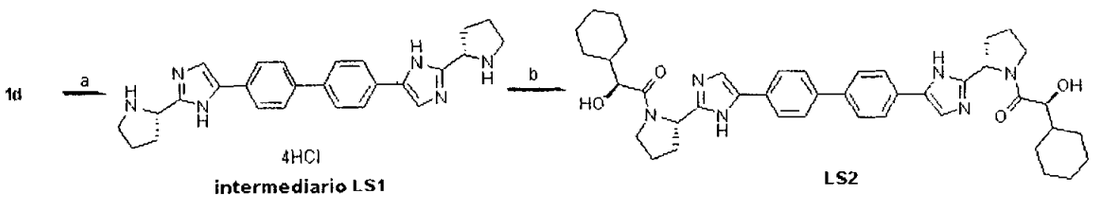
Condición 6: Solvente A: 10% Acetonitrilo/90% agua/0.1% TFA; Solvente B: 90% Acetonitrilo/10% agua/0.1% TFA; Columna: Phenomenex-Luna 21 x 100 mm S10; Longitud de onda: 220nM; Relación de flujo: 25 mL/min; 0% B hasta 60% B durante 10 min con 5 min de

tiempo de espera.

Experimentales:

Compuesto LS2

(1S,1'S)-2,2'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(1-ciclohexil-2-oxoetanol)

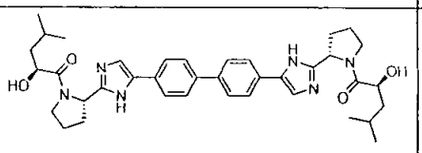
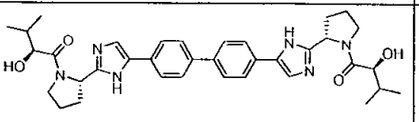


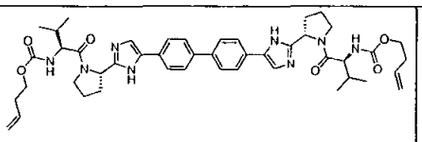
Extremo a: Al 1d (1.4 g; 2.24 mmol) se le agregó 30 mL de HCl 4N en dioxano. Después de 3 h, 60 mL de éter se le agregó y el precipitado se filtró y se secó bajo alto vacío proporcionando 1.02g (80%) del intermediario LS1 como un polvo amarillo pálido. ^{1}H RMN (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 10.41 (s, 2H), 9.98 (s, 2H), 8.22 (s, 2H), 8.06 (d, J = 8.54Hz, 4H), 7.92 (d, J = 8.55Hz, 4H), 5.07 (s, 2H), 3.43-3.54 (m, 2H), 3.33-3.43 (m, 2H), 2.43-2.59 (m, 4H), 2.16-2.28 (m, 2H), 1.94-2.09 (m, 2H). CL (Cond. 1): TR = 1.28 min; EM: Anal. Calculado para $[M+H]^+$ $C_{26}H_{28}N_6$: 425.24; encontrado 425.56.

Extremo b: Al intermediario LS1 (200 mg; 0.35 mmol) en 2 mL DMF se le agregó DIPEA (0.30 mL; 1.75mmol), ácido (S)-2-ciclohexil-2-hidroxiacético (61 mg; 0.39 mmol), seguido por HATU (147 mg; 0.38 mmol). Después de agitar a temperatura ambiente durante 18 h, la mezcla

de reacción se dividió en dos porciones y se purifica por medio de HPLC preparativa (Cond'n 1). Las fracciones que contienen el producto deseado se agruparon y pasaron a través de un cartucho MCX (Oasis; 6g; previamente acondicionado con dos longitudes de columna de metanol). El cartucho se lavó con dos longitudes de columna de metanol y el producto se eluyó con amoniaco/metanol. La concentración proporciona 65 mg de LS2 (26%) como un polvo incoloro. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 0.87-1.30 (m, 12H) 1.38-1.53 (m, J=24.72, 11.90 Hz, 4H) 1.54-1.75 (m, 8H) 1.95-2.21 (m, 6H) 3.72-3.86 (m, 6H) 5.13 (t, J=6.56 Hz, 2H) 7.87 (d, J=7.93 Hz, 4H) 7.96 (d, J=6.41 Hz, 4H) 8.13 (s, 2H) (imidazol NH y protones de hidroxilo no contados para). CL (Cond'n 2): TR = 3.07 min; EM: Anal. Calculado para $[M+H]^+$ $C_{42}H_{52}N_6O_4$: 705.9; encontrado 705.6.

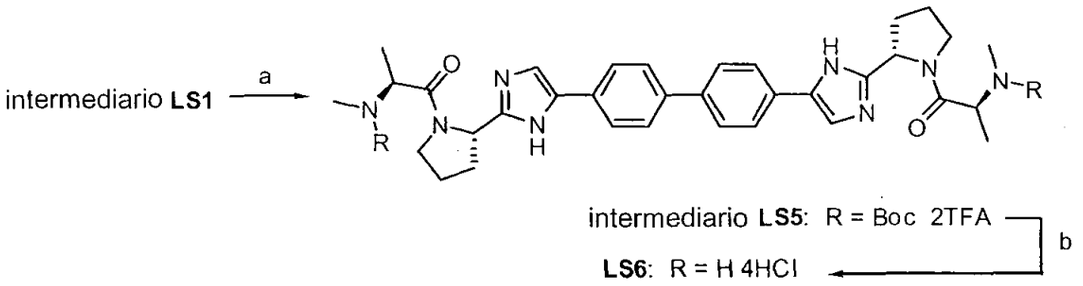
Los siguientes análogos se prepararon de manera similar a la preparación de LS2 del intermediario LS1 empleando el ácido carboxílico apropiado:

Número del Ejemplo	Nombre del Compuesto	Estructura	Datos Analíticos
LS3	(2S,2'S)-1,1'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(4-metil-1-oxo-2-pentanol)		LC/MS: 2.02 min (Cond'n 1); Análisis calculado para $[M+H]^+$ $C_{38}H_{48}N_6O_4$: 653.4; encontrado 653.2.
LS4	(2S,2'S)-1,1'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(3-metil-1-oxo-2-butanol)		LC/MS: 1.99 min (Cond'n 3); Análisis calculado para $[M+H]^+$ $C_{36}H_{44}N_6O_4$: 625.3; encontrado 625.3.

LS16	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(((3-buten-1-iloxi)carbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil) carbamato de 3-buten-1-ilo	 del intermediario LS1 y (S)-2-((but-3-eniloxi)carbonilamino)-3-metilbutanoico que se preparó de L-valina y butenilcloroformiato de manera similar a la preparación de el extremo-51	^{1}H RMN (500 MHz, CH_3OD) δ ppm 0.81-1.10 (m, 12H) 1.90-2.15 (m, 4H) 2.15-2.51 (m, 8H) 3.82-3.96 (m, 2H) 3.97-4.05 (m, 2H) 4.05-4.19 (m, 4H) 4.25 (d, J=7.02 Hz, 2H) 4.62 (s, 2H) 5.00-5.17 (m, 4H) 5.20 (t, J=5.65 Hz, 2H) 5.79-5.93 (m, 2H) 7.20-7.47 (m, 2H) 7.59-7.90 (m, 8H)

Ejemplo LS6

(2S,2'S)-1,1'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(N-metil-1-oxo-2-propanamina)



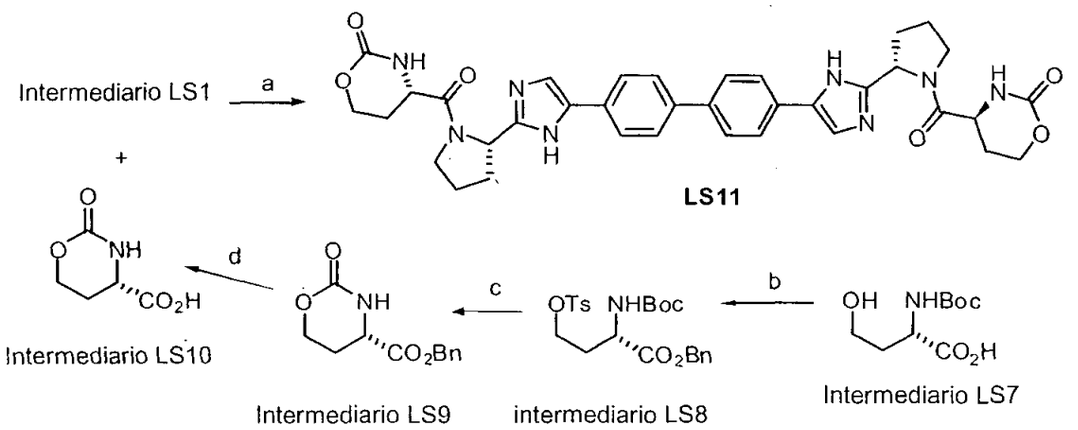
Extremo a: Al intermediario LS1 (64mg; 0.11mmol) en 1 mL de DMF se le agregó ácido (S)-2-(tert-butoxicarbonil(metil)amino)propanoico (48mg; 0.24mmol), base Hunig (0.12mL; 0.67mmol) y HATU (90mg; 0.24mmol). Después de 3h, la reacción se purificó por medio de HPLC preparativa (Cond'n 2). Las fracciones que contienen el intermediario LS5 se agruparon y concentraron proporcionando el intermediario LS5 como un polvo incoloro (43mg; 48%) después de secar bajo alto vacío. CL (Cond'n 4): TR = 2.12 min; EM: Anal. Calculado para $[M+H]^+$ $C_{44}H_{58}N_8O_6$: 795.4; encontrado 795.5.

Extremo b: El Intermediario LS5 se permitió agitar en 2 mL de HCl/Dioxano (4N) durante 18 h en cuyo tiempo 10 mL de éter se le agregó y el precipitado resultante se filtró y se secó bajo alto vacío proporcionando el LS6 (45mg; 155%) como un sólido incoloro. ^1H RMN (500

MHz, DMSO-d_6) δ ppm 2.00-2.11 (m, 2H) 2.12-2.27 (m, 4H) 2.38-2.47 (m, 2H) 2.39-2.48 (m, 2H) 2.58 (t, J=5.19 Hz, 2H) 3.78-3.85 (m, 2H) 3.91-4.02 (m, 2H) 4.21-4.32 (m, 2H) 5.26 (t, J=7.17 Hz, 2H) 7.93 (d, J=7.32 Hz, 4H) 8.02 (d, J=7.94 Hz, 4H) 8.12-8.21 (m, 2H) 8.69-8.81 (m, 2H) 9.09-9.17 (m, 2H); protones N-Me oscurecidos por pico DMSO con otros 2 protones sin contar para. CL (Cond'n 5): TR = 1.71 min; EM: Anal. Calculado para $[M+H]^+$ $C_{34}H_{42}N_8O_2$: 595.3; encontrado 595.6.

Ejemplo LS11

(4S,4'S)-4,4'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiilcarbonil))bis(1,3-oxazinan-2-ona)



Extremo a: Al intermediario LS1 (65mg; 0.11mmol) en 1 mL DMF se le agregó HATU (91mg; 0.24mmol), ácido (S)-2-oxo-1,3-oxazinan-4-carboxílico (intermediario LS10; 35mg; 0.24mmol), seguido por DIPEA (0.12 mL; 0.68mmol. Después de 3h, la mezcla de reacción se purificó dos veces por medio de HPLC

preparativa (Cond'n 3). Las fracciones apropiadas se agruparon y concentraron bajo alto vacío proporcionando 8 mg (10%) bis TFA LS11 como un aceite incoloro. ^{1}H RMN (500 MHz, CH_3OD) δ ppm ^{1}H RMN (500 MHz, CH_3OD) δ ppm 1.99-2.43 (m, 10H) 2.48-2.66 (m, 1.98 Hz, 2H) 3.82-3.95 (m, 4H) 4.17-4.40 (m, 4H) 4.57 (t, J=5.80 Hz, 2H) 5.23-5.41 (m, 2H) 7.73-7.97 (m, 10H); imidazol y carbamato los protones NH no se cuentan para. CL (Cond'n 6): TR = 2.28 min; EM: Anal. Calculado para $[M+H]^+$ $C_{34}H_{42}N_8O_2$: 679.3; encontrado 679.4.

Extremo b: Realizado como en Baldwin et al, Tetrahedron 1988, 44, 637

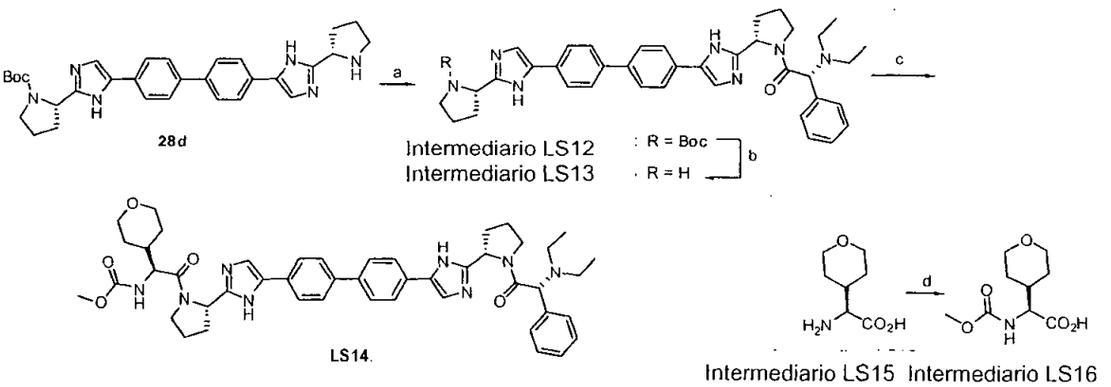
Extremo c: Realizado como en Sakaitani y Ohfune, J. Am. Chem. Soc. 1990, 112, 1150 para la conversión del compuesto 1 hasta 5. La purificación por medio de Biotage (cartucho 40M; 1:1 éter/acetato de etilo) luego HPLC preparativa (Cond'n 4) proporcionó 77mg (8%) intermediario LS9 como un aceite viscoso. ^{1}H RMN (300 MHz, $CDCl_3$) δ ppm 2.02-2.21 (m, 1H) 2.23-2.41 (m, 1H) 4.11-4.38 (m, 3H) 5.11-5.31 (m, 2H) 6.15 (s, 1H) 7.27-7.46 (m, 5H). CL (Cond'n 7): TR = 1.24 min; EM: Anal. Calculado para $[M+H]^+$ $C_{34}H_{42}N_8O_2$: 236.1; encontrado 236.4.

Extremo d: El Intermediario LS9 se hidrogenó bajo 1 atmósfera de H_2 en 3 mL metanol con 10 mg Pd/C (10%) durante 18 h. La mezcla de reacción se filtró a través de una almohadilla de tierra diatomácea (Celite®) y se concentró para proporcionar el intermediario LS10 (40 mg; 83%) como un

polvo incoloro. ^{1}H RMN (500 MHz, CH_3OD) δ ppm 2.08-2.18 (m, 1H) 2.26-2.38 (m, 1H) 4.19 (t, J=5.95 Hz, 1H) 4.25-4.40 (m, 2H).

Ejemplo LS14

((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo



Extremo a: Al 28 (1.5g; 2.86mmol) en 25 mL DMF se le agregó secuencialmente Extremo-2 (697 mg; 2.86 mmol), HATU (1.2g; 3.14 mmol), y base Hunig (1.5 mL; 8.57 mmol). Después de 3 h, la solución se concentró hasta 10mL y se divide entre cloroformo y agua. La capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio, se filtró, y se concentró in vacuo a un aceite ambar el cual se sometió a cromatografía en gel de sílice (Biotage; cargado en muestreador 40 con diclorometano; eluido en cartucho 40M con 0 hasta 12% diclorometano/metanol sobre 1200mL). Las fracciones que

contienen el intermediario LS12 se agruparon y concentraron para proporcionar material que contiene DMF residual. Este material se volvió a disolver en diclorometano y se lavó con agua (3 x 50mL) y luego salmuera. La capa orgánica se secó sobre sulfato de magnesio, se filtró, y se concentró a polvo 761 mg el cual se volvió a purificar por medio de cromatografía en gel de sílice (Biotage; cargado en muestreador 40 con diclorometano; eluido en cartucho 40M con 0 hasta 80% 4:1 cloroformo: metanol/acetato de etilo sobre 1500 mL) para proporcionar el intermediario LS12 (501 mg; 25%) como un polvo incoloro. CL (Cond'n 8): TR = 1.24 min.

Extremo b: Al intermediario LS12 (490mg; 0.69mmol) se le agregó 6 mL HCl/Dioxano seguido por 25 mL diclorometano. Después de 24 h, 75 mL éter se agregó, la mezcla de reacción se filtró y el precipitado se secó bajo vacío proporcionando el intermediario LS13 · 4HCl (434mg; cuant) como un sólido color canela. ^{1}H RMN (300 MHz, CH_3OD) δ ppm 1.16-1.29 (m, 3H) 1.37 (t, J=6.95 Hz, 3H) 1.89-2.06 (m, 6.95 Hz, 1H) 2.12-2.51 (m, 5H) 2.52-2.85 (m, 4H) 3.02-3.24 (m, 2H) 3.42-3.55 (m, 7.32 Hz, 1H) 3.58-3.71 (m, 2H) 4.26-4.41 (m, 1H) 5.18-5.37 (m, 2H) 5.65 (s, 1H) 7.57-7.66 (m, 3H) 7.67-7.75 (m, 1H) 7.86-8.04 (m, 10H) 8.14 (s, 1H). CL (Cond'n 8): TR = 1.92 min.

Extremo c: Al intermediario LS13 · 4HCl (75mg; 0.099mmol) en 0.7mL DMF se le agregó secuencialmente intermediario LS16

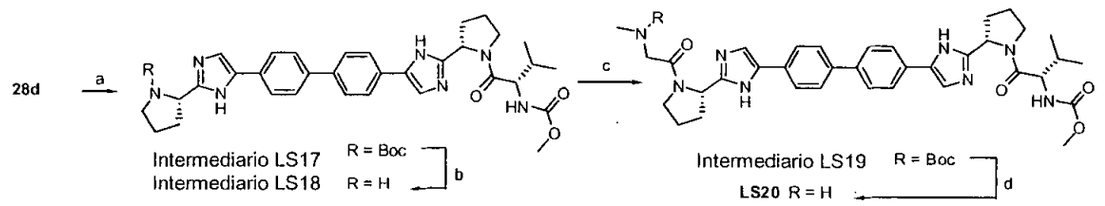
(26mg; 0.118mmol), HATU (45mg; 0.118mmol), y base Hunig (0.10mL; 0.591mmol). Después de 2h, la mezcla de reacción se filtró a través de tierra diatomácea (Celite®), la almohadilla se lavó con 0.3 mL metanol y el filtrado resultante se purificó por medio de HPLC preparativa (Cond'n 5) en dos inyecciones separadas. Las fracciones que contienen el producto deseado se pasaron a través de un cartucho MCX (Oasis; 1g; previamente acondicionado con dos longitudes de columna de metanol). El cartucho se lavó con dos longitudes de columna de metanol y el producto se eluyó con amoniaco/metanol. La concentración proporciona 36mg de LS14 como un polvo incoloro el cual se evaluó para ser de 82% de pureza diaestereomérica (más posiblemente epimérico en el carbono estereogénico en el intermediario 16). Se vuelve a someter a purificación de HPLC preparativa (2x) proporcionando LS14 (13mg; 16%) como un sólido incoloro. ^{1}H RMN (500 MHz, CH_3OD) δ ppm 0.99 (q, J=6.92 Hz, 6H) 1.25-1.72 (m, 5H) 1.80-2.42 (m, 10H) 2.47-2.61 (m, 3H) 2.66-2.78 (m, 2H) 3.35-3.43 (m, 2H) 3.65-3.71 (m, 3H) 3.89-4.01 (m, 4H) 4.01-4.10 (m, 1H) 4.32 (d, J=8.24 Hz, 1H) 5.11-5.22 (m, 1H) 6.95-7.17 (m, 3H) 7.30-7.44 (m, 3H) 7.53 (d, J=7.02 Hz, 1H) 7.62-7.89 (m, 8H). CL (Cond'n 9): TR = 5.31 min.

Extremo d: El Intermediario LS16 se preparó en una manera análoga al procedimiento describiendo la síntesis de

Extremo-51 substituyendo ácido (S)-2-amino-2-(tetrahidro-2H-piran-4-il)acético (disponible de Astatech) para L-Valina. ^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 1.15-1.63 (m, 5H) 1.75-2.03 (m, 1H) 3.54 (s, 3H) 3.76-3.98 (m, 4H) 7.45 (d, J=8.42 Hz, 1H); un protón obscurecido por pico de agua.

Ejemplo LS20

((1S)-2-metil-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-metilglicil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo



Extremo a & b: El Intermediario LS18 se preparó de manera análoga al procedimiento que describe la síntesis del intermediario LS13 substituyendo Extremo-51 por el Extremo-2.

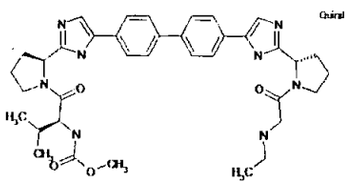
Extremo c: Al intermediario LS18 (100mg; 0.14mmol) en 1.4mL DMF se le agregó secuencialmente Sarcosina N-Boc (30mg; 0.16mmol), base Hunig (0.13mL; 0.72mmol) y HATU (60mg; 0.16mmol). Después de 2h la mezcla de reacción se dividió en diclorometano, se lavó con $NaHCO_3$ (ac),

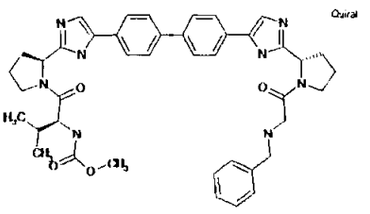
salmuera, se secó sobre sulfato de magnesio, se filtró y concentró al intermediario crudo LS19 que se usó directamente en la siguiente Extremo. CL (Cond'n 5): TR = 2.42 min; EM: Anal. Calculado para $[M+H]^+$ $C_{41}H_{52}N_8O_6$: 753.4; encontrado 753.9.

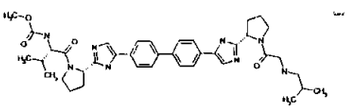
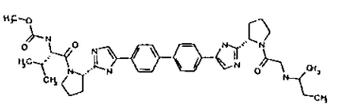
Extremo d: Intermediario crudo LS19 se disolvió en 0.5mL metanol y 5 mL 4N HCl/Dioxano. Después de iniciar durante 1 h, la reacción se concentró y purificó por medio de HPLC preparativa (Cond'n 6) y las fracciones que contienen el producto deseado se pasaron a través de un cartucho MCX (Oasis; 1g; previamente acondicionado con dos longitudes de columna de metanol). El cartucho se lavó con dos longitudes de columna de metanol y el producto se eluyó con amoniaco/metanol. La concentración proporciona LS20 (32mg; 34%). ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 0.74-0.98 (m, 6H) 1.79-2.24 (m, 9H) 2.29-2.38 (m, 2H) 3.19-3.51 (m, 8H) 3.50-3.56 (m, 3H) 3.59-3.71 (m, 1H) 3.81 (s, 1H) 3.97-4.17 (m, 1H) 5.01-5.16 (m, 2H) 7.30 (d, J=7.93 Hz, 1H) 7.51 (s, 1H) 7.59-7.74 (m, 4H) 7.79 (d, J=7.63 Hz, 4H) 11.78 (s, 1H). CL (Cond'n 5): TR = 2.00 min; EM: Anal. Calculado para $[M+H]^+$ $C_{36}H_{44}N_8O_4$: 653.4; encontrado 653.7.

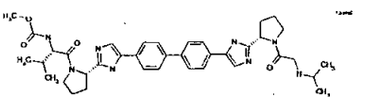
Los siguientes análogos se prepararon de manera similar a la preparación de LS20 de LS18 substituyendo

el ácido carboxílico apropiado por N-Boc Sarcosina:

Número del Ejemplo	Nombre del Compuesto	Estructura	Datos Analíticos
LS21	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-etilglicil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo		LC/MS: 2.34 min (Cond'n 2); Análisis calculado para $[M+H]^+$ $C_{37}H_{46}N_8O_4$: 667.4; encontrado 667.7.

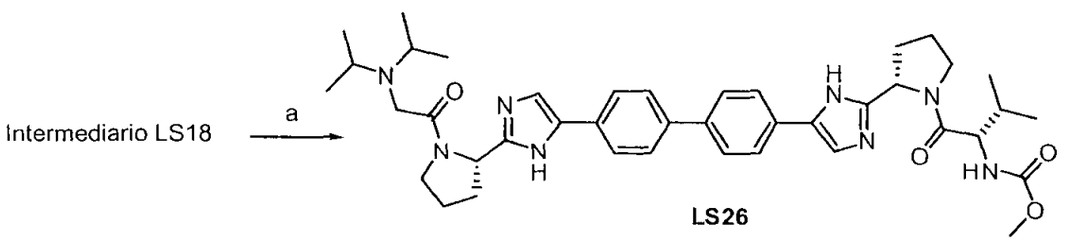
LS22	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-bencilglicil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo		LC/MS: 2.34 min (Cond'n 5); Análisis calculado para $[M+H]^+$ $C_{42}H_{48}N_8O_4$: 729.4; encontrado 729.8.

LS23	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-isobutilglicil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo		LC/MS: 2.07 min (Cond'n 5); Análisis calculado para $[M+H]^+$ $C_{39}H_{50}N_8O_4$: 695.4; encontrado 695.8.
LS24	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-sec-butilglicil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo		LC/MS: 2.03 min (Cond'n 5); Análisis calculado para $[M+H]^+$ $C_{39}H_{50}N_8O_4$: 695.4; encontrado 695.9.

LS25	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-isopropilglicil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo		LC/MS: 1.97 min (Cond'n 5); Análisis calculado para $[M+H]^+$ $C_{38}H_{48}N_8O_4$: 681.4; encontrado 681.7.

Ejemplo LS26

((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-diisopropilglicil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo



Extremo a: El compuesto LS26 se preparó en una forma similar a la preparación del intermediario LS19 empleando ácido 2-(diisopropilamino)acético como el compañero de acoplamiento del

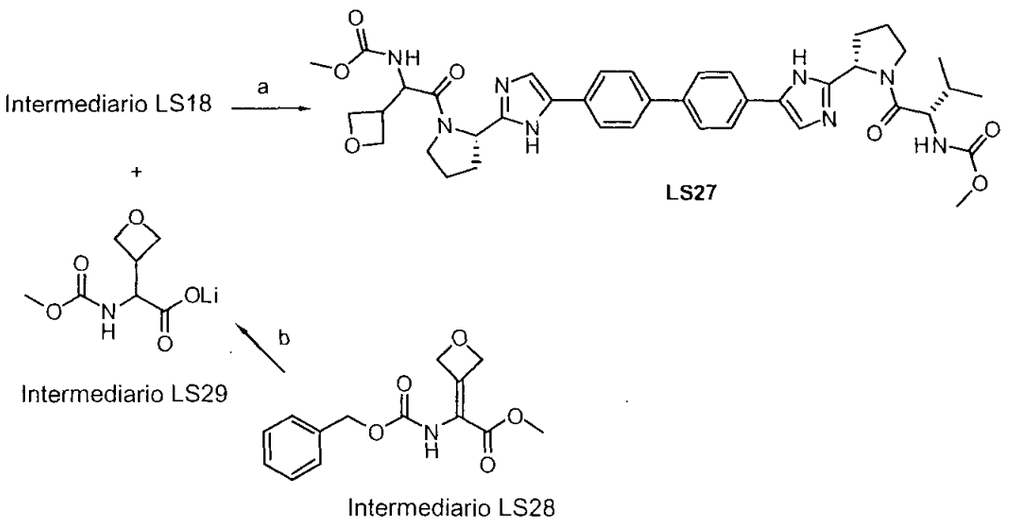
ácido carboxílico. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 0.74-1.04 (m, 18H) 1.74-2.21 (m, 13H) 2.86-3.09 (m, 3H) 3.54 (s, 3H) 3.71-3.89 (m, 3H) 4.06 (t, J=8.55 Hz, 1H) 4.98-5.13 (m, 2H) 5.56 (d, J=8.55 Hz, 1H) 7.21-7.34 (m, 1H) 7.42-7.54 (m, 1H) 7.61-7.87 (m, 8H). CL (Cond'n 5): TR = 1.98 min; EM: Análisis calculado para $[M+H]^+$ $C_{41}H_{54}N_8O_4$: 723.4; encontrado 723.4.

Ejemplo LS27 Diaestereómero 1

((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-(3-oxetanil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

Ejemplo LS27 Diaestereómero 2

((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-2-(3-oxetanil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo



Extremo a: El compuesto LS27 se preparó en una forma similar a la preparación del intermediario LS19 empleando ácido 2-(metoxicarbonilamino)-2-(oxetan-3-il)acético (intermediario LS29) como el compañero de acoplamiento del ácido carboxílico. Los dos diaestereómeros de LS27 se separaron por medio de HPLC preparativa (Xbridge C18, 100 x 19 mm I.D. S-5µm; Fase Móvil A: 95% Agua-5% Acetonitrilo con 10 mM acetato de amonio (pH=5); Fase Móvil B: 95% Acetonitrilo-5% agua con 10 mM acetato de amonio (pH = 5); Isocrático 30% B durante 7 min; Relación de flujo: 25 mL/min; detección UV: 220 nm; Cantidad de muestra: ~5 mg/cada inyección, 300 µl solución de muestra en metanol (~17 mg/mL)). Diaestereómero 1: ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 0.80-0.96 (m, 6H) 1.91-2.06 (m, 6H) 2.09-2.21 (m, 3H) 3.54 (s, 3H) 3.59 (s, 3H) 3.77-3.83 (m, 2H) 3.87 (t, J=7.63 Hz, 1H) 4.06 (t, J=8.24 Hz, 1H) 4.31 (t, J=6.41 Hz, 1H) 4.43 (t, J=6.10 Hz, 1H) 4.49 (t, J=7.17 Hz, 1H) 4.51-4.57 (m, 1H) 4.80 (t, J=8.55 Hz, 1H) 5.00-5.05 (m, 1H) 5.06-5.11 (m, 1H) 7.30 (d, J=8.55 Hz, 1H) 7.50 (s, 1H) 7.58-7.89 (m, 8H) 11.77 (s, 2H). CL (Cond'n 10): TR = 7.14 min; EM: Análisis calculado para $[M+H]^+$ $C_{40}H_{48}N_8O_7$: 753.4; encontrado 753.9. Diaestereómero 2: ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 0.79-0.98 (m, 6H) 1.91-2.06 (m, 4H) 2.07-2.23 (m, 4H) 3.51-3.69 (m, 8H) 3.74-3.90 (m, 2H) 4.06 (t, J=7.48 Hz, 1H) 4.20-4.33 (m, 1H) 4.36-4.49 (m, 2H) 4.55 (s, 2H) 4.71 (s, 1H) 4.97-5.05 (m, 1H) 5.08 (s, 1H) 5.53 (s, 1H) 7.30 (d, J=7.93

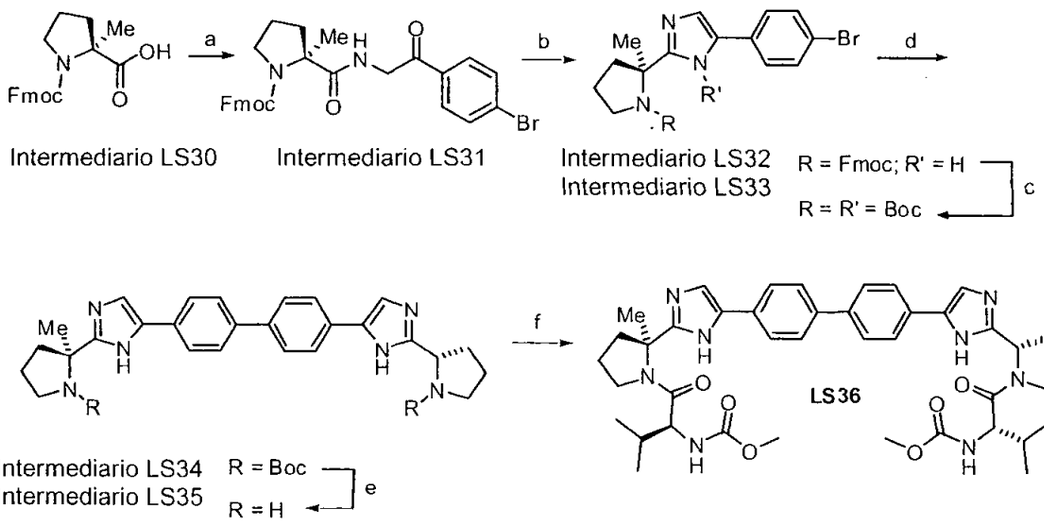
Hz, 1H) 7.51 (s, 1H) 7.58-7.91 (m, 8H) 11.53 (s, 1H) 11.78 (s, 1H). CL (Cond'n 10): TR = 8.79 min; EM: Análisis calculado para $[M+H]^+$ $C_{40}H_{48}N_8O_7$: 753.4; encontrado 753.9.

Extremo b: Una solución de 2-(benciloxicarbonilamino)-2-(oxetan-3-iliden)acetato de metilo (intermediario LS28; Fuente: Moldes et al, Il Farmaco, 2001, 56, 609 and Wuitschik et al, Ang. Chem. Int. Ed. Engl, 2006, 45, 7736; 200 mg, 0.721 mmol) en acetato de etilo (7 mL) y CH_2Cl_2 (4.00 mL) se desgasificó al burbujear nitrógeno durante 10 min. El dicarbonato de dimetilo (0.116 mL, 1.082 mmol) y Pd/C (20 mg, 0.019 mmol) se agregaron entonces, la mezcla de reacción se equipó con un globo de hidrógeno y se permitió agitar a temperatura ambiente durante la noche. La mezcla de reacción se filtró a través de tierra diatomácea (Celite®) y se concentró. El residuo se purificó por medio de Biotage (cargado con diclorometano en un muestreador 25; eluiod en 25S Columna con diclorometano por 3CV luego 0 hasta 5% metanol/diclorometano sobre 250 mL luego mantenido a 5% metanol/diclorometano durante 250 mL; 9 mL fracciones). Las fracciones que contienen el producto deseado se concentraron para proporcionar 167 mg 2-(metoxicarbonilamino)-2-(oxetan-3-il)acetato de metilo como un aceite incoloro que solidificó durante el reposo. ^1H RMN (500 MHz, CLOROFORMO-D) δ ppm 3.29-3.40 (m, 1H) 3.70 (s, 3H) 3.74 (s, 3H) 4.55 (t, J=6.41 Hz, 1H) 4.58-4.68 (m, 2H) 4.67-4.78 (m, 2H) 5.31 (br s, 1H). EM: Análisis calculado para $[M+H]^+$ $C_8H_{13}NO_5$: 204.1; encontrado 204.0. A 2-

(metoxicarbonilamino)-2-(oxetan-3-il)acetato de metilo (50 mg, 0.246 mmol) en THF (2 mL) y agua (0.5mL) se le agregó monohidrato de hidróxido de litio (10.33 mg, 0.246 mmol). La solución resultante se permitió hasta agitar durante la noche a temperatura ambiente luego se concentró hasta secarse para proporcionar el intermediario LS29 como un polvo incoloro. ^{1}H RMN (500 MHz, CH_3OD) δ ppm 3.38-3.50 (m, 1H) 3.67 (s, 3H) 4.28 (d, J=7.63 Hz, 1H) 4.57-4.79 (m, 4H).

Ejemplo LS36

((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-2-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo



Extremo a: Al ácido (S)-1-(((9H-fluoren-9-il)metoxi)carbonil)-2-metilpirrolidin-2-carboxílico (intermediario LS30; 1.5g; 4.3 mmol) en 50 mL DMF se le agregó secuencialmente clorohidrato de 2-amino-1-(4-bromofenil)etanona (1.2g; 4.7 mmol), HOAT (290 mg; 2.1 mmol), base Hunig (0.7 mL; 4.3mmol) y EDCI (1.2g; 6.4mmol). Después de 1 h, la mezcla de reacción se vació en 150 mL agua y se permitió agitar durante 15 min antes de filtrar el precipitado resultante el cual se disolvió en diclorometano y se secó sobre sulfato de magnesio. La mezcla de diclorometano se filtró y aplicó a un Biotage 40 samplet. La cromatografía en una Columna 40M (25 hasta 60% acetato de etilo/hexano sobre 1200 mL) proporcionó 2-(2-(4-bromofenil)-2-oxoetilcarbamoil)-2-metilpirrolidin-1-carboxilato de (S)-(9H-fluoren-9-il)metilo (intermediario LS31; 2.4g; cuant) como una espuma amarilla. CL (Cond'n 11): TR = 3.75 min; EM: Análisis calculado para $[M+H]^+$ $C_{29}H_{27}BrN_2O_4$: 547.1; encontrado 547.0.

Extremo b: Una mezcla de acetato de amonio (844 mg; 10.97mmol) y 2-(2-(4-bromofenil)-2-oxoetilcarbamoil)-2-metilpirrolidin-1-carboxilato de (S)-(9H-fluoren-9-il)metilo (intermediario LS31; 1.00g; 1.83mmol) se calentó a 140°C en 25 mL xileno durante 2.5 h en cuyo tiempo la mezcla de reacción se concentró y cargó con diclorometano sobre un Biotage 40 samplet. La purificación por medio de Biotage (5

hasta 60% acetato de etilo/hexano sobre 1000 mL con 400 mL tiempo de espera) proporcionó 2-(5-(4-bromofenil)-1H-imidazol-2-il)-2-metilpirrolidin-1-carboxilato de (S)-(9H-fluoren-9-il)metilo (intermediario LS32; 469 mg; 49%) como un líquido ambar. CL (Cond'n 12): TR = 3.09 min; EM: Análisis calculado para $[M+H]^+$ $C_{29}H_{26}BrN_3O_2$: 528.1; encontrado 528.5.

Extremo c: A 2-(5-(4-bromofenil)-1H-imidazol-2-il)-2-metilpirrolidin-1-carboxilato de (S)-(9H-fluoren-9-il)metilo (intermediario LS32; 329 mg; 0.62 mmol) en 3 mL DMF se le agregó 1.5 mL piperidina. La mezcla de reacción se concentró por medio de una corriente de nitrógeno durante la noche. El residuo resultante se lavó con hexano y se pasó a través de un cartucho MCX (Oasis; 6g; previamente acondicionado con dos longitudes de columna de metanol). El cartucho se lavó con dos longitudes de columna de metanol y el producto se eluyó con amoniaco/metanol. La concentración proporciona 193 mg de (S)-5-(4-bromofenil)-2-(2-metilpirrolidin-2-il)-1H-imidazol el cual se disolvió en 6 mL diclorometano y combinó con di-t-butildicarbonato (413 mg; 1.89 mmol), DMAP (15mg; 0.13mmol) y TEA (0.17 mL; 1.30 mmol). Después de 48 h, la mezcla de reacción se concentró y purificó por medio de cromatografía en un sistema Biotage proporcionando 5-(4-bromofenil)-2-(1-(tert-butoxicarbonil)-2-metilpirrolidin-2-il)-1H-imidazol-1-carboxilato de (S)-tert-butilo (intermediario LS33; 150 mg; 48%) como un sólido blanco opaco. CL (Cond'n 5): TR = 3.75

min; EM: Análisis calculado para $[M+H]^+$ $C_{24}H_{32}BrN_3O_4$: 506.2; encontrado 506.4

Extremo d: 2-(5-(4'-(2-((S)-1-(tert-butoxicarbonil)pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)-2-metilpirrolidin-1-carboxilato de (S)-tert-butilo (intermediario LS34) se preparó en una forma similar a la preparación de 1d empleando intermediario LS33 en lugar de 1b. ^{1}H RMN (300 MHz, DMSO-d_6; 100°C) δ ppm 1.18-1.29 (m, 9H) 1.29-1.40 (m, 9H) 1.75-1.82 (m, 3H) 1.81-2.39 (m, 8H) 3.35-3.75 (m, 4H) 4.81-4.92 (m, 1H) 7.36-7.45 (m, 1H) 7.57-7.74 (m, 5H) 7.76-7.89 (m, 4H) 11.29-11.63 (m, 2H). CL (Cond'n 5): TR = 2.49 min; EM: Análisis calculado para $[M+H]^+$ $C_{37}H_{46}N_6O_4$: 639.4; encontrado 639.9.

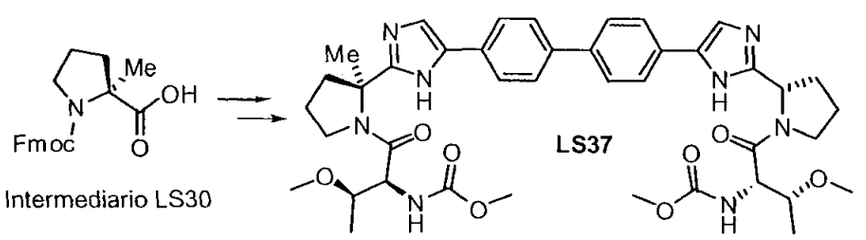
Extremo e: 2-((S)-2-metilpirrolidin-2-il)-5-(4'-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol (intermediario LS35) se preparó en una forma similar a la preparación de 1e empleando intermediario LS34 en lugar de 1d. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.76-1.83 (m, 3H) 1.92-2.23 (m, 6H) 3.31-3.49 (m, 4H) 4.88-4.97 (m, 1H) 7.76-7.88 (m, 5H) 7.90-8.04 (m, 5H) 9.72-9.82 (m, 1H) 10.04-10.16 (m, 1H); imidazol y protónes NH de pirrolidina inexplicables. CL (Cond'n 5): TR = 1.79 min; EM: Análisis calculado para $[M+H]^+$ $C_{27}H_{30}N_6$: 439.2; encontrado 439.5.

Extremo f: Compuesto LS36 se preparó en una forma similar a la preparación del ejemplo 1 empleando intermediario LS35 en lugar de 1e y Extremo-51 en lugar de Extremo-1. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 0.72-0.97 (m, 12H) 1.77 (s, 3H) 1.86-2.08 (m, 8H) 2.09-2.19 (m, 2H) 2.25-2.39 (m, 2H) 3.49-3.59 (m, 6H) 3.81 (d, J=6.71 Hz, 4H) 4.06 (q, J=7.83

Hz, 2H) 5.08 (dd, J=7.02, 3.05 Hz, 1H) 7.12 (d, J=8.85 Hz, 1H) 7.27-7.34 (m, 1H) 7.46-7.55 (m, 1H) 7.59-7.73 (m, 4H) 7.75-7.86 (m, 3H) 11.66 (s, 1H) 11.77 (s, 1H). CL (Cond'n 5): TR = 2.25 min; EM: Análisis calculado para $[M+H]^+$ $C_{41}H_{52}N_8O_6$: 753.4; encontrado 754.0.

Ejemplo LS37

((1S,2R)-2-metoxi-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-treonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-2-metil-1-pirrolidinil)carbonil)propil)carbamato de metilo



El Compuesto LS37 se preparó en una forma similar a la preparación de LS36 del intermediario LS30 usando Extremo-86 en lugar de Extremo-51. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 0.99-1.17 (m, 6H) 1.76 (s, 3H) 1.87-2.09 (m, 4H) 2.10-2.23 (m, 2H) 2.34-2.38 (m, 2H) 2.56-2.60 (m, 1H) 2.63 (d, J=1.83 Hz, 1H) 3.17 (s, 3H) 3.19 (s, 3H) 3.37-3.51 (m, 2H) 3.54 (s, 6H) 3.75-3.96 (m, 4H) 4.13-4.36 (m, 2H) 5.07 (dd, J=7.48, 3.20 Hz, 1H) 7.20 (d, J=8.54 Hz, 1H) 7.24-7.34 (m, 1H) 7.50 (dd, J=7.17, 1.98 Hz, 1H) 7.59-7.73 (m, 4H) 7.76-7.86 (m, 3H) 11.65 (s, 1H) 11.77 (s, 1H). CL (Cond'n 13): TR = 4.30 min; EM: Análisis calculado para $[M+H]^+$ $C_{41}H_{52}N_8O_8$: 785.4; encontrado 785.4.

Sección F Condiciones CL para determinar el tiempo de

retención

Condición 1

Columna: Phenomenex-Luna 4.6 X 50 mm S10

% B de Inicio = 0

% B Final = 100

Tiempo de Gradiente = 4 min

Relación de flujo = 4 mL/Min

Longitud de onda = 220

Solvente A = 10% metanol - 90% H_2O - 0.1% TFA

Solvente B = 90% metanol - 10% H_2O - 0.1% TFA

Condición 2

Columna: Waters-Sunfire 4.6 X 50 mm S5

% B de Inicio = 0

% B Final = 100

Tiempo de Gradiente = 2 min

Relación de flujo = 4 mL/Min

Longitud de onda = 220

Solvente A = 10% metanol - 90% H_2O - 0.1% TFA

Solvente B = 90% metanol - 10% H_2O - 0.1% TFA

Condición 3

Columna: Phenomenex 10u 3.0 X 50 mm

% B de Inicio = 0

% B Final = 100

Tiempo de Gradiente = 2 min

Relación de flujo = 4 mL/Min

Longitud de onda = 220

Solvente A = 10% metanol - 90% H_2O - 0.1% TFA

Solvente B = 90% metanol - 10% H_2O - 0.1% TFA

Condición 4

Columna: Phenomenex-Luna 3.0 X 50 mm S10

% B de Inicio = 0

% B Final = 100

Tiempo de Gradiente = 3 min

Relación de flujo = 4 mL/Min

Longitud de onda = 220

Solvente A = 10% metanol - 90% H_2O - 0.1% TFA

Solvente B = 90% metanol - 10% H_2O - 0.1% TFA

Condición 5

Columna: Phenomenex-Luna 4.6 X 50 mm S10

% B de Inicio = 0

% B Final = 100

Tiempo de Gradiente = 3 min

Relación de flujo = 4 mL/Min

Longitud de onda = 220

Solvente A = 10% metanol - 90% H_2O - 0.1% TFA

Solvente B = 90% metanol - 10% H_2O - 0.1% TFA

Condición 6

Columna: Xbridge C18 4.6 X 50 mm S5

% B de Inicio = 0

% B Final = 100

Tiempo de Gradiente = 3 min

Relación de flujo = 4 mL/Min

Longitud de onda = 220

Solvente A = H_2O: ACN 95%: 5% 10 mm acetato de amonio

Solvente B = H_2O: ACN 5%: 95% 10 mm acetato de amonio

Condición 7

Columna: Phenomenex C18 10u 4.6 X 30 mm

% B de Inicio = 0

% B Final = 100

Tiempo de Gradiente = 3 min

Relación de flujo = 4 mL/Min

Longitud de onda = 220

Solvente A = 10% metanol - 90% H_2O - 0.1% TFA

Solvente B = 90% metanol - 10% H_2O - 0.1% TFA

Condición 8

Columna: Phenomenex LunaC18 10u 4.6 X 30 mm

% B de Inicio = 0

% B Final = 100

Tiempo de Gradiente = 2 min

Relación de flujo = 5 mL/Min

Longitud de onda = 220

Solvente A = 10% metanol - 90% H_2O - 0.1% TFA

Solvente B = 90% metanol - 10% H_2O - 0.1% TFA

Condición 9

Columna: Phenomenex C18 10u 4.6 X 30 mm

% B de Inicio = 0

% B Final = 100

Tiempo de Gradiente = 10 min

Relación de flujo = 4 mL/Min

Longitud de onda = 220

Solvente A = H_2O: ACN 95%: 5% 10 mm acetato de amonio

Solvente B = H_2O: ACN 5%: 95% 10 mm acetato de amonio

Condición 10

Columna: Phenomenex 10u 3.0 X 50 mm

% B de Inicio = 0

% B Final = 100

Tiempo de Gradiente = 3 min

Relación de flujo = 4 mL/Min

Longitud de onda = 220

Solvente A = 10% metanol - 90% H_2O - 0.1% TFA

Solvente B = 90% metanol - 10% H_2O - 0.1% TFA

Condición 11

Columna: Xterra 4.6 X 30 mm S5

% B de Inicio = 0

% B Final = 100

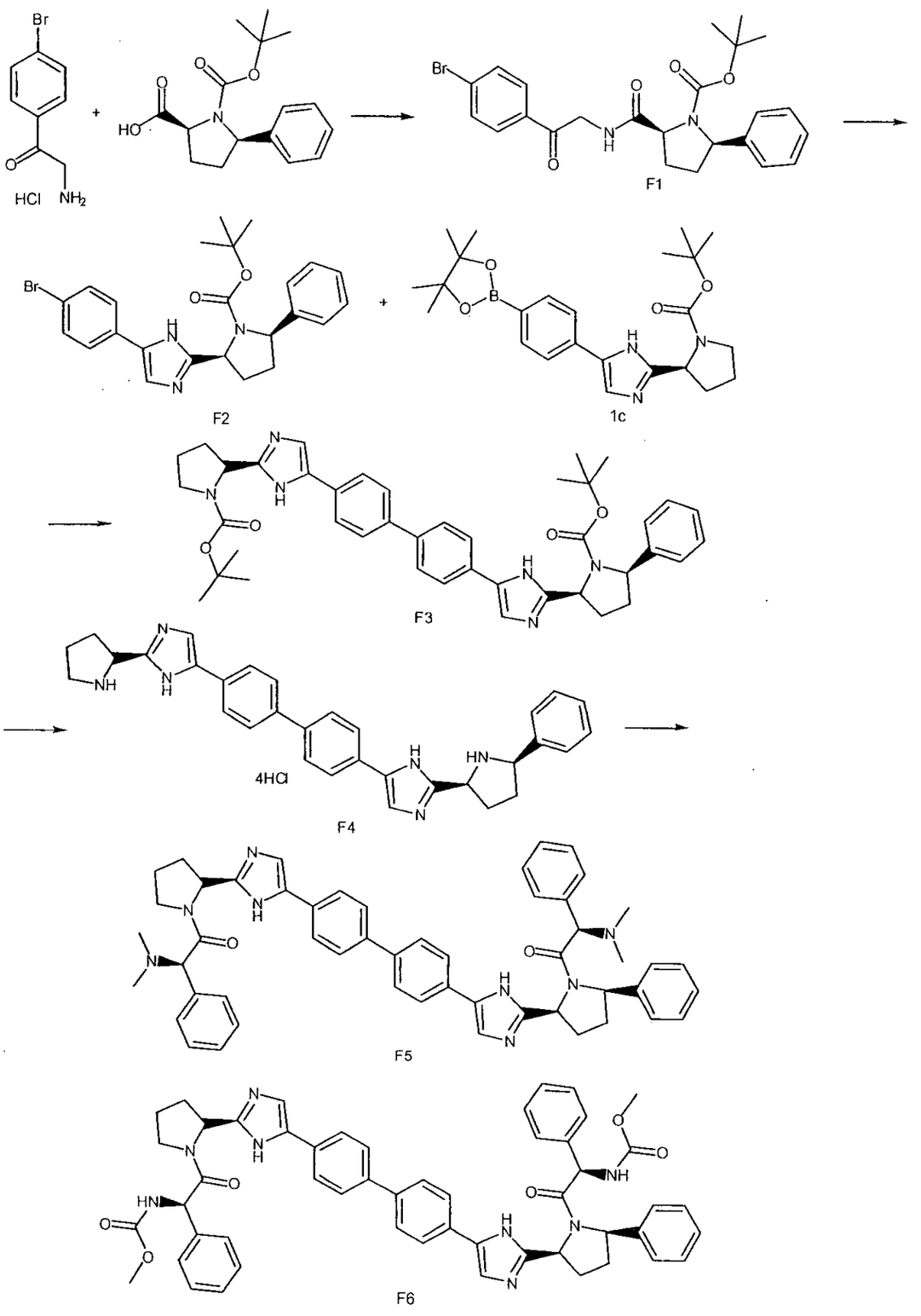
Tiempo de Gradiente = 2 min

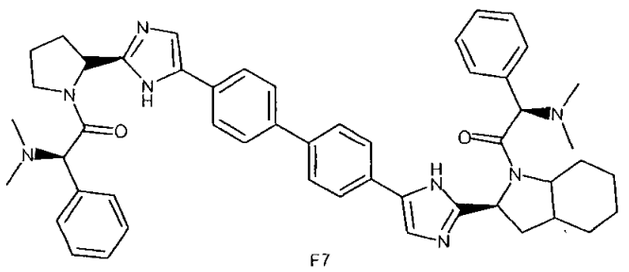
Relación de flujo = 5 mL/Min

Longitud de onda = 220

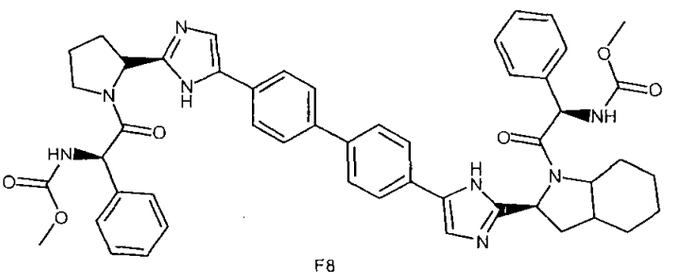
Solvente A = H_2O: ACN 95%: 5% 10 mm acetato de amonio

Solvente B = H_2O: ACN 5%: 95% 10 mm acetato de amonio


Br
HCl NH2
HO
F1
F2
1c
F3
4HCl
F4
F5
F6



F7



F8

El Compuesto F1 se preparó en una manera análoga al procedimiento usado para sintetizar 1a con la siguiente modificación: Ácido (2S,5R)-1-(tert-butoxicarbonil)-5-fenilpirrolidin-2-carboxílico se usó en lugar de N-Boc-L-prolina.

El Compuesto F2 se preparó en una manera análoga al procedimiento usado para sintetizar 1b.

El Compuesto F3 se preparó en una manera análoga al procedimiento usado para sintetizar 1d.

El Compuesto F4 se preparó en una manera análoga al procedimiento usado para sintetizar 1e.

El Compuesto F5, F6 se preparó en una manera análoga al procedimiento usado para sintetizar el ejemplo 1 del Compuesto F4.

El Compuesto F7, F8 se preparó en una manera análoga al

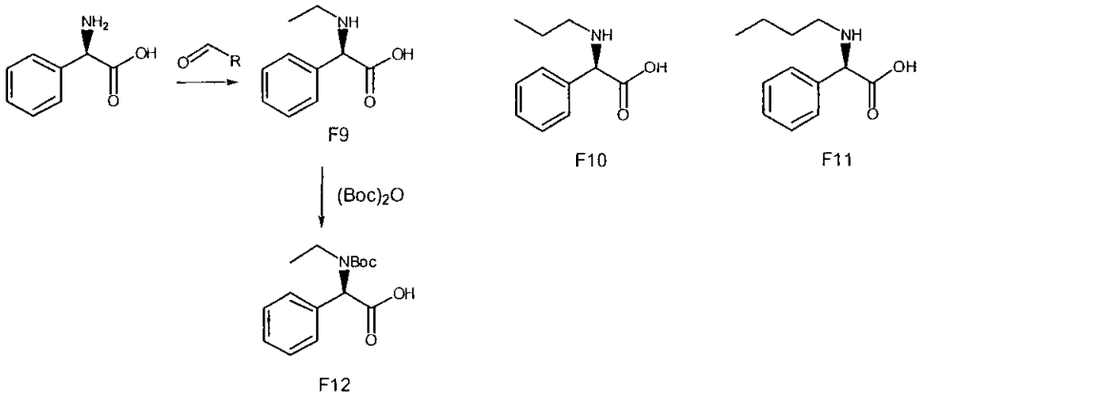
procedimiento usado para sintetizar F5 con la siguiente modificación: Ácido (2S)-1-(tert-butoxicarbonil)octahidro-1H-indol-2-carboxílico se usó en lugar de ácido (2S,5R)-1-(tert-butoxicarbonil)-5-fenilpirrolidin-2-carboxílico.

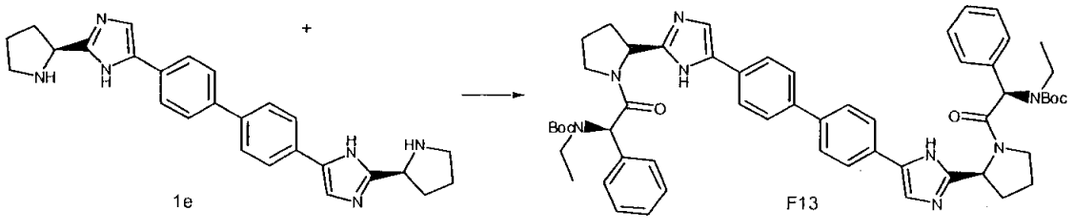
Entrada	Nombre del Compuesto	Tiempo de retención (Condición CL); índice de homogeneidad datos EM
F1		TR = 3.838 minutos (condición 1, 94%); EMBR: Análisis calculado para C24H27BrN2O4 486.12; encontrado: 487.26 $(M+H)^+$.
F2		TR = 3.175 minutos (condición 1, 83%); EMBR: Análisis calculado para C24H27BrN2O4 467.12; encontrado: 468.26 $(M+H)^+$.

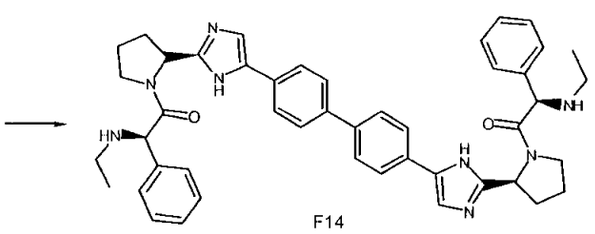
F3		TR = 2.965 minutos (condición 1, 93%); EMBR: Análisis calculado para C42H48N6O4 700.37; encontrado: 701.49 $(M+H)^+$.
F4		TR = 2.083 minutos (condición 1, 98%); EMBR: Análisis calculado para C32H32N6 500.27; encontrado: 501.40 $(M+H)^+$.
F5		TR = 1.222 minutos (condición 3, 98%); EMBR: Análisis calculado para C52H54N8O2 822.44; encontrado: 823.5 $(M+H)^+$.

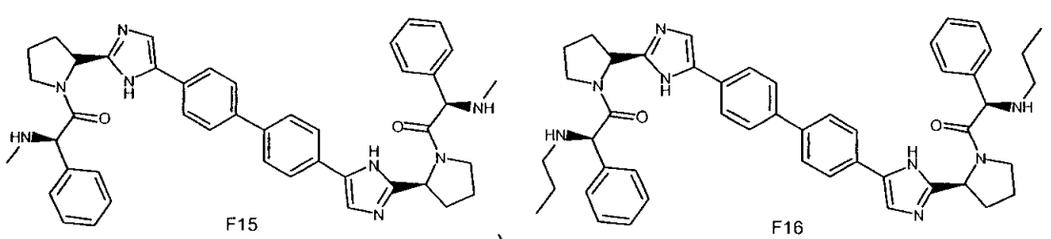
F6	((1R)-2-((2R)-2-(5-(4'-(2-((2S,5R)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-5-fenil-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	TR = 1.512 minutos (condición 3, 98%); EMBR: Análisis calculado para C52H50N8O6 882.39; encontrado: 883.45 $(M+H)^+$.
F7	rel-(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(dimetilamino)-2-fenilacetil)octahidro-1H-indol-2-il)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina	TR = 1.223 minutos (condición 3, 98%); EMBR: Análisis calculado para C50H56N8O2 800.45; encontrado: 801.51 $(M+H)^+$.

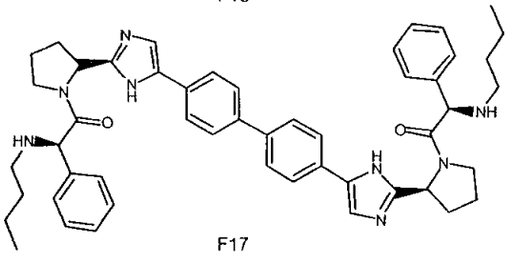
F8	rel-((1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)octahidro-1H-indol-2-il)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	TR = 1.513 minutos (condición 3, 98%); EMBR: Análisis calculado para C50H56N8O2 860.40; encontrado: 861.42 $(M+H)^+$.


F9
F10
F11
(Boc)2O
F12


1e
F13


F14


F15
F16


F17

El Compuesto F9, F10, y F11 se preparó en una manera análoga al procedimiento usado para sintetizar el procedimiento de primera mitad de Extremo 3 usando acetaldehído, propionaldehído, y butiraldehído respectivamente.

Compuesto F12

El $(Boc)_2O$ (2.295 g, 10.20 mmol) se le agregó a la mezcla del compuesto F9 (1.0 g, 4.636 mmol), base Hunig (1.78 mL, 10.20 mmol) en CH_2Cl_2 (12 mL), y la mezcla resultante se agitó durante la noche. El componente volátil se removió in vacuo, y el residuo se purificó por un sistema HPLC de fase inversa (H_2O/metanol/TFA) para proporcionar el compuesto F12 como una cera transparente (0.993 g). CL (Cond.3): TR = 1.663 min; >95% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ C15H21NO4: 279.33; encontrado $[M+Na]^+$ 302.30

El Compuesto F13 se preparó en una manera análoga al procedimiento usado para sintetizar el ejemplo 1 del Compuesto 1e y F12.

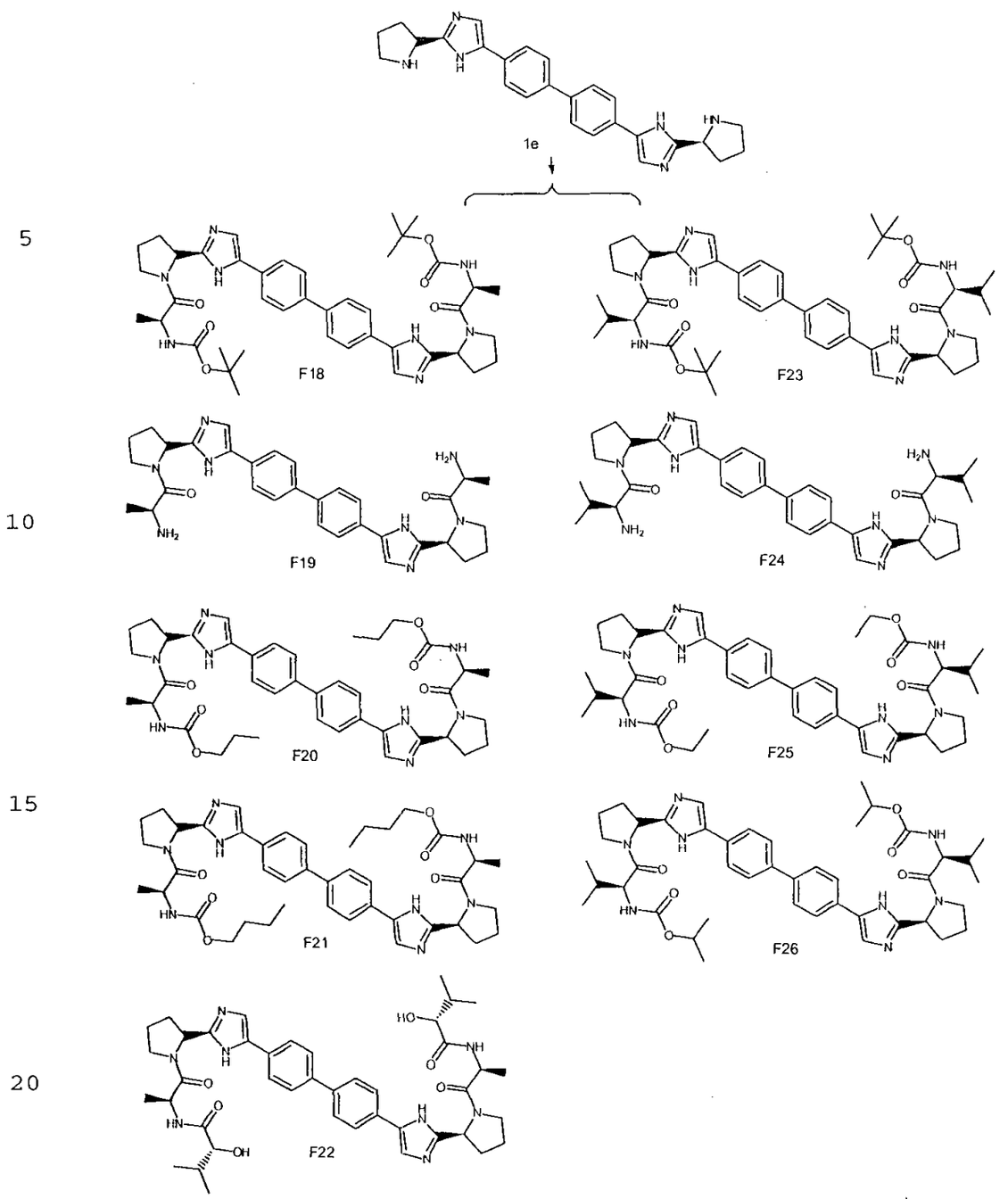
El Compuesto F14 se preparó en una manera análoga al procedimiento usado para sintetizar 132e.

El Compuesto F15, F16, y F17 se preparó en una manera análoga al procedimiento usado para sintetizar F14.

Entrada	Nombre del Compuesto	Tiempo de retención (Condición CL); índice de homogeneidad datos EM
F9		TR = 0.580 minutos (condición 1, 94%); EMBR: Análisis calculado para C10H13NO2 179.09; encontrado: 180.26 $(M+H)^+$.
F10		TR = 0.563 minutos (condición 3, 94%); EMBR: Análisis calculado para C11H15NO2 193.11; encontrado: 194.26 $(M+H)^+$.
F11		TR = 1.023 minutos (condición 3, 94%); EMBR: Análisis calculado para C12H17NO2 207.13; encontrado: 208.31 $(M+H)^+$.

F12		TR = 1.663 minutos (condición 3, 95%); EMBR: Análisis calculado para C15H21NO4 279.15; encontrado: 302.30 $(Na+H)^+$.
F13		TR = 2.595 minutos (condición 4, 94%); EMBR: Análisis calculado para C56H66N8O6 946.51; encontrado: 947.64 $(M+H)^+$.
F14	(1R)-N-etil-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(etilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletanamina	TR = 1.55 minutos (condición 5, 90%); EMBR: Análisis calculado para C46H50N8O2 746.41; encontrado: 747.72 $(M+H)^+$.

F15	(1R)-N-metil-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(metilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletanamina	TR = 1.50 minutos (condición 5, 94%); EMBR: Análisis calculado para C44H46N8O2 718.37; encontrado: 719.69 $(M+H)^+$.
F16	N-((1R)-2-oxo-1-fenil-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-fenil-2-(propilamino)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)-1-propanamina	TR = 1.63 minutos (condición 5, 90%); EMBR: Análisis calculado para C48H54N8O2 774.43; encontrado: 775.76 $(M+H)^+$.
F17	N-((1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(butilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)-1-butanamina	TR = 1.81 minutos (condición 5, 85%); EMBR: Análisis calculado para C50H58N8O2 802.47; encontrado: 803.79 $(M+H)^+$.



El Compuesto F18 y F23 se preparó en una manera análoga al procedimiento usado para sintetizar el ejemplo 1 con la siguiente modificación: N-Boc-L-alanina y N-Boc-L-valina se

usó en lugar de N-Boc-L-prolina respectivamente.

El Compuesto F22 se preparó en una manera análoga al procedimiento usado para sintetizar el ejemplo 1 del Compuesto F19.

El Compuesto F19, F24 se preparó en una manera análoga al procedimiento usado para sintetizar 132e.

Compuesto F25

((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((etoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de etilo

A una solución de F24 (0.06 g, 0.074 mmol) en DMF (1 mL) se le agregó base Hunig (0.105 mL, 0.593 mmol) y carbonoclorohidrato de etilo (0.016 mL, 0.163 mmol) luego se agita a temperatura ambiente. Dos horas más tarde, se revisa por LCMS. Estos fueron tres picos principales que indican el compuesto deseado, compuesto tri-acoplado, y tetra-acoplado. La reacción se detiene y se concentra por presión reducida para conseguir aceite café ligero el cual se trató con 10 mL de 2 M NH_3 en metanol durante 20 minutos luego se concentra de nuevo a un sólido amarillo el cual se purificó por CL preparativa para proporcionar el compuesto F25 como una sal TFA blanca (57.6 mg).

CL (Cond.6): TR = 1.932 min, LC/MS: Análisis calculado para $[M+H]^+$ C42H54N8O6: 766.42; encontrado 767.55.

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 0.69-0.94 (m, 12H) 1.16 (t, J=7.02 Hz, 6H) 1.90-2.26 (m, 8H) 2.40 (d, J=4.88 Hz, 2H) 3.73-3.92 (m, 4H) 3.94-4.08 (m, 4H) 4.12 (t, J=7.78 Hz, 2H) 5.15 (t, J=7.02 Hz, 2H) 7.26 (d, J=8.54 Hz, 2H) 7.85-7.93 (m, 4H) 7.93-8.01 (m, 4H) 8.13 (s, 2H) 14.68 (s, 2H)

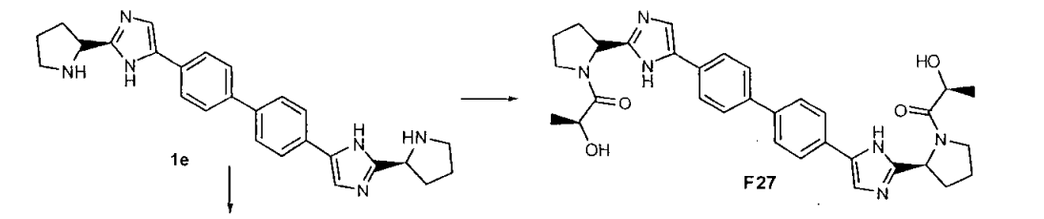
El Compuesto F20, F21, y F26 se preparó en una manera análoga al procedimiento usado para sintetizar el ejemplo 1.

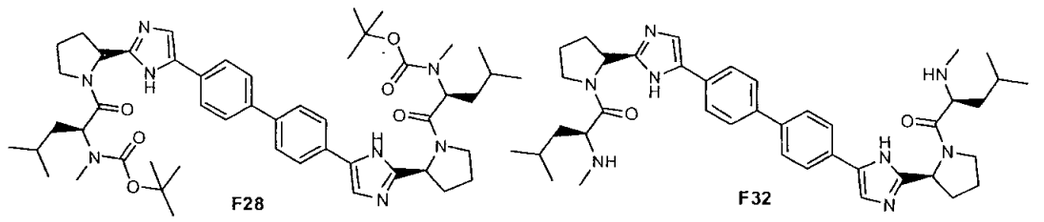
Entrada	Nombre del Compuesto	Tiempo de retención (Condición CL); índice de homogeneidad datos EM
F18		TR = 2.257 minutos (condición 5, 96%); EMBR: Análisis calculado para C42H54N8O6 766.42; encontrado: 767.88 $(M+H)^+$.

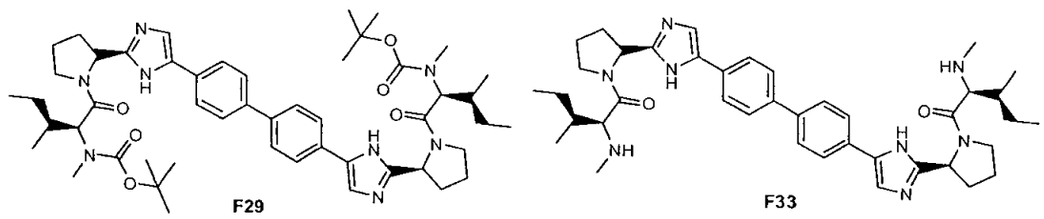
F19		TR = 1.462 minutos (condición 5, 95%); EMBR: Análisis calculado para C32H38N8O2 566.31; encontrado: 567.79 $(M+H)^+$.
F20	((1S)-1-metil-2-oxo-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(propoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)carbamato de propilo	TR = 1.338 minutos (condición 3, 89%); EMBR: Análisis calculado para C40H50N8O6 738.39; encontrado: 739.95 $(M+H)^+$.
F21	((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(butoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de butilo	TR = 1.447 minutos (condición 3, 96%); EMBR: Análisis calculado para C42H54N8O6 766.93; encontrado: 768.02 $(M+H)^+$.

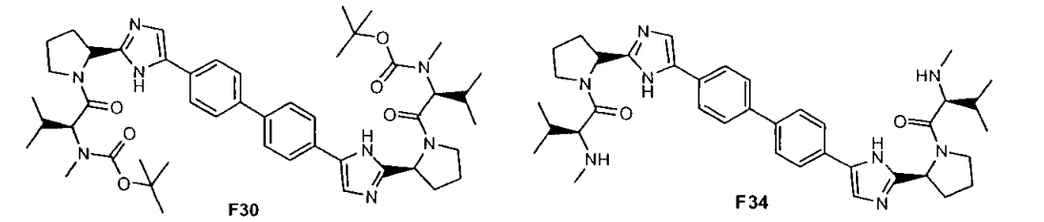
F22	(2S)-2-hidroxi-N-((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-((2S)-2-hidroxi-3-metilbutanoil)-L-alanil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)-3-metilbutanamida	TR = 1.703 minutos (condición 4, 98%); EMBR: Análisis calculado para C42H54N8O 766.93; encontrado: 768.02 $(M+H)^+$.
F23		TR = 2.881 minutos (condición 7, 93%); EMBR: Análisis calculado para C46H62N8O6 822.48; encontrado: 823.95 $(M+H)^+$.
F24		TR = 1.743 minutos (condición 7, 98%); EMBR: Análisis calculado para C36H46N8O2 622.37; encontrado: 624.07 $(M+H)^+$.

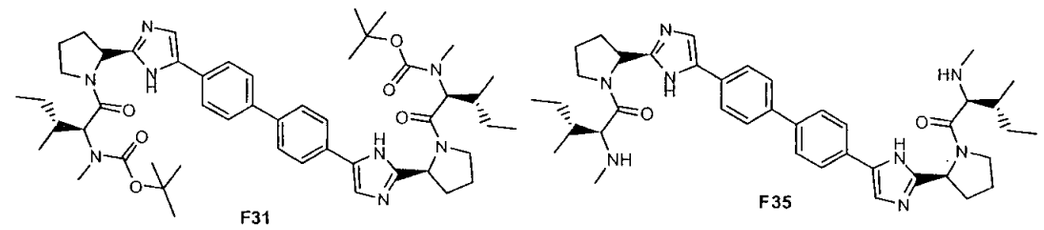
F25	((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((etoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de etilo	TR = 1.932 minutos (condición 6, 97%); EMBR: Análisis calculado para C42H54N8O6 766.42; encontrado: 767.55 $(M+H)^+$.
F26	((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((isopropoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de isopropilo	TR = 2.122 minutos (condición 6, 98%); EMBR: Análisis calculado para C44H58N8O6 794.45; encontrado: 795.58 $(M+H)^+$.


1e
F27


F28
F32


F29
F33


F30
F34


F31
F35

Entrada	Nombre del Compuesto	Tiempo de retención (Condición CL); índice de homogeneidad datos EM
F27	(2S)-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-hidroxipropanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-oxo-2-propanol	TR = 1.03 minutos (condición 3, 98%); EMBR: Análisis calculado para C32H36N6O4 568.28; encontrado: 569.76 $(M+H)^+$.
F28	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((tert-butoxicarbonil)(metil)amino)-4-metilpentanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-3-metilbutil)metilcarbamato de tert-butilo	TR = 1.847 minutos (condición 3, 95%); EMBR: Análisis calculado para C50H70N8O6 878.54; encontrado: 879.53 $(M+H)^+$.

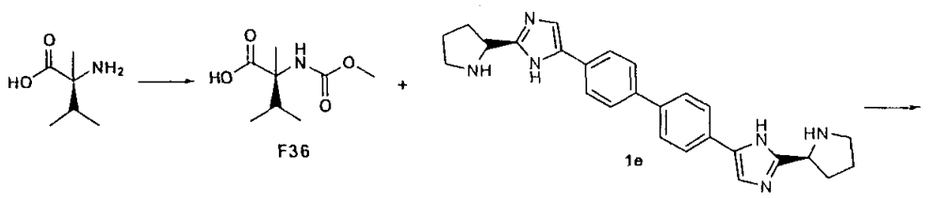
F29	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((tert-butoxicarbonil)(metil)amino)-3-metilpentanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilbutil)metilcarbamato de tert-butilo	TR = 2.202 minutos (condición 8, 98%); EMBR: Análisis calculado para C50H70N8O6 878.54; encontrado: 879.57 $(M+H)^+$.
F30	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((tert-butoxicarbonil)(metil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)metilcarbamato de tert-butilo	TR = 1.743 minutos (condición 8, 96%); EMBR: Análisis calculado para C48H66N8O6 850.51; encontrado: 851.52 $(M+H)^+$.

F31	((1S,2R)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tert-butoxicarbonil)-N-metil-L-alloisoleucil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilbutil)metilcarbamato de tert-butilo	TR = 1.82 minutos (condición 8, 98%); EMBR: Análisis calculado para C50H70N8O6 878.54; encontrado: 879.54 $(M+H)^+$.
F32	(2S)-N,4-dimetil-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-4-metil-2-(metilamino)pentanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-oxo-2-pentanamina	TR = 3.715 minutos (condición 9, 98%); EMBR: Análisis calculado para C40H54N8O2 678.44; encontrado: 679.46 $(M+H)^+$.
F33	(2S)-N,3-dimetil-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-metil-2-(metilamino)pentanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-oxo-2-pentanamina	TR = 3.058 minutos (condición 9, 99%); EMBR: Análisis calculado para C36H46N8O2 678.44; encontrado: 679.61 $(M+H)^+$.

F34	(2S)-N,3-dimetil-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-metil-2-(metilamino)butanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-oxo-2-butanamina	TR = 3.206 minutos (condición 9, 99%); EMBR: Análisis calculado para C38H50N8O2 650.41; encontrado: 651.41 $(M+H)^+$.
F35	(2S,3R)-N,3-dimetil-1-((2S)-2-(4-(4'-(2-((2S)-1-((2S,3R)-3-metil-2-(metilamino)pentanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-oxo-2-pentanamina	TR = 3.43 minutos (condición 9, 98%); EMBR: Análisis calculado para C40H54N8O2 678.44; encontrado: 679.44 $(M+H)^+$.

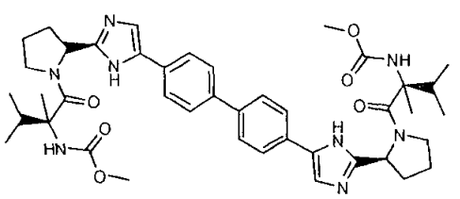
El Compuesto F27 hasta F31 se preparó en una manera análoga al procedimiento usado para sintetizar el ejemplo 1.

El Compuesto F32 hasta F35 se preparó en una manera análoga al procedimiento usado para sintetizar 1e.

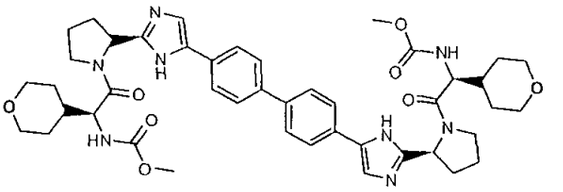


F36

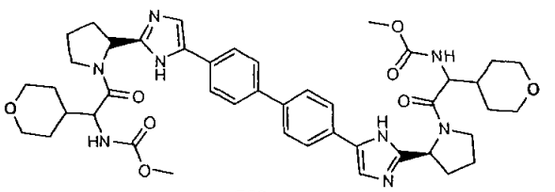
1e



F37



F38



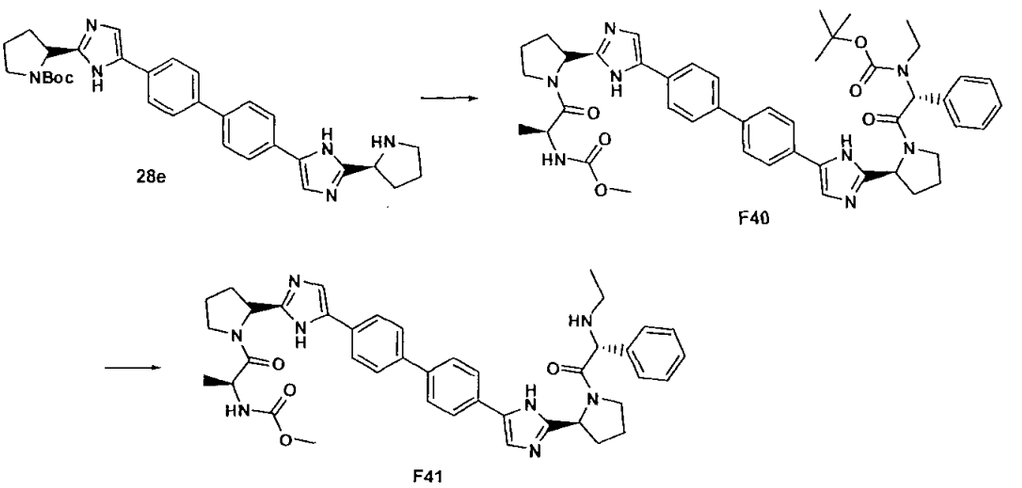
F39

El Compuesto F36 se preparó en una manera análoga al procedimiento usado para sintetizar Extremo-52.

El Compuesto F37, F38, y F39 se preparó en una manera análoga al procedimiento usado para sintetizar el ejemplo 1 del Compuesto F36 y LS16 respectivamente.

Entrada	Compuesto	Tiempo de retención (Condición CL); índice de homogeneidad datos EM
F36		TR = 1.55 minutos (condición 10); EMBR: Análisis calculado para C10H13NO2 189.1; encontrado: 190.13 $(M+H)^+$. ^1H RMN (500 MHz, DMSO-d_6) δ ppm 0.71-1.00 (m, 6H) 1.16-1.41 (m, 3H) 1.75-2.09 (m, 1H) 3.39-3.64 (m, 3H) 7.13 (s, 1H) 12.27 (s, 1H)
F37	((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-2,3-dimetilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-1,2-dimetilpropil)carbamato de metilo	TR = 2.572 minutos (condición 4, 98%); EMBR: Análisis calculado para C42H54N8O6 766.42; encontrado: 767.48 $(M+H)^+$.

F38	((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo	TR = 2.128 minutos (condición 7, 98%); EMBR: Análisis calculado para C44H54N8O8 822.41; encontrado: 823.45 $(M+H)^+$.
F39	(2-((2S)-2-(4-(4'-(2-((2S)-1-(((metoxicarbonil)amino)(tetrahidro-2H-piran-4-il)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(tetrahidro-2H-piran-4-il)etil)carbamato de metilo	TR = 2.162 minutos (condición 7, 98%); EMBR: Análisis calculado para C44H54N8O8 822.42; encontrado: 823.49 $(M+H)^+$.

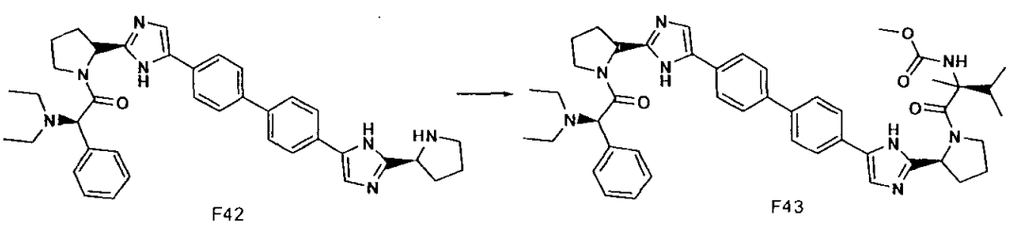


El Compuesto F41 se preparó en una manera análoga al procedimiento usado para sintetizar el ejemplo 1.

El Compuesto F42 se preparó en una manera análoga al procedimiento usado para sintetizar 1e.

Entrada	Nombre del Compuesto	Tiempo de retención (Condición CL); índice de homogeneidad datos EM
F40		TR = 2.72 minutos (condición 10); EMBR: Análisis calculado para C46H54N8O6 814.42; encontrado: 815.98 $(M+H)^+$.

F41	((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(etilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	TR = 2.048 minutos (condición 10, 95%); EMBR: Análisis calculado para C41H46N8O4 714.36; encontrado: 715.84 $(M+H)^+$.

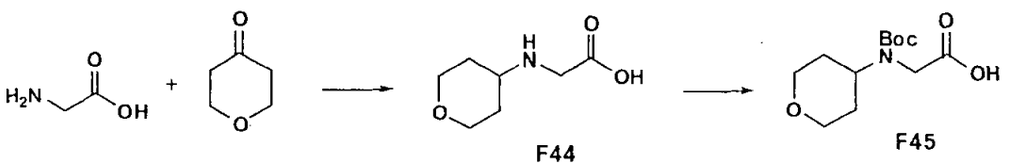


F42 F43

El Compuesto F42 se preparó en una manera análoga al procedimiento usado para sintetizar el ejemplo 28f empleando Extremo-2 en lugar de Extremo-4.

El Compuesto F43 se preparó en una manera análoga al procedimiento usado para sintetizar 2 del Compuesto F42.

Entrada	Nombre del Compuesto	Tiempo de retención (Condición CL); índice de homogeneidad datos EM
F42		TR = 2.0 minutos (condición 10, 95%); EMBR: Análisis calculado para C38H43N7O 613.35; encontrado: 614.40 $(M+H)^+$.
F43	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-1,2-dimetilpropil)carbamato de metilo	TR = 2.308 minutos (condición 10, 98%); EMBR: Análisis calculado para C50H70N8O6 784.44; encontrado: 785.49 $(M+H)^+$.



El Compuesto F44 se preparó siguiendo el documento a continuación con la siguiente modificación: glicina se usó en lugar de leucina.

Un método simple para la preparación de N-mono- y N,N-di-alquilado α-aminoácidos Yuntao Song et al., Tetrahedron Lett. 41, Octubre 2000, Paginas 8225-8230.

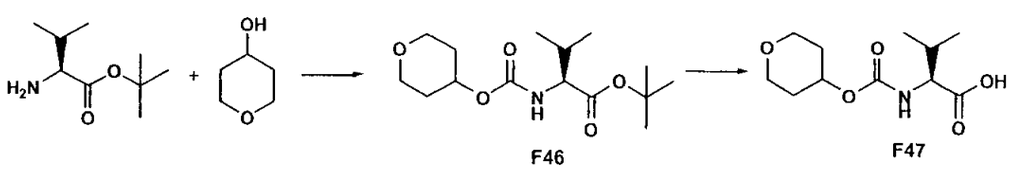
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.37-1.62 (m, 2H) 1.86 (dd, J=12.36, 1.98 Hz, 2H) 3.01-3.12 (m, 1H) 3.15 (s, 2H) 3.25 (t, J=11.75 Hz, 2H) 3.86 (dd, J=11.44, 4.12 Hz, 2H) 7.67-8.48 (m, 1H).

Compuesto F45

El ácido 2-(tetrahidro-2H-piran-4-ilamino)acético (0.2 g, 1.256 mmol) F44 se disolvió en DMF (22.5 mL) y Et_3N (2.5 mL, 17.94 mmol). Después de 5 minutos BOC_2O (0.583 mL, 2.51 mmol) se le agregó y la solución de reacción se calentó a 60°C durante 1 h. La reacción se concentró por presión reducida proporcionando un aceite amarillo ligero al cual se le agregó 20 mL HCl/H_2O el cual se ajustó a PH3 a 0°C y se agitó durante 10 minutos. La mezcla de reacción se extrajo

por acetato de etilo 3 X 20 mL, se secó ($MgSO_4$), filtró, y concentró hasta secarse. El éter se agregó y la mezcla se procesó por sonicación y filtró proporcionando un sólido blanco F45 ácido 2-(tert-butoxicarbonil(tetrahidro-2H-piran-4-il)amino)acético (0.14 g, 0.540 mmol, 43.0% de rendimiento).

^{1}H RMN (300 MHz, DMSO-d_6) δ ppm 1.27-1.44 (m, 9H) 1.43-1.69 (m, 4H) 3.19-3.39 (m, 2H) 3.74 (s, 2H) 3.79-3.92 (m, 2H) 3.97-4.16 (m, 1H) 12.46 (s, 1H).



F46 F47

El Compuesto F46 se preparó siguiendo el procedimiento de referencia a continuación con la siguiente modificación: 2-amino-3-metilbutanoato de (S)-tert-butilo se usó en lugar de 2-(((9H-fluoren-9-il)metoxi)carbonilamino)-3-metilbutanoato de (S)-metilo.

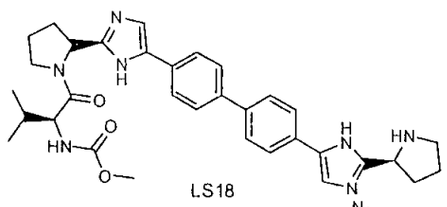
Hans-Joachim Knölker, et al. Synlett 1997; 925-928

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 0.77-0.97 (m, 6H) 1.32-1.45 (m, 9H) 1.45-1.56 (m, 2H) 1.74-1.91 (m, 2H) 1.94-2.11 (m, 1H) 3.36-3.53 (m, 2H) 3.76 (dd, J=8.09, 6.26 Hz, 1H) 3.77-3.90 (m, 2H) 4.69 (dd, J=9.00, 4.73 Hz, 1H) 7.35 (d, J=8.24 Hz, 1H)

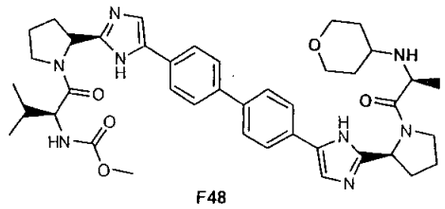
Compuesto F47

A un Compuesto 46 3-metil-2-((tetrahidro-2H-piran-4-iloxi)carbonilamino)butanoato de (S)-tert-butilo (0.21 g, 0.697 mmol) se le agregó HCl en dioxano (15 mL, 60.0 mmol) y la mezcla se agitó a temperatura ambiente bajo nitrógeno durante tres horas. La reacción se hizó y se concentró bajo presión reducida para proporcionar F47 ácido (S)-3-metil-2-((tetrahidro-2H-piran-4-iloxi)carbonilamino)butanoico (0.1694g, 0.691 mmol, 100% de rendimiento) como una cera transparente.

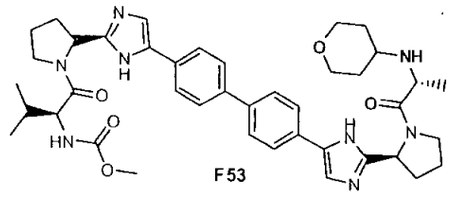
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 0.88 (t, J=6.71 Hz, 6H) 1.41-1.60 (m, 2H) 1.85 (d, J=12.21 Hz, 2H) 1.97-2.08 (m, 1H) 3.41 (t, J=10.68 Hz, 1H) 3.45-3.52 (m, 1H) 3.64-3.74 (m, 1H) 3.77-3.89 (m, 2H) 4.63-4.72 (m, 1H) 7.32 (d, J=8.55 Hz, 1H) 12.52 (s, 1H)



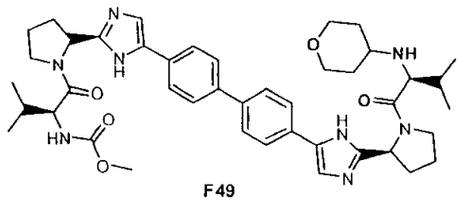
LS18



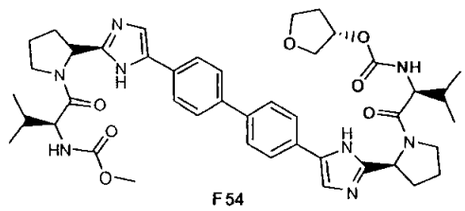
F48



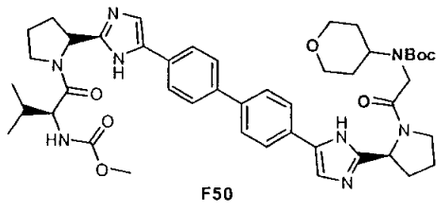
F53



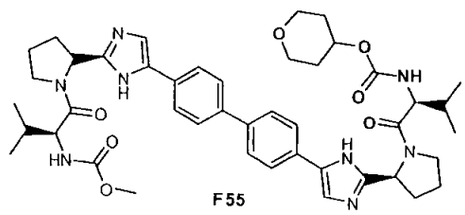
F49



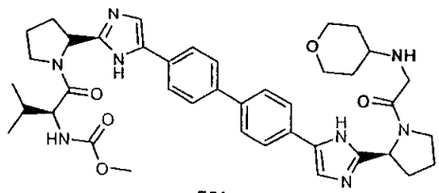
F54



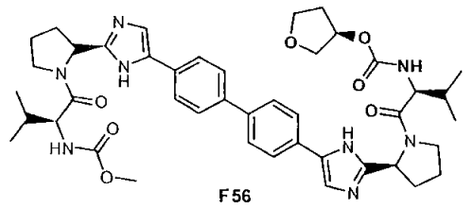
F50



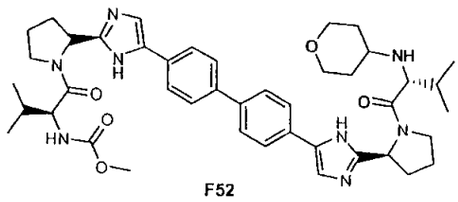
F55



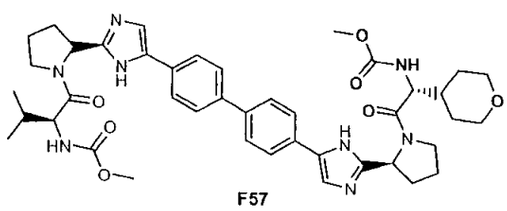
F51



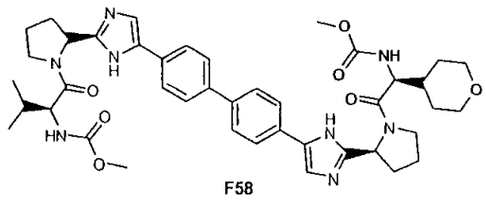
F56



F52



F57



F58

El Compuesto F48 hasta F58 excepto F51 se preparó en una manera análoga al procedimiento usado para sintetizar el ejemplo 1 de LS18.

El Compuesto F51 se preparó en una manera análoga al procedimiento usado para sintetizar 1e de F50.

Entrada	Nombre del Compuesto	Tiempo de retención (Condición CL); índice de homogeneidad datos EM
F48	((1S)-2-metil-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahidro-2H-piran-4-il)-L-alanil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo	TR = 2.103 minutos (condición 7, 98%); EMBR: Análisis calculado para C41H52N8O5 736.41; encontrado: 737.07 $(M+H)^+$.

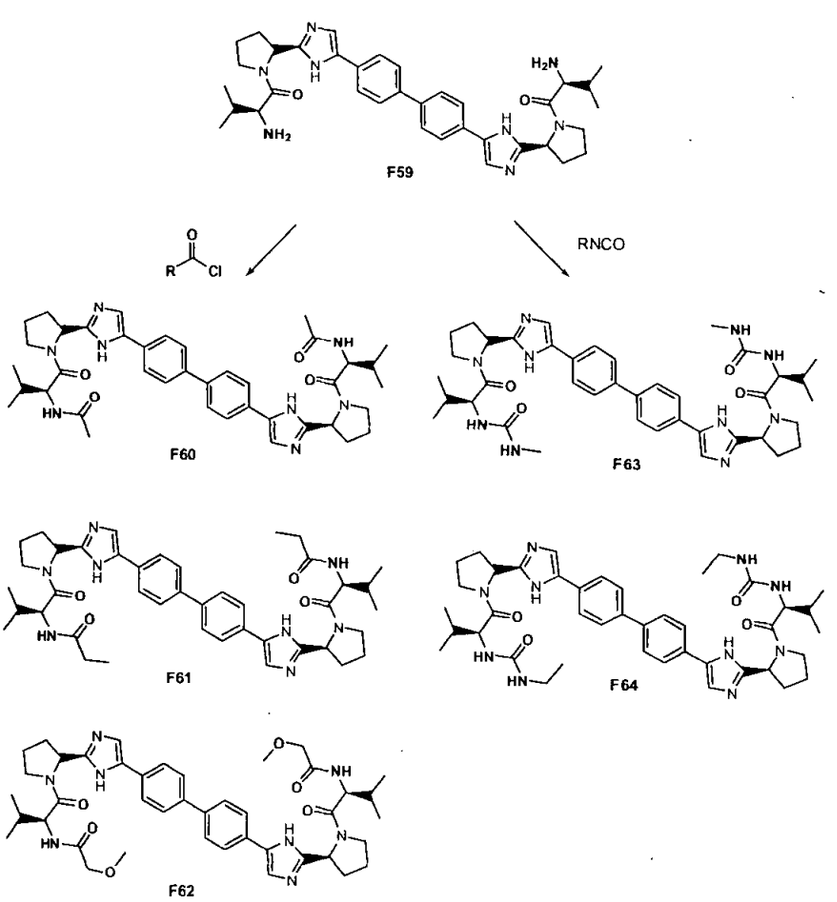
F49	((1S)-2-metil-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahidro-2H-piran-4-il)-L-valil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo	TR = 2.117 minutos (condición 7, 98%); EMBR: Análisis calculado para C43H56N8O5 764.44; encontrado: 765.75 $(M+H)^+$.
F50		TR = 2.547 minutos (condición 7, 98%); EMBR: Análisis calculado para C45H58N8O7 822.44; encontrado: 823.17 $(M+H)^+$.
F51	((1S)-2-metil-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahidro-2H-piran-4-il)glicil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo	TR = 2.138 minutos (condición 7, 96%); EMBR: Análisis calculado para C40H50N8O5 722.39; encontrado: 723.63 $(M+H)^+$.

F52	((1S)-2-metil-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahidro-2H-piran-4-il)-D-valil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo	TR = 2.083 minutos (condición 7, 98%); EMBR: Análisis calculado para C43H56N8O5 764.44; encontrado: 765.78 $(M+H)^+$.
F53	((1S)-2-metil-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(tetrahidro-2H-piran-4-il)-D-alanil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo	TR = 0.963 minutos (condición 11, 95%); EMBR: Análisis calculado para C43H54N8O7 736.41; encontrado: 737.54 $(M+H)^+$.

F54	((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de (3S)-tetrahidro-3-furanilo	TR = 2.378 minutos (condición 7, 95%); EMBR: Análisis calculado para C43H54N8O7 794.41; encontrado: 795.94 $(M+H)^+$.
F55	((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de tetrahidro-2H-piran-4-il	TR = 2.447 minutos (condición 7, 99%); EMBR: Análisis calculado para C44H56N8O7 808.43; encontrado: 809.42 $(M+H)^+$.

F56	((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de (3R)-tetrahidro-3-furanilo	TR = 2.398 minutos (condición 7, 96%); EMBR: Análisis calculado para C43H54N8O7 794.41; encontrado: 795.36 $(M+H)^+$.
F57	((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo	TR = 2.272 minutos (condición 7, 98%); EMBR: Análisis calculado para C42H52N8O7 780.40; encontrado: 781.34 $(M+H)^+$.

F58	((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-2-(tetrahidro-2H-piran-4-il)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo	TR = 2.225 minutos (condición 7, 98%); EMBR: Análisis calculado para C42H52N8O7 780.40; encontrado: 781.27 $(M+H)^+$.



Compuesto F59

El Compuesto F59 se preparó en una manera análoga al procedimiento usado para sintetizar 26a con la siguiente modificación: Boc-L-val-OH se usó en lugar de Boc-D-val-OH.

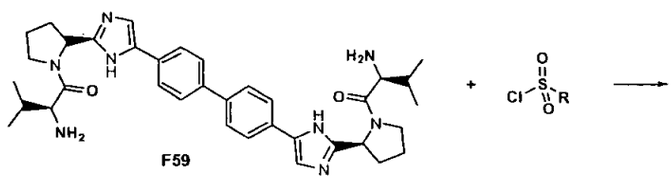
El Compuesto F60 hasta F62 se prepararon en una manera análoga al procedimiento usado para sintetizar el ejemplo 29 de F59.

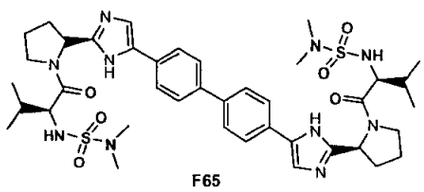
El Compuesto F63 y F64 se prepararon en una manera análoga al procedimiento usado para sintetizar Extremo 45.

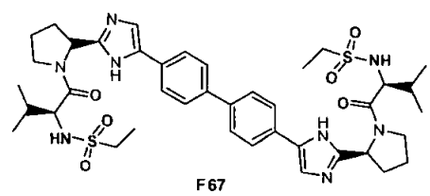
Entrada	Nombre del Compuesto	Tiempo de retención (Condición CL); índice de homogeneidad datos EM
F59		TR = 1.743 minutos (condición 7, 98%); EMBR: Análisis calculado para C36H46N8O2 622.37; encontrado: 624.07 $(M+H)^+$.

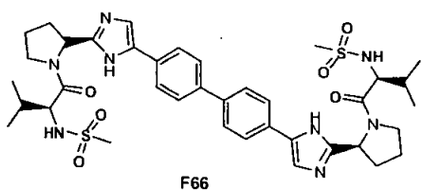
F60	N-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-acetamido-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)acetamida	TR = 2.047 minutos (condición 10, 98%); EMBR: Análisis calculado para C40H50N8O4 706.44; encontrado: 707.77 $(M+H)^+$.
F61	N-((1S)-2-metil-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-metil-2-(propionilamino)butanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)propanamida	TR = 2.215 minutos (condición 10 98%); EMBR: Análisis calculado para C42H54N8O4 734.43; encontrado: 735.87 $(M+H)^+$.

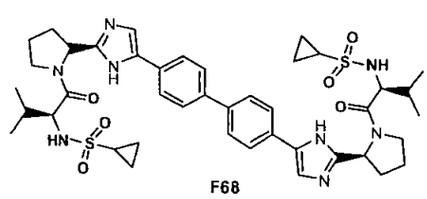
F64	1-etil-3-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((etilcarbamoil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)urea	TR = 1.617 minutos (condición 12, 93%); EMBR: Análisis calculado para C42H56N10O4 764.45; encontrado: 765.57 $(M+H)^+$.

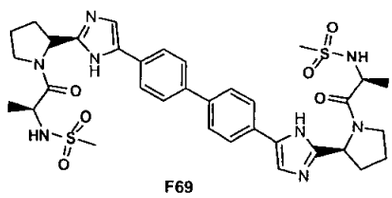












Compuesto F65

A una solución de F59 (0.06 g, 0.074 mmol en DMF (1 mL) se le agregó cloruro de dimetilsulfamoilo (0.016 mL, 0.148 mmol) y Base Hunig (0.078 mL, 0.445 mmol) luego se agita a temperatura ambiente durante 3 h. El solvente se removió por presión reducida para conseguir aceite café ligero el cual se purificó por HPLC Preparativa proporcionando F65 N-((S)-1-((S)-2-(5-(4'-(2-((S)-1-((S)-2-(N,N-dimetilsulfamoilamino)-3-metilbutanoil)pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2-il)propan-2-sulfonamida (19.0 mg, 0.018 mmol, 24.08% de rendimiento)

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 0.65-1.03 (m, 12H) 1.87-2.08 (m, 4H) 2.06-2.27 (m, 4H) 2.37-2.46 (m, 2H) 2.56-2.69 (m, 12H) 3.66-3.92 (m, 6H) 5.14 (t, J=7.63 Hz, 2H) 7.49 (d, J=9.16 Hz, 2H) 7.89 (d, J=8.24 Hz, 4H) 7.96 (s, 4H) 8.14 (s, 2H) 14.72 (s, 2H)

TR = 2.047 minutos (condición 10, 98%); EMBR: Análisis calculado para C40H50N8O4 706.38; encontrado: 707.77 $(M+H)^+$.

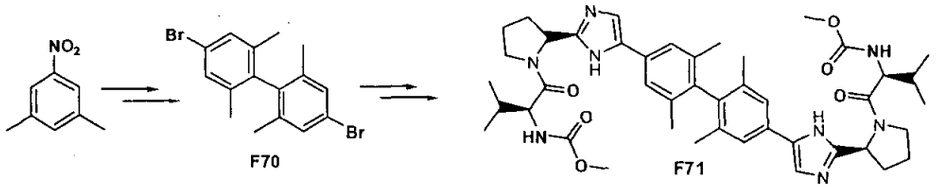
1b Fret (EC50,uM) = 0.21

El Compuesto F66 hasta F69 se preparó en una manera análoga al procedimiento usado para sintetizar F65 del Compuesto F59.

F62	2-metoxi-N-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((metoxiacetil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)acetamida	TR = 2.232 minutos (condición 10, 99%); EMBR: Análisis calculado para C42H54N8O6 766.93; encontrado: 768.05 $(M+H)^+$.
F63	1-metil-3-((1S)-2-metil-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(metilcarbamoil)-L-valil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)urea	TR = 2.082 minutos (condición 10, 95%); EMBR: Análisis calculado para C40H52N10O4 736.42; encontrado: 737.86 $(M+H)^+$.

Entrada	Nombre del Compuesto	Tiempo de retención (Condición CL); índice de homogeneidad datos EM
F66	N-((1S)-2-metil-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-metil-2-((metilsulfonil)amino)butanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)metansulfonamida	TR = 2.02 minutos (condición 10, 98%); EMBR: Análisis calculado para C38H50N8O6S2 778.38; encontrado: 779.60 $(M+H)^+$.
F67	N-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((etilsulfonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)etansulfonamida	TR = 2.172 minutos (condición 10 98%); EMBR: Análisis calculado para C40H54N8O6S2 807.04; encontrado: 808.42 $(M+H)^+$.

F68	N-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((ciclopropilsulfonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)ciclopropansulfonamida	TR = 2.217 minutos (condición 10, 93%); EMBR: Análisis calculado para C42H54N8O6S2 831.06; encontrado: 832.49 $(M+H)^+$.
F69	N-((1S)-1-metil-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metilsulfonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)metansulfonamida	TR = 1.983 minutos (condición 10, 95%); EMBR: Análisis calculado para C34H42N8O6S2 722.27; encontrado: 723.68 $(M+H)^+$.



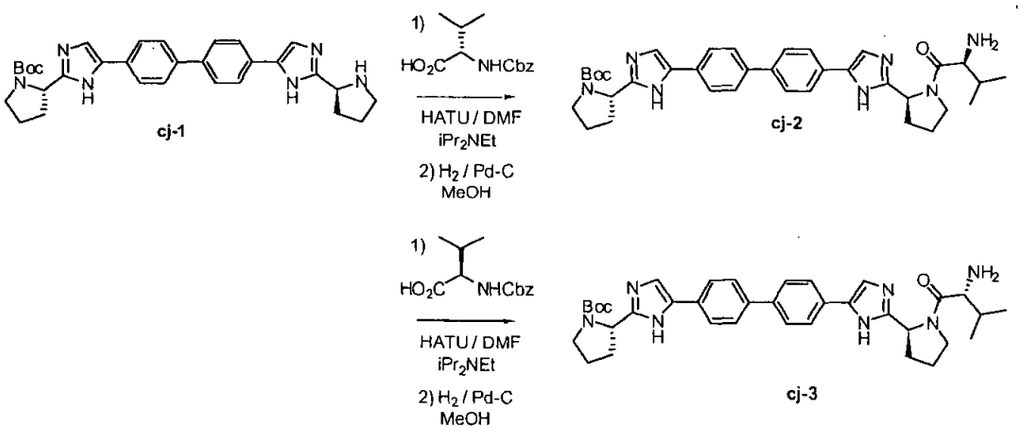
El Compuesto F70 se preparó siguiendo el procedimiento descrito en Anna Helms et al., *J. Am. Chem. Soc.* 1992 114 (15) pp 6227-6238.

El Compuesto F71 se preparó en una manera análoga al procedimiento usado para sintetizar el ejemplo 1.

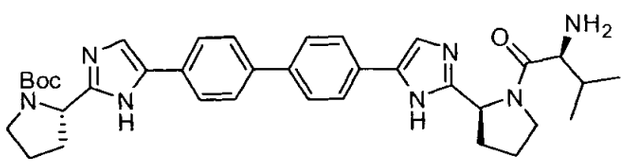
^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 0.69-0.95 (m, 12H) 1.92 (s, 12H) 1.97-2.27 (m, 8H) 2.40 (s, 2H) 3.55 (s, 6H) 3.73-3.97 (m, 4H) 4.12 (t, J=7.78 Hz, 2H) 5.14 (t, J=7.02 Hz, 2H) 7.34 (d, J=8.24 Hz, 2H) 7.49-7.70 (m, 4H) 8.04 (s, 2H) 14.59 (s, 2H) TR = 2.523 minutos (condición 7, 96%); EMBR: Análisis calculado para C44H58N8O6 794.45; encontrado: 795.48 $(M+H)^+$.

Sección cj: Síntesis de Reemplazos de Carbamato

Ejemplo cj-2 y cj-3



Preparación de 2-(5-(4'-(2-((S)-1-((S)-2-amino-3-metilbutanoil)pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-tert-Butilo (cj-2)



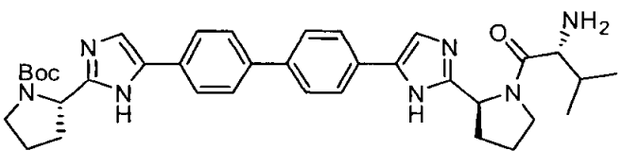
A una solución de 2-(5-(4'-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-tert-butilo (cj-1) (1.00 g, 1.91 mmol), iPr_2NEt (1.60 mL, 9.19 mmol) y N-Z-valina (0.62 g, 2.47 mmol) en DMF (10 mL) se le agregó HATU (0.92 g, 2.42 mmol). La solución se permitió agitar a temperatura ambiente durante 1 h y luego se vació en agua con hielo (ca. 250 mL) y se permitió reposar durante 20 min. La mezcla se filtró y el sólido se lavó con agua y luego se secó in vacuo durante la noche para proporcionar un sólido incoloro (1.78 g) el cual se usó como tal en la siguiente Extremo. 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% Pd-C (0.37 g) en MeOH (100 mL) se hidrogenó (presión del globo) durante 12 h. La mezcla se filtró luego y el solvente se removió in vacuo. El residuo se purificó por cromatografía en gel de sílice (sistema Biotage / 0-10% MeOH-CH_2Cl_2) para proporcionar el

compuesto del título como una espuma amarilla ligera (0.90 g, 76%).

^{1}HRMN (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)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-tert-Butilo (cj-3)

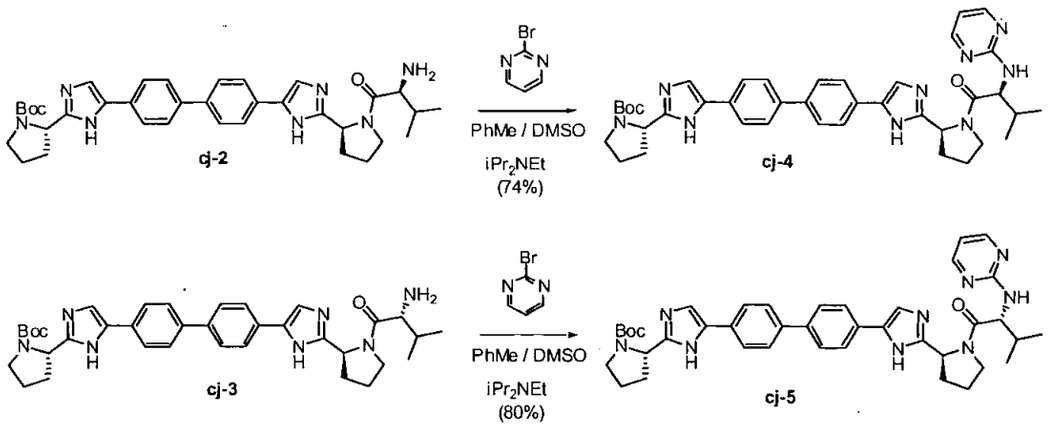


El 2-(5-(4'-(2-((S)-1-((R)-2-amino-3-metilbutanoil)pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-tert-Butilo (cj-3) se preparó usando el mismo método usado para preparar cj-2 para dar una espuma incolora (1.15 g, 76%).

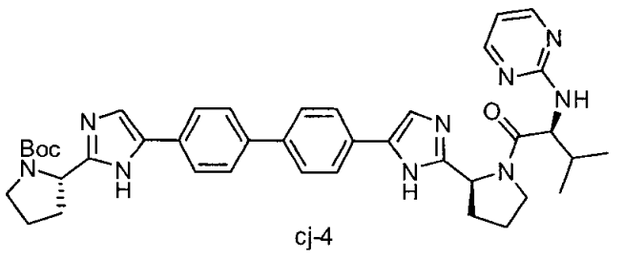
^{1}HRMN (400 MHz, DMSO-d_6) δ 12.17 (s, 0.35H), 12.04 (s, 0.65H),

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 $(M+H)^+$.

Ejemplo cj-4 y cj-5



Preparación de 2-(5-(4'-(2-((S)-1-((S)-3-metil-2-(pirimidin-2-ilamino)butanoil)pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-tert-Butilo (cj-4)



cj-4

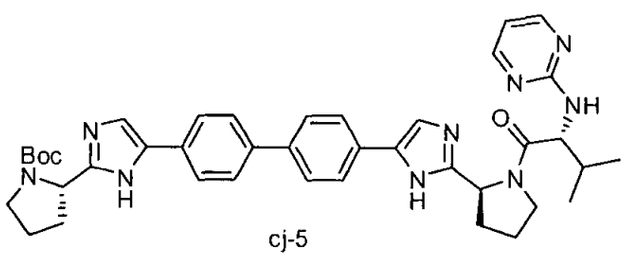
Una mezcla de 2-(5-(4'-(2-((S)-1-((S)-2-amino-3-

metilbutanoil)pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-tert-butilo (cj-2) (0.45 g, 0.72 mmol), 2-bromopirimidina (0.37 g, 2.34 mmol) y iPr_2NEt (0.20 mL, 1.18 mmol) en tolueno-DMSO (4:1, 5 mL) se calentó a 90°C durante la noche. Los volatiles se removieron in vacuo y el residuo se purificó por HPLC preparativa (YMC Pack C-18, 30 X 100 mm/MeCN-H_2O-TFA). El compuesto del título (0.56 g, 74%), como su sal TFA, se obtuvo como un vidrio amarillo anaranjado.

^{1}HRMN (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)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-tert-Butilo (cj-5)



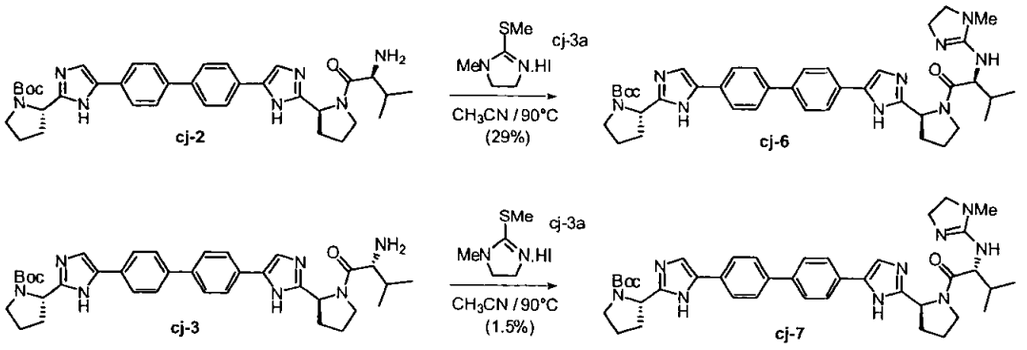
cj-5

La sal TFA del compuesto del título se preparó siguiendo el mismo método usado para preparar cj-4 para dar un sólido amarillo ligero (0.375 g, 59%).

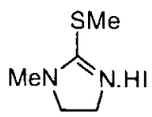
^{1}HRMN (400 MHz, DMSO-d_6) δ 14.67 (br s, 2H), 8.30 (d, J = 4.3 Hz, 1H), 8.04 - 8.19 (m, 2H), 7.84 - 7.96 (m, 8H), 6.88 (d, J = 8.6 Hz, 1H), 6.61 (app t, J = 4.5 Hz, 1H), 5.17 (dd, J = 4.4, 8.0 Hz, 1H), 5.00 - 5.07 (m, 1H), 4.67 (dd, J = 7.3, 8.1 Hz, 1H), 3.91 - 3.96 (m, 1H), 3.70-3.75 (m, 1H), 3.56 - 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: Análisis calculado para $C_{40}H_{47}N_9O_3$: 701; encontrado: 702 $(M+H)^+$.

Ejemplo cj-6 y cj-7



Preparación de yodohidrato de 1-Metil-2-(metiltio)-4,5-dihidro-1H-imidazol



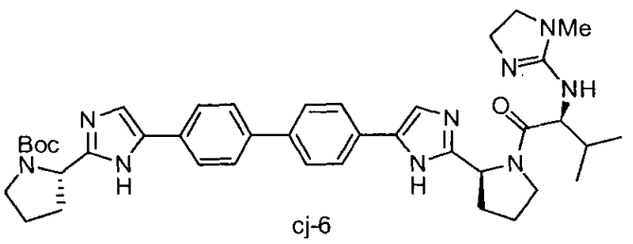
cj-3a

El compuesto del título se preparó de conformidad con: Kister, J.; Assef, G.; Dou, H. J.-M.; Metzger, J. Tetrahedron 1976, 32, 1395. Así, una solución de N-metiletilendiamina (10.8 g, 146 mmol) en EtOH-H_2O (1:1, 90 mL) se precalentó a 60°C y CS_2 (9.0 mL, 150 mmol) se le agregó gota a gota. La mezcla resultante se calentó a 60°C durante 3 h y luego HCl concentrado (4.7 mL) se agregó lentamente. La temperatura se elevó a 90°C y la agitación se continuó durante 6 h. Después de que la mezcla fría se había almacenado a -20°C, esto se filtró y el sólido resultante se secó in vacuo para proporcionar 1-metilimidazolidin-2-tiona (8.43g, 50%) como un sólido beige. ^{1}HRMN (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 mmol) en acetona (50 mL) se le agregó MeI (2.9 mL, 46.6 mmol). La solución se permitió agitar a temperatura ambiente durante 4 h y el sólido resultante se filtró rápidamente y luego se secó in vacuo para dar yodohidrato de 1-metil-2-(metiltio)-4,5-dihidro-1H-imidazol (8.79 g, 77%) como un sólido beige.

^{1}HRMN (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)-1-((S)-3-metil-2-(1-metil-4-5-dihidroimidazol-2-ilamino)butanoil)pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-tert-Butilo (cj-6)



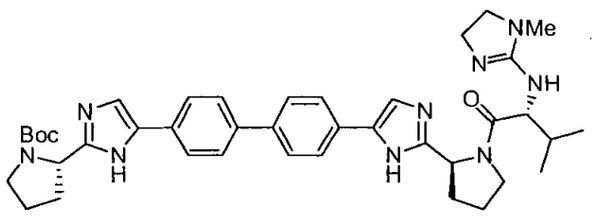
cj-6

Una mezcla de 2-(5-(4'-(2-((S)-1-((S)-2-amino-3-metilbutanoil)pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)-pirrolidin-1-carboxilato de (S)-tert-butilo (cj-2) (0.280 g, 0.448 mmol) y yodohidrato de 1-metil-2-(metiltio)-4,5-dihidro-1H-imidazol (cj-3a) (0.121 g, 0.468 mmol) en CH_3CN (5 mL) se calentó a 90°C durante 12 h. Otros 0.030 g de yodohidrato de 1-metil-2-(metiltio)-4,5-dihidro-1H-imidazol (cj-3a) se le agregó y el calentamiento continuo durante 12 horas adicionales. La mezcla de reacción cruda se purificó directamente por 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 ligero el cual se usó como tal en las Extremos posteriores.

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)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-tert-Butilo (cj-7)

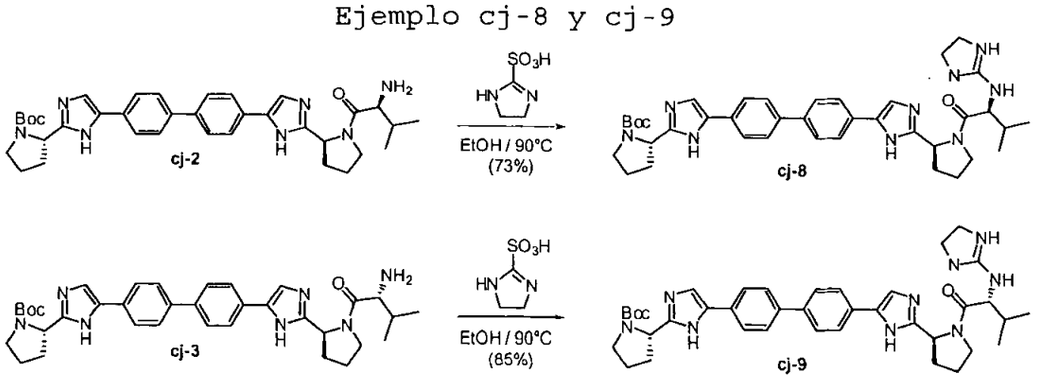


cj-7

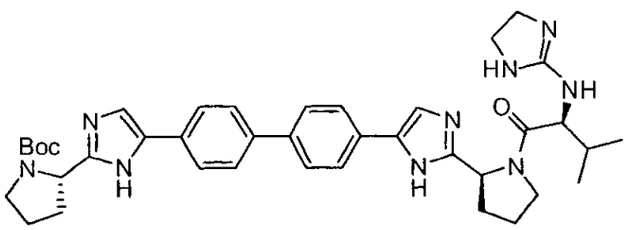
El compuesto del título se preparó de cj-3 de conformidad con el método descrito para la síntesis de cj-6, excepto que la mezcla de reacción se purificó inicialmente por HPLC preparativa (YMC-Pack 25 X 250 mm/MeCN-H_2O-NH_4OAc) y luego se volvió a purificar por HPLC preparativa (Luna Fenil-hexil//MeCN-H_2O-NH_4OAc). Esto dio el producto deseado (0.005 g) como una espuma la cual se usó como tal en las Extremos posteriores.

LCMS: Análisis calculado para $C_{40}H_{51}N_9O_3$: 705; encontrado: 706 $(M+H)^+$.

Ejemplo 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)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-tert-Butilo (cj-8)



cj-8

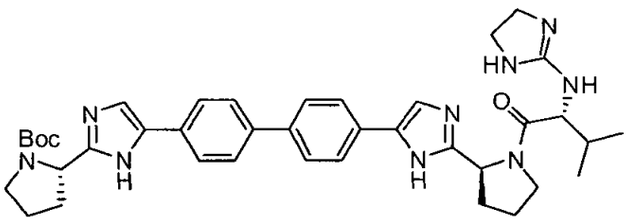
Una mezcla de 2-(5-(4'-(2-((S)-1-((S)-2-amino-3-metilbutanoil)pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-tert-butilo (cj-2) (0.298 g, 0.480 mmol), ácido 4,5-dihidro-1H-imidazol-2-sulfónico (AstaTech) (0.090 g, 0.60 mmol) y iPr_2NEt (0.083 mL, 0.48 mmol) en EtOH (4 mL) se calentó a 100°C durante 12 h. La mezcla fría se evaporó hasta secarse y el residuo se purificó por HPLC preparativa (Luna 5u C18/MeCN-H_2O-TFA, x2) para proporcionar la sal TFA del compuesto del título (0.390 g, 73%) como un sólido amarillo ligero.

^{1}HRMN (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)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-tert-Butilo (cj-9)



cj-9

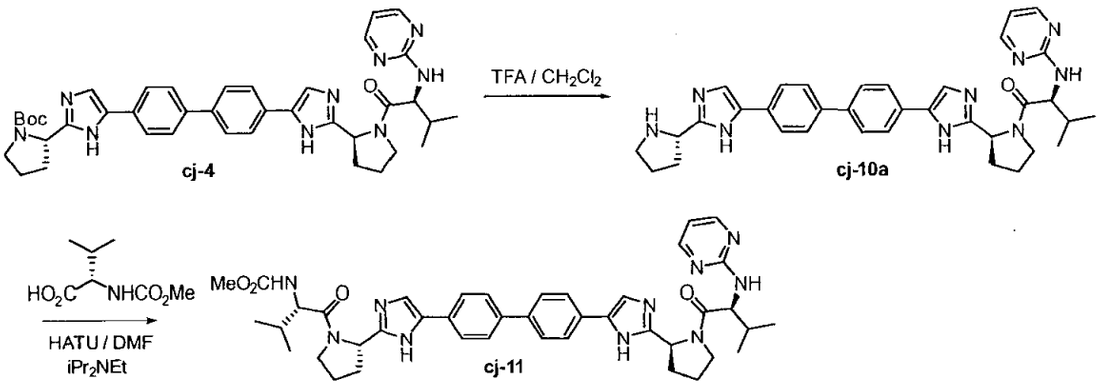
El compuesto del título se preparó de cj-3 de conformidad con el mismo método usado para preparar cj-8 para proporcionar la sal TFA (0.199 g, 57%) como un vidrio amarillo.

^{1}HRMN (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, 2.5H), 0.85 (d, J = 6.5 Hz, 2.5H), 0.66 (d, J = 7.0 Hz,

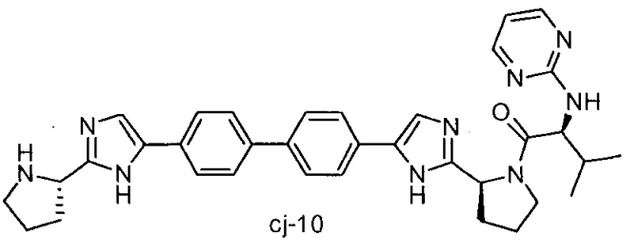
0.5H), 0.54 (d, J = 6.5 Hz, 0.5H).

LCMS: 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)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-il)butan-1-ona (cj-10a).



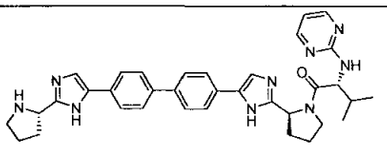
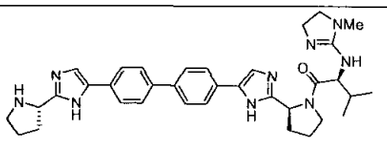
Extremo 1: Una solución de la sal TFA de 2-(5-(4'-(2-((S)-1-((S)-3-metil-2-(pirimidin-2-ilamino)butanoil)pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-tert-butilo (cj-4) (0.208 g, 0.199 mmol) en una mezcla CH_2Cl_2 (4 mL) y TFA (3 mL) se agitó a temperatura ambiente durante 1.5 h. Los solventes se removieron luego in vacuo y el residuo se purificó por HPLC preparativa (Luna 5u C18/MeCN-H_2O-TFA) para dar la sal TFA del

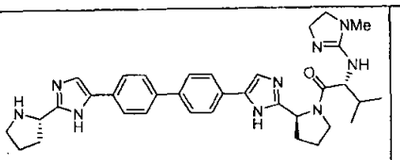
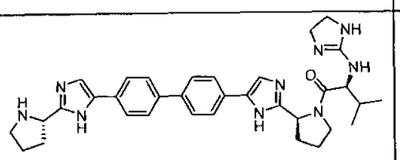
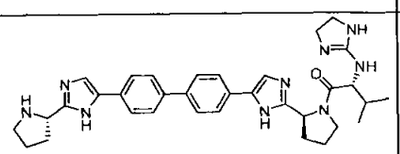
compuesto del título (0.391 g) como una goma anaranjada.

^{1}HRMN (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).

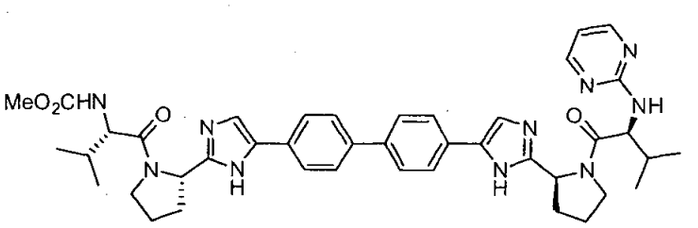
LCMS: Análisis calculado para $C_{35}H_{39}N_9O$: 601; encontrado: 602 $(M+H)^+$.

Similarmente, los siguientes ejemplos se prepararon de conformidad con el método representativo anterior;

Ejemplo	Estructura	LCMS
cj-10a (del cj-3)		LCMS: Análisis calculado para $C_{35}H_{39}N_9O$: 601; encontrado: 602 $(M+H)^+$.
cj-10b (del cj-2)		LCMS: Análisis calculado para $C_{35}H_{43}N_9O$: 605; encontrado: 606 $(M+H)^+$.

cj-10c (del cj-3)		LCMS: Análisis calculado para $C_{35}H_{43}N_9O$: 605; encontrado: 606 $(M+H)^+$.
cj-10d (del cj-2)		LCMS: Análisis calculado para $C_{34}H_{41}N_9O$: 591; encontrado: 592 $(M+H)^+$.
cj-10e (del cj-3)		LCMS: Análisis calculado para $C_{34}H_{41}N_9O$: 591; encontrado: 592 $(M+H)^+$.

Preparación de *((1S)-2-metil-1-(((2S)-2-(5-(4'-(2-((2S)-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

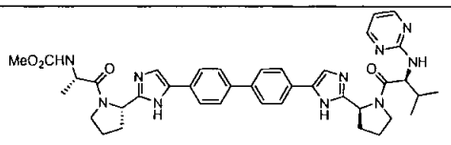
((1S)-2-metil-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pirimidinil-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo

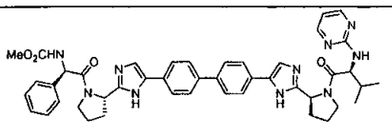
Extremo 2: A una solución de la sal TFA de (S)-3-metil-2-(pirimidin-2-ilamino)-1-((S)-2-(5-(4'-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-il)butan-1-ona (cj-10) (0.208 g, 0.197 mmol) en DMF (4 mL) se le agregó iPr_2NEt (0.20 mL, 1.15 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (0.049 g, 0.28 mmol) y HATU (0.105 g, 0.276 mmol). La solución se agitó durante 1.5 h a temperatura ambiente, se diluyó con MeOH (2 mL) y se purificó directamente por HPLC preparativa (Luna 5u C18/MeCN-H_2O-NH_4OAc). Este material se volvió a purificar por cromatografía instantánea (SiO_2/2-10% MeOH-CH_2Cl_2) para dar un sólido el cual se liofilizó a partir de CH_3CN-H_2O para dar el compuesto del título (48.6 mg, 32%) como un sólido incoloro. ^{1}HRMN (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).

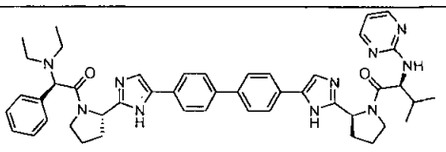
LCMS: Análisis calculado para $C_{42}H_{50}N_{10}O_4$:758; encontrado: 759

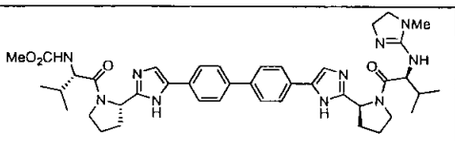
$(M+H)^+$.

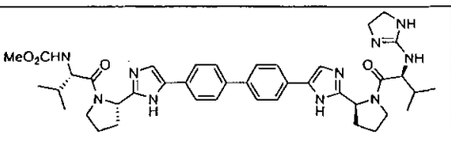
Similarmente, los siguientes ejemplos se prepararon de conformidad con el método representativo anterior;

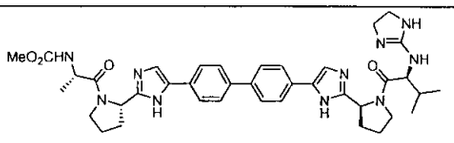
Ejemplo	Nombre del Compuesto	Estructura	LCMS
cj-11a (del cj-10 y Extremo -52)	((1S)-1-metil-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pirimidinil-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{40}H_{46}N_{10}O_4$: 730; encontrado: 731 $(M+H)^+$.

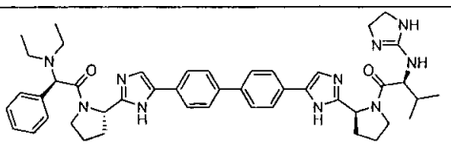
cj-11b (del cj-10 y Extremo -4)	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pirimidinil-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{45}H_{48}N_{10}O_4$: 792; encontrado: 793 $(M+H)^+$.

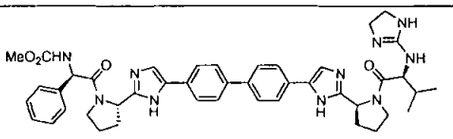
cj-11c (del cj-10 y Extremo-2)	N-((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil)-2-pirimidin Amina		LCMS: Análisis calculado para $C_{47}H_{54}N_{10}O_2$: 790; encontrado: 791 $(M+H)^+$.

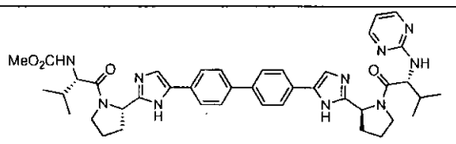
cj-11d (del cj-10b y Extremo-51)	((1S)-2-metil-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(1-metil-4,5-dihidro-1H-imidazol-2-il)-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil) propil) carbamato de metilo		LCMS: Análisis calculado para $C_{42}H_{54}N_{10}O_4$: 762; encontrado: 763 $(M+H)^+$.

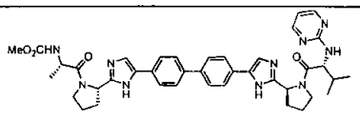
cj-11e (del cj-10d y Extremo-51)	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihidro-1H-imidazol-2-il)-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo		LCMS: Análisis calculado para $C_{41}H_{52}N_{10}O_4$: 748; encontrado: 749 $(M+H)^+$.

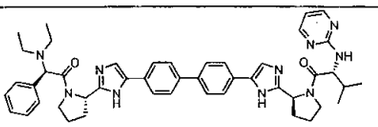
cj-11f (del cj-10d y Extremo-52)	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihidro-1H-imidazol-2-il)-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)arbamato de metilo		LCMS: Análisis calculado para $C_{39}H_{48}N_{10}O_4$: 720; encontrado: 721 $(M+H)^+$.

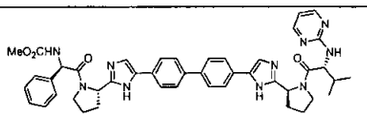
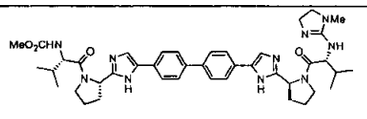
cj-11g (del cj-10d y Extremo-2)	N-((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)-4,5-dihidro-1H-imidazol-2-amina		LCMS: Análisis calculado para $C_{46}H_{56}N_{10}O_2$: 780; encontrado: 781 $(M+H)^+$.

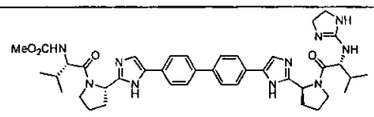
cj11h (del cj-10d y Extremo-4)	((1R)-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pirimidinil-D-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{44}H_{50}N_{10}O_4$: 782; encontrado: 783 $(M+H)^+$.

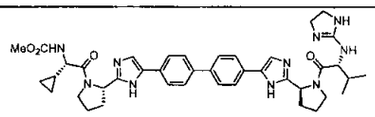
cj-11i (del cj-10a y Extremo-51)	((1S)-2-metil-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pirimidinil-D-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil) carbamato de metilo		LCMS: Análisis calculado para $C_{42}H_{50}N_{10}O_4$: 758; encontrado: 759 $(M+H)^+$.

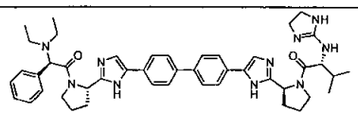
cj-11j (del cj-10a y Extremo-52)	((1S)-1-metil-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pirimidinil-D-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{40}H_{46}N_{10}O_4$: 730; encontrado: 731 $(M+H)^+$.

cj-11k (del cj-10a y Extremo -2)	N-((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)-2-pirimidin amina		LCMS: Análisis calculado para $C_{47}H_{54}N_{10}O_2$: 790; encontrado: 791 $(M+H)^+$.

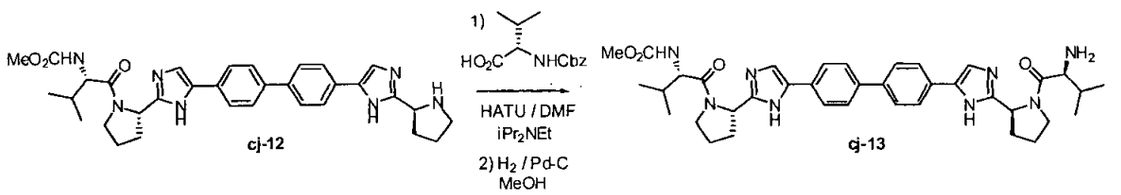
cj-11l (del cj-10a y Extremo -4)			LCMS: Análisis calculado para $C_{45}H_{48}N_{10}O_4$: 792; encontrado: 793 $(M+H)^+$.
cj-11m (del cj-10c y Extremo -51)	((1S)-2-metil-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(1-metil-4,5-dihidro-1H-imidazol-2-il)-D-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil) carbamato de metilo		LCMS: Análisis calculado para $C_{42}H_{54}N_{10}O_4$: 762; encontrado: 763 $(M+H)^+$.

cj-11n (del cj-10e y Extremo-51)	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihidro-1H-imidazol-2-il)-D-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo		LCMS: Análisis calculado para $C_{41}H_{52}N_{10}O_4$: 748; encontrado: 749 $(M+H)^+$.

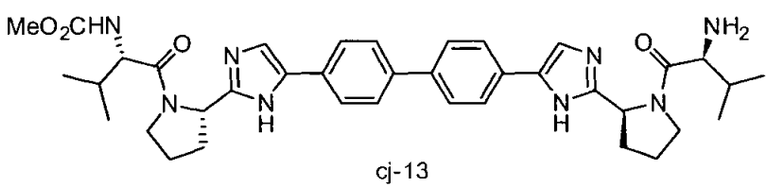
cj-11o (del cj-10e y Extremo-54b)	((1S)-1-ciclopropil-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihidro-1H-imidazol-2-il)-D-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil) carbamato de metilo		LCMS: Análisis calculado para $C_{41}H_{50}N_{10}O_4$: 746; encontrado: 747 $(M+H)^+$.

cj-11p (del cj-10e y Extremo-2)	N-((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)-4,5-dihidro-1H-imidazol-2-amina		LCMS: Análisis calculado para $C_{46}H_{56}N_{10}O_2$: 780; encontrado: 781 $(M+H)^+$.

Ejemplo-cj-13



Preparación de (S)-1-((S)-2-(5-(4'-(2-((S)-1-((S)-2-amino-3-metilbutanoil)pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (cj-13)



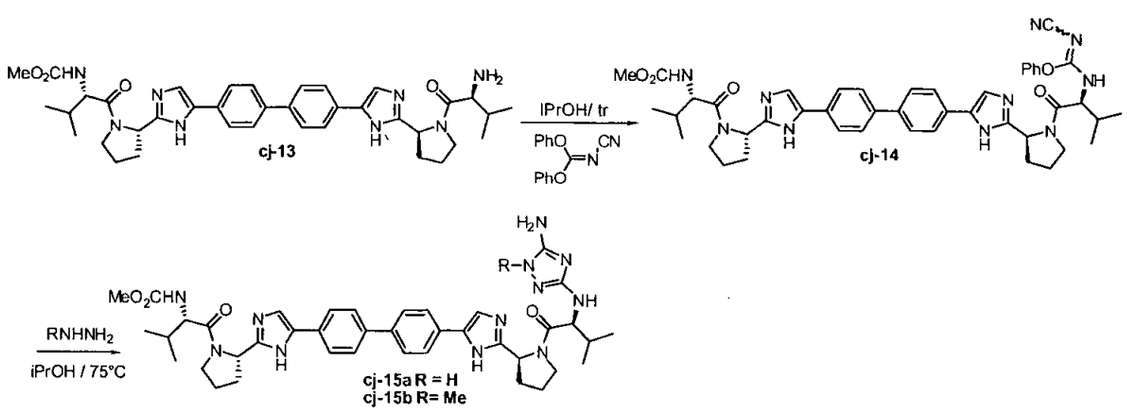
cj-13

A una solución de (S)-3-metil-1-oxo-1-((S)-2-(5-(4'-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-il)butan-2-ilcarbamato de metilo (cj-12) (1.16 g, 1.99 mmol), Z-Val-OH (0.712 g, 2.83 mmol) y iPr_2NEt (0.70 mL, 5.42 mmol) en DMF (40 mL) se le agregó HATU (1.10 g, 2.89 mmol) en porciones. La mezcla se permitió agitar a temperatura ambiente durante 1 h y luego se vació en agua con hielo (400 mL) y se permitió reposar durante 20 min. La mezcla se filtró y el sólido se lavó con agua fría y se permitió 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 $(M+H)^+$.

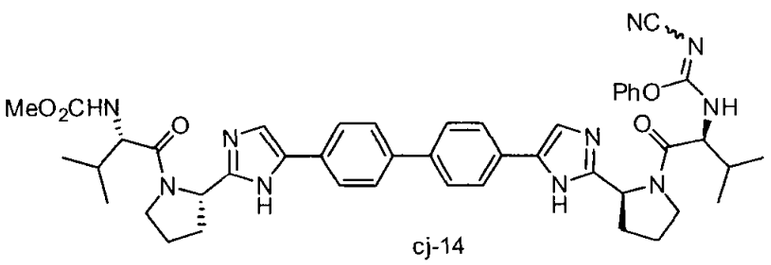
El sólido obtenido se disolvió en MeOH (80 mL), 10% Pd-C (1.0 g) se le agregó y la mezcla se hidrogenó a temperatura ambiente y a presión atmósferica durante 3 h. La mezcla se filtró luego y el filtrado se concentró in vacuo. El residuo resultante se purificó por cromatografía instantánea (SiO_2/ 5-20% MeOH-CH_2Cl_2) para proporcionar el compuesto del título (1.05 g, 77%) como una espuma incolora. ^{1}HRMN (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)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (cj-14)

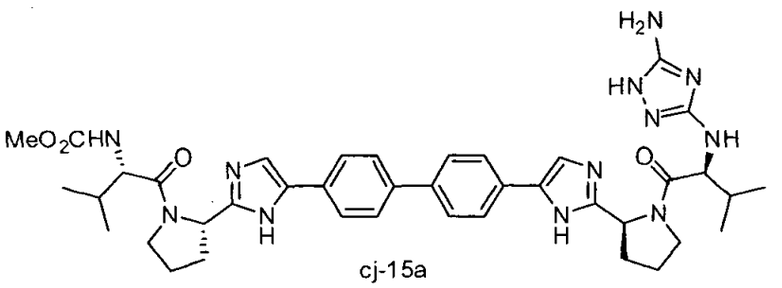


cj-14

Una mezcla de (S)-1-((S)-2-(5-(4'-(2-((S)-1-((S)-2-amino-3-metilbutanoil)pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (cj-13) (0.329 g, 0.527 mmol) y cianocarbonimidato de difenilo (0.128 g, 0.537 mmol) 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 Extremo sin purificación adicional.

LCMS: Análisis calculado para $C_{46}H_{52}N_{10}O_5$: 824; encontrado: 825 $(M+H)^+$.

Preparación de ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(5-amino-1-metil-1H-1,2,4-triazol-3-il)-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (cj-15a, R=H)



cj-15a

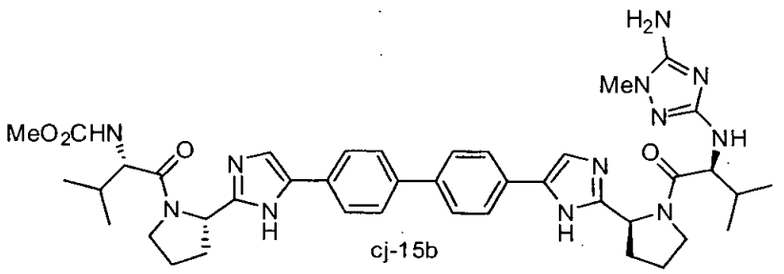
Una solución de (S)-1-((S)-2-(5-(4'-(2-((S)-1-((S)-2-((Z/E)-(cianoimino)(fenoxi)metilamino)-3-metilbutanoil)pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (cj-14) (0.074 g, 0.090 mmol) e hidrato de hidrazina (0.05 mL, 0.88 mmol) en iPrOH (2 mL) se calentó a 75°C durante 7 h. El solvente se removió entonces in vacuo y el residuo se purificó por HPLC preparativa (Luna 5u C18/MeCN-H_2O-NH_4OAc) para dar una espuma la cual se liofilizó a partir de CH_3CN-H_2O para dar el compuesto del título (0.032 g, 46%) como un sólido incoloro.

^{1}HRMN (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-1H-1,2,4-triazol-3-ilamino)-3-metilbutanoil)pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-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)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (cj-14) (0.105 g, 0.128 mmol) y N-metilhidrazina (0.010 mL, 0.188 mmol) en iPrOH (2 mL) se calentó a 75°C durante 3 h. Una segunda porción de N-metilhidrazina (0.010 mL, 0.188 mmol) se le agregó y se continuó agitando durante 7 h. Los volátiles se removieron luego in vacuo y el residuo se purificó por HPLC preparativa (Luna 5u C18/MeCN-H_2O-

NH_4OAc) para dar una espuma la cual se purificó además por cromatografía instantánea (SiO_2/0-20% 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.

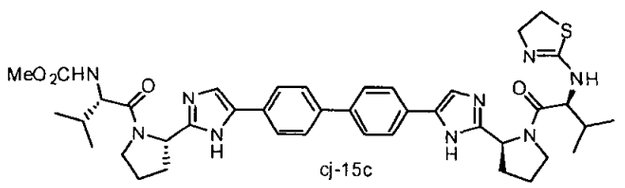
^{1}HRMN (400 MHz, DMSO-d_6) δ 13.79 (s, 0.4H), 12.19 (s, 1H), 11.76 (m, 1.6H), 7.77 - 7.85 (m, 4H), 7.62 - 7.71 (m, 4H), 7.49 - 7.51 (m, 1H), 7.24 - 7.29 (m, 1H), 6.31 (d, J = 9.1 Hz, 0.5H), 6.09 (d, J = 9.1 Hz, 1.5H), 5.87 (s, 1H), 5.34 - 5.36 (m, 1H), 5.04 - 5.08 (m, 2H), 4.89 (s, 1H), 4.75 (s, 2H), 3.53 (s, 3H), 2.10 - 2.17 (s, 3H), 1.94 - 2.02 (m, 6H), 0.81 - 0.98 (m, 12H).

LCMS: 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 $(M+H)^+$.

Ejemplo cj-15c

((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(4,5-dihidro-1,3-thiazol-2-il)-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo



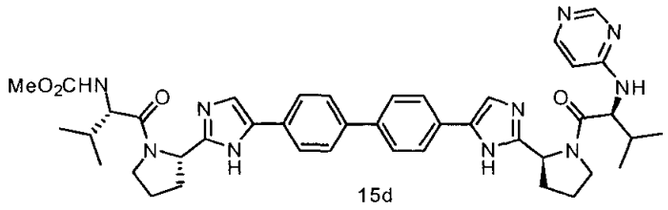
cj-15c

El ejemplo cj-15c se preparó por la condensación del intermediario cj-13 con 2-(metiltio)-4,5-dihidrotiazol (Aldrich) usando condiciones análogas a aquellas en la preparación del intermediario cj-4. LCMS: Análisis calculado para $C_{41}H_{51}N_9O_4S$: 765; encontrado: 766

$(M+H)^+$.

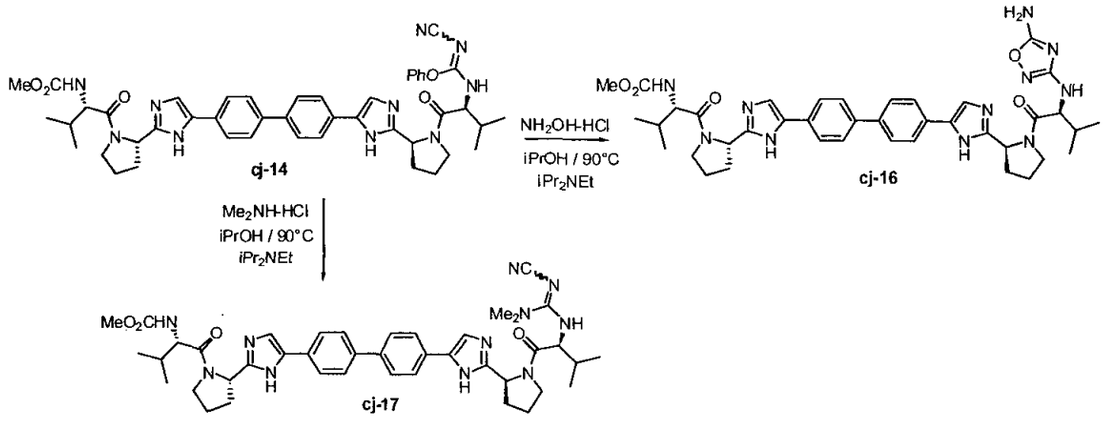
Ejemplo 15-d

((1S)-2-metil-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-4-pirimidinil-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo

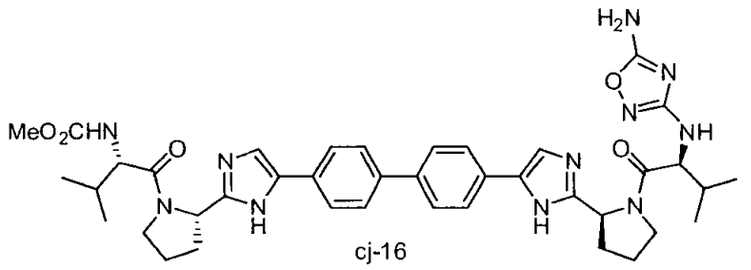


El ejemplo cj-15d se preparó por la condensación del intermediario cj-13 con 4,6-dicloropirimidina (Aldrich) usando condiciones análogas a aquellas en la preparación del intermediario cj-4, seguido por hidrogenación con 10% Pd-C. LCMS: Análisis calculado para $C_{42}H_{50}N_{10}O_4$: 758; encontrado: 759 $(M+H)^+$.

Ejemplo cj-16 y cj-17



Preparación de ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(5-amino-1,2,4-oxadiazol-3-il)-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (cj-16)



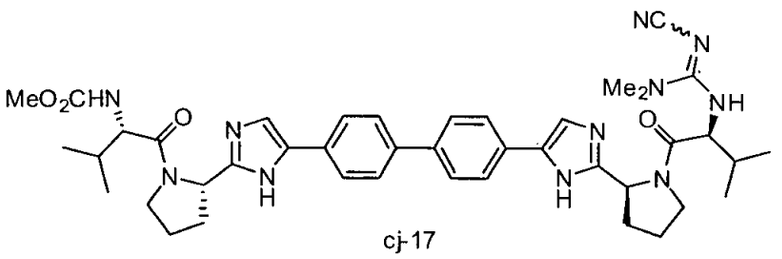
Una solución de (S)-1-((S)-2-(5-(4'-(2-((S)-1-((S)-2-((Z/E)-(cianoimino)(fenoxi)metilamino)-3-metilbutanoil)pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (cj-14) (0.120 g, 0.205 mmol) y clorohidrato de hidroxilamina (0.0213 g, 0.307 mmol) en iPrOH (5 mL) se calentó a 75°C durante 3 h. Una segunda porción de clorohidrato de hidroxilamina (0.0213 g, 0.307 mmol) se le agregó y se continuó calentando durante 7 h. Los volátiles se removieron luego in vacuo y el residuo se purificó por HPLC preparativa (Luna 5u C18/MeCN-H_2O-NH_4OAc) para dar una espuma la cual se purificó además por cromatografía instantánea (SiO_2/5% 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.

^{1}HRMN (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 (sin resolver 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: Análisis calculado para $C_{40}H_{49}N_{11}O_5$: 763; encontrado: 764 $(M+H)^+$.

Preparación de ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(ciano(dimetil)carbamimidoil)-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo (cj-17)



cj-17

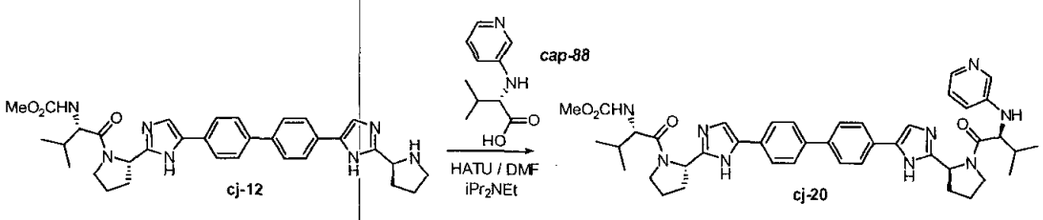
Una solución de (S)-1-((S)-2-(5-(4'-(2-((S)-1-((S)-2-((Z/E)-(cianoimino)(fenoxi)metilamino)-3-metilbutanoil)pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (cj-14) (0.115 g, 0.198 mmol) y clorohidrato de dimetilamina (0.0257 g, 0.315 mmol) en iPrOH (5 mL) se calentó a 90°C durante 12 h. Una segunda porción de clorohidrato de dimetilamina (0.0257 g, 0.315 mmol) se le agregó y se

continuó calentando durante 48 h. Los volátiles se removieron luego in vacuo y el residuo se purificó por HPLC preparativa (Luna 5u C18/MeCN-H_2O-NH_4OAc) y luego se repurificó por cromatografía instantánea (SiO_2/5% MeOH-CH_2Cl_2). La cera incolora resultante se liofilizó a partir de CH_3CN-H_2O para dar el compuesto del título (0.0318 g, 21%) como un sólido incoloro.

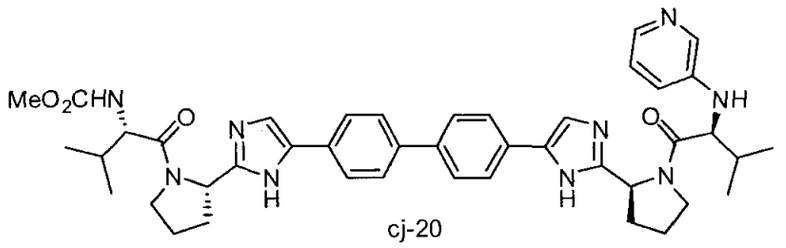
^{1}HRMN (400 MHz, DMSO-d_6) δ 12.22 (m, 0.6H), 11.81 (s, 1H), 11.75 (s, 1H), 12.17 - 12.22 (m, 0.5H), 11.99 - 12.04 (m, 0.5H), 11.75-11.81 (m, 1H), 7.76 - 7.79 (m, 3H), 7.62 - 7.73 (m, 5H), 7.50 (t, J = 2.0 Hz, 1H), 7.23 - 7.29 (m, 1H), 6.64 (d, J = 8.1 Hz, 1H), 5.06 - 5.08 (m, 2H), 4.47 (t, J = 8.1 Hz, 2H), 4.06 (sin resolver 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 $(M+H)^+$.

Ejemplo cj-20



Preparación de ((1S)-2-metil-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-3-piridinil-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo (cj-20)



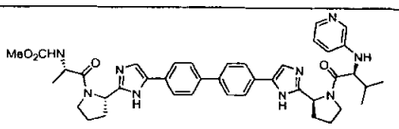
cj-20

A una solución de (S)-3-metil-1-oxo-1-((S)-2-(5-(4'-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-il)butan-2-ilcarbamato de metilo (cj-13) (0.060 g, 0.103 mmol) en DMF (2 mL) se le agregó iPr_2NEt (0.18 mL, 1.02 mmol), ácido (S)-3-metil-2-(piridin-3-ilamino)butanoico (extremo-88) (0.040 g, 0.206 mmol) y HATU (0.078 g, 0.205 mmol). La mezcla de reacción se agitó durante 1.5 h a temperatura ambiente y luego se purificó directamente por HPLC preparativa (Luna 5u C18/MeCN-H_2O-NH_4OAc). El sólido resultante se volvió a purificar por cromatografía instantánea (SiO_2/0-10% MeOH-CH_2Cl_2) y el producto obtenido se liofilizó a partir de CH_3CN-H_2O para dar el compuesto del título (0.044 g, 56%) como un sólido. ^{1}HRMN (400 MHz, DMSO-d_6) δ 12.19 (s, 1H), 11.76 (s, 1H), 8.07 (d, J = 2.6 Hz, 1H), 7.62 - 7.85 (m, 8H), 7.49 - 7.51 (m, 2H), 7.24 - 7.29 (m, 1H), 6.99 - 7.06 (m, 2H), 6.46 - 6.49 (m, 0.5H), 5.97 - 5.99 (m, 0.5H), 5.71 (d, J = 9.0 Hz, 1H), 5.55 (d, J = 10.6 Hz, 1H), 5.22 - 5.44 (m, 1H), 5.03 - 5.09 (m, 2H), 4.04 - 4.13 (m, 2H), 3.78 - 3.90 (m, 3H), 3.66 - 3.71 (m, 1H), 3.53 (s, 3H), 2.03 - 2.19 (m, 2H), 1.84

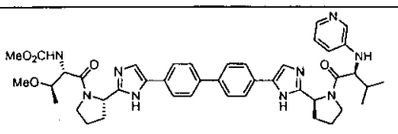
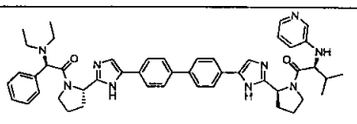
- 2.01 (m, 4H), 0.81 - 1.01 (m, 12H).

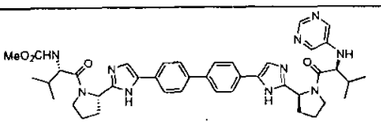
LCMS: Anal. Calculado para $C_{43}H_{51}N_9O_4$: 757; encontrado: 758 $(M+H)^+$.

Similarmente, los siguientes ejemplos se prepararon de conformidad con el método representativo anterior;

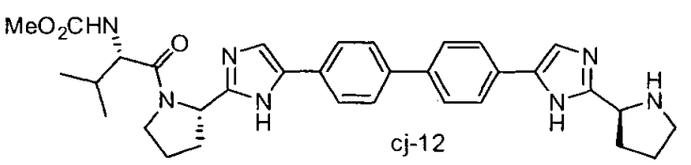
Ejemplo	Nombre del Compuesto	Estructura	LCMS
cj-20a (del cj-22 y extremo -88)	((1S)-1-metil-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-3-piridinil-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etil)carbamato de metilo		LCMS: Análisis calculado para $C_{41}H_{47}N_9O_4$: 729; encontrado: 730 $(M+H)^+$.

601458

cj-20b (del cj-23 y extremo -88)	((1S,2R)-2-metoxi-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-3-piridinil-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)propil) carbamato de metilo		LCMS: Análisis calculado para $C_{43}H_{51}N_9O_5$: 773; encontrado: 774 $(M+H)^+$.
cj-20c (del cj-24 y extremo -88)	N-((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil)-3-piridinamina		LCMS: Análisis calculado para $C_{48}H_{55}N_9O_2$: 789; encontrado: 790 $(M+H)^+$.

cj-20d (del cj-12 y extremo -88)	((1S)-2-metil-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-5-pirimidinil-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)propil) carbamato de metilo		LCMS: Análisis calculado para $C_{42}H_{50}N_{10}O_4$: 758; encontrado: 759 $(M+H)^+$.

Preparación de (S)-3-metil-1-oxo-1-((S)-2-(5-(4'-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-il)butan-2-ilcarbamato de metilo (cj-12)



cj-12

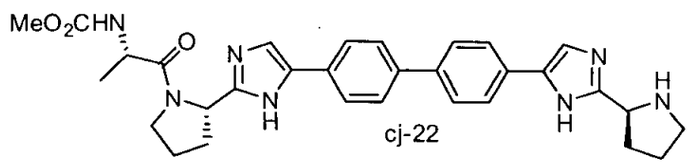
Sintetizado del intermediario-28d y extremo-51 como en el Ejemplo 28e, seguido por remoción de Boc con TFA/CH_2Cl_2 y

formación de base libre con resina MCX.

^{1}HRMN (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 $(M+H)^+$.

Preparación de (S)-1-oxo-1-((S)-2-(5-(4'-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-il)propan-2-ilcarbamato de metilo (cj-22).



cj-22

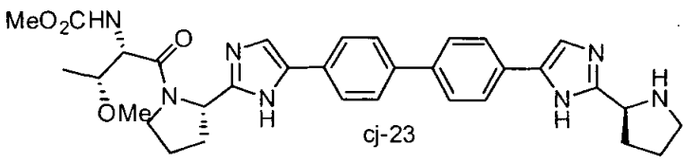
Sintetizado del intermediario-28d y extremo-52 como en el Ejemplo 28e, seguido por remoción Boc con TFA/CH_2Cl_2 y formación de base libre con resina MCX.

^{1}HRMN (400 MHz, MeOH-d_4) δ 7.68 - 7.79 (m, 4H), 7.59-7.65 (m, 4H), 7.44 (d, J = 6.6 Hz, 1H), 7.37 (s, 0.3H), 7.27 (s, 0.7H), 5.18 (dd, J = 4.0, 7.6 Hz, 1H), 4.74 (t, J = 8.0 Hz, 1H), 4.46 (dd, J = 6.8, 13.9 Hz, 1H), 3.84 (sin resolver dd, J = 6.1, 6.5 Hz, 1H), 3.62 (s, 3H), 3.54 (s, 1H), 3.32 - 3.46 (m, 3H), 2.40 - 2.46 (m, 1H), 2.26 - 2.39 (m, 2H), 2.14

- 2.24 (m, 2H), 2.01 - 2.12 (m, 2H), 0.32 (d, J = 7.1 Hz, 3H).

LCMS: Análisis calculado para $C_{31}H_{35}N_7O_3$: 553; encontrado: 554 $(M+H)^+$.

Preparación de (2S,3R)-3-metoxi-1-oxo-1-((S)-2-(5-(4'-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-il)butan-2-ilcarbamato de metilo (cj-23).

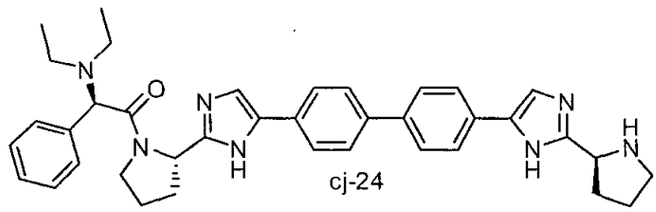


Sintetizado del intermediario -28d y extremo-86 como en el Ejemplo 28e, seguido por remoción Boc con TFA/CH_2Cl_2 y formación de base libre con resina MCX.

^{1}HRMN (400 MHz, MeOH-d_4) δ 7.72 (m, 4H), 7.64 -7.69 (m, 4H), 7.48 (d, J = 4.1 Hz, 1H), 7.38 (s, 0.3H), 7.33 (s, 0.7H), 5.51 - 5.54 (m, 0.2H), 5.22 (dd, J = 4.9, 7.6 Hz, 0.8H), 4.76 (t, J = 8.0 Hz, 1H), 4.48 (d, J = 5.1 Hz, 0.8H), 4.35 - 4.36 (m, 0.2H), 3.90 - 3.99 (m, 1H), 3.68 (s, 3H), 3.54 (s, 1H), 3.35 - 3.48 (m, 4H), 3.29 (s, 3H), 2.42 - 2.50 (m, 1H), 2.30 - 2.37 (m, 2H), 2.19 - 2.26 (m, 2H), 2.05 - 2.15 (m, 2H), 1.19 (d, J = 6.1 Hz, 3H).

LCMS: Análisis calculado para $C_{33}H_{39}N_7O_4$: 597; encontrado: 598 $(M+H)^+$.

Preparación de (R)-2-(Dietilamino)-2-fenil-1-((S)-2-(5-(4'-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)bifenil-4-il)-1H-imidazol-2-il)pirrolidin-1-il)etanona (cj-24).



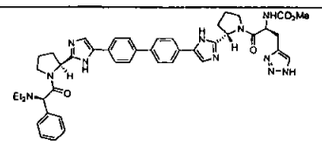
cj-24

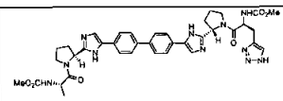
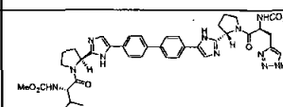
Sintetizado del intermediario-28d y extremo-2 como en el Ejemplo 28e, seguido por remoción Boc con TFA/CH_2Cl_2 y formación de base libre con resina MCX.

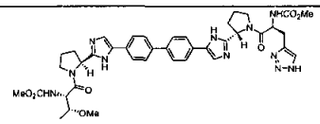
^{1}HRMN (400 MHz, MeOH-d_4) δ 7.59 - 7.82 (m, 10H), 7.36 - 7.51 (m, 4H), 7.01 - 7.15 (m, 1H), 5.09 - 5.13 (m, 2H), 4.77 (t, J = 8.5 Hz, 1H), 4.03 - 4.05 (m, 1H), 3.67 - 3.93 (m, 1H), 3.35 - 3.47 (m, 2H), 3.18 - 3.23 (m, 1H), 2.91-3.07 (m, 2H), 2.70 - 2.84 (m, 2H), 2.34 - 2.60 (m, 2H), 1.97 - 2.24 (m, 5H), 1.07 - 1.17 (m, 6H).

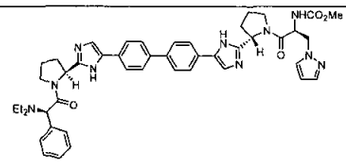
LCMS: Análisis calculado para $C_{38}H_{43}N_7O$: 613; encontrado: 614 $(M+H)^+$.

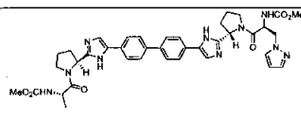
Los siguientes se prepararon de conformidad al procedimiento en el ejemplo 28 iniciando con 28d. Las extremos se dan en la Tabla en el orden en el que se anexaron hasta 28d. Donde un número de extremo no da el ácido carboxílico correspondiente es comercialmente disponible.

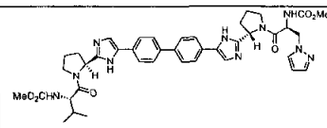
Ejemplo	Nombre del Compuesto	Estructura	LCMS	Extremo
cj-32	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(1H-1,2,3-triazol-4-ilmetil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{45}H_{51}N_{11}O_4$: 809; encontrado: 810 $(M+H)^+$.	2/128

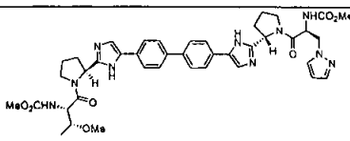
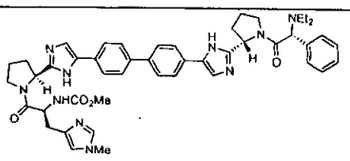
cj-33	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(1H-1,2,3-triazol-4-ilmetil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{38}H_{43}N_{11}O_6$: 749; encontrado: 750 $(M+H)^+$.	52/128
cj-34	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil) amino)-3-(1H-1,2,3-triazol-4-il)propanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo		LCMS: Análisis calculado para $C_{40}H_{47}N_{11}O_6$: 777; encontrado: 777 $(M+H)^+$.	51/128

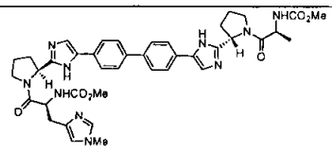
cj-35	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-metoxi-2-((metoxicarbonil)amino)butanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(1H-1,2,3-triazol-4-ilmetil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{40}H_{47}N_{11}O_7$: 793; encontrado: 794 $(M+H)^+$.	86/128

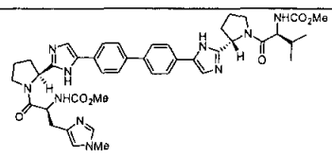
cj-36	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(1H-pirazol-1-ilmetil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{46}H_{52}N_{10}O_4$: 808; encontrado: 809 $(M+H)^+$.	2/129

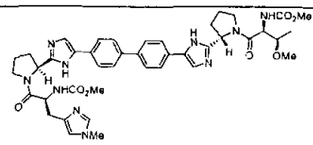
cj-37	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(1H-pirazol-1-ilmetil)etil) carbamato de metilo		LCMS: Análisis calculado para C39H44N10O6: 748; encontrado: 749 $(M+H)^+$.	52/129

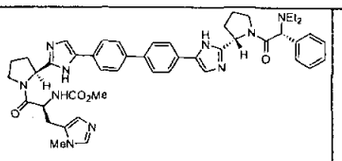
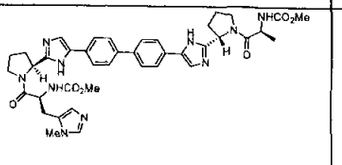
cj-38	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-(1H-pirazol-1-il)propanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil) carbamato de metilo		LCMS: Análisis calculado para $C_{40}H_{47}N_{11}O_7$: 776; encontrado: 777 $(M+H)^+$.	51/129

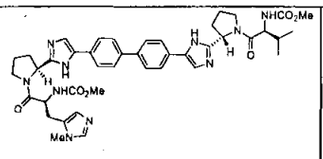
cj-39	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-treonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(1H-pirazol-1-ilmetil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{41}H_{48}N_{10}O_7$: 792; encontrado: 793 $(M+H)^+$.	86/129
cj-40	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-((1-metil-1H-imidazol-4-il)metil)-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{47}H_{54}N_{10}O_4$: 822; encontrado: 823 $(M+H)^+$.	2/127

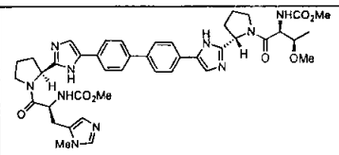
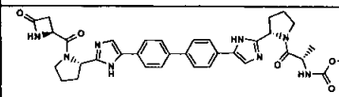
cj-41	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-((1-metil-1H-imidazol-4-il)metil)-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{40}H_{46}N_{10}O_6$: 762; encontrado: 763 $(M+H)^+$.	52/127

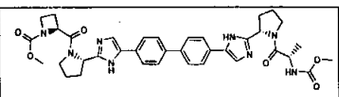
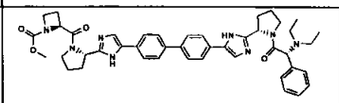
cj-42	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-(1-metil-1H-imidazol-4-il)propanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil) carbamato de metilo		LCMS: Análisis calculado para $C_{42}H_{50}N_{10}O_6$ 790; encontrado: 791 $(M+H)^+$.	51/127

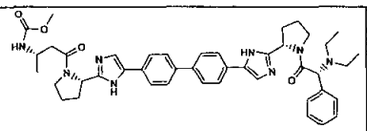
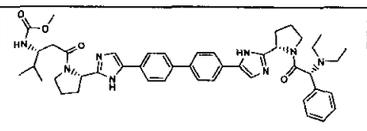
cj-43	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-metoxi-2-((metoxicarbonil)amino)butanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-((1-metil-1H-imidazol-4-il)metil)-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{42}H_{50}N_{10}O_7$ 806; encontrado: 806 $(M+H)^+$.	86/127

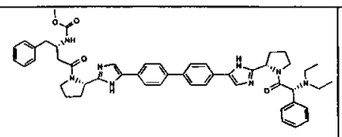
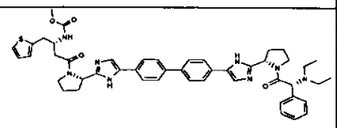
cj-44	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-((1-metil-1H-imidazol-5-il)metil)-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{47}H_{54}N_{10}O_4$ 822; encontrado: 823 $(M+H)^+$.	2/126
cj-45	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-((1-metil-1H-imidazol-5-il)metil)-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{40}H_{46}N_{10}O_6$: 762; encontrado: 763 $(M+H)^+$.	52/126

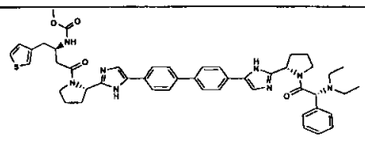
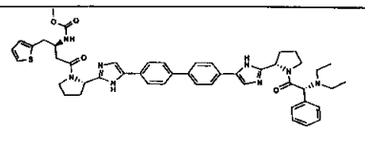
cj-46	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-(1-metil-1H-imidazol-5-il)propanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil) carbamato de metilo		LCMS: Análisis calculado para $C_{42}H_{50}N_{10}O_6$ 790; encontrado: 791	51/126

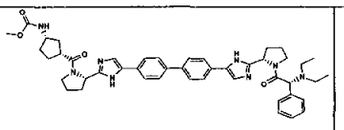
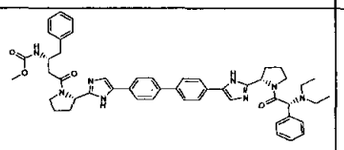
cj-47	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-metoxi-2-((metoxicarbonil)amino)butanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-((1-metil-1H-imidazol-5-il)metil)-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{42}H_{50}N_{10}O_7$ 806; encontrado: 807 $(M+H)^+$.	86/126
cj-48	((1S)-1-metil-2-oxo-2-((2S)-2-(5-(4'-(2-((2S)-1-(((2S)-4-oxo-2-azetidinil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)etil)carbamato de metilo		LCMS: Análisis calculado para $C_{35}H_{38}N_8O_5$ 650; encontrado: 651 $(M+H)^+$.	52/-

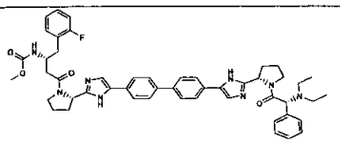
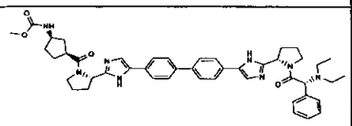
cj-49	(2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-1-azetidin carboxilato de metilo		LCMS: Análisis calculado para $C_{37}H_{42}N_8O_6$ 694; encontrado: 695 $(M+H)^+$.	52/114
cj-50	(2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-1-azetidin carboxilato de metilo		LCMS: Análisis calculado para $C_{44}H_{50}N_8O_4$ 754; encontrado: 755 $(M+H)^+$.	2/114

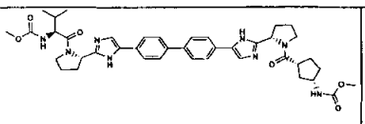
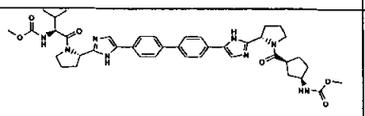
cj-51	((1S)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-3-oxopropil) carbamato de metilo		LCMS: Análisis calculado para $C_{44}H_{52}N_8O_4$ 756; encontrado: 757 $(M+H)^+$.	2/115
cj-52	((1R)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-isopropil-3-oxopropil) carbamato de metilo		LCMS: Análisis calculado para $C_{46}H_{56}N_8O_4$ 784; encontrado: 785 $(M+H)^+$.	2/116

cj-53	((1S)-1-bencil-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-3-oxopropil) carbamato de metilo		LCMS: Análisis calculado para $C_{50}H_{56}N_8O_4$ 833; encontrado: 834 $(M+H)^+$.	2/96
cj-54	((1R)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-3-oxo-1-(2-tienilmetil) propil)carbamato de metilo		LCMS: Análisis calculado para $C_{48}H_{54}N_8O_4S$ 838; encontrado: 839 $(M+H)^+$.	2/119

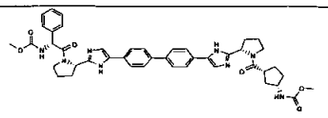
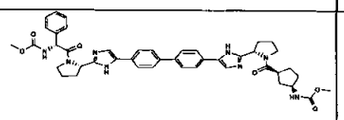
cj-55	((1R)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-3-oxo-1-(3-tienilmetil) propil)carbamato de metilo		LCMS: Análisis calculado para $C_{48}H_{54}N_8O_4S$ 838; encontrado: 839 $(M+H)^+$.	2/120
cj-56	((1S)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-3-oxo-1-(2-tienilmetil) propil)carbamato de metil		LCMS: Análisis calculado para $C_{48}H_{54}N_8O_4S$ 838; encontrado: 839 $(M+H)^+$.	2/118

cj-57	((1S,3R)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil) ciclopentil) carbamato de metil		LCMS: Análisis calculado para $C_{46}H_{54}N_8O_4$ 782; encontrado: 783 $(M+H)^+$.	2/99a
cj-58	((1R)-1-bencil-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-3-oxopropil) carbamato de metilo		LCMS: Análisis calculado para $C_{50}H_{56}N_8O_4$ 832; encontrado: 833 $(M+H)^+$.	2/117

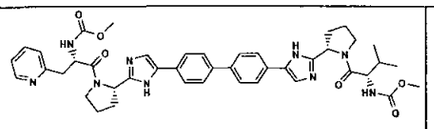
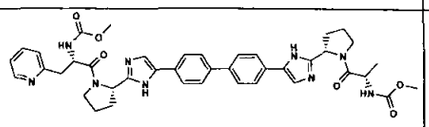
cj-59	((1R)-3-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-(2-fluorobencil)-3-oxopropil) carbamato de metilo		LCMS: Análisis calculado para $C_{50}H_{55}N_8O_4F$ 850; encontrado: 851 $(M+H)^+$.	2/100
cj-60	((1R,3S)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil) ciclopentil) carbamato de metilo		LCMS: Análisis calculado para $C_{46}H_{54}N_8O_4$ 782; encontrado: 783 $(M+H)^+$.	2/99

cj-61	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(((1R,3S)-3-((metoxicarbonil) amino)ciclopentil) carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo		LCMS: Análisis calculado para $C_{41}H_{50}N_8O_6$ 750; encontrado: 751 $(M+H)^+$.	52/99a
cj-62	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(((1S,3R)-3-((metoxicarbonil) amino)ciclopentil) carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo		LCMS: Análisis calculado para $C_{41}H_{50}N_8O_6$ 750; encontrado: 751 $(M+H)^+$.	52/99

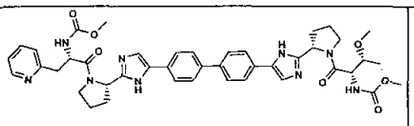
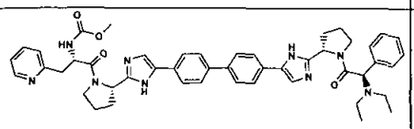
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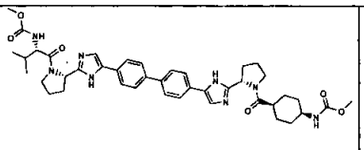
cj-63	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1R,3S)-3-((metoxicarbonil)amino)ciclopentil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) carbamato de metilo		LCMS: Análisis calculado para $C_{44}H_{48}N_8O_6$ 784; encontrado: 785 $(M+H)^+$.	4/99a
cj-64	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1S,3R)-3-((metoxicarbonil)amino)ciclopentil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) carbamato de metilo		LCMS: Análisis calculado para $C_{44}H_{48}N_8O_6$ 784; encontrado: 785 $(M+H)^+$.	4/99

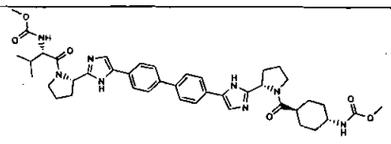
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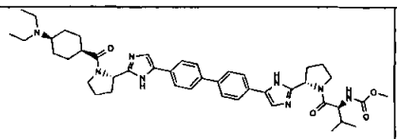
cj-65	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-(2-piridinil)propanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo		LCMS: Análisis calculado para $C_{43}H_{49}N_9O_6$ 787; encontrado: 788 $(M+H)^+$.	51/93
cj-66	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(2-piridinilmetil) etil)carbamato de metilo		LCMS: Análisis calculado para $C_{41}H_{45}N_9O_6$ 759; encontrado: 760 $(M+H)^+$.	52/93

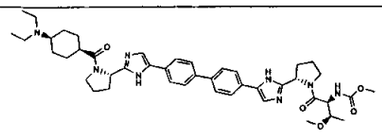
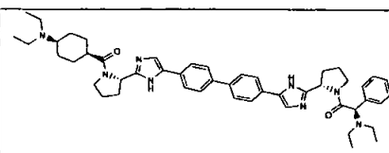
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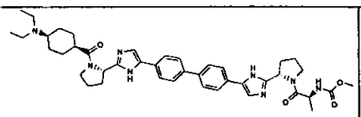
cj-67	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-metoxi-2-((metoxicarbonil)amino)butanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(2-piridinilmetil)etil)carbamato de metilo		LCMS: Análisis calculado para $C_{43}H_{49}N_9O_7$ 803; encontrado: 804 $(M+H)^+$.	86/93
cj-68	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(2-piridinilmetil)etil)carbamato de metilo		LCMS: Análisis calculado para $C_{48}H_{53}N_9O_4$ 819; encontrado: 820 $(M+H)^+$.	2/93

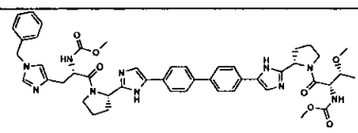
cj-69	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-((metoxicarbonil)amino)ciclohexil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo		LCMS: Análisis calculado para $C_{42}H_{52}N_8O_6$ 764; encontrado: 765 $(M+H)^+$.	51/104

cj-70	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((trans-4-((metoxicarbonil)amino)ciclohexil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil) carbamato de metilo		LCMS: Análisis calculado para $C_{42}H_{52}N_8O_6$ 764; encontrado: 765 $(M+H)^+$.	51/105

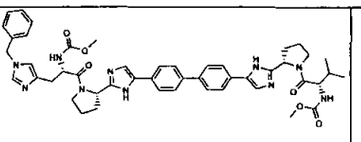
cj-71	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-(dietilamino) ciclohexil) carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo		LCMS: Análisis calculado para $C_{44}H_{58}N_8O_4$ 762; encontrado: 763 $(M+H)^+$.	51/106

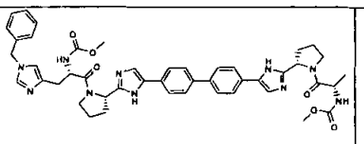
cj-72	((1S,2R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-(dietilamino) ciclohexil) carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metoxipropil) carbamato de metilo		LCMS: Análisis calculado para $C_{44}H_{58}N_8O_5$ 778; encontrado: 779 $(M+H)^+$.	86/106
cj-73	cis-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-N,N-dietilciclo hexanamina		LCMS: Análisis calculado para $C_{49}H_{62}N_8O_2$ 794; encontrado: 795 $(M+H)^+$.	2/106

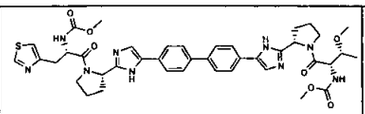
cj-74	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-(dietilamino) ciclohexil) carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{42}H_{54}N_8O_4$ 734; encontrado: 735 $(M+H)^+$.	52/106

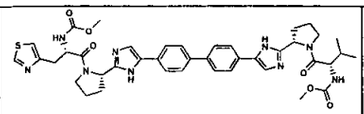
cj-75	((1S)-1-((1-bencil-1H-imidazol-4-il)metil)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-metoxi-2-((metoxicarbonil)amino)butanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{48}H_{54}N_{10}O_7$ 882; encontrado: 883 $(M+H)^+$.	86/108

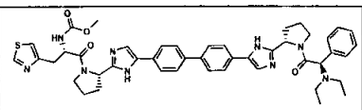
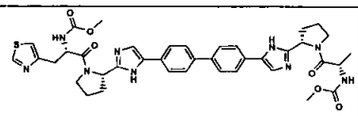
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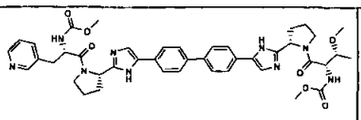
cj-76	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1-bencil-1H-imidazol-4-il)-2-((metoxicarbonil)amino)propanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo		LCMS: Análisis calculado para $C_{48}H_{54}N_{10}O_6$ 866; encontrado: 867 $(M+H)^+$.	51/108

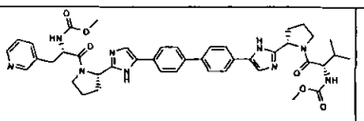
cj-77	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1-bencil-1H-imidazol-4-il)-2-((metoxicarbonil)amino)propanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{46}H_{50}N_{10}O_6$ 838; encontrado: 839 $(M+H)^+$.	52/108

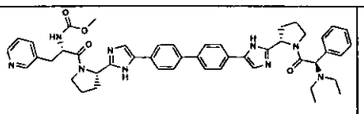
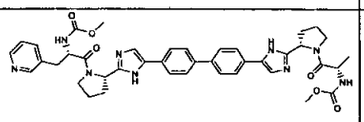
cj-78	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-metoxi-2-((metoxicarbonil)amino)butanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(1,3-tiazol-4-ilmetil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{41}H_{47}N_9O_7S$ 809; encontrado: 810 $(M+H)^+$.	86/107

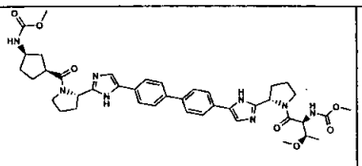
cj-79	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-(1,3-tiazol-4-il)propanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil) carbamato de metilo		LCMS: Análisis calculado para $C_{41}H_{47}N_9O_6S$ 793; encontrado: 794 $(M+H)^+$.	51/107

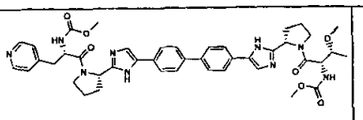
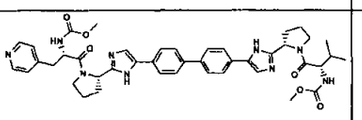
cj-80	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(1,3-tiazol-4-ilmetil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{46}H_{51}N_9O_4S$ 825; encontrado: 826 $(M+H)^+$.	2/107
cj-81	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(1,3-tiazol-4-ilmetil)etil) carbamato de metilo		LCMS: Análisis calculado para $C_{39}H_{43}N_9O_6S$ 765; encontrado: 766 $(M+H)^+$.	51/107

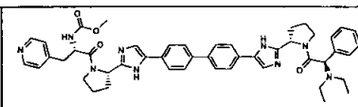
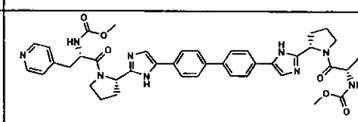
cj-82	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-metoxi-2-((metoxicarbonil)amino)butanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(3-piridinilmetil)etil)carbamato de metilo		LCMS: Análisis calculado para $C_{43}H_{49}N_9O_7$ 803; encontrado: 804 $(M+H)^+$.	86/109

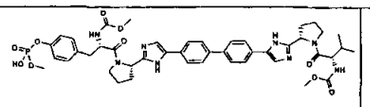
cj-83	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(3-piridinilmetil)etil)carbamato de metilo		LCMS: Análisis calculado para $C_{43}H_{49}N_9O_6$ 787; encontrado: 788 $(M+H)^+$.	51/109

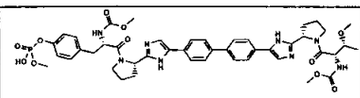
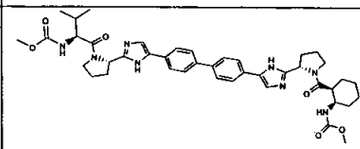
cj-84	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(3-piridinilmetil) etil)carbamato de metilo		LCMS: Análisis calculado para $C_{48}H_{53}N_9O_4$ 819; encontrado: 820 $(M+H)^+$.	2/109
cj-85	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(3-piridinilmetil) etil)carbamato de metilo		LCMS: Análisis calculado para $C_{41}H_{45}N_9O_6$ 759; encontrado: 760 $(M+H)^+$.	52/109

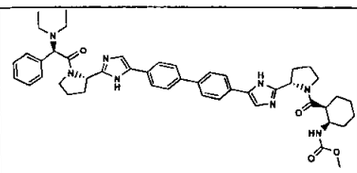
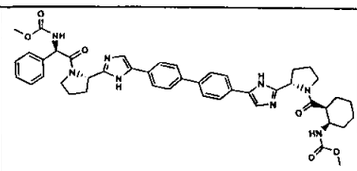
cj-86	((1R,3S)-3-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-metoxi-2-((metoxicarbonil)amino)butanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil) ciclopentil) carbamato de metilo		LCMS: Análisis calculado para $C_{42}H_{50}N_8O_7$ 766; encontrado: 767 $(M+H)^+$.	86/99

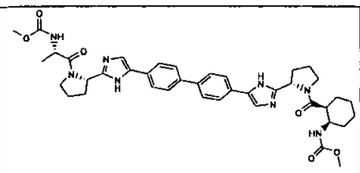
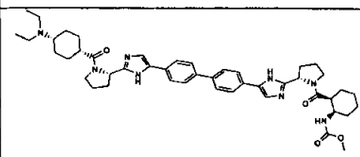
cj-87	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-metoxi-2-((metoxicarbonil)amino)butanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(4-piridinilmetil)etil)carbamato de metilo		LCMS: Análisis calculado para $C_{43}H_{49}N_9O_7$ 803; encontrado: 804 $(M+H)^+$.	86/110
cj-88	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(4-piridinilmetil)etil)carbamato de metilo		LCMS: Análisis calculado para $C_{43}H_{49}N_9O_6$ 787; encontrado: 788 $(M+H)^+$.	51/110

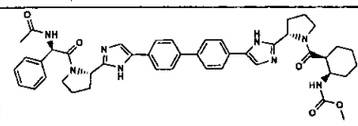
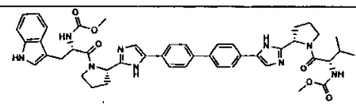
cj-89	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(4-piridinilmetil) etil)carbamato de metilo		LCMS: Análisis calculado para $C_{48}H_{53}N_9O_4$ 819; encontrado: 820 $(M+H)^+$.	2/110
cj-90	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(4-piridinilmetil) etil)carbamato de metilo		LCMS: Análisis calculado para $C_{41}H_{45}N_9O_6$ 759; encontrado: 760 $(M+H)^+$.	52/110

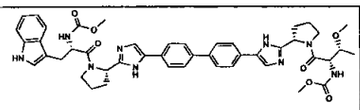
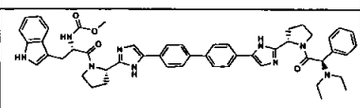
cj-91	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(O-(hidroxi(metoxi) fosforil)-N-(metoxicarbonil)-L-tirosil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo		LCMS: Análisis calculado para $C_{45}H_{53}N_8O_{10}P$ 896; encontrado: 897 $(M+H)^+$.	51/111

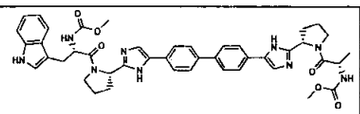
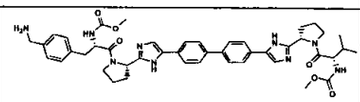
cj-92	((1S,2R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(O-(hidroxi(metoxi)fosforil)-N-(metoxicarbonil)-L-tirosil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metoxipropil)carbamato de metilo		LCMS: Análisis calculado para $C_{45}H_{53}N_8O_{11}P$ 912; encontrado: 913 $(M+H)^+$.	86/111
cj-93	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(((1S,2R)-2-((metoxicarbonil)amino)ciclohexil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo		LCMS: Análisis calculado para $C_{42}H_{52}N_8O_6$ 764; encontrado: 765 $(M+H)^+$.	98/51

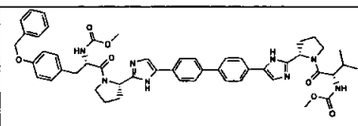
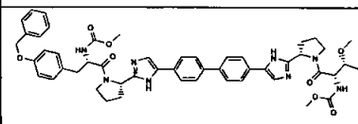
cj-94	((1R,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil) ciclohexil) carbamato de metilo		LCMS: Análisis calculado para $C_{47}H_{56}N_8O_4$ 796; encontrado: 797 $(M+H)^+$.	98/2
cj-95	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1S,2R)-2-((metoxicarbonil)amino)ciclohexil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) carbamato de metilo		LCMS: Análisis calculado para $C_{45}H_{50}N_8O_6$ 798; encontrado: 799 $(M+H)^+$.	98/4

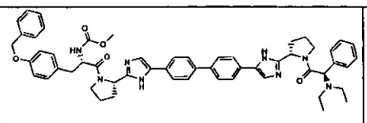
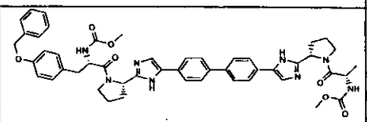
cj-96	((1R,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil) ciclohexil) carbamato de metilo		LCMS: Análisis calculado para $C_{40}H_{48}N_8O_6$ 736; encontrado: 737 $(M+H)^+$.	98/51
cj-97	((1R,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((cis-4-(dietilamino) ciclohexil) carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil) ciclohexil) carbamato de metilo		LCMS: Análisis calculado para $C_{46}H_{60}N_8O_4$ 788; encontrado: 789 $(M+H)^+$.	98/106

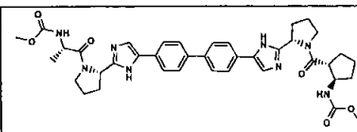
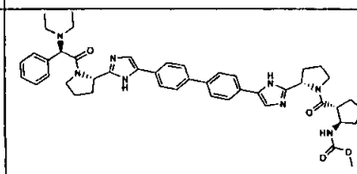
cj-98	((1R,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-acetamido-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil) ciclohexil) carbamato de metilo		LCMS: Análisis calculado para $C_{45}H_{50}N_8O_5$ 782; encontrado: 783 $(M+H)^+$.	98/130
cj-99	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1H-indol-3-il)-2-((metoxicarbonil)amino) propanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo		LCMS: Análisis calculado para $C_{56}H_{51}N_9O_6$ 825; encontrado: 826 $(M+H)^+$.	51/112

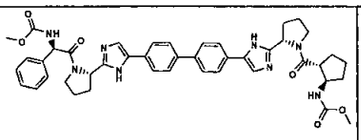
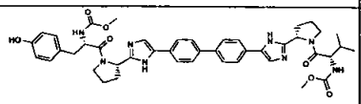
cj-100	((1S)-1-(1H-indol-3-ilmetil)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-metoxi-2-((metoxicarbonil)amino)butanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{46}H_{51}N_9O_7$ 841; encontrado: 842 $(M+H)^+$.	86/112
cj-101	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-(1H-indol-3-ilmetil)-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{51}H_{55}N_9O_4$ 857; encontrado: 858 $(M+H)^+$.	2/112

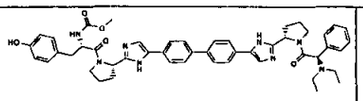
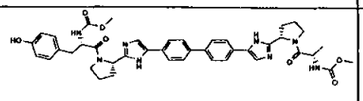
cj-102	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1H-indol-3-il)-2-((metoxicarbonil)amino)propanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{44}H_{47}N_9O_6$ 797; encontrado: 798 $(M+H)^+$.	52/112
cj-103	((1S)-1-(4-(aminometil) bencil)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil) amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{45}H_{53}N_9O_6$ 815; encontrado: 816 $(M+H)^+$.	ver texto

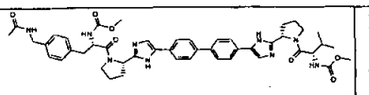
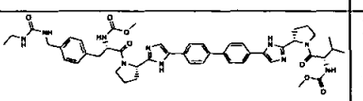
cj-104	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(O-bencil-N-(metoxicarbonil)-L-tirosil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo		LCMS: Análisis calculado para $C_{51}H_{56}N_8O_7$ 892; encontrado: 893 $(M+H)^+$.	51/113
cj-105	((1S,2R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(O-bencil-N-(metoxicarbonil)-L-tirosil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metoxipropil) carbamato de metilo		LCMS: Análisis calculado para $C_{51}H_{56}N_8O_8$ 908; encontrado: 909 $(M+H)^+$.	86/113

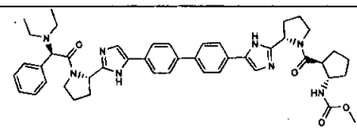
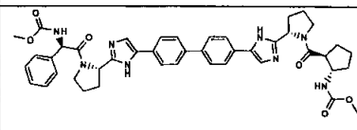
cj-106	((1S)-1-(4-(benciloxi) bencil)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{56}H_{60}N_8O_5$ 924; encontrado: 925 $(M+H)^+$.	2/113
cj-107	((1S)-1-(4-(benciloxi) bencil)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{49}H_{52}N_8O_7$ 864; encontrado: 865 $(M+H)^+$.	52/113

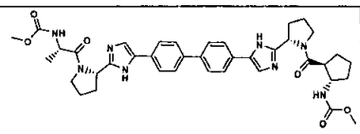
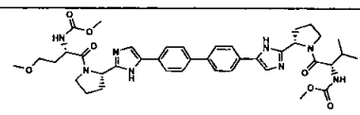
cj-108	((1R,2R)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil) ciclopentil) carbamato de metilo		LCMS: Análisis calculado para $C_{39}H_{46}N_8O_6$ 722; encontrado: 723 $(M+H)^+$.	122/52
cj-109	((1R,2R)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil) ciclopentil) carbamato de metilo		LCMS: Análisis calculado para $C_{46}H_{54}N_8O_4$ 782; encontrado: 783 $(M+H)^+$.	122/2

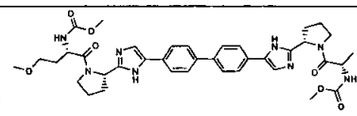
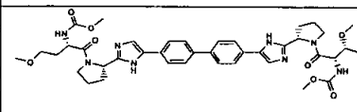
cj-110	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1R,2R)-2-((metoxicarbonil)amino)ciclopentil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) carbamato de metilo		LCMS: Análisis calculado para $C_{44}H_{48}N_8O_6$ 784; encontrado: 785 $(M+H)^+$.	122/4
cj-111	((1S)-1-(4-hidroxibencil)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{44}H_{50}N_8O_7$ 802; encontrado: 803 $(M+H)^+$.	ver texto

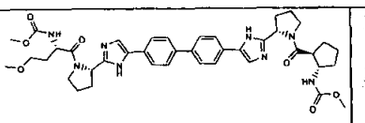
cj-112	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-(4-hidroxibencil)-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{49}H_{54}N_8O_5$ 834; encontrado: 835 $(M+H)^+$.	ver texto
cj-113	((1S)-1-(4-hidroxibencil)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{42}H_{46}N_8O_7$ 774; encontrado: 775 $(M+H)^+$.	ver texto

cj-114	((1S)-1-(4-(acetamidometil) bencil)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil) amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{47}H_{55}N_9O_7$ 857; encontrado: 585 $(M+H)^+$.	ver texto
cj-115	((1S)-1-(4-(((etilcarbamoil)amino)metil) bencil)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo		LCMS: Análisis calculado para $C_{48}H_{58}N_{10}O_7$ 886; encontrado: 887 $(M+H)^+$.	ver texto

cj-116	((1S,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil) ciclopentil) carbamato de metilo		LCMS: Análisis calculado para $C_{46}H_{54}N_8O_4$ 782; encontrado: 783 $(M+H)^+$.	121/2
cj-117	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(((1S,2S)-2-((metoxicarbonil) amino)ciclopentil)carb onil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) carbamato de metilo		LCMS: Análisis calculado para $C_{44}H_{48}N_8O_6$ 784; encontrado: 785 $(M+H)^+$.	121/4

cj-118	((1S,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil) ciclopentil) carbamato de metilo		LCMS: Análisis calculado para $C_{39}H_{46}N_8O_6$ 722; encontrado: 723 $(M+H)^+$.	121/52
cj-119	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-homoseril)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo		LCMS: Análisis calculado para $C_{40}H_{50}N_8O_7$ 754; encontrado: 755 $(M+H)^+$.	51/87

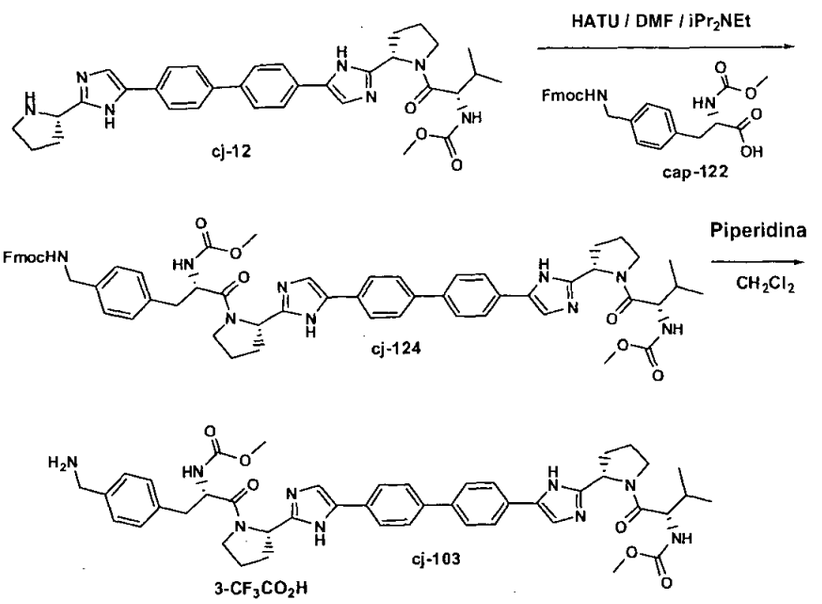
cj-120	((1S)-3-metoxi-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)propil) carbamato de metilo		LCMS: Análisis calculado para $C_{38}H_{46}N_8O_7$ 726; encontrado: 727 $(M+H)^+$.	52/87
cj-121	((1S,2R)-2-metoxi-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-homoseril)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)propil) carbamato de metilo		LCMS: Análisis calculado para $C_{40}H_{50}N_8O_8$ 770; encontrado: 771 $(M+H)^+$.	86/87

cj-122	((1S,2S)-2-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-homoseril)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil) ciclopentil) carbamato de metilo		LCMS: Análisis calculado para $C_{41}H_{50}N_8O_7$ 766; encontrado: 767 $(M+H)^+$.	121/87

Ejemplos cj-111 hasta cj-113.

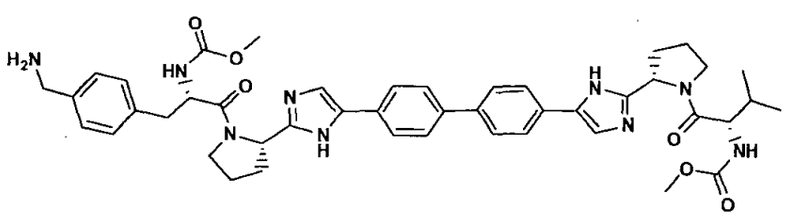
Para los ejemplos cj-111 hasta cj-113 los compuestos de los Ejemplos cj-105 hasta cj-107 se hidrogenaron bajo condiciones analogas a aquellas uadas en el Ejemplo 28, Extremo d (con la excepción de que K_2CO_3 no se empleó).

Preparación de los ejemplos cj-103, cj-114 y cj-115.



El intermediario cj-124 se preparó por acoplamiento del intermediario cj-12 y Extremo-122, como se describe en el Ejemplo 28, Extremo e. LCMS: Análisis calculado para $C_{60}H_{63}N_9O_8$ 1037; encontrado: 520 $(1/2M+H)^+$. Esto corresponde al ion molecular cargado doblemente.

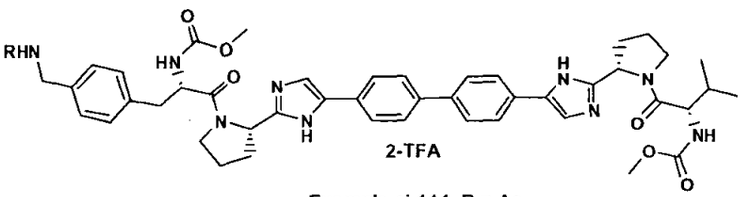
Ejemplo cj-103.



El intermediario cj-124 (83.0 mg, 0.08 mmol) se disolvió en DMF (5 mL) y piperidina (1 mL) se le agregó a

temperatura ambiente. Después de 2h los volatiles se removieron in vacuo y el residuo se purificó por HPLC preparativa (YMC-Pack C-18, 30X100mm, CH_3CN-H_2O-TFA) para dar la sal TFA de la amina (87.0 mg, 94%). LCMS: Análisis calculado para $C_{45}H_{53}N_9O_6$ 815; encontrado: 816 $(M+H)^+$.

Ejemplos cj-114 hasta cj-115.

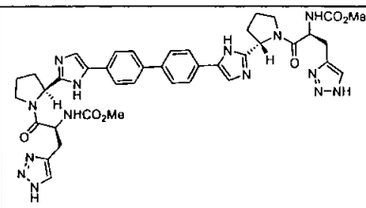


Example cj-114, R = Ac
cj-115, R = CONHEt

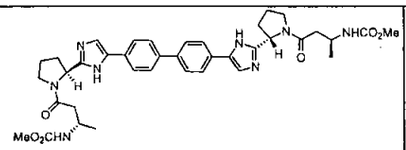
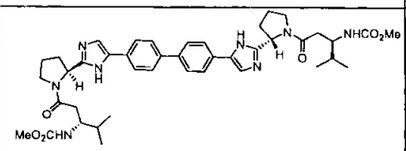
El producto del Ejemplo cj-103 se aciló con ya sea anhídrido acético o isocianato de etilo como se muestra en el esquema de reacción bajo condiciones análogas a aquellas en el Ejemplo 25. Ejemplo cj-114, LCMS: Análisis calculado para $C_{47}H_{55}N_9O_7$ 857; encontrado: 858 $(M+H)^+$.

Ejemplo cj-115, LCMS: Análisis calculado para $C_{48}H_{58}N_{10}O_7$ 886; encontrado: 887 $(M+H)^+$.

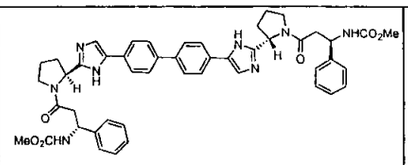
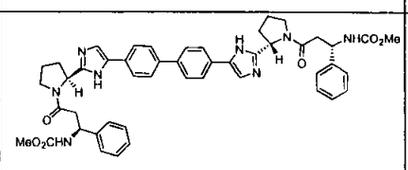
Los siguientes ejemplos se prepararon del intermediario 1e usando un procedimiento análogo al Ejemplo 1. El extremo anexada se indica en la Tabla y donde el número sin extremo se da el ácido carboxílico que es comercialmente disponible.

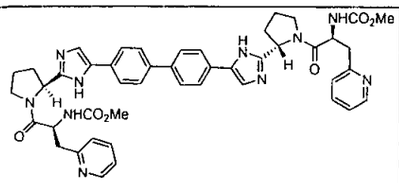
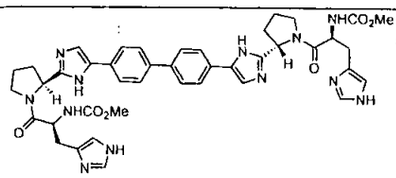
Ejemplo	Nombre del Compuesto	Estructura	Extremo	LCMS
cj-125	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-(1H-1,2,3-triazol-4-il)propanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(1H-1,2,3-triazol-4-ilmetil)etil) carbamato de metilo		128	LCMS: Análisis calculado para $C_{40}H_{44}N_{14}O_6$: 816; encontrado: 817 $(M+H)^+$.

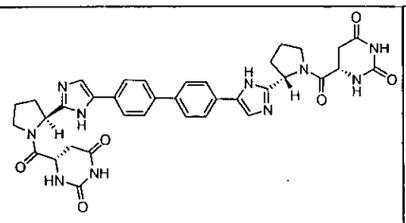
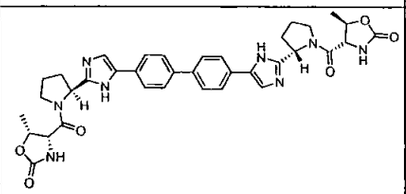
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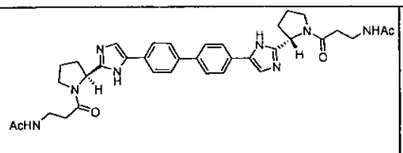
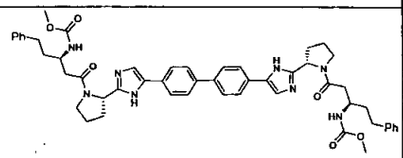
cj-126	(4,4'-bifenildiilbis (1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((2S)-4-oxo-4,2-butandiil))) biscarbamato de dimetilo		115	LCMS: Análisis calculado para $C_{38}H_{46}N_8O_6$ 710; encontrado: 711 $(M+H)^+$.
cj-127	(4,4'-bifenildiilbis (1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((3R)-4-metil-1-oxo-1,3-pentandiil))) biscarbamato de dimetilo		116	LCMS: Análisis calculado para $C_{42}H_{54}N_8O_6$ 766; encontrado: 777 $(M+H)^+$.

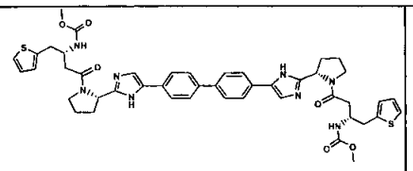
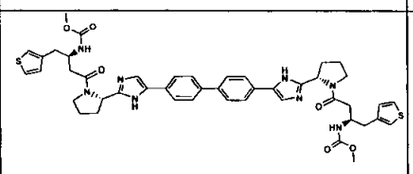
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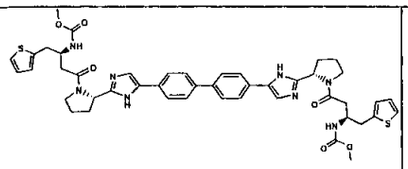
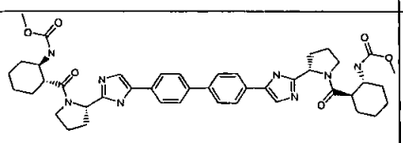
cj-128	((1R)-3-((2S)-2-(5-(4'-(2-(1-((3R)-3-((metoxicarbonil)amino)-3-fenilpropanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-3-oxo-1-fenilpropil) carbamato de metilo		92	LCMS: Análisis calculado para $C_{48}H_{50}N_8O_6$ 834; encontrado: 835 $(M+H)^+$.
cj-129	((1S)-3-((2S)-2-(5-(4'-(2-(1-((3S)-3-((metoxicarbonil)amino)-3-fenilpropanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-3-oxo-1-fenilpropil) carbamato de metilo		91	LCMS: Análisis calculado para $C_{48}H_{50}N_8O_6$ 834; encontrado: 835 $(M+H)^+$.

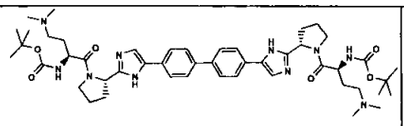
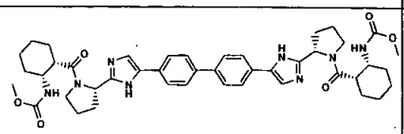
cj-130	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-(2-piridinil)propanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(2-piridinilmetil)etil)carbamato de metilo		93	LCMS: Análisis calculado para $C_{46}H_{48}N_{10}O_6$ 836; encontrado: 837 $(M+H)^+$.
cj-131	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1H-imidazol-4-il)-2-((metoxicarbonil)amino)propanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-(1H-imidazol-4-ilmetil)-2-oxoetil)carbamato de metilo		94	LCMS: Análisis calculado para $C_{42}H_{46}N_{12}O_6$ 814; encontrado: 815 $(M+H)^+$.

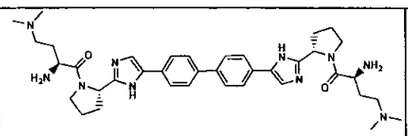
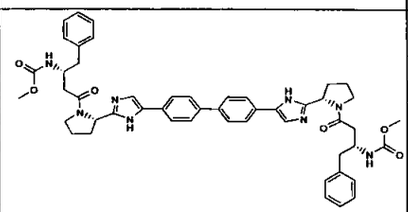
cj-132	(6S,6'S)-6,6'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil carbonil)) didihidro-2,4(1H,3H)-pirimidindiona		-	LCMS: Análisis calculado para $C_{36}H_{36}N_{10}O_6$ 704; encontrado: 705 $(M+H)^+$.
cj-133	(4S,5R,4'S,5'R)-4,4'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil carbonil))bis(5-metil-1,3-oxazolidin-2-ona)		124	LCMS: Análisis calculado para $C_{37}H_{40}N_8O_5$ 676; encontrado: 677 $(M+H)^+$.

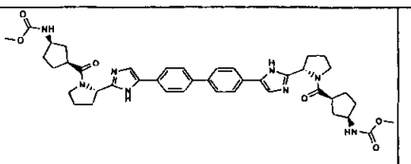
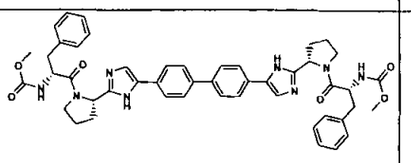
cj-134	N-(3-((2S)-2-(5-(4'-(2-((2S)-1-(3-acetamidopropanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-3-oxopropil) acetamida		-	LCMS: Análisis calculado para $C_{36}H_{42}N_8O_4$ 650; encontrado: 651 $(M+H)^+$.
cj-135	(4,4'-bifenildiilbis (1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil ((3R)-1-oxo-5-fenil-1,3-pentandiil))) biscarbamato de dimetilo		95	LCMS: Análisis calculado para $C_{52}H_{58}N_8O_6$ 890; encontrado: 890 $(M+H)^+$.

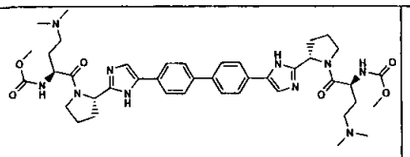
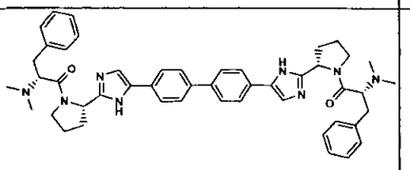
cj-136	(4,4'-bifenildiilbis (1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil ((2R)-4-oxo-1-(2-tienil)-4,2-butandiil))) biscarbamato de dimetilo		119	LCMS: Análisis calculado para $C_{46}H_{50}N_8O_6S_2$ 874; encontrado: 875 $(M+H)^+$.
cj-137	(4,4'-bifenildiilbis (1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil ((2R)-4-oxo-1-(3-tienil)-4,2-butandiil))) biscarbamato de dimetilo		120	LCMS: Análisis calculado para $C_{46}H_{50}N_8O_6S_2$ 874; encontrado: 875 $(M+H)^+$.

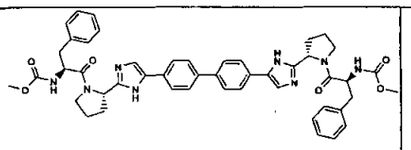
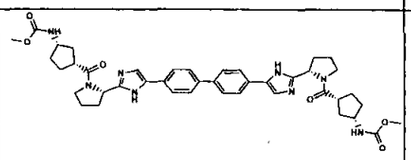
cj-138	(4,4'-bifenildiilbis (1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil ((2S)-4-oxo-1-(2-tienil)-4,2-butandiil))) biscarbamato de dimetilo		118	LCMS: Análisis calculado para $C_{46}H_{50}N_8O_6S_2$ 874; encontrado: 875 $(M+H)^+$.
cj-139	(4,4'-bifenildiilbis (1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil carbonil(1R,2R)-2,1-ciclohexandiil))bis-carbamato de dimetilo		97	LCMS: Análisis calculado para $C_{44}H_{54}N_8O_6$ 790; encontrado: 791 $(M+H)^+$.

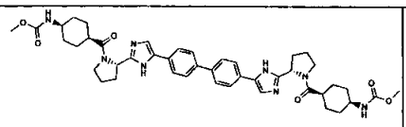
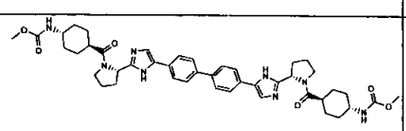
cj-140	(4,4'-bifenildiilbis (1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil ((2S)-4-(dimetilamino)-1-oxo-1,2-butandiil))) biscarbamato de di-tert-butilo		125	LCMS: Análisis calculado para $C_{48}H_{68}N_{10}O_6$ 880; encontrado: 881 $(M+H)^+$.
cj-141	(4,4'-bifenildiilbis (1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil carbonil(1R,2S)-2,1-ciclohexandiil))bis-carbamato de dimetilo		98	LCMS: Análisis calculado para $C_{44}H_{54}N_8O_6$ 790; encontrado: 791 $(M+H)^+$.

cj-142	(3S,3'S)-4,4'-(4,4'-bifenildiilbis (1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(N~1~,N~1~-dimetil-4-oxo-1,3-butandiamina)		ver texto	LCMS: Análisis calculado para $C_{38}H_{52}N_{10}O_2$ 680; encontrado: 681 $(M+H)^+$.
cj-143	(4,4'-bifenildiilbis (1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil ((2R)-4-oxo-1-fenil-4,2-butandiil))) biscarbamato de dimetilo		117	LCMS: Análisis calculado para $C_{50}H_{54}N_8O_6$ 862; encontrado: 863 $(M+H)^+$.

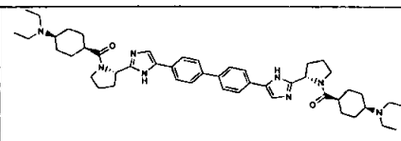
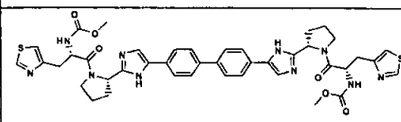
cj-144	(4,4'-bifenildiilbis (1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil carbonil(1R,3S)-3,1-ciclopentandiil))biscarbamato de dimetilo		99	LCMS: Análisis calculado para $C_{42}H_{50}N_8O_6$ 762; encontrado: 763 $(M+H)^+$.
cj-145	((1R)-1-bencil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-3-fenilpropanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo		101	LCMS: Análisis calculado para $C_{48}H_{50}N_8O_6$ 834; encontrado: 835 $(M+H)^+$.

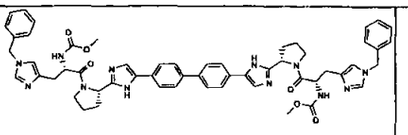
cj-146	(4,4'-bifenildiilbis (1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil ((2S)-4-(dimetilamino)-1-oxo-1,2-butandiil))) biscarbamato de dimetilo		ver texto	LCMS: Análisis calculado para $C_{42}H_{56}N_{10}O_6$ 796; encontrado: 797 $(M+H)^+$.
cj-147	(2R,2'R)-1,1'-(4,4'-bifenildiilbis (1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(N,N-dimetil-1-oxo-3-fenil-2-propanamina)		90	LCMS: Análisis calculado para $C_{48}H_{54}N_8O_2$ 774; encontrado: 775 $(M+H)^+$.

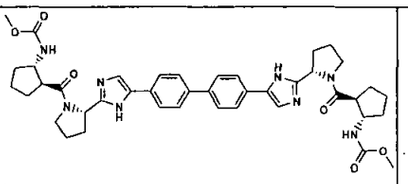
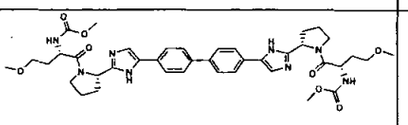
cj-148	((1S)-1-bencil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-fenilpropanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo		102	LCMS: Análisis calculado para $C_{48}H_{50}N_8O_6$ 834; encontrado: 835 $(M+H)^+$.
cj-149	(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil carbonil(1R,3S)-3,1-ciclopentandiil))biscarbamato de dimetilo		99a	LCMS: Análisis calculado para $C_{42}H_{50}N_8O_6$ 806; encontrado: 807 $(M+H)^+$.

cj-150	(4,4'-bifenildiilbis (1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil carbonilcis-4,1-ciclohexandiil)) biscarbamato de dimetilo		104	LCMS: Análisis calculado para $C_{44}H_{54}N_8O_6$ 790; encontrado: 791 $(M+H)^+$.
cj-151	(4,4'-bifenildiilbis (1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil carboniltrans-4,1-ciclohexandiil)) biscarbamato de dimetilo		105	LCMS: Análisis calculado para $C_{44}H_{54}N_8O_6$ 790; encontrado: 791 $(M+H)^+$.

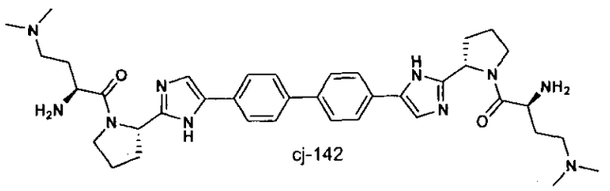
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cj-152	({cis)-4,4'-(4,4'-bifenildiilbis (1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil carbonil))bis(N,N-dietilciclo hexanamina)		106	LCMS: Análisis calculado para $C_{48}H_{66}N_8O_2$ 766; encontrado: 777 $(M+H)^+$.
cj-153	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-(1,3-tiazol-4-il)propanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-(1,3-tiazol-4-ilmetil)etil) carbamato de metilo		107	LCMS: Análisis calculado para $C_{42}H_{44}N_{10}O_6S_2$ 848; encontrado: 849 $(M+H)^+$.

cj-154	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-(1-bencil-1H-imidazol-4-il)-2-((metoxicarbonil)amino)propanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-((1-bencil-1H-imidazol-4-il)metil)-2-oxoetil) carbamato de metilo		108	LCMS: Análisis calculado para $C_{56}H_{58}N_{12}O_6$ 994; encontrado: 995 $(M+H)^+$.

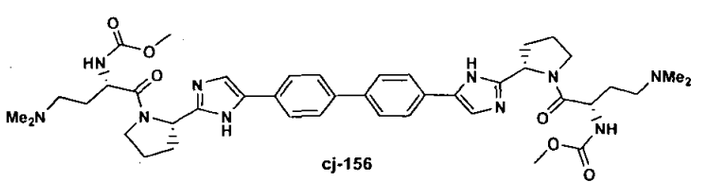
cj-155	(4,4'-bifenildiilbis (1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil carbonil(1S,2S)-2,1-ciclopentandiil))bis carbamato de dimetilo		121	LCMS: Análisis calculado para $C_{42}H_{50}N_8O_6$ 762; encontrado: 763 $(M+H)^+$.
cj-156	((1S)-3-metoxi-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-homoseril)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)propil) carbamato de metilo		87	LCMS: Análisis calculado para $C_{40}H_{50}N_8O_8$ 770; encontrado: 771 $(M+H)^+$.

Ejemplo cj-142.



El ejemplo cj-142 se preparó a partir del producto obtenido en el ejemplo cj-140 por el tratamiento con 40% TFA en CH_2Cl_2. La mezcla se permitió agitar durante 3 h a temperatura ambiente y luego se concentró in vacuo. El residuo se purificó por HPLC preparativa (YMC-Pack, C18 30X100mm, CH_3CN-H_2O-TFA).

Ejemplo cj-156.



El compuesto del ejemplo-cj-156 se preparó por carbamoilación del compuesto preparado en el ejemplo-cj-142 de conformidad al método mostrado por el extremo-51.

Sección JG

Método A: LCMS - Xterra MS C-18 3.0 x 50mm, 0 hasta 100% B durante 30.0 minuto gradiente, tiempo de espera 1 minuto, A = 5% acetonitrilo, 95% agua, 10mm acetato de

amonio, B = 95% acetonitrilo, 5% agua, 10mm acetato de amonio.

Método B: HPLC - X-Terra C-18 4.6 x 50mm, 0 hasta 100% B durante 10.0 minuto gradiente, tiempo de espera 1 minuto, A = 10% metanol 90% agua 0.1% TFA, B = 90% metanol 10% agua 0.1% TFA

Método C: HPLC - YMC C-18 4.6 x 50mm, 0 hasta 100% B durante 10.0 minuto gradiente, tiempo de espera 1 minuto, A = 10% metanol 90% agua 0.2% H_3PO_4, B = 90% metanol 10% agua 0.2% H_3PO_4.

Método D: HPLC - Phenomenex C-18 4.6 x 150mm, 0 hasta 100% B durante 10.0 minuto gradiente, tiempo de espera 1 minuto, A = 10% metanol 90% agua 0.2% H_3PO_4, B = 90% metanol 10% agua 0.2% H_3PO_4

Método E: LCMS - Gemini C-18 4.6 x 50mm, 0 hasta 100% B durante 10.0 minuto gradiente, tiempo de espera 1 minuto, A = 5% acetonitrilo, 95% agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% agua, 10mm acetato de amonio.

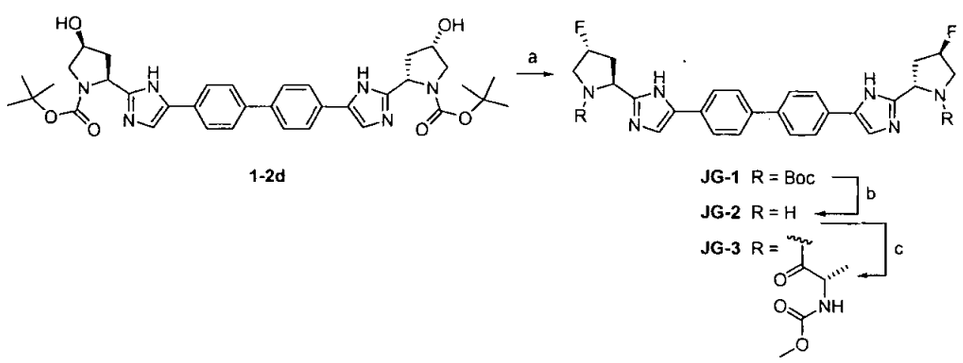
Método F: LCMS-Luna C-18 3.0 x 50mm, 0 hasta 100% B durante 7.0 minuto gradiente, tiempo de espera 1 minuto, A = 5% acetonitrilo, 95% agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% agua, 10mm acetato de amonio.

Método G: HPLC - Phenomenex Gemini C-18 4.6 x 150mm, 10 hasta 80% B durante 35 minuto gradiente, tiempo de espera 1 minuto, A = 5% acetonitrilo, 95% agua, 10mm acetato de

amonio, B = 95% acetonitrilo, 5% agua, 10mm acetato de amonio

Método H: HPLC - Phenomenex Gemini C-18 4.6 x 150mm, 10 hasta 80% B durante gradiente de 25 minutos, tiempo de espera 1 minuto, A = 5% acetonitrilo, 95% agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% agua, 10mm acetato de amonio

Método I: HPLC -Waters-X-Bridge C-18 4.6 x 150mm, 10 hasta 70% B durante gradiente de 30 minutos, tiempo de espera 1 minuto, A = 5% acetonitrilo, 95% agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% agua, 10mm acetato de amonio



Extremo a:

El 5,5'-(5,5'-(bifenil-4,4'-diil)bis(1H-imidazol-5,2-diil))bis(3-hidroxipirrolidin-1-carboxilato) de (3S,3'S,5S,5'S)-tert-butilo (1.40g, 2.13mmol) se le agregó como un sólido a una solución de trifluoruro de bis(2-metoxietil)aminoazufre (0.87mL, 4.69mmol) en 14.0mL CH_2Cl_2 se enfrió a -78°C. La reacción se agitó a -78°C durante dos horas y luego se calentó a temperatura ambiente y se agitó durante 2 horas. La reacción se vació en solución de bicarbonato de

sodio saturado y se agitó hasta que el burbujeo se detuvo. Las capas se separaron y la capa acuosa se lavaron una vez con CH_2Cl_2. Los orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron, y se concentraron para dar un aceite amarillo. El aceite se trituró con CH_2Cl_2 y pentano para proporcionar el 5,5'-(5,5'-(bifenil-4,4'-diil)bis(1H-imidazol-5,2-diil))bis(3-fluoropirrolidin-1-carboxilato) de (3R,3'R,5S,5'S)-tert-butilo JG-1 como un sólido color canela (0.98g, 71%).

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 12.10 (2H, m) 7.60-7.82 (8H, m) 7.35 (2H, m) 5.45 (1H, s) 5.35 (1H, s) 4.85-4.90 (2H, m) 3.69-3.79 (4H, m) 2.53-2.61 (2H, m) 2.28-2.37 (2H, m) 1.40 (8H, s) 1.12 (10H, s)

LCMS - Phenomenex C-18 3.0 x 50mm, 0 hasta 100% B durante 4.0 minuto gradiente, tiempo de espera 1 minuto, A = 10% metanol 90% agua 0.1% TFA, B = 90% metanol 10% agua 0.1% TFA, (t_R= 3.04 min) Anal Calculado para $C_{36}H_{42}F_2N_6O_4$ 660.70; encontrado 661.68 $(M+H)^+$

Extremo b:

A una solución de 5,5'-(5,5'-(bifenil-4,4'-diil)bis(1H-imidazol-5,2-diil))bis(3-hidroxipirrolidin-1-carboxilato) de (3R,3'R,5S,5'S)-

tert-butilo (0.098g, 1.48mmol) en 4mL dioxano se le agregó 2.0mL de una solución 4.0M de HCl en dioxano. La reacción se agitó durante 2 horas a temperatura ambiente y se concentró bajo presión reducida. El sólido color canela resultante se secó bajo vacío para dar el tetraclorohidrato de 4,4'-bis(2-((2S,4S)-4-fluoropirrolidin-2-il)-1H-imidazol-5-il)bifenilo JG-2 (0.89g, 100% de rendimiento). Sin purificación adicional.

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 9.05 (2H, s), 8.18 (2H, s), 8.00-8.09 (4H, m) 7.89 (4H, d, J=7.63 Hz) 5.71 (1H, s) 5.61 (1H, s) 5.24-5.33 (2H, m) 3.92 (2H, d, J=10.68Hz) 3.63-3.71 (2H, m) 2.79-2.89 (2H, m)

LCMS - Phenomenex C-18 3.0 x 50mm, 0 hasta 100% B durante 4.0 minuto gradiente, tiempo de espera 1 minuto, A = 10% metanol 90% agua 0.1% TFA, B = 90% metanol 10% agua 0.1% TFA, (t_R= 2.12 min) Análisis calculado para $C_{26}H_{26}F_2N_6$ 460.53; encontrado 461.37 $(M+H)^+$.

Extremo c:

A una solución agitada de tetraclorohidrato de 4,4'-bis(2-((2S,4R)-4-fluoropirrolidin-2-il)-1H-imidazol-5-il)bifenilo (0.060g, 0.10mmol), ácido (S)-2-(metoxicarbonilamino)propanoico (0.031g, 0.21mmol), y HATU (0.081g, 0.21mmol) en 3mL DMF se le agregó

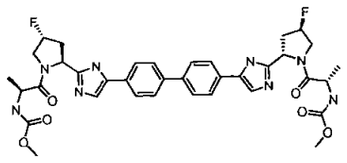
diisopropiletil amina (0.11mL, 0.61mmol). La reacción se agitó a temperatura ambiente durante la noche (16 horas) y se concentró bajo presión reducida. El producto crudo se purificó por HPLC preparativa de fase inversa y en segundo término por pasarse a través de un cartuchos de extracción Waters MCX para proporcionar el (2S,2'S)-1,1'-((3R,3'R,5S,5'S)-5,5'-(5,5'-(bifenil-4,4'-diil)bis(1H-imidazol-5,2-diil))bis(3-fluoropirrolidin-5,1-diil))bis(1-oxopropano-2,1-diil)dicarbamato de dimetilo JG-3, base libre (0.0097g, 7.5%).

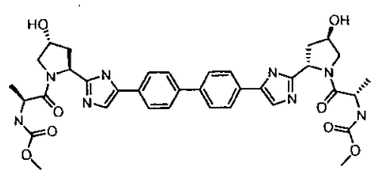
^{1}H RMN (500MHz, DMSO-d_6) δ ppm 11.91 (2H, m), 7.76-7.84 (3H, m), 7.64-7.84 (5H, m), 7.48-7.58 (2H, m), 5.55 (1H, s), 5.11 (1H, s), 4.29-4.38 (2H, m), 4.13 (2H, d, J=12.51 Hz), 3.89-3.98 (2H, m), 3.53 (6H, s), 2.54-2.64 4H, m), 1.21 (6H, s).

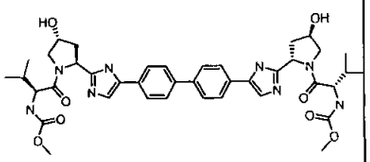
LCMS - Luna C-18 3.0 x 50mm, 0 hasta 100% B durante 7.0 minuto gradiente, tiempo de espera 1 minuto, A = 5% acetonitrilo, 95% agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% agua, 10mm acetato de amonio, (t_R=2.40 min).

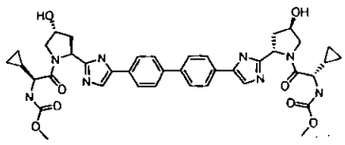
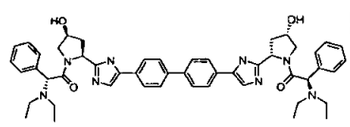
Nominal/EMBR - Calculado para $C_{36}H_{40}F_2N_8O_6$ 718.30; encontrado 719.24$(M+H)^+$.

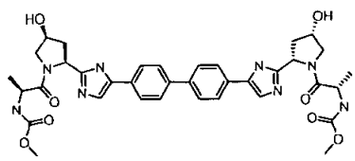
Exacto/HRMS - Calculado para $C_{36}H_{41}F_2N_8O_6$ 719.3117; encontrado 719.3114$(M+H)^+$

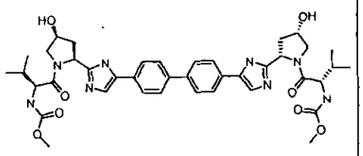
Estructura	Nombre del Compuesto	Datos
JG-3 	((1S)-2-((2S,4R)-4-fluoro-2-(5-(4'-(2-((2S,4R)-4-fluoro-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	TR = 13.60 min, método I EMBR: Análisis calculado para $C_{36}H_{40}F_2N_8O_6$ 718.30 encontrado: 719.24 $(M+H)^+$ HRMS: Análisis calculado para $C_{36}H_{41}F_2N_8O_6$ 719.3117 encontrado 719.3114 $(M+H)^+$

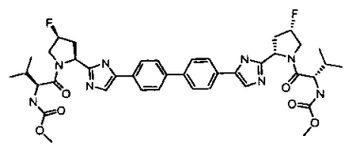
JG-4  Apartir de 1-1e y Extremo-12	((1S)-2-((2S,4R)-4-hidroxi-2-(5-(4'-(2-((2S,4R)-4-hidroxi-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	TR = 9.27 min, método H EMBR: Análisis calculado para $C_{36}H_{42}N_8O_8$ 714.77 encontrado: 715.33 $(M+H)^+$ HRMS: Análisis calculado para $C_{36}H_{43}N_8O_8$ 715.3204 encontrado: 715.3186 $(M+H)^+$

JG-5  A partir de 1-1e y Extremo-51	((1S)-1-(((2S,4R)-4-hidroxi-2-(5-(4'-(2-((2S,4R)-4-hidroxi-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	TR = 15.08 min, método G EMBR: Análisis calculado para $C_{40}H_{50}N_8O_8$ 770.88 encontrado: 771.76 $(M+H)^+$ HRMS: Análisis calculado para $C_{40}H_{51}N_8O_8$ 771.3830 encontrado: 771.3798 $(M+H)^+$

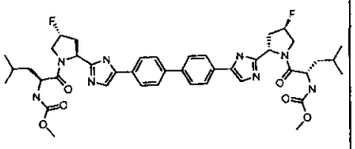
JG-6  A partir de 1-1e y Extremo-54b	(4,4'-bifenildiilbis(1H-imidazol-5,2-diil((2S,4R)-4-hidroxi-2,1-pirrolidindiil)((1S)-1-ciclopropil-2-oxo-2,1-etanediil)))biscarbamato de dimetil	TR = 13.67 min, método G EMBR: Análisis calculado para $C_{40}H_{46}N_8O_8$ 766.85 encontrado: 767.65 $(M+H)^+$ HRMS: calculado para $C_{40}H_{47}N_8O_8$ 767.3517 encontrado: 767.3483 $(M+H)^+$
JG-7  A partir de 1-2e y Extremo-2	(3S,5S,3'S,5'S)-5,5'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil))bis(1-((2R)-2-(dietilamino)-2-fenilacetil)-3-pirrolidinol)	TR = 15.88min, método H EMBR: Análisis calculado para $C_{50}H_{58}N_8O_4$ 834.45 encontrado: 835.38 $(M+H)^+$ HRMS: Análisis calculado para $C_{50}H_{59}N_8O_4$ 835.4659 encontrado: 835.4627 $(M+H)^+$

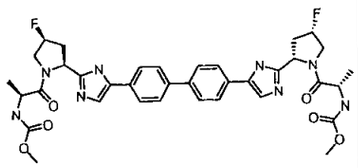
JG-8  A partir de 1-2e y Extremo-52	((1S)-2-((2S,4S)-4-hidroxi-2-(5-(4'-(2-((2S,4S)-4-hidroxi-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	TR = 9.99 min, método H EMBR: Análisis calculado para $C_{36}H_{42}N_8O_8$ 714.77 encontrado: 715.71 $(M+H)^+$ HRMS: Análisis calculado para $C_{36}H_{43}N_8O_8$ 715.3204 encontrado: 715.3188 $(M+H)^+$

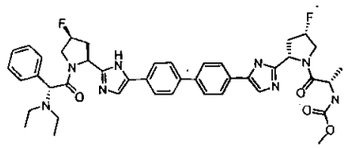
JG-9  A partir de 1-2e y Extremo-51	((1S)-1-(((2S,4S)-4-hidroxi-2-(5-(4'-(2-((2S,4S)-4-hidroxi-1-((2S)-2-((metoxi carbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil) carbamato de metilo	TR = 14.12 min, método H EMBR: Análisis calculado para $C_{40}H_{50}N_8O_8$ 770.88 encontrado: 771.74 $(M+H)^+$ HRMS: Análisis calculado para $C_{40}H_{51}N_8O_8$ 771.3830 encontrado: 771.3799 $(M+H)^+$

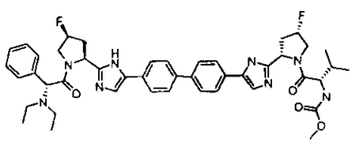
JG-10  A partir de 1-2e2 y Extremo-51	((1S)-1-(((2S,4S)-4-fluoro-2-(5-(4'-(2-((2S,4S)-4-fluoro-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil)carbamato de metilo	TR = 17.66 min, método I EMBR: Análisis calculado para $C_{40}H_{48}F_2N_8O_6$ 774.86 encontrado: 775.49 $(M+H)^+$ HRMS: Análisis calculado para $C_{40}H_{49}F_2N_8O_6$ 775.3743 encontrado: 775.3717 $(M+H)^+$

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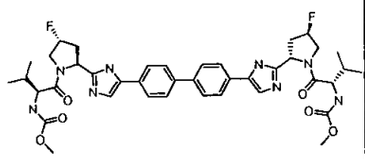
JG-12  A partir de ácido (S)-2-(metoxicarbonilamino)-4-metilpentanoico y JG-2	((1S)-1-(((2S,4R)-4-fluoro-2-(5-(4'-(2-((2S,4R)-4-fluoro-1-((2S)-2-((metoxi carbonil)amino)-4-metilpentanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-3-metilbutil) carbamato de metilo	TR = 9.69 min, método I EMBR: Análisis calculado para $C_{42}H_{52}F_2N_8O_6$ 802.92 encontrado: 803.42 $(M+H)^+$ HRMS: Análisis calculado para $C_{42}H_{53}F_2N_8O_6$ 803.4056 encontrado: 803.4018 $(M+H)^+$

JG-13  A partir de 1-2e2 y Extremo-52	((1S)-2-((2S,4S)-4-fluoro-2-(5-(4'-(2-((2S,4S)-4-fluoro-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil) carbamato de metilo	TR = 13.60 min, método I EMBR: Análisis calculado para $C_{36}H_{40}F_2N_8O_6$ 718.30 encontrado: 719.45 $(M+H)^+$ HRMS: Análisis calculado para $C_{36}H_{41}F_2N_8O_6$ 719.3117 encontrado 719.3090 $(M+H)^+$

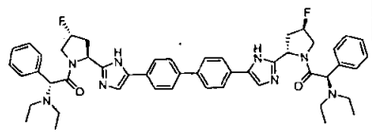
JG-14  A partir de JG-25 y Extremo-52	((1S)-2-((2S,4S)-2-(5-(4'-(2-((2S,4S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-4-fluoro-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-4-fluoro-1-pirrolidinil)-1-metil-2-oxoetil) carbamato de metilo	TR = 15.13 min, método I LCMS: Análisis calculado para $C_{43}H_{48}F_2N_8O_4$ 778.91 encontrado: 779.79 $(M+H)^+$

JG-15  A partir de JG-25 y Extremo-51	((1S)-1-(((2S,4S)-2-(5-(4'-(2-((2S,4S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-4-fluoro-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-4-fluoro-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	TR = 17.51 min, método I LCMS: Análisis calculado para $C_{45}H_{52}F_2N_8O_4$ 806.96 encontrado: 807.50 $(M+H)^+$

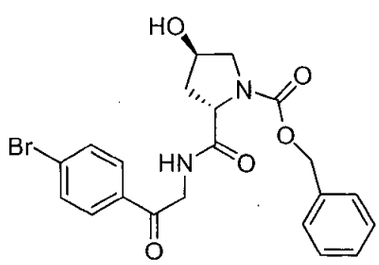
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JG-16  A partir de JG-2 y Extremo-51	((1S)-1-(((2S,4R)-4-fluoro-2-(5-(4'-(2-((2S,4R)-4-fluoro-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	TR =16.51 min, método I EMBR: Análisis calculado para $C_{40}H_{48}F_2N_8O_6$ 774.86 encontrado: 775.39 $(M+H)^+$ HRMS: Análisis calculado para $C_{40}H_{49}F_2N_8O_6$ 775.3743 encontrado: 775.3740 $(M+H)^+$

001557

JG-17  A partir de JG-2 y Extremo-2	(1R,1'R)-2,2'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil((2S,4R)-4-fluoro-2,1-pirrolidindiil))bis(N,N-dietil-2-oxo-1-feniletanamina)	TR = 8.13 min, método I LCMS: Análisis calculado para $C_{50}H_{56}F_2N_8O_2$ 839.04 encontrado: 839.46 $(M+H)^+$ HRMS: Análisis calculado para $C_{50}H_{57}F_2N_8O_2$ 839.4572 encontrado: 839.4543 $(M+H)^+$

La síntesis del JG-18 como en el ejemplo 28 Extremo a usando hidroxiprolina en lugar de prolina.



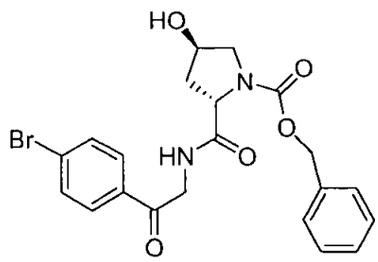
JG-18

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 7.89(2H, t, J=8.39 Hz)

7.74 (2H, t, J=8.24 Hz) 7.28-7.37 (5H, m) 5.01-5.08 (3H, m) 4.27-4.57 (4H, m) 3.44-3.53 (1H, m) 3.37(1H, d, J=10.99 Hz) 2.12 (1H, d, J=11.60 Hz) 1.93 (1H, dd, J=12.05 Hz, 6.56 Hz)

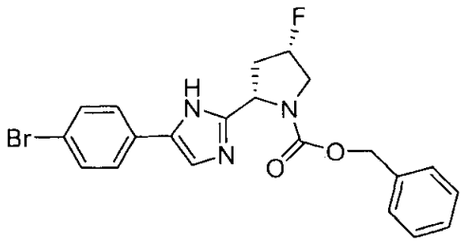
LCMS - Phenomenex C-18 3.0 x 50mm, 0 hasta 100% B durante 4.0 minuto gradiente, tiempo de espera 1 minuto, A = 10% metanol 90% agua 0.1% TFA, B = 90% metanol 10% agua 0.1% fase móvil TFA, t_R= 3.62 min, Análisis calculado para $C_{21}H_{21}BrN_2O_5$ 461.32; encontrado 462.64 $(M+H)^+$.

La síntesis del JG-19 a partir de JG-18 como en el ejemplo 28 Extremo b.



JG-19

LCMS - Luna C-18 3.0 x 50mm, 0 hasta 100% B durante 4.0 minuto gradiente, tiempo de espera 1 minuto, A = 5% acetonitrilo, 95% agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% agua, 10mm acetato de amonio, t_R= 1.88 min, Análisis calculado para $C_{21}H_{20}BN_3O_3$ 441.07; encontrado 442.22 $(M+H)^+$

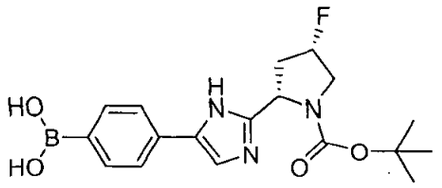


JG-20

El 2-(5-(4-bromofenil)-1H-imidazol-2-il)-4-hidroxipirrolidin-1-carboxilato de (2S,4R)-bencilo (1.5g, 3.4mmol) se le agregó como un sólido a una solución de trifluoruro de bis(2-metoxietil) aminoazufre (0.98mL, 5.1mmol) en 15mL CH_2Cl_2 se enfrió a -78°C. La reacción se agitó a -78°C durante dos horas y luego se calentó a temperatura ambiente y se agitó durante 2 horas. La reacción se vació en solución de bicarbonato de sodio saturado y se agitó hasta que el burbujeo se detuvo. Las capas se separaron y la capa acuosa se lavó una vez con CH_2Cl_2. Los orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron, y se concentraron para dar un aceite amarillo. El aceite se trituró con CH_2Cl_2 y pentano para proporcionar el 2-(5-(4-bromofenil)-1H-imidazol-2-il)-4-fluoropirrolidin-1-carboxilato de (2S,4S)-bencilo JG-20 como un sólido amarillo (0.96g, 62%).

^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 7.70 (2H, d, J=7.02 Hz) 7.48-7.55 (3H, m) 7.41 -7.35 (3H, m) 7.19-7.11 (2H, m) 5.15 - 5.02 (3H, m) 3.84 -3.78 (2H, m) 3.33 (2H, s) 2.53-2.61 (1H, m) 2.33-2.42 (1H, m)

LCMS - Luna C-18 3.0 x 50mm, 0 hasta 100% B durante 4.0 minuto gradiente, tiempo de espera 1 minuto, A = 5% acetonitrilo, 95% agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% agua, 10mm acetato de amonio, t_R= 2.10 min, Análisis calculado para $C_{21}H_{19}Br_1F_1N_3O_2$ 443.06; encontrado 444.05 $(M+H)^+$



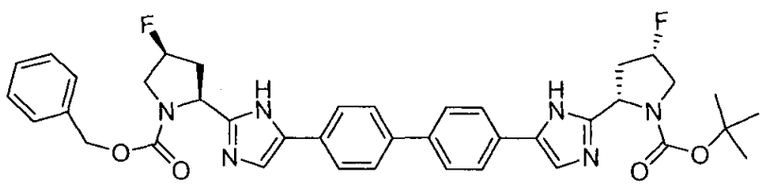
JG-21

El 4-hidroxi-2-(5-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (2S,4R)-tert-butilo, 1-2c (1.5g, 3.3mmol) se le agregó como un sólido a una solución de trifluoruro de bis(2-metoxietil) aminoazufre (0.91mL, 5.0mmol) en 15mL CH_2Cl_2 se enfrió a -78°C. La reacción se agitó a -78°C durante dos horas y luego se calentó a temperatura ambiente y se agitó durante 2 horas. La reacción se vació en solución de bicarbonato de sodio saturado y se agitó hasta que el burbujeo se detuvo. Las capas se separaron y la capa acuosa se lavó una vez con CH_2Cl_2. Los orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron, y se concentraron para dar un aceite café. El aceite se sometió a cromatografía en gel de sílice con 5% MeOH/CH_2Cl_2 para

proporcionar el ácido 4-(2-((2S,4S)-1-(tert-butoxicarbonil)-4-fluoropirrolidin-2-il)-1H-imidazol-5-il)fenilborónico como un sólido color canela (0.46g, 37%).

LCMS - Luna C-18 3.0 x 50mm, 0 hasta 100% B durante 4.0 minuto gradiente, tiempo de espera 1 minuto, A = 5% acetonitrilo, 95% agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% agua, 10mm acetato de amonio, t_R= 1.46 min, Análisis calculado para $C_{18}H_{23}B_1F_1N_3O_4$ 375.18; encontrado 376.12 $(M+H)^+$.

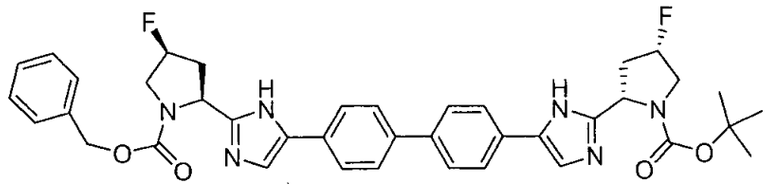
El JG-22 se sintetizó a partir del JG-20 y JG-21 como se describe en el ejemplo 28 Extremo c.



JG-22

LCMS - Luna C-18 3.0 x 50mm, 0 hasta 100% B durante 4.0 minuto gradiente, tiempo de espera 1 minuto, A = 5% acetonitrilo, 95% agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% agua, 10mm acetato de amonio, t_R= 2.27 min, Análisis calculado para $C_{39}H_{40}F_2N_6O_4$ 694.31; encontrado 695.35 $(M+H)^+$

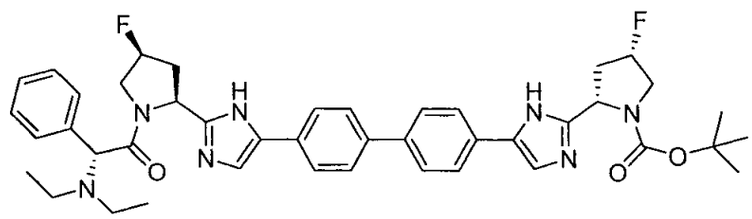
El JG-23 se sintetizó a partir del JG-22 como se describe en el ejemplo 28 Extremo d.



JG-23

LCMS - Phenomenex C-18 3.0 x 50mm, 0 hasta 100% B durante 4.0 minuto gradiente, tiempo de espera 1 minuto, A = 10% metanol 90% agua 0.1% TFA, B = 90% metanol 10% agua 0.1% Fase móvil TFA, t_R= 2.62 min, Análisis calculado para $C_{31}H_{34}F_2N_6O_2$ 560.27; encontrado 561.52 $(M+H)^+$.

El JG-24 se sintetizó a partir del JG-22 y Extremo-2 como en el ejemplo 28 Extremo e.

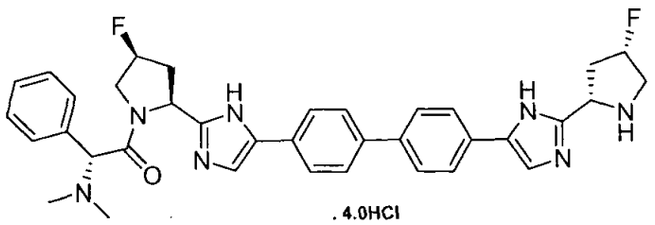


JG-24

LCMS - Luna C-18 3.0 x 50mm, 0 hasta 100% B durante 4.0 minuto gradiente, tiempo de espera 1 minuto, A = 5% acetonitrilo, 95% agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% agua, 10mm acetato de amonio, t_R= 2.30 min, Análisis calculado para $C_{41}H_{45}F_2N_7O_3$ 721.36; encontrado 722.42 $(M+H)^+$

El JG-25 se sintetizó a partir del JG-24 por medio de la

reacción con HCl metanolico como se describe en el ejemplo LS14 Extremo b.



JG-25

LCMS - Luna C-18 3.0 x 50mm, 0 hasta 100% B durante 4.0 minuto gradiente, tiempo de espera 1 minuto, A = 5% acetonitrilo, 95% agua, 10mm acetato de amonio, B = 95% acetonitrilo, 5% agua, 10mm acetato de amonio, t_R= 1.98 min, Análisis calculado para $C_{36}H_{37}F_2N_7O_1$ 621.30; encontrado 622.48 $(M+H)^+$

Sección OL Condiciones CL:

Condición 1: Solvente A: 5% acetonitrilo/95% agua/10mmol acetato de amonio; Solvente B: 95% acetonitrilo/5% agua/10mmol acetato de amonio; Columna: Phenomenex GEMINI 5u C18 4.6 x 5.0mm; Longitud de onda: 220nM; Relación de flujo: 4 ml / min; 0%B hasta 100% B durante 3 min con un tiempo de espera de 1 minuto.

Condición 2: Solvente A: 5% acetonitrilo/95% agua/10mmol acetato de amonio; Solvente B: 95% acetonitrilo/5% agua/10mmol acetato de amonio; Columna: Phenomenex GEMINI 5u

C18 4.6 x 5.0mm; Longitud de onda: 220nM; Relación de flujo: 4 ml/min; 0%B hasta 100% B durante 2 min con un tiempo de espera de 1 minuto.

Condición 3: Solvente A: 5% acetonitrilo/95% agua/10mmol acetato de amonio; Solvente B: 95% acetonitrilo/5% agua/10mmol acetato de amonio; Columna: Phenomenex GEMINI 5u C18 4.6 x 5.0mm; Longitud de onda: 220nM; Relación de flujo: 4 ml/min; 0%B hasta 100% B durante 4 min con un tiempo de espera de 1 minuto.

Condición 4: Solvente A: 10%MeOH/90% agua/0.1% TFA; Solvente B: 90% MeOH/10% agua/0.1% TFA; Columna: Phenomenex 10u C18 3.0 x 5.0mm; Longitud de onda: 220nM; Relación de flujo: 4ml/min; 0%B hasta 100% B durante 4 min con un tiempo de espera de 1 minuto.

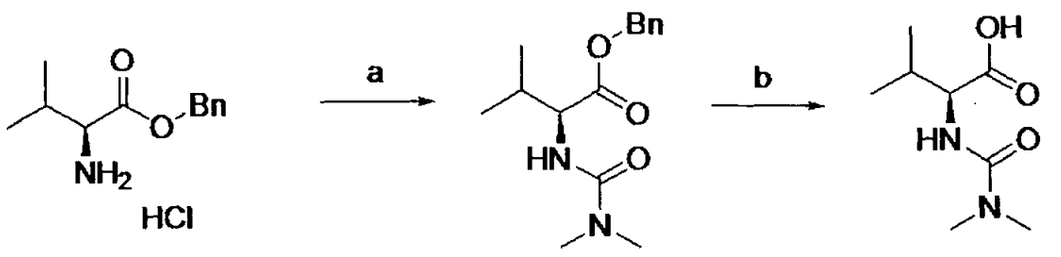
Condición 5: Solvente A: 5% acetonitrilo/95% agua/10mmol acetato de amonio; Solvente B: 95% acetonitrilo/5% agua/10mmol acetato de amonio; Columna: Phenomenex GEMINI 5u C18 4.6 x 5.0mm; Longitud de onda: 220nM; Relación de flujo: 4 ml/min; 0%B hasta 100% B durante 9 min con un tiempo de espera de 1 minuto.

Condición 6: Solvente A: 10% MeOH/90% agua/0.2% H_3PO_4; Solvente B: 90% MeOH/10% agua/0.2% H_3PO_4; Columna: Phenomenex 5u C-18 4.6 x 50mm; Longitud de onda: 220nM; Relación de flujo: 1.5ml/min; 0%B hasta 100% B durante 14 min con un tiempo de espera de 3 minutos.

Condición 7: Solvente A: 10% MeOH/90% agua/0.1% TFA; Solvente B: 90% MeOH/10% agua/0.1% TFA; Columna: Phenomenex 10u C18 3.0 x 5.0mm; Longitud de onda: 220nM; Relación de flujo: 4ml/min; 0%B hasta 100% B durante 3 min con un tiempo de espera de 1 minuto.

Condición 8: Solvente A: 10%MeOH/90% agua/0.1% TFA; Solvente B: 90% MeOH/10% agua/0.1% TFA; Columna: Phenomenex 10u C18 3.0 x 5.0mm; Longitud de onda: 220nM; Relación de flujo: 4ml/min; 0%B hasta 100% B durante 2 min con un tiempo de espera de 1 minuto.

Extremos experimentales:



Extremo del intermdiario OL-1 Extremo OL-2

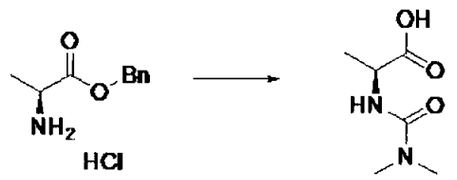
Extremo a: El cloruro de dimetilcarbamoilo (0.92 mL, 10 mmol) se le agregó lentamente a una solución de clorohidrato de 2-amino-3-metilbutanoato de (S)-bencilo (2.44 g; 10 mmol) y base Hunig (3.67 mL, 21 mmol) en THF (50 mL). La suspensión blanca resultante se agitó a temperatura ambiente durante la noche (16 horas) y se concentró 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 por cromatografía instantánea, se eluyó con acetato de etilo:hexanos (1:1). Las fracciones colectadas se concentraron bajo vacío proporcionando 2.35 g (85%) del extremo del intermediario OL-1 como un aceite claro. ^1H 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). CL (Cond. 1): TR = 1.76 min; EM: Análisis calculado para $[M+H]^+$ $C_{16}H_{22}N_2O_3$: 279.17; encontrado 279.03.

Extremo b: A el extremo del intermediario OL-1 (2.35 g; 8.45 mmol) en 50 ml MeOH se le agregó Pd/C (10%; 200 mg) y la suspensión negra resultante se mojó con N_2 (3x) y se colocó bajo 1 átomo 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 clara resultante luego se concentró bajo presión reducida para obtener 1.43 g (89%) del extremo OL-2 como una espuma blanca, la cual se usó sin purificación adicional. ^1H 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,

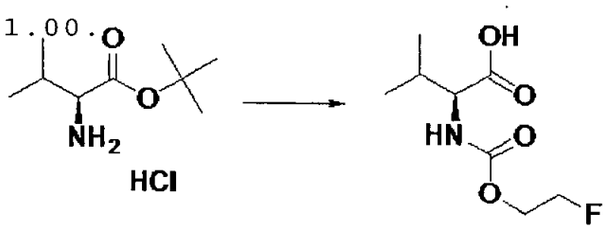
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J=8.39, 6.87 Hz, 1H) 5.93 (d, J=8.54 Hz, 1H) 12.36 (s, 1H).). CL (Cond. 1): TR = 0.33 min; EM: Análisis calculado para $[M+H]^+$ $C_8H_{17}N_2O_3$: 1898.12; encontrado 189.04.



Extremo OL-3

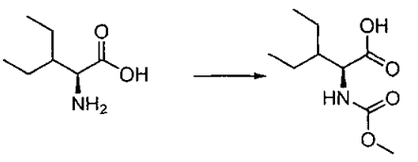
El extremo OL-3 se preparó a partir de clorohidrato de 2-aminopropanoato de (S)-bencilo de conformidad al método descrito por el extremo OL-2. ^1H RMN (500 MHz, DMSO-d_6) δ ppm 1.27 (d, J=7.32 Hz, 3H) 2.80 (s, 6H) 4.06 (qt, 1H) 6.36 (d, J=7.32 Hz, 1H) 12.27 (s, 1H). CL (Cond. 1): TR = 0.15 min; EM: Análisis calculado para $[M+H]^+$ $C_6H_{13}N_2O_3$: 161.09; encontrado 161.00.



Extremo OL-4

El extremo OL-4 se preparó a partir de clorohidrato de 3-metilbutanoato de (S)-tert-butilo y

cloroformiato de 2-fluoroetilo de conformidad al método descrito por el 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)

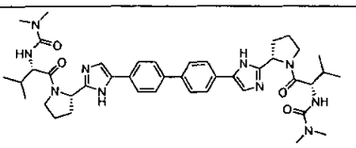


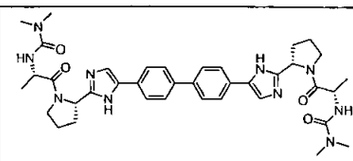
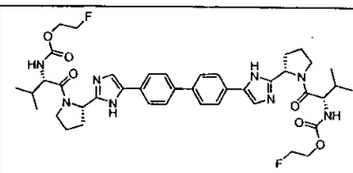
Extremo OL-5

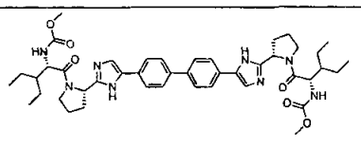
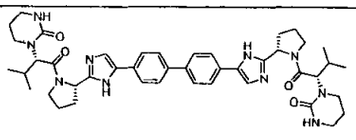
El extremo OL-5 se preparó a partir de (S)-dietil alanina y cloroformiato de metilo de conformidad al método descrito por el extremo-51. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 0.72-0.89 (m, 6H) 1.15-1.38 (m, 4H) 1.54-1.66 (m, 1H) 3.46-3.63 (m, 3H) 4.09 (dd, J=8.85, 5.19 Hz, 1H) 7.24 (d, J=8.85 Hz, 1H) 12.55 (s, 1H). CL (Cond. 2): TR = 0.66 min; EM: Análisis calculado para $[M+H]^+$ $C_9H_{18}NO_4$:204.12; encontrado 204.02.

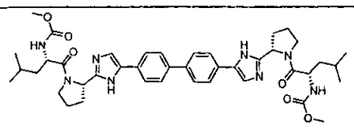
Nuevos ejemplos:

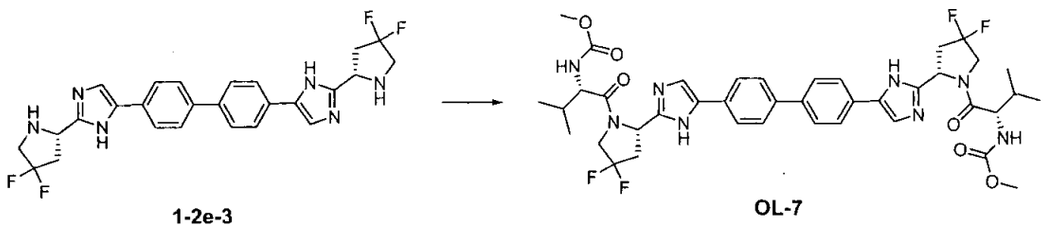
Los siguientes análogos se prepararon a partir del 1e de manera similar a la preparación del ejemplo 1 y empleando el extremo apropiada.

Número de Ejemplo	Nombre del Compuesto	Estructura	Datos Analíticos
OL-1	3-((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((dimetil carbamoil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil)-1,1-dimetilurea	 A partir de 1e y extremo OL-2	LC/MS: 2.16 min (Cond'n 3); Análisis calculado para $[M+H]^+$ $C_{42}H_{57}N_{10}O_4$: 765.45; encontrado 765.47.

OL-2	3-((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(dimetil carbamoil)-L-alanil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)-1,1-dimetilurea	 A partir de 1e y extremo OL-3	LC/MS: 1.86 min (Cond'n 3); Análisis calculado para $[M+H]^+$ $C_{38}H_{49}N_{10}O_4$: 709.39; encontrado 709.43.
OL-3	((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-(((2-fluoroetoxi) carbonil) amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de 2-fluoroetilo	 A partir de 1e y extremo OL-4	LC/MS: 2.83 min (Cond'n 4); Análisis calculado para $[M+H]^+$ $C_{42}H_{53}F_2N_8O_6$: 803.40; encontrado 803.47.

OL-4	((1S)-2-etil-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-3-etil-2-((metoxicarbonil)amino)pentanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)butil)carbamato de metilo	 A partir de 1e y Extremo OL-5	LC/MS: 2.64 min (Cond'n 3); Análisis calculado para $[M+H]^+$ $C_{44}H_{59}N_8O_6$: 795.45; encontrado 795.48.
OL-5	1,1'-(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(2S)-2,1-pirrolidindiil((2S)-3-metil-1-oxo-1,2-butanodiil)))ditetrahidro-2(1H)-pirimidinona	 A partir de 1e y ácido (S)-3-metil-2-(2-oxotetrahidropirimidin-1(2H)-il)butanoico	LC/MS: 2.95 min (Cond'n 4); Análisis calculado para $[M+H]^+$ $C_{44}H_{57}N_{10}O_6$: 789.46; encontrado 789.52.

OL-6	((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-4-metilpentanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-3-metilbutil) carbamato de metilo	 A partir de 1e y ácido (S)-2-(metoxicarbonilamino)-4-metilpentanoico que se preparó de L-Isoleucina y metilcloroformiato de manera similar a la preparación de el extremo-51	LC/MS: 2.95 min (Cond'n 3); Análisis calculado para $[M+H]^+$ $C_{42}H_{53}N_8O_6$: 767.42; encontrado 767.43.



1-2e-3 OL-7

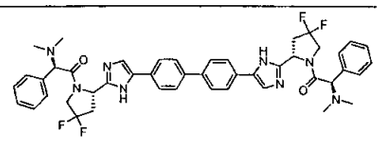
Ejemplo OL-7

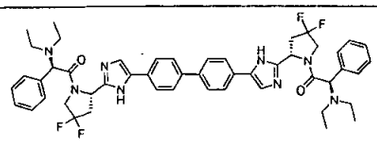
((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-4,4-difluoro-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

El ejemplo OL-7 se preparó a partir de 1-2e-3 de manera similar a la preparación del ejemplo 1, usando el extremo-51 como el compañero de acoplamiento. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 0.80 (dd, J=6.41, 2.44 Hz, 12H) 1.87-1.98 (m, 2H) 2.79-2.91 (m, 2H) 3.01-3.13 (m, 2H) 3.54 (s, 6H) 3.98 (t, J=7.93 Hz, 2H) 4.22-4.37 (m, 2H) 4.52 (t, J=14.19 Hz, 2H) 5.31 (t, J=8.39 Hz, 2H) 7.50 (d, J=7.93 Hz, 2H) 7.82-7.87 (m, 4H) 7.88-7.97 (m, 6H) 8.08 (s, 2H). CL (Cond'n 6): 7.64 min; EM: Análisis calculado para $[M+H]^+$ $C_{40}H_{47}F_4N_8O_6$: 811.35; encontrado 811.46. HRMS: Análisis calculado para $(M+H)^+$ $C_{40}H_{47}F_4N_8O_6$ 811.3549 encontrado 811.3553.

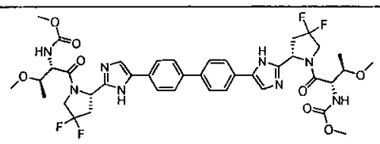
Los siguientes análogos se prepararon a partir de 1-2e-3 de manera similar a la preparación del ejemplo 1 y empleando

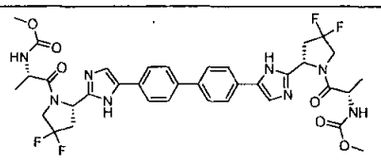
el extremo apropiada.

Número de Ejemplo	Nombre del Compuesto	Estructura	Datos Analíticos
OL-8	(1R,1'R)-2,2'-(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((2S)-4,4-difluoro-2,1-pirrolidindiil)))bis(N,N-dimetil-2-oxo-1-fenil etanamina)	 A partir de 1-2e-3 y Extremo-1	LC/MS: 3.98 min (Cond'n 5); Análisis calculado para $[M+H]^+$ $C_{46}H_{47}F_4N_8O_2$: 819.37; encontrado 819.78.

OL-9	(1R,1'R)-2,2'-(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((2S)-4,4-difluoro-2,1-pirrolidindiil)))bis(N,N-dietil-2-oxo-1-fenil etanamina)	 A partir de 1-2e-3 y Extremo-2	LC/MS: 4.58 min (Cond'n 5); Análisis calculado para $[M+H]^+$ $C_{50}H_{55}F_4N_8O_2$: 875.449; encontrado 875.90.

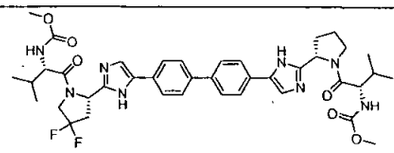
001576

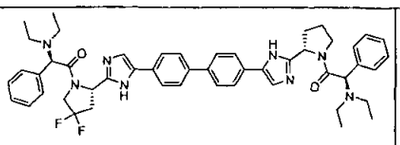
OL-10	((1S,2R)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-(N-(metoxicarbonil)-O-metil-L-threonyl)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-4,4-difluoro-1-pirrolidinil)carbonil)-2-metoxipropil)carbamato de metilo	 A partir de 1-2e-3 y Extremo-86	LC/MS: 2.18 min (Cond'n 7); Análisis calculado para $[M+H]^+$ $C_{40}H_{47}F_4N_8O_8$: 843.84; encontrado 844.04.

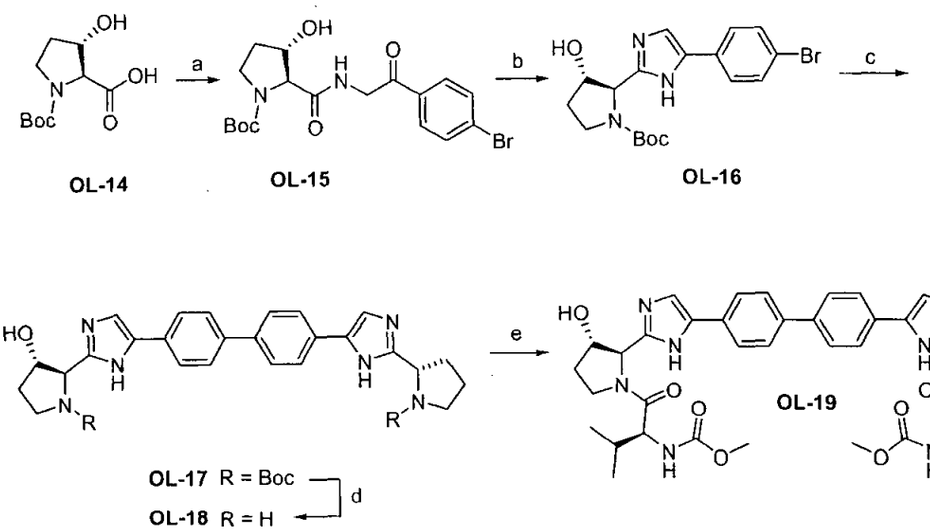
OL-11	((1S)-2-((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-4,4-difluoro-1-pirrolidinil)-1-metil-2-oxoetil) carbamato de metilo	 A partir de 1-2e-3 y Extremo-52	LC/MS: 2.04 min (Cond'n 7); Análisis calculado para $[M+H]^+$ $C_{36}H_{39}F_4N_8O_6$: 755.29; encontrado 755.78.

001578

Los siguientes análogos se prepararon a partir de 1-3e de manera similar a la preparación del ejemplo 1 y empleando el extremo apropiada.

Número de Ejemplo	Nombre del Compuesto	Estructura	Datos Analíticos
OL-12	((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2S)-2-((metoxi carbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 A partir de 1-3e y Extremo-51	LC/MS: 2.33 min (Cond'n 3); Análisis calculado para $[M+H]^+$ $C_{40}H_{49}F_2N_8O_2$: 775.37; encontrado 775.37.

OL-13	rac-(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-4,4-difluoro-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dietil-2-oxo-1-feniletanamina	 A partir de 1-3e y Extremo-2	LC/MS: 3.93 min (Cond'n 5); Análisis calculado para $[M+H]^+$ $C_{50}H_{57}F_2N_8O_2$: 839.40; encontrado 839.93.



Ejemplo OL-19

((1S)-1-(((2R,3S)-3-hidroxi-2-(4-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

Extremo a: El intermediario OL-15 se preparó en una manera similar como el intermediario 1a, en donde N-Boc-L-prolina se substituyó por N-Boc-trans-3-hidroxi-L-prolina. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.34/1.4) (2 br. s., 9H) 1.65-1.77 (m, 1H) 1.83-1.95 (m, 1H) 3.33-3.42 (m, 1H) 3.43-3.51 (m, 1H) 3.96-4.07 (m, 1H) 4.16 (s, 1H) 4.44-4.65 (m, 2H) 5.22-5.28 (m, 1H) 7.74 (d, J=8.54 Hz, 2H) 7.86-7.94 (m, 2H) 8.15-8.32 (m, 1H). CL (Cond. 4): TR = 3.33 min; EM: Análisis calculado para $[2M+Na]^+$ $C_{36}H_{46}Br_2N_4NaO_{10}$: 877.57;

encontrado 877.11.

Extremo b: El intermediario OL-16 se preparó del intermediario OL-15 en una manera similar como el intermediario 1b. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.16/1.39 (2 br. s., 9H) 1.71-1.81 (m, J=6.10 Hz, 1H) 2.01-2.17 (m, 1H) 3.37-3.50 (m, 1H) 3.50-3.62 (m, 1H) 4.15 (s, 1H) 4.49-4.70 (m, 1H) 5.36 (dd, J=6.71, 3.66 Hz, 1H) 7.44-7.62 (m, 3H) 7.68 (d, J=7.02 Hz, 2H) 11.96/11.99/12.26/12.30 (m, 1H). CL (Cond. 8): TR = 1.87 min; EM: Análisis calculado para $[M+H]^+$ $C_{18}H_{23}BrN_3O_3$: 408.08; encontrado 408.09.

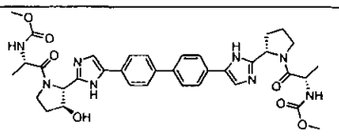
Extremo c: El intermediario OL-17 se preparó por acoplar el intermediario OL-16 con 1c de manera similar a la preparación de 1d. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.09-1.49 (m, 18H) 1.71-2.04 (m, 4H) 2.06-2.28 (m, 2H) 3.33-3.40 (m, 1H) 3.41-3.65 (m, 3H) 4.18 (s, 1H) 4.52-4.69 (m, 1H) 4.70-4.88 (m, 1H) 5.38 (s, 1H) 6.64-7.35 (m, 1H) 7.39-7.96 (m, 9H) 11.71 - 12.0/12.10 - 12.36 (m, 2H). CL (Cond. 2): TR = 1.36 min; EM: Análisis calculado para $[M+H]^+$ $C_{36}H_{45}N_6O_5$: 641.77; encontrado 641.39.

Extremo d: El intermediario OL-18 se preparó por desprotección del intermediario OL-17 con HCl de manera similar a la preparación de 1-1e. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.92-2.07 (m, 2H) 2.14-2.25 (m, 1H) 2.35-2.44 (m, 1H) 3.15 (s, 4H) 3.32-3.41 (m, J=7.02, 7.02, 7.02 Hz, 1H) 3.41-3.51 (m, J=7.32 Hz, 2H) 3.54-3.66 (m, 1H) 4.68 (d, J=4.27 Hz,

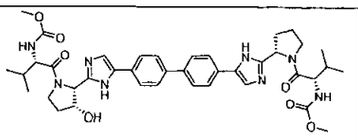
1H) 4.78-4.89 (m, J=4.88 Hz, 1H) 5.04 (s, 1H) 6.89/7.73 (2d, J= 8.70 Hz, 1H) 7.89 (dd, J=8.24, 4.58 Hz, 4H) 7.96-8.07 (m, 4H) 8.15 (d, J=23.19 Hz, 2H) 9.62-10.12 (m, 2H) 10.21-10.74 (m, 2H).). CL (Cond. 8): TR = 1.30 min; EM: Análisis calculado para $[M+H]^+$ $C_{26}H_{29}N_6O$: 441.24; encontrado 441.18.

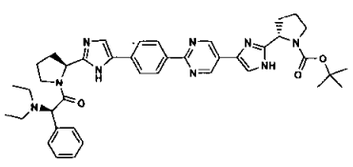
Extremo e: El ejemplo OL-19 se preparó por el acoplamiento del intermediario OL-18 con el extremo-51 de manera similar a la preparación del ejemplo 1. ^1H RMN (500 MHz, DMSO-d_6) δ ppm 0.78 (d, J=6.41 Hz, 6H) 0.83 (d, J=6.71 Hz, 6H) 1.92-2.12 (m, 5H) 2.12-2.21 (m, 1H) 2.31 (dd, J=12.21, 5.80 Hz, 1H) 2.35-2.43 (m, 1H) 3.54 (d, J=4.27 Hz, 6H) 3.78-3.89 (m, 3H) 3.91-4.02 (m, 1H) 4.07-4.19 (m, 2H) 4.36-4.50 (m, 1H) 4.81 (d, J=3.66 Hz, 1H) 5.13 (t, J=7.17 Hz, 1H) 5.79 (s, 1H) 7.34 (dd, J=11.29, 8.85 Hz, 2H) 7.83-7.90 (m, 4H) 7.90-8.01 (m, 4H) 8.12 (s, 2H) [Nota: la señal para el NH de imidazol fue muy amplia para asignar un cambio químico].). CL (Cond. 4): TR = 2.76 min; EM: Análisis calculado para $[M+H]^+$ $C_{40}H_{51}N_8O_7$: 755.39; encontrado 755.38. HRMS: Análisis calculado para $(M+H)^+$ $C_{40}H_{51}N_8O_7$ 755.3881 encontrado 755.3873.

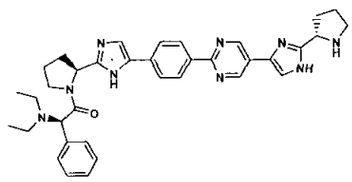
El siguiente análogo se preparó del intermediario OL-18 de manera similar a la preparación del ejemplo 1 y empleando el extremo-52.

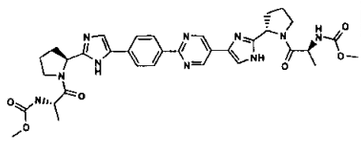
Número de Ejemplo	Nombre del Compuesto	Estructura	Datos Analíticos
OL-20	((1S)-2-((2S)-2-(4-(4'-(2-((2R,3S)-3-hidroxi-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	 A partir de OL-18 y Extremo-52	LC/MS: 2.32 min (Cond'n 4); Análisis calculado para $[M+H]^+$ $C_{36}H_{43}N_8O_7$: 699.78; encontrado 699.32.

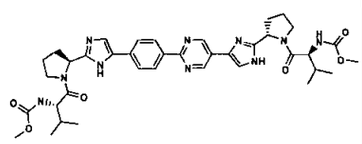
El siguiente análogo se preparó de manera similar a la preparación de OL-19 pero usando N-Boc-cis-3-hidroxi-L-prolina como material de partida.

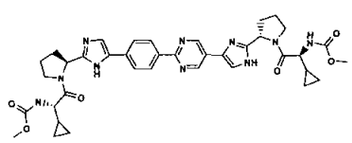
Número de Ejemplo	Nombre del Compuesto	Estructura	Datos Analíticos
OL-21	((1S)-1-(((2R)-3-hidroxi-2-(4-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil) carbamato de metilo	 A partir de N-Boc-cis-3-hidroxi-L-prolina y Extremo-51	LC/MS: 2.74 min (Cond'n 4); Análisis calculado para $[M+H]^+$ $C_{40}H_{51}N_8O_7$: 755.39; encontrado 755.34.

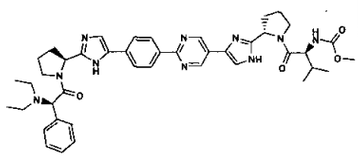
Número de Ejemplo	Nombre del Compuesto	Heterociclos con nuevas extremos	*Datos Analíticos* (Cond 1: 3 min gradiente, 4 min de corrida; Cond 2: 2 min gradiente, 3 min de corrida)
D71	(2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-5-pirimidinil)-1H-imidazol-2-il)-1-pirrolidina carboxilato de tert-butilo	 Preparado a partir de 152i-1 (en lugar de 148e) y Extremo-2 usando condiciones experimentales resumidas en el ejemplo 148	t_R = 1.82 min, (97.7%), (Cond 1) EMBR: Análisis calculado para $C_{41}H_{50}N_9O_3$ 716.40; encontrado: 716.44 $(M+H)^+$. HRMS: Análisis calculado para $C_{41}H_{50}N_9O_3$ 716.4037; encontrado: 716.4056 $(M+H)^+$.

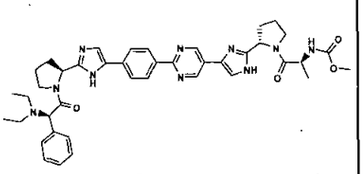
D72	(1R)-N,N-dietil-2-oxo-1-fenil-2-((2S)-2-(5-(4-(5-(2-((2S)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirimidinil)fenil)-1H-imidazol-2-il)-1-pirrolidinil)etanamina	 Preparado a partir de la entrada 71 (en lugar de 152j-27) usando condiciones experimentales resumidas en el ejemplo 152k-1.	t_R = 1.56 min, (~95.3%, tiene borde), (Cond 1) EMBR: Análisis calculado para $C_{36}H_{42}N_9O$ 616.35; encontrado: 616.37 $(M+H)^+$. HRMS: Análisis calculado para $C_{36}H_{42}N_9O$ 616.3512; encontrado: 616.3540 $(M+H)^+$.

D73	((1S)-2-((2S)-2-(5-(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 a partir de 152h-1 (en lugar de 148e) y Extremo-52 usando condiciones experimentales resumidas en el ejemplo 148	t_R = 1.52 min, (96.2%), (Cond 1) EMBR: Análisis calculado para $C_{34}H_{41}N_{10}O_6$ 685.32; encontrado: 685.21 $(M+H)^+$. HRMS: Análisis calculado para $C_{34}H_{41}N_{10}O_6$ 685.3211; encontrado: 685.3196 $(M+H)^+$.

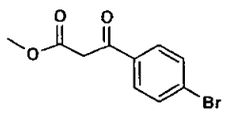
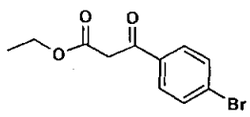
D74	((1S)-1-(((2S)-2-(5-(2-(4-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-5-pirimidinil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo	 Preparado a partir de 152h-1 (en lugar de 148e) y Extremo-51 usando condiciones experimentales resumidas en el ejemplo 148	t_R = 2.09 min, (95%), (Cond 1) EMBR: Análisis calculado para $C_{38}H_{49}N_{10}O_6$ 741.38; encontrado: 741.26 $(M+H)^+$. HRMS: Análisis calculado para $C_{38}H_{49}N_{10}O_6$ 741.3837; encontrado: 741.3824 $(M+H)^+$.

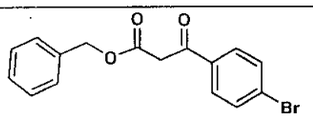
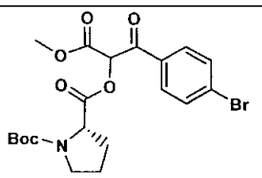
D75	((1S)-1-ciclopropil-2-((2S)-2-(5-(2-(4-(2-((2S)-1-((2S)-2-ciclopropil-2-((metoxi carbonil) amino)acetil) -2-pirrolidinil) -1H-imidazol-5-il)fenil)-5-pirimidinil)-1H-imidazol-2-il)-1-pirrolidinil) -2-oxoetil) carbamato de metilo	 Preparado a partir de 152h-1 (en lugar de 148e) y Extremo-54b usando condiciones experimentales resumidas en el ejemplo 148	t_R = 1.98 min, (95%), (Cond 1) EMBR: Análisis calculado para $C_{38}H_{45}N_{10}O_6$ 737.35; encontrado: 737.22 $(M+H)^+$. HRMS: Análisis calculado para $C_{38}H_{45}N_{10}O_6$ 737.3524; encontrado: 737.3555 $(M+H)^+$.

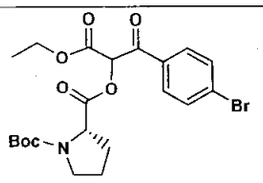
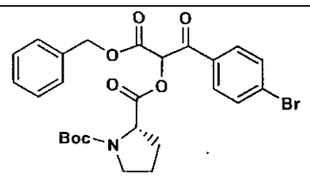
D76	((1S)-1-(((2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-5-pirimidinil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo	 Preparado a partir de la entrada D72 (en lugar de 148e) y Extremo-51 usando condiciones experimentales resumidas en el ejemplo 148	t_R = 1.69 min, (95%), (Cond 1) EMBR: Análisis calculado para $C_{43}H_{53}N_{10}O_4$ 773.43; encontrado: 773.30 $(M+H)^+$. HRMS: Análisis calculado para $C_{43}H_{53}N_{10}O_4$ 773.4251; encontrado: 773.4280 $(M+H)^+$.

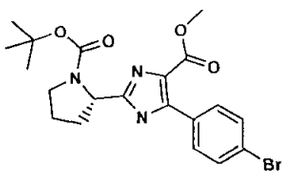
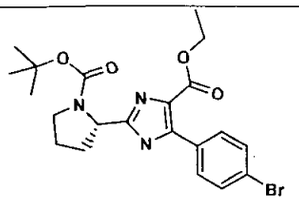
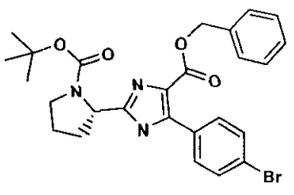
D77	((1S)-2-((2S)-2-(5-(2-(4-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-5-pirimidinil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil) carbamato de metilo	 Preparado a partir de la entrada D72 (en lugar de 148e) y Extremo-52 usando condiciones experimentales resumidas en el ejemplo 148	t_R = 1.81 min, (97.5%), (Cond 1) EMBR: Análisis calculado para $C_{41}H_{49}N_{10}O_4$ 745.39; encontrado: 745.27 $(M+H)^+$. HRMS: Análisis calculado para $C_{41}H_{49}N_{10}O_4$ 745.3938; encontrado: 745.3939 $(M+H)^+$.

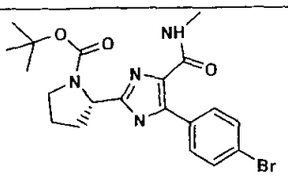
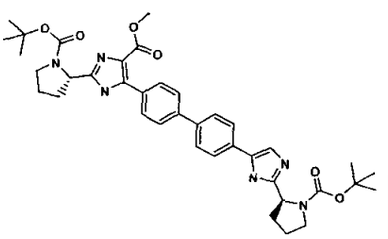
Sección J

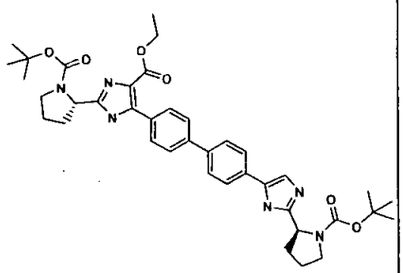
Número de Ejemplo	Nombre del Compuesto	Estructura	Datos Analíticos
J.1a		 Preparado a partir de 4-bromoacetofenona y dimetilcarbonato a partir de Bioorg.Med.Chem.Lett (2001)11, 641	t_R = 1.7 min, (Cond 2); LCMS: $C_{10}H_9BrO_3$ encontrado: 257 $(M+H)^+$.
J.1b		 Preparado a partir de 4-bromoacetofenona y dietilcarbonato a partir de Bioorg.Med.Chem.Lett (2001)11, 641.	t_R = 1.9 min, (Cond 2); LCMS: $C_{11}H_{11}BrO_3$ encontrado: 271 $(M+H)^+$.

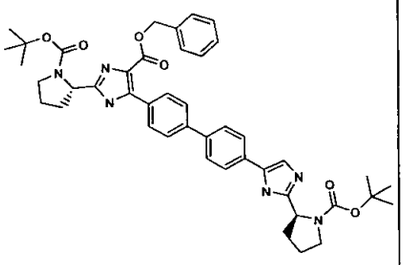
J.1c		 Preparado a partir de 4-bromoacetofenona y dibencilcarbonato a partir de Bioorg.Med.Chem.Lett (2001)11, 641.	t_R = 2.1min, (Cond 2); LCMS: $C_{16}H_{13}BrO_3$ encontrado: 332 $(M+H)^+$.
J1		 Preparado a partir de la entrada J.1a (en lugar de J.1b) y prolina usando condiciones experimentales en el ejemplo J2.	t_R = 2.2min, (Cond 2); LCMS: $C_{20}H_{24}BrNO_7$ encontrado: 470 $(M+H)^+$.

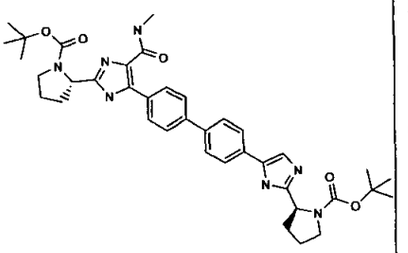
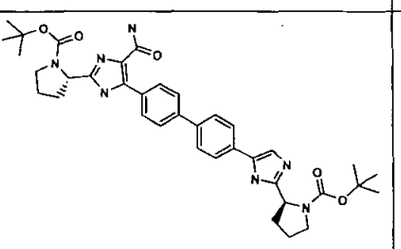
J2		 Preparado a partir de la entrada J.1b y prolina usando condiciones experimentales en el ejemplo J2.	t_R = 2.2min, (Cond 2); LCMS: $C_{21}H_{26}BrNO_7$ encontrado: 484 $(M+H)^+$.
J3		 Preparado a partir de la entrada J.1c (en lugar de J.1b) y prolina usando condiciones experimentales en el ejemplo J2.	t_R = 2.3min, (Cond 2); LCMS: $C_{26}H_{28}BrNO_7$ encontrado: 546 $(M+H)^+$.

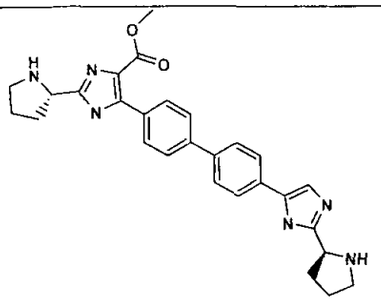
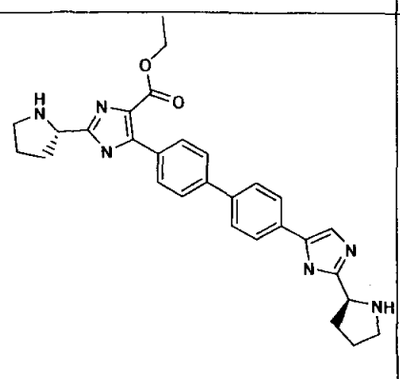
J4		 Preparado a partir de la entrada J.1 y (en lugar de J.2) usando condiciones experimentales en el ejemplo J2.	t_R = 1.84 min, (100%) (Cond 2); EMBR: Análisis calculado para $C_{20}H_{24}BrN_3O_4$; 450.10; encontrado: 450.13 y 452.13 $(M+H)^+$.
J5		 Preparado a partir de la entrada J2 usando condiciones experimentales en J5.	t_R = 1.93 min, (99%) (Cond 2); Reportado en J5.
J6		 Preparado a partir de la entrada J3 (en lugar de entrada J1) usando condiciones experimentales en J5.	t_R = 2.1 min, (93%) (Cond 2); EMBR: Análisis calculado para $C_{26}H_{29}BrN_3O_4$ 526.13; encontrado: 526.16 y 528.16 $(M+H)^+$.

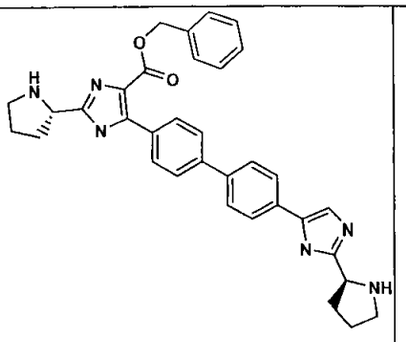
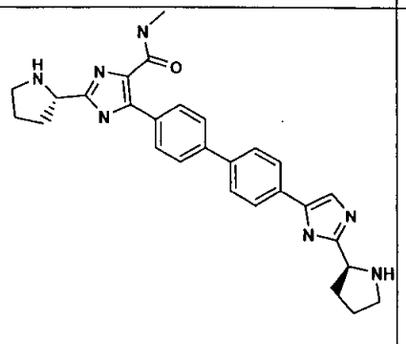
J7		 Preparado a partir de la entrada J5 usando experimental en J7.	t_R = 1.7 min, (100%) (Cond 2); Reportado en J7.
J8	2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-5-(4'-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-4-carboxilato de metilo	 Preparado a partir de la entrada J4 (en lugar de 152e-1) y 1c usando condiciones experimentales resumidas en el ejemplo 152g-1.	t_R = 1.70 min, (95%) (Cond 2); EMBR: Análisis calculado para $C_{38}H_{47}N_6O_6$ 683.36; encontrado: 683.42 $(M+H)^+$.

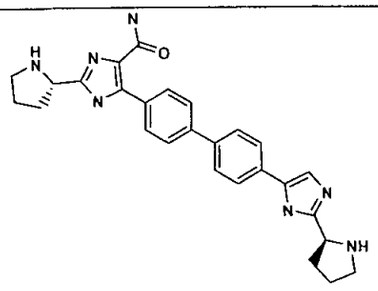
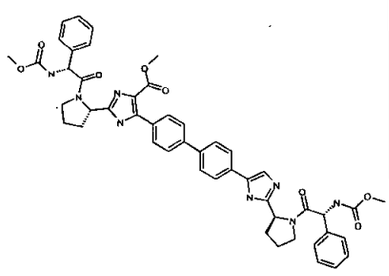
J9	2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-5-(4'-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-4-carboxilato de etilo	 Preparado a partir de la entrada J5 (en lugar de 152e-1) y 1c usando condiciones experimentales resumidas en el ejemplo 152g-1.	t_R = 1.78 min, (97.5%) (Cond 2); EMBR: Análisis calculado para $C_{39}H_{49}N_6O_6$ 697.37; encontrado: 697.38 $(M+H)^+$.

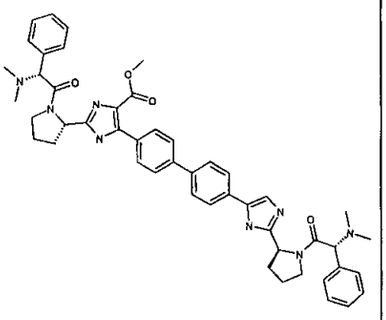
	J10	2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-5-(4'-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-4-carboxilato de bencilo	 Preparado a partir de la entrada J6 (en lugar de 152e-1) y 1c usando condiciones experimentales resumidas en el ejemplo 152g-1.	t_R = 1.88 min, (85%) (Cond 2); EMBR: Análisis calculado para $C_{44}H_{51}N_6O_6$ 759.39; encontrado: 759.48 $(M+H)^+$.

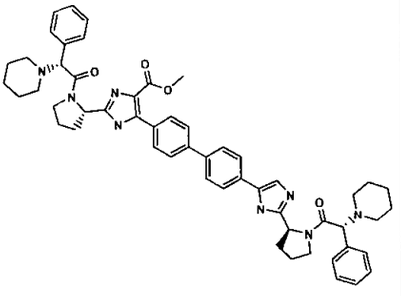
J11	(2S)-2-(5-(4'-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-4-(metilcarbamoil)-1H-imidazol-2-il)-1-pirrolidinacarboxilato de tert-butilo	 Preparado a partir de la entrada J7 (en lugar de 152e-1) y 1c usando condiciones experimentales resumidas en el ejemplo 152g-1.	t_R = 1.65 min, (90%) (Cond 2); EMBR: Análisis calculado para $C_{38}H_{48}N_7O_5$ 682.37; encontrado: 682.42 $(M+H)^+$.
J11.a		 Preparado a partir de la entrada J9 como se deescribe en J11.a.	t_R = 1.60 min, (Cond 2); LCMS: $C_{37}H_{46}N_7O_5$ encontrado: 668 $(M+H)^+$.

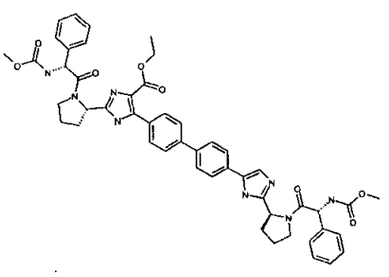
J12		 Preparado a partir de la entrada J8 (en lugar de 152j-27) usando condiciones experimentales resumidas en el ejemplo 152k-1.	t_R = 1.25min, (97%) (Cond 2); LCMS: $C_{28}H_{31}N_6O_2$ encontrado: 483 $(M+H)^+$.
J13		 Preparado a partir de la entrada J9 (en lugar de 152j-27) usando condiciones experimentales resumidas en el ejemplo 152k-1.	t_R = 1.34 min, (Cond 2); LCMS: $C_{29}H_{33}N_6O_2$ encontrado: 497 $(M+H)^+$.

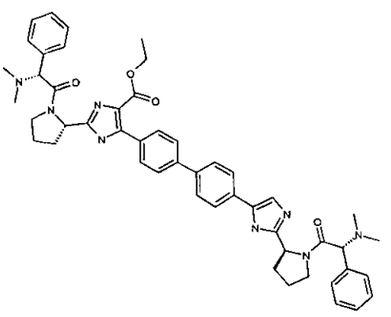
J14		 Preparado a partir de la entrada J10 (en lugar de 152j-27) usando condiciones experimentales resumidas en el ejemplo 152k-1.	t_R = 1.51 min, (90%) (Cond 2); LCMS: $C_{34}H_{35}N_6O_2$ encontrado: 559 $(M+H)^+$.
J15		 Preparado a partir de la entrada J11 (en lugar de 152j-27) usando condiciones experimentales resumidas en el ejemplo 152k-1.	t_R = 1.32 min, (99%) (Cond 2); LCMS: $C_{28}H_{32}N_7O$ encontrado: 482 $(M+H)^+$.

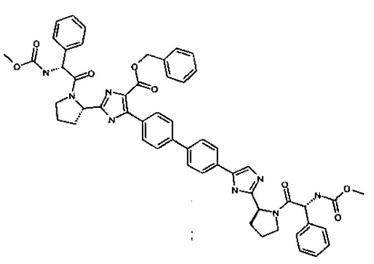
J15.a		 Preparado a partir de la entrada J11.a (en lugar de 152j-27) usando condiciones experimentales resumidas en el ejemplo 152k-1.	t_R = 1.07 min, (98%) (Cond 2); LCMS: $C_{27}H_{30}N_7O$ encontrado: 468 $(M+H)^+$.
J16	2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-5-(4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-4-carboxilato de metilo	 Preparado a partir de la entrada J12 (en lugar de 148e) y Extremo-4 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.62 min, (99.5%) (Cond 2); EMBR: Análisis calculado para C48H49N8O8 865.37; encontrado: 865.34 $(M+H)^+$. HRMS: Análisis calculado para C48H49N8O8 865.3673; encontrado: 865.3715 $(M+H)^+$.

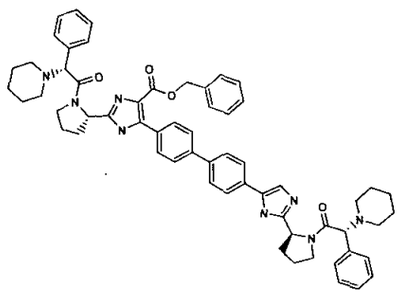
J17	2-((2S)-1-((2R)-2-(dimetil amino)-2-fenilacetil)-2-pirrolidinil)-5-(4'-(2-((2S)-1-((2R)-2-(dimetil amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-4-carboxilato de metilo	 Preparado a partir de la entrada J12 (en lugar de 148e) y Extremo-1 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.37 min, (92%) (Cond 2); EMBR: Análisis calculado para C48H53N8O4 804.42; encontrado: 805.51 $(M+H)^+$. HRMS: Análisis calculado para C48H53N8O4 805.4190; encontrado: 805.4211 $(M+H)^+$.

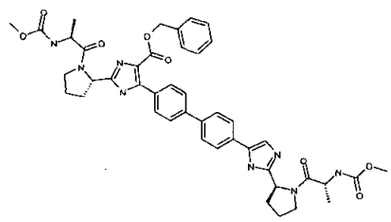
J18	2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-4-carboxilato de metilo	 Preparado a partir de la entrada J12 (en lugar de 148e) y Extremo-14 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.46 min, (94%) (Cond 2); EMBR: Análisis calculado para C54H61N8O6 885.48; encontrado: 885.48 $(M+H)^+$. HRMS: Análisis calculado para C54H61N8O6 885.4816; encontrado: 885.4852 $(M+H)^+$.

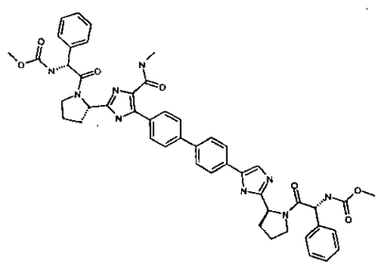
J19	2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-5-(4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-4-carboxilato de etilo	 Preparado a partir de la entrada J13 (en lugar de 148e) y Extremo-4 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.68 min, (99%) (Cond 2); EMBR: Análisis calculado para C49H51N8O8 879.38; encontrado: 879.37 $(M+H)^+$. HRMS: Análisis calculado para C49H51N8O8 879.3830; encontrado: 879.3814 $(M+H)^+$.

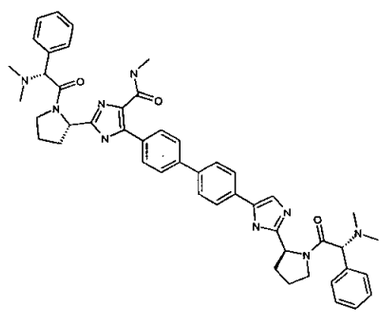
	J20	2-((2S)-1-((2R)-2-(dimetil amino)-2-fenilacetil)-2-pirrolidinil)-5-(4'-(2-((2S)-1-((2R)-2-(dimetil amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-4-carboxilato de etilo	 Preparado a partir de la entrada J13 (en lugar de 148e) y Extremo-1 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.45 min, (89%) (Cond 2); EMBR: Análisis calculado para C49H55N8O4 818.44; encontrado: 818.40 $(M+H)^+$. HRMS: Análisis calculado para C49H55N8O4 819.4346; encontrado: 819.4340 $(M+H)^+$.

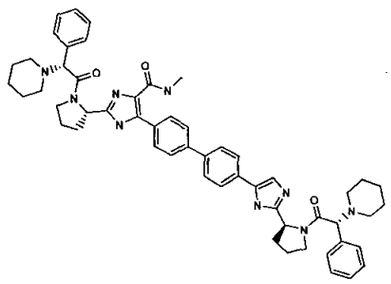
J21	2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-5-(4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-4-carboxilato de bencilo	 Preparado a partir de la entrada J14 (en lugar de 148e) y Extremo-4 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.80 min, (92%) (Cond 2); EMBR: Análisis calculado para C54H53N8O8 941.40; encontrado: 941.39 $(M+H)^+$. HRMS: Análisis calculado para C54H53N8O8 941.3986; encontrado: 941.4033 $(M+H)^+$.

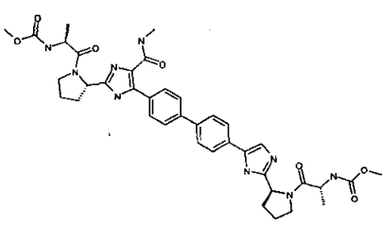
J23	2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil) acetil)-2-pirroli dinil)-5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil) acetil)-2-pirroli dinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-4-carboxilato de bencilo	 Preparado a partir de la entrada J14 (en lugar de 148e) y Extremo-14 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.63 min, (96%) (Cond 2); EMBR: Análisis calculado para C60H65N8O4 961.51; encontrado: 961.54 $(M+H)^+$. HRMS: Análisis calculado para C60H65N8O4 961.5129; encontrado: 961.5164 $(M+H)^+$.

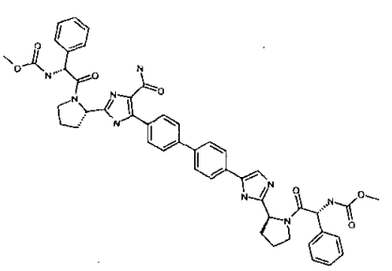
J24	2-((2S)-1-(N-(metoxi carbonil)-L-alanil)-2-pirrolidinil)-5-(4'-(2-((2S)-1-(N-(metoxi carbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-4-carboxilato de bencilo	 Preparado a partir de la entrada J14 (en lugar de 148e) y Extremo-52 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.64 min, (94%) (Cond 2); EMBR: Análisis calculado para C44H49N8O8 817.37; encontrado: 817.38 $(M+H)^+$. HRMS: Análisis calculado para C44H49N8O8 817.3673; encontrado: 817.3675 $(M+H)^+$.

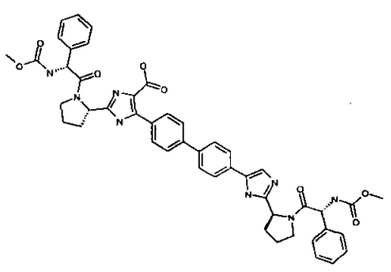
J25	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-4-(metilcarbamoil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) carbamato de metilo	 Preparado a partir de la entrada J15 (en lugar de 148e) y Extremo-4 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.58 min, (99.6%) (Cond 2); EMBR: Análisis calculado para C48H50N9O7 864.38; encontrado: 864.47 $(M+H)^+$. HRMS: Análisis calculado para C48H50N9O7 864.3833; encontrado: 864.3849 $M+H)^+$.

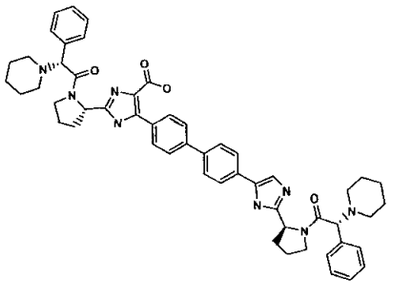
J26	2-((2S)-1-((2R)-2-(dimetil amino)-2-fenilacetil)-2-pirrolidinil)-5-(4'-(2-((2S)-1-((2R)-2-(dimetil amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-N-metil-1H-imidazol-4-carboxamida	 Preparado a partir de la entrada J15 (en lugar de 148e) y Extremo-1 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.31 min, (93.2%) (Cond 2); EMBR: Análisis calculado para C48H54N9O3 804.44; encontrado: 804.51 $(M+H)^+$. HRMS: Análisis calculado para C48H54N9O3 804.4350; encontrado: 804.4369$(M+H)^+$.

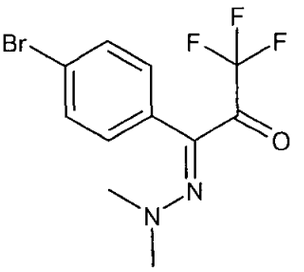
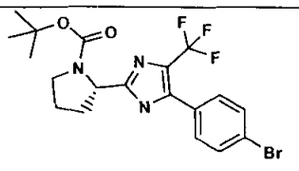
J27	N-metil-2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-4-carboxamida	 Preparado a partir de la entrada J15 (en lugar de 148e) y Extremo-14 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.39 min, (95.4%) (Cond 2); EMBR: Análisis calculado para C54H62N9O3 884.50; encontrado: 884.52 $(M+H)^+$. HRMS: Análisis calculado para C54H62N9O3 884.4976; encontrado: 884.4973 $(M+H)^+$.

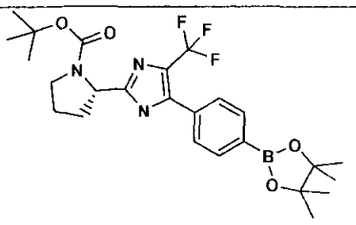
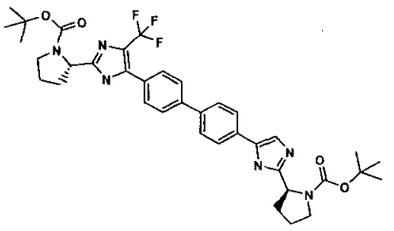
	J28	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-4-(metilcarbamoil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil) carbamato de metilo	 Preparado a partir de la entrada J15 (en lugar de 148e) y Extremo-52 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.34 min, (89.3%) (Cond 2); EMBR: Análisis calculado para C38H46N9O7 740.35; encontrado: 740.31 $(M+H)^+$. HRMS: Análisis calculado para C38H46N9O7 740.3520; encontrado: 740.3497$(M+H)^+$.

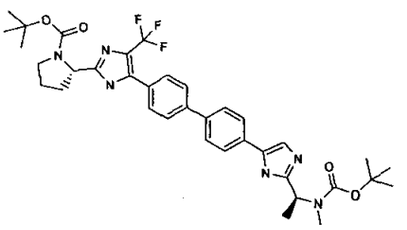
J29	((1R)-2-((2S)-2-(4-carbamoil-5-(4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) carbamato de metilo	 Preparado a partir de la entrada J15.a (en lugar de 148e) Y Extremo-4 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.55 min, (96.4%) (Cond 2); EMBR: Análisis calculado para C47H48N9O7 740.35; encontrado: 740.31 $(M+H)^+$. HRMS: Análisis calculado para C47H48N9O7 740.3520; encontrado: 740.3497 $M+H)^+$.

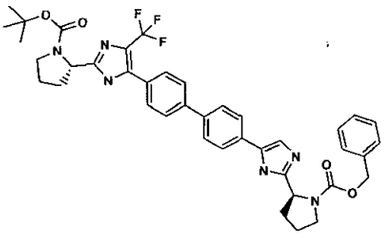
J30	Ácido 2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-5-(4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-4-carboxílico	 Preparado a partir de la entrada 21 (en lugar de 28c) usando condiciones experimentales resumidas en el ejemplo 28 eextremo d.	t_R = 1.52 min, (92.8%) (Cond 2); EMBR: Análisis calculado para C47H47N8O8 851.35; encontrado: 851.37 $(M+H)^+$. HRMS: Análisis calculado para C47H47N8O8 851.3517; encontrado: 851.3553 $(M+H)^+$.

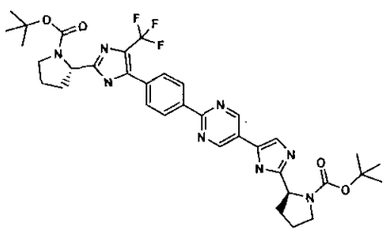
J31	Ácido 2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-5-(4'-(2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-4-carboxílico	 Preparado a partir de la entrada 23 (en lugar de 28c) usando condiciones experimentales resumidas en el ejemplo 28 eextremo d.	t_R = 1.36 min, (96.5%) (Cond 2); EMBR: Análisis calculado para C53H59N8O4 871.47; encontrado: 871.47 $(M+H)^+$. HRMS: Análisis calculado para C53H59N8O4 871.4659; encontrado: 871.4692 $(M+H)^+$.

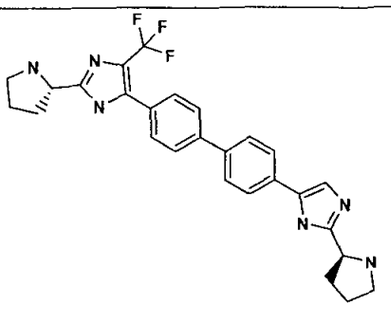
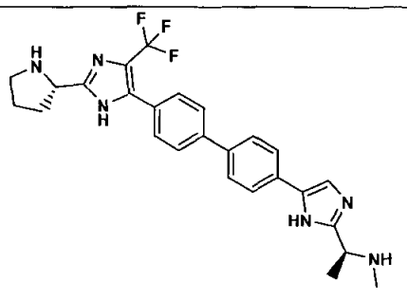
J32		 Preparado a partir de 4-bromobenzaldehído de conformidad al procedimiento descrito en J.Org.Chem. (1988), 53, 129.	t_R = 1.96 min, (96%) (Cond 2); EMBR: Análisis calculado para $C_{11}H_{11}BrF_3N_2O$ 323.00; encontrado: 323.05 y 325.05 $(M+H)^+$. ^1H RMN (300 MHz, DMSO-d_6) δ 7.58 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 3.06 (s, 6H).
J32.a		 Preparado a partir de la entrada J32 usando condiciones experimentales en J32.a	t_R = 2.19 min, (96%) (Cond 2); Reportado en J32.a

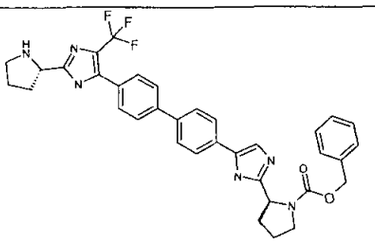
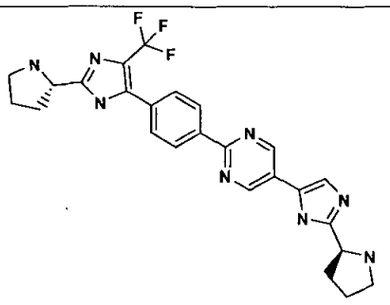
J32.b		 Preparado a partir de la entrada J32.a (en lugar de 1b) usando condiciones experimentales resumidas en el ejemplo 1 eextremo c.	t_R = 2.3 min, (73%) (Cond 2); LCMS: $C_{25}H_{34}BF_3N_3O_4$ encontrado: 508 $(M+H)^+$.
J33	(2S)-2-(5-(4'-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-4-(trifluorometil)-1H-imidazol-2-il)-1-pirrolidinacarboxilato de tert-butilo	 Preparado a partir de la entrada J32.a (en lugar de 152e-1) y 1c usando condiciones experimentales resumidas en el ejemplo 152g-1.	t_R = 2.7 min, (95%) (Cond 2); EMBR: Análisis calculado para $C_{37}H_{44}F_3N_6O_4$ 693.34; encontrado: 693.33 $(M+H)^+$. HRMS: Análisis calculado para $C_{37}H_{44}F_3N_6O_4$ 693.3376; encontrado: 693.3370 $(M+H)^+$.

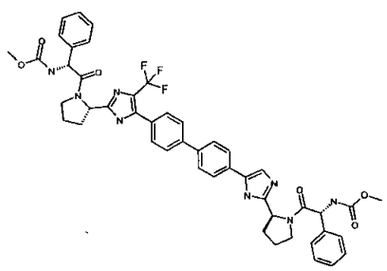
J33.a	(2S)-2-(5-(4'-(2-((1S)-1-((tert-butoxicarbonil)(metil)amino)etil)-1H-imidazol-5-il)-4-bifenilil)-4-(trifluoro metil)-1H-imidazol-2-il)-1-pirrolidina carboxilato de tert-butilo	 Preparado a partir de la entrada J32.a (en lugar de 152e-1) y 1-8c usando condiciones experimentales resumidas en el ejemplo 152g-1.	t_R = 1.97 min, (97%) (Cond 2); EMBR: Análisis calculado para $C_{36}H_{44}F_3N_6O_4$ 681.34; encontrado: 681.31 $(M+H)^+$. HRMS: Análisis calculado para $C_{36}H_{44}F_3N_6O_4$ 681.3376; encontrado: 681.3383 $(M+H)^+$.

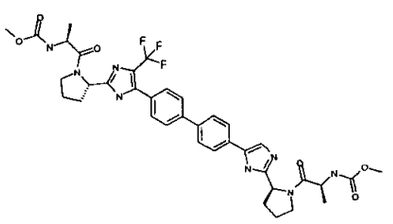
J34	(2S)-2-(5-(4'-(2-((2S)-1-((benciloxi)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-4-(trifluorometil)-1H-imidazol-2-il)-1-pirrolidina carboxilato de tert-butilo	 Preparado a partir de la entrada J32.a (en lugar de 152e-1) y 1-5c usando condiciones experimentales resumidas en el ejemplo 152g-1.	t_R = 2.0 min, (95%) (Cond 2); EMBR: Análisis calculado para $C_{40}H_{42}F_3N_6O_4$ 727.32; encontrado: 727.19 $(M+H)^+$. HRMS: Análisis calculado para $C_{40}H_{42}F_3N_6O_4$ 727.3220; encontrado: 727.3251 $(M+H)^+$.

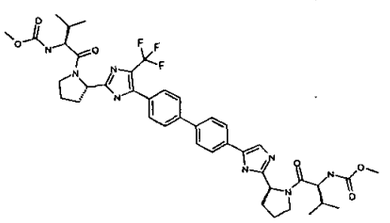
	J34.a	(2S)-2-(5-(4-(5-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirimidinil)fenil)-4-(trifluorometil)-1H-imidazol-2-il)-1-pirrolidina carboxilato de tert-butilo	 Preparado a partir de la entrada J32.b (en lugar de 152e-1) y 152d-1 usando condiciones experimentales resumidas en el ejemplo 152g-1.	t_R = 1.97 min, (93%) (Cond 2); EMBR: Análisis calculado para $C_{35}H_{42}F_3N_8O_4$ 695.33; encontrado: 695.28 $(M+H)^+$.

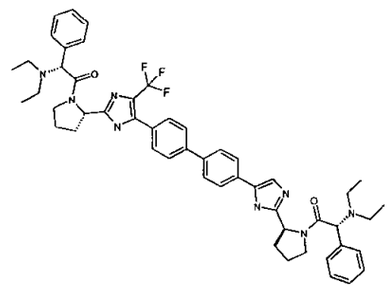
J35		 Preparado a partir de la entrada J33 (en lugar de 152j-27) usando condiciones experimentales resumidas en el ejemplo 152k-1.	t_R = 1.46 min, (92%) (Cond 2); LCMS: $C_{27}H_{28}F_3N_6O$ encontrado: 493 $(M+H)^+$.
J35.a		 Preparado a partir de la entrada J33.a (en lugar de 152j-27) usando condiciones experimentales resumidas en el ejemplo 152k-1.	LCMS: $C_{26}H_{28}F_3N_6$ encontrado: 481 $(M+H)^+$.

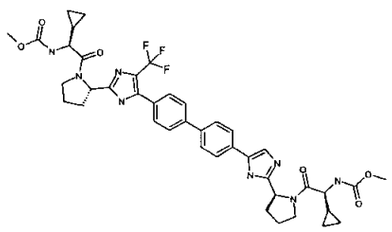
J36		 Preparado a partir de la entrada J34 (en lugar de 152j-27) usando condiciones experimentales resumidas en el ejemplo 152k-1.	LCMS: $C_{35}H_{34}F_3N_6O_2$ encontrado: 626 $(M+H)^+$.
J36.a		 Preparado a partir de la entrada J34.a (en lugar de 152j-27) usando condiciones experimentales resumidas en el ejemplo 152k-1.	t_R = 1.45 min, (Cond 2); LCMS: $C_{25}H_{26}F_3N_8$ encontrado: 495 $(M+H)^+$.

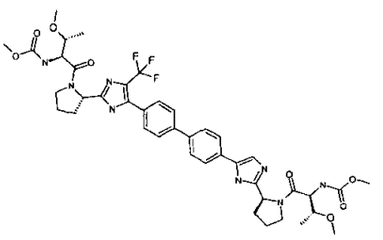
J37	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-4-(trifluorometil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) carbamato de metilo	 Preparado a partir de la entrada J35 (en lugar de 148e) y Extremo-4 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.9 min, (95%) (Cond 2); EMBR: Análisis calculado para $C_{47}H_{46}F_3N_8O_4$ 875.35; encontrado: 875.35 $(M+H)^+$. HRMS: Análisis calculado para $C_{47}H_{46}F_3N_8O_4$ 875.3492; encontrado: 875.3504 $(M+H)^+$.

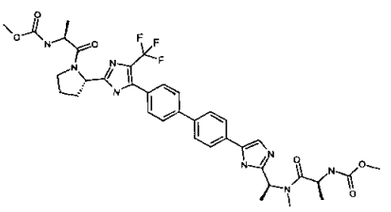
J38	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-4-(trifluorometil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil) carbamato de metilo	 Preparado a partir de la entrada J35 (en lugar de 148e) y Extremo-52 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.7 min, (95.5%) (Cond 2); EMBR: Análisis calculado para $C_{37}H_{42}F_3N_8O_6$ 751.32; encontrado: 751.32 $(M+H)^+$. HRMS: Análisis calculado para $C_{37}H_{42}F_3N_8O_6$ 751.3179; encontrado: 751.3163 $(M+H)^+$.

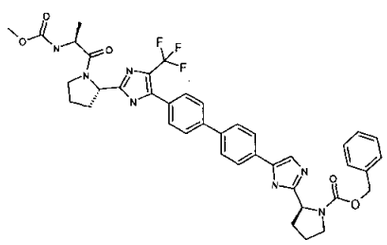
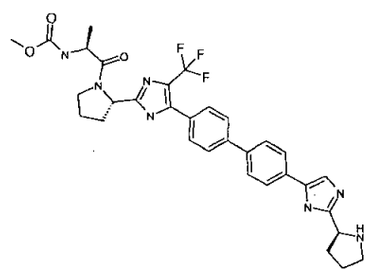
J39	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-4-(trifluorometil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo	 Preparado a partir de la entrada J35 (en lugar de 148e) y Extremo-51 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.9 min, (96%) (Cond 2); EMBR: Análisis calculado para $C_{41}H_{50}F_3N_8O_6$ 807.38; encontrado: 807.33 $(M+H)^+$. HRMS: Análisis calculado para $C_{41}H_{50}F_3N_8O_6$ 807.3805; encontrado: 807.3773 $(M+H)^+$.

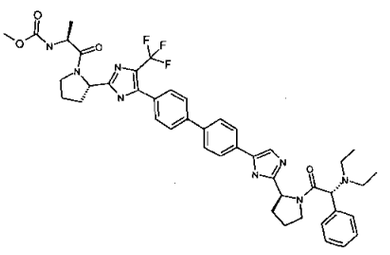
J40	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietil amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-4-(trifluorometil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dietil-2-oxo-1-feniletanamina	 Preparado a partir de la entrada J35 (en lugar de 148e) y Extremo-2 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.6 min, (95%) (Cond 2); EMBR: Análisis calculado para $C_{51}H_{58}F_3N_8O_2$ 871.46; encontrado: 871.48 $(M+H)^+$. HRMS: Análisis calculado para $C_{51}H_{58}F_3N_8O_2$ 871.4635; encontrado: 871.4647 $(M+H)^+$.

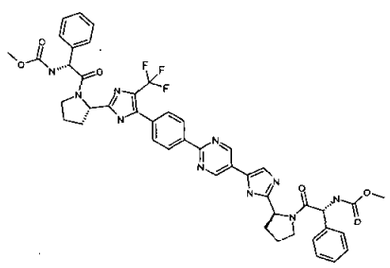
J41	((1S)-1-ciclopropil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-ciclopropil-2-((metoxicarbonil)amino)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-4-(trifluorometil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil) carbamato de metilo	 Preparado a partir de la entrada J35 (en lugar de 148e) y Extremo-54b usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.8 min, (96.9%) (Cond 2); EMBR: Análisis calculado para $C_{41}H_{46}F_3N_8O_6$ 803.35; encontrado: 803.35 $(M+H)^+$. HRMS: Análisis calculado para $C_{41}H_{46}F_3N_8O_6$ 803.3492; encontrado: 803.3507 $(M+H)^+$.

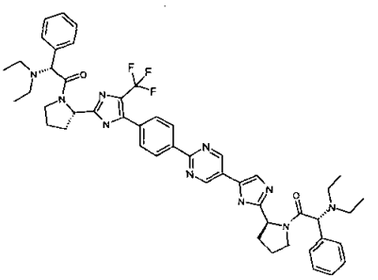
	J42	((1S,2R)-2-metoxi-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-treonil)-2-pirrolidinil)-4-(trifluoro metil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil) propil)carba mato de metilo	 Preparado a partir de la entrada J35 (en lugar de 148e) y Extremo-86 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.8 min, (92%) (Cond 2); EMBR: Análisis calculado para $C_{41}H_{50}F_3N_8O_8$ 839.37; encontrado: 839.30 $(M+H)^+$. HRMS: Análisis calculado para $C_{41}H_{50}F_3N_8O_8$ 839.3704; encontrado: 839.3677 $(M+H)^+$.

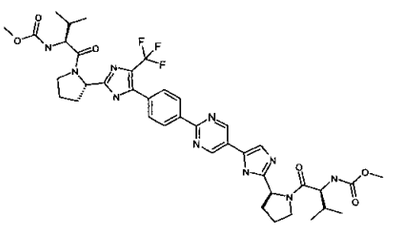
J42.a	((1S)-2-((2S)-2-(5-(4'-(2-((1S)-1-((N-(metoxicarbonil)-L-alanil)(metil)amino)etil)-1H-imidazol-5-il)-4-bifenilil)-4-(trifluoro metil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil) carbamato de metilo	 Preparado a partir de la entrada J35.a (en lugar de 148e) y Extremo-52 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.69 min, (100%) (Cond 2); EMBR: Análisis calculado para $C_{36}H_{42}F_3N_8O_6$ 739.32; encontrado: 739.31 $(M+H)^+$. HRMS: Análisis calculado para $C_{36}H_{42}F_3N_8O_6$ 739.3179; encontrado: 739.3195 $(M+H)^+$.

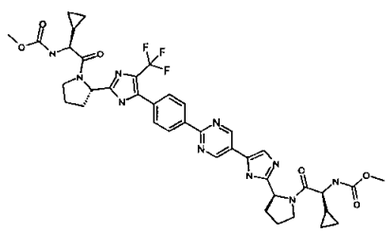
J43	(2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-4-(trifluoro metil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinacarboxilato de bencilo	 Preparado a partir de la entrada J36 (en lugar de 148e) y Extremo-52 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.9 min, (95%) (Cond 2); EMBR: Análisis calculado para $C_{40}H_{41}F_3N_7O_5$ 756.31; encontrado: 756.19 $(M+H)^+$. HRMS: Análisis calculado para $C_{40}H_{41}F_3N_7O_5$ 756.3121; encontrado: 756.3127 $(M+H)^+$.
J44		 Preparado a partir de la entrada J43 (en lugar de 152g-8) usando condiciones experimentales resumidas en el ejemplo 152i-1.	LCMS: $C_{32}H_{35}F_3N_7O_3$ encontrado: 622 $(M+H)^+$.

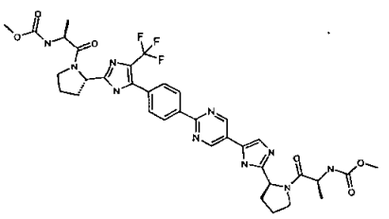
J45	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietil amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-4-(trifluoro metil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil) carbamato de metilo	 Preparado a partir de la entrada J44 (en lugar de 148e) y Extremo-2 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.7 min, (93%) (Cond 2); EMBR: Análisis calculado para $C_{44}H_{50}F_3N_8O_4$ 811.39; encontrado: 811.34 $(M+H)^+$. HRMS: Análisis calculado para $C_{44}H_{50}F_3N_8O_4$ 811.3907; encontrado: 811.3913 $(M+H)^+$.

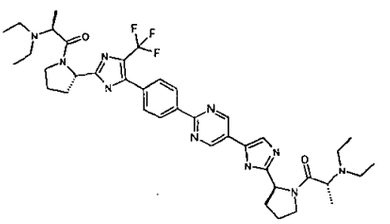
J46	((1R)-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirimidinil)fenil)-4-(trifluorometil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) carbamato de metilo	 Preparado a partir de la entrada J34.a (en lugar de 148e) y Extremo-4 usando condiciones experimentales resumidas en el ejemplo 148	t_R = 1.82 min, (98%) (Cond 2); EMBR: Análisis calculado para $C_{45}H_{44}F_3N_{10}O_6$ 877.34; encontrado: 877.29 $(M+H)^+$. HRMS: Análisis calculado 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-(dietil amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-pirimidinil)fenil)-4-(trifluoro metil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dietil-2-oxo-1-fenileta-namina	 Preparado a partir de la entrada J34.a (en lugar de 148e) y Extremo-2 usando condiciones experimentales resumidas en el ejemplo 148	t_R = 1.58 min, (97%) (Cond 2); EMBR: Análisis calculado para $C_{49}H_{56}F_3N_{10}O_2$ 873.44; encontrado: 873.40 $(M+H)^+$. HRMS: Análisis calculado 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-pirimidinil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil) carbamato de metilo	 Preparado a partir de la entrada J34.a (en lugar de 148e) y Extremo-51 usando condiciones experimentales resumidas en el ejemplo 148	t_R = 1.85 min, (99%) (Cond 2); EMBR: Análisis calculado para $C_{39}H_{48}F_3N_{10}O_6$ 809.37; encontrado: 809.37 $(M+H)^+$. HRMS: Análisis calculado para $C_{39}H_{48}F_3N_{10}O_6$ 809.3710; encontrado: 809.3683 $(M+H)^+$.

J49	((1S)-1-ciclopropil-2-((2S)-2-(5-(4-(5-(2-((2S)-1-((2S)-2-ciclopropil-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 a partir de la entrada J34.a (en lugar de 148e) y Extremo-54b usando condiciones experimentales resumidas en el ejemplo 148	t_R = 1.75 min, (100%) (Cond 2); EMBR: Análisis calculado para $C_{39}H_{44}F_3N_{10}O_6$ 805.34; encontrado: 805.34 $(M+H)^+$. HRMS: Análisis calculado 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 a partir de la entrada J34.a (en lugar de 148e) y Extremo-52 usando condiciones experimentales resumidas en el ejemplo 148	t_R = 1.61 min, (94%) (Cond 2); EMBR: Análisis calculado para $C_{35}H_{40}F_3N_{10}O_6$ 753.31; encontrado: 753.31 $(M+H)^+$. HRMS: Análisis calculado para $C_{35}H_{40}F_3N_{10}O_6$ 753.3084; encontrado: 753.3099 $(M+H)^+$.

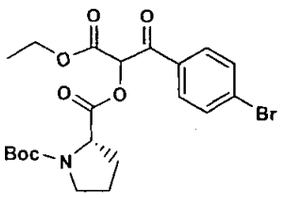
J51	(2R)-1-((2S)-2-(5-(4-(5-(2-((2S)-1-((2R)-2-(dietil amino)propanoil)-2-pirroli *dinil)-1H-imidazol-5-*il)-2-pirimidinil)fenil)-4-(trifluoro metil)-1H-imidazol-2-il)-1-pirroli dinil)-N,N-dietil-1-oxo-2-propanamina	 Preparado a partir de la entrada J34.a (en lugar de 148e) y Extremo-70b usando condiciones experimentales resumidas en el ejemplo 148	t_R = 1.41 min, (92%) (Cond 2); EMBR: Análisis calculado para $C_{39}H_{52}F_3N_{10}O_2$ 749.42; encontrado: 749.37 $(M+H)^+$. HRMS: Análisis calculado para $C_{39}H_{52}F_3N_{10}O_2$ 749.4227; encontrado: 749.4223 $(M+H)^+$.

Cond 1: Condiciones LCMS: Phenomenex-Luna 4.6 x 50 mm S10, 0 hasta 100%B durante 3 min, 4 min tiempo de paro, 4 mL/min, 220nm, A: 10% MeOH-90%H2O - 0.1% TFA; B: 90% MeOH-10%H2O-0.1% TFA.

Cond 2: Condiciones LCMS: Phenomenex-Luna 4.6 x 50 mm S10, 0

hasta 100%B durante 2 min, 3 min tiempo de paro, 4 mL/min, 220nm, A: 10% MeOH-90%H2O - 0.1% TFA; B: 90% MeOH-10%H2O-0.1% TFA.

Ejemplo J2. Pirrolidin-1,2-dicarboxilato de (2S)-2-(1-(4-bromofenil)-3-etoxi-1,3-dioxopropan-2-il) 1-tert-butilo



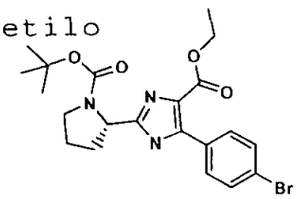
J2

El 3-(4-bromofenil)-3-oxopropanoato de etilo (15 g, 55 mmol) se disolvió en CH_2Cl_2 (600 mL) y NBS frescamente recristalizado (9.8 g, 55 mmol) se le agregó y la solución se agitó 18 hr. La mezcla de reacción se lavó con una solución de $NaHCO_3$, salmuera, y se secó ($MgSO_4$), se filtró, y se concentró para dar un residuo el cualno se purificó. El 2-bromo-3-(4-bromofenil)-3-oxopropanoato de etilo (16.5 g, 48 mmol) y N-Boc-L-prolina (10 g, 48 mmol) se tomaron en acetonitrilo (450 mL) y base Hunig (16 mL, 95 mmol) se le agregó y la solución se agitó 18 hr. El solvente se removió por evaporación rotatoria y el residuo se tomó en acetato de etilo, se lavó con 0.1 N HCl, y salmuera. ^1H 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 = 7.3Hz, 3H).

EMBR: Análisis calculado para $C_{21}H_{26}BrNO_7$ 484.09; encontrado: 410.08 $(M+H)^+$.

Ejemplo J5.

5-(4-bromofenil)-2-(1-(tert-butoxicarbonil)pirrolidin-2-il)-1H-imidazol-4-carboxilato de (S)-etilo

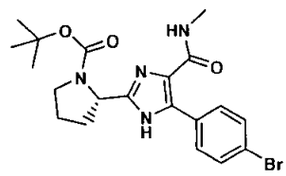


J5

Una botella de presión de 1L se cargó con pirrolidin-1,2-dicarboxilato de (2S)-2-(1-(4-bromofenil)-3-etoxi-1,3-dioxopropan-2-il) 1-tert-butilo J2 (7 g, 35 mmol) y 11 g de NH_4OAc en 125 mL de xileno, y la reacción se calentó a 140°C durante 3.5 hr. Después de enfriarse, la solución se dividió entre acetato de etilo y agua. El extremo orgánica se concentró y el residuo resultante se aplicó a un cartucho de gel de sílice Biotage 40m y se eluyó por 20 -100% gradiente, acetato de etilo/Hex para dar 3g (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 = 7.3Hz, 3H). EMBR: 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)-tert-butilo

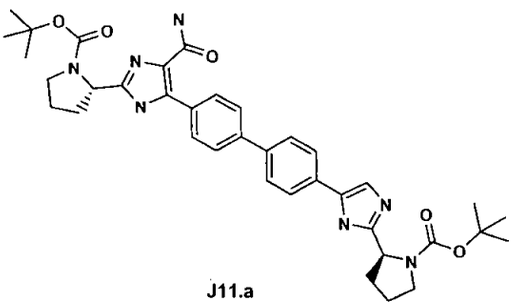


J7

El 5-(4-bromofenil)-2-(1-(tert-butoxicarbonil)pirrolidin-2-il)-1H-imidazol-4-carboxilato de (S)-etilo (1g, 2.1 mmol) se disolvió en 2M metilamina en MeOH (35 mL) y se calentó en un recipiente de presión a 70°C durante 48 h. La mezcla de reacción se concentró y el residuo se aplicó en un cartucho de gel desílice Biotage 25 m y se eluyó por 10 -100% gradiente, acetato de etilo/Hex 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).

EMBR: Análisis calculado para $C_{20}H_{26}BrN_4O_3$ 449.12; encontrado: 449.15 y 451.14 $(M+H)^+$.

Ejemplo J11.a.

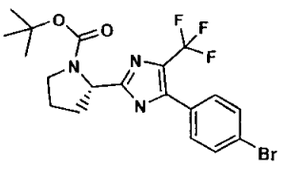


J11.a

La entrada J9 (1.1g, 1.58 mmol) se tomó en etanol (60 mL), 28% soln de hidróxido de amonio concentrado (10 mL) se agregó, y la reacción se calentó en un recipiente de presión a 75°C durante 48 h. El solvente se removió por evaporación rotatoria y el residuo se tomó en acetato de etilo y se lavó con agua, salmuera. La concentración y aplicación a un cartucho Biotage 25 M, gradiente de elución con 10% - 100% acetato de etilo/CH_2Cl_2, dio el J11.a 90 mg (8.5%) y recuperó el material de partida J9 696 mg (63%).

Ejemplo J32.a.

2-(5-(4-bromofenil)-4-(trifluorometil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-tert-butilo

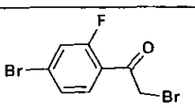
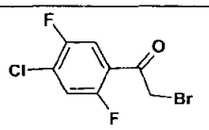


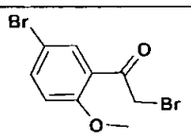
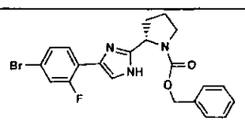
J32.a

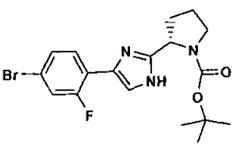
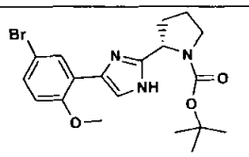
La 3-(4-bromofenil)-3-(2,2-dimetilhidrazono)-1,1,1-trifluoropropan-2-ona (2.0g, 6.2 mmol) se suspendió en 5N de ácido sulfúrico (60 mL) y se calentó a 45°C durante 6 h. La temperatura se elevó a 85°C durante 2 h, y durante el enfriamiento un precipitado se formó. Este material el cual se aisló por filtración para dar 1-(4-bromofenil)-3,3,3-trifluoropropane-1,2-diona 1.6g (92%) como un sólido amarillo. La diona (1.6g, 5.7 mmol) se tomó en metanol (30 mL), N-(tert-butoxicarbonil)-L-prolinal (1g, 5.0 mmol) se agregó, seguido la adición de 28% solución de hidróxido de amonio (10 mL). La reacción se agitó a temperatura ambiente durante 18 h, se vació en diclorometano (200 mL), se lavó con agua y se secó con $MgSO_4$. El filtrado, concentración y aplicación a un cartucho Biotage 40M, gradiente de elución con 5% - 30% acetato de etilo/Hexanos, dio J32.a 1.3g (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). EMBR: 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

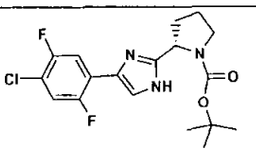
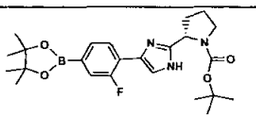
462.0840 $(M+H)^+$.

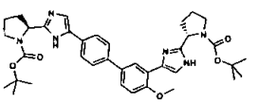
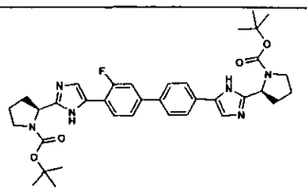
Sección D

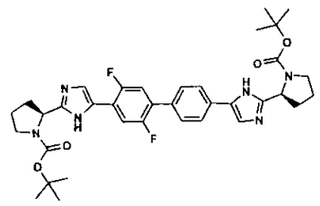
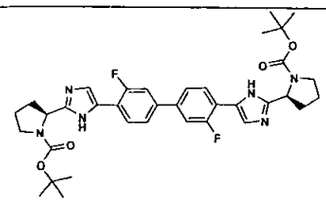
Entrada	Nombre del Compuesto	Estructura	**Datos
D1		 Preparado a partir de 1-(4-bromo-2-fluorofenil)etanona (Distribuidor: Marshalton 50043) usando condiciones de bromación resumidas en D5.	t_R = 2.65 min, (86.7%) LCMS: Análisis calculado para $C_8H_{15}BrFO$ 296.88; encontrado: 296.91 $(M+H)^+$.
D2		 Preparado a partir de 1-(4-cloro-2,5-difluorofenil)etanona (Distribuidor: Oakwood products, 001626) usando condiciones de bromación resumidas en D5.	t_R = 2.66 min, (80%) LCMS: Análisis calculado para $C_8H_4BrClFO$ 270.92; encontrado: ND $(M+H)^+$.

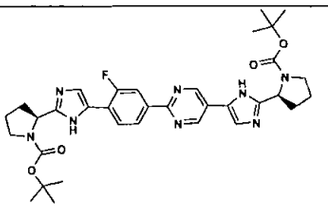
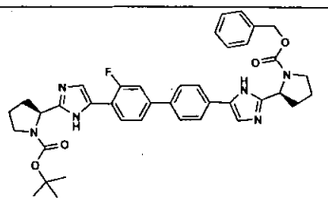
D3		 Preparado a partir de 2-bromo-1-(5-bromo-2-metoxifenil)etanona (Andersh et al., Synth. Comm. 2000, 30 (12), 2091-98) usando condiciones de bromación resumidas en D5.	t_R = 2.57 min, (95%) LCMS: Análisis calculado para $C_9H_9BrO_2$ 228.99; encontrado: 229.00 $(M+H)^+$.
D4		 Preparado a partir de la entrada D1 y CBz-L-prolina (en lugar de Boc-L-prolina) usando condiciones experimentales resumidas en D5.	t_R = 2.38 min, (95.0%) EMBR: Análisis calculado para $C_{19}H_{20}{}^{79}BrFN_3O_2$ 444.07; encontrado: 444.04 $(M+H)^+$. HRMS: Análisis calculado para $C_{19}H_{20}{}^{79}BrFN_3O_2$ 444.0721; encontrado: 444.0736 $(M+H)^+$

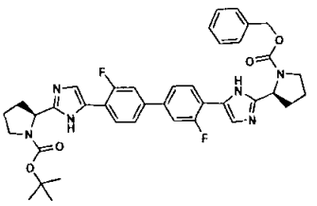
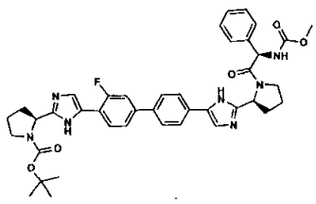
D5		 Condiciones experimentales en D5	t_R = 2.27min, (95%) EMBR: Análisis calculado para $C_{18}H_{22}BrFN_3O_2$ 410.09 y 412.08; encontrado: 410.08 y 412.08 $(M+H)^+$. HRMS: Análisis calculado para $C_{18}H_{22}{}^{79}BrFN_3O_2$ 410.0879; encontrado: 410.0893 $(M+H)^+$.
D6		 Preparado a partir de la entrada D3 (en lugar de entrada D1) usando condiciones experimentales resumidas en D5.	t_R = 2.26 min, (95%) EMBR: Análisis calculado para $C_{19}H_{25}BrN_3O_3$ 422.11 y 424.11; encontrado: 422.10 y 424.10 $(M+H)^+$. HRMS: Análisis calculado para $C_{19}H_{25}{}^{79}BrN_3O_3$ 422.1079; encontrado: 422.1089 $(M+H)^+$.

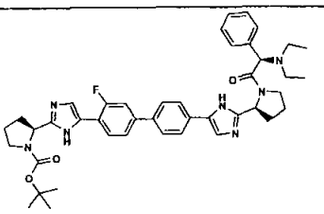
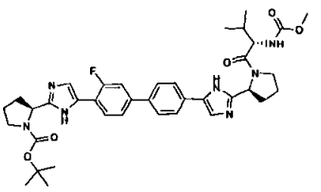
D7		 Preparado a partir de la entrada D2 (en lugar de entrada D1) usando condiciones experimentales resumidas en el experimento adjunto.	t_R = 2.28 min, (95%) EMBR: Análisis calculado para $C_{18}H_{21}ClF_2N_3O_2$ 384.13; encontrado: 384.13 $(M+H)^+$. HRMS: Análisis calculado para $C_{18}H_{21}ClF_2N_3O_2$ 384.1290; encontrado: 384.1301 $(M+H)^+$.
D8		 Preparado a partir de la entrada D5 (en lugar de 1b) usando condiciones experimentales resumidas en el Ejemplo 1, Eextremo c.	t_R = 2.62 min, (~50%) y 1.95 min (~50%, ácido borónico) EMBR: Análisis calculado para $C_{24}H_{34}BFN_3O_4$ 458.26; encontrado: 458.23 $(M+H)^+$. HRMS: Análisis calculado para $C_{24}H_{34}BFN_3O_4$ 458.2626; encontrado: 458.2610 $(M+H)^+$.

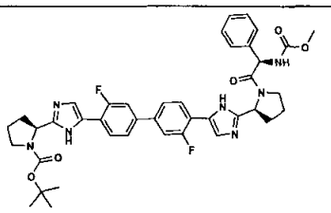
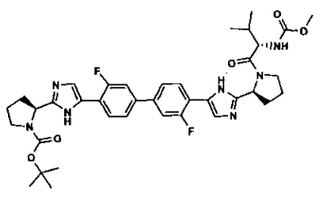
D9	(2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-metoxi-3-bifenilil)-1H-imidazol-2-il)-1-pirrolidinacarboxilato de tert-butilo	 Preparado a partir de la entrada D6 (en lugar de 152e-1) y 1c usando condiciones experimentales resumidas en el ejemplo 152g-1.	t_R = 2.28 min, (95%) EMER: Análisis calculado para $C_{37}H_{47}N_6O_5$ 655.36; encontrado: 655.37 $(M+H)^+$. HRMS: Análisis calculado para $C_{37}H_{47}N_6O_5$ 655.3608; encontrado: 655.3627 $(M+H)^+$.
D10	(2S,2'S)-2,2'-((3-fluoro-4,4'-bifenildiil)bis(1H-imidazol-4,2-diil))di(1-pirrolidinacarboxilato) de di-tert-butilo	 Preparado a partir de la entrada D5 (en lugar de 152e-1) y 1c usando condiciones experimentales resumidas en el ejemplo 152g-1.	t_R = 2.21 min, (99.2%) LCMS: Análisis calculado para $C_{38}H_{42}FN_6O_4$ 643.34; encontrado: 643.51 $(M+H)^+$. HRMS: Análisis calculado para $C_{38}H_{42}FN_6O_4$ 643.3403; encontrado: 643.3390 $(M+H)^+$.

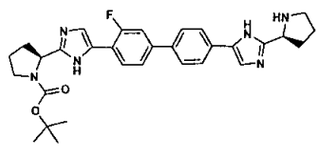
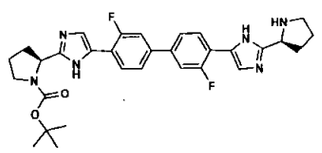
D11	(2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-2,5-difluoro-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinacarboxilato de tert-butilo	 Preparado a partir de la entrada D7 (en lugar de 152e-1) y 1c usando condiciones experimentales resumidas en el ejemplo 152g-1.	t_R = 2.24 min, (95%) EMBR: Análisis calculado para $C_{38}H_{42}F_2N_6O_4$ 661.33; encontrado: 661.35 $(M+H)^+$. HRMS: Análisis calculado para $C_{38}H_{42}F_2N_6O_4$ 661.3314; encontrado: 661.3336 $(M+H)^+$.
D12	(2S,2'S)-2,2'-((3,3'-difluoro-4,4'-bifenildiil)bis(1H-imidazol-5,2-diil))di(1-pirrolidinacarboxilato) de di-tert-butilo	 Preparado a partir de la entrada D5 (en lugar de 152e-1) usando condiciones experimentales resumidas en el ejemplo 153a-1.	t_R = 2.20min, (95%) EMBR: Análisis calculado para $C_{38}H_{42}F_2N_6O_4$ 661.33; encontrado: 661.22 $(M+H)^+$. HRMS: Análisis calculado para $C_{38}H_{42}F_2N_6O_4$ 661.3314; encontrado: 661.3307 $(M+H)^+$

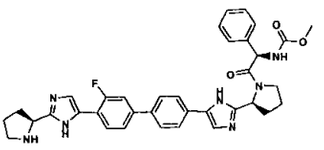
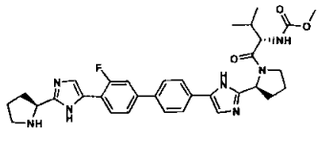
D13	(2S)-2-(5-(2-(4-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-3-fluorofenil)-5-pirimidinil)-1H-imidazol-2-il)-1-pirrolidinacarboxilato de tert-butilo	 Preparado a partir de la entrada D8 (en lugar de 1c) y 152b-1 usando condiciones experimentales resumidas en el ejemplo 152g-1.	t_R = 2.27min, (95%) EMBR: Análisis calculado para $C_{39}H_{42}FN_9O_4$ 645.33; encontrado: 645.34 $(M+H)^+$. HRMS: Análisis calculado para $C_{39}H_{42}FN_9O_4$ 645.3313; encontrado: 645.3323 $(M+H)^+$.
D14	(2S)-2-(4-(4'-(2-((2S)-1-((benciloxi)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-3-fluoro-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinacarboxilato de tert-butilo	 Preparado a partir de la entrada D5 (en lugar de 152e-1) y 1-5c usando condiciones experimentales resumidas en el ejemplo 152g-1.	t_R = 2.26min, (95%) EMBR: Análisis calculado para $C_{43}H_{42}FN_9O_4$ 677.33; encontrado: 677.33 $(M+H)^+$. HRMS: Análisis calculado para $C_{43}H_{42}FN_9O_4$ 677.3252; encontrado: 677.3278 $(M+H)^+$.

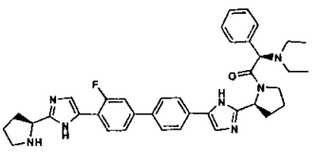
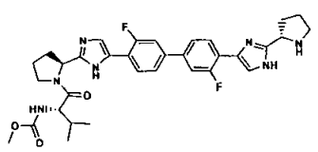
D15	(2S)-2-(4-(4'-(2-((2S)-1-((benciloxi)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-3,3'-difluoro-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinacarboxilato de tert-butilo	 Preparado a partir de la entrada D8 (en lugar de 1c) y entrada D4 usando condiciones experimentales resumidas en el ejemplo 152g-1.	t_R = 2.36min, (97.3%) EMER: Análisis calculado para $C_{39}H_{41}F_2N_6O_4$ 695.32; encontrado: 695.33 $(M+H)^+$. HRMS: Análisis calculado para $C_{39}H_{41}F_2N_6O_4$ 695.3157; encontrado: 695.3151 $(M+H)^+$.
D16	(2S)-2-(5-(3-fluoro-4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinacarboxilato de tert-butilo	 Preparado a partir de la entrada D21 (en lugar de 148e) y Extremo-4 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 2.16 min, (91.0%) EMER: Análisis calculado para $C_{41}H_{45}FN_8O_5$ 734.35; encontrado: 734.36 $(M+H)^+$. HRMS: Análisis calculado para $C_{41}H_{45}FN_8O_5$ 734.3466; encontrado: 734.3474 $(M+H)^+$.

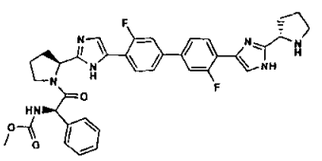
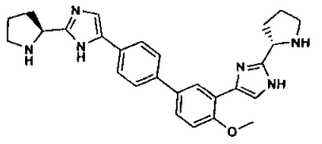
D17	(2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-3-fluoro-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinacarboxilato de tert-butilo	 Preparado a partir de la entrada D21 (en lugar de 148e) y Extremo-2 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.95 min, (95%) EMBR: Análisis calculado para $C_{43}H_{51}FN_7O_3$ 732.40; encontrado: 732.44 $(M+H)^+$. HRMS: Análisis calculado para $C_{43}H_{51}FN_7O_3$ 732.4037; encontrado: 732.4065 $(M+H)^+$.
D18	(2S)-2-(5-(3-fluoro-4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinacarboxilato de tert-butilo	 Preparado a partir de la entrada D21 (en lugar de 148e) y Extremo-51 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 2.14 min, (95%) EMBR: Análisis calculado para $C_{38}H_{47}FN_7O_5$ 700.36; encontrado: 700.37 $(M+H)^+$. HRMS: Análisis calculado para $C_{38}H_{47}FN_7O_5$ 700.3623; encontrado: 700.3596 $(M+H)^+$.

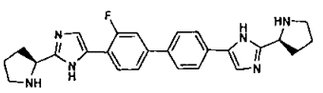
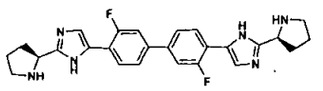
D19	(2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinacarboxilato de tert-butilo	 Preparado a partir de la entrada D22 (en lugar de 148e) y Extremo-4 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 2.23 min, (95%) EMBR: Análisis calculado para $C_{41}H_{44}F_2N_7O_5$ 752.34; encontrado: 752.35 $(M+H)^+$. HRMS: Análisis calculado para $C_{41}H_{44}F_2N_7O_5$ 752.3372; encontrado: 752.3385 $(M+H)^+$.
D20	(2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinacarboxilato de tert-butilo	 Preparado a partir de la entrada D22 (en lugar de 148e) y Extremo-51 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 2.16 min, (90%) EMBR: Análisis calculado para $C_{38}H_{46}F_2N_7O_5$ 718.35; encontrado: 718.36 $(M+H)^+$. HRMS: Análisis calculado para $C_{38}H_{46}F_2N_7O_5$ 718.3528; encontrado: 718.3505 $(M+H)^+$.

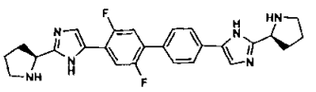
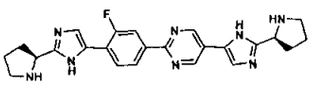
D21	(2S)-2-(5-(3-fluoro-4'-(2-((2S)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinacarboxilato triacetato de tert-butilo	 Preparado a partir de la entrada D14 (en lugar de 152g-8) usando condiciones experimentales resumidas en el ejemplo 152i-1.	t_R = 1.94 min, (95%) EMBR: Análisis calculado para $C_{31}H_{36}FN_6O_2$ 543.29; encontrado: 543.30. HRMS: Análisis calculado para $C_{31}H_{36}FN_6O_2$ 543.2884; encontrado: 543.2872 $(M+H)^+$.
D22	(2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinacarboxilato de tert-butilo	 Preparado a partir de la entrada D15 (en lugar de 152g-8) usando condiciones experimentales resumidas en el ejemplo 152i-1.	t_R = 2.14 min, (95%) EMBR: Análisis calculado para $C_{31}H_{35}F_2N_6O_2$ 561.28; encontrado: 561.29 $(M+H)^+$. HRMS: Análisis calculado para $C_{31}H_{35}F_2N_6O_2$ 561.2790; encontrado: 561.2766 $(M+H)^+$.

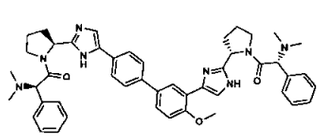
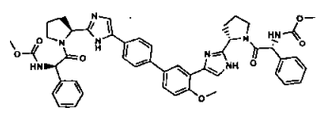
D23	((1R)-2-((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Preparado a partir de la entrada D16 (en lugar de 152j-27) usando condiciones experimentales resumidas en el ejemplo 152k-1.	t_R = 1.90 min, (94%) EMBR: Análisis calculado para $C_{36}H_{37}FN_7O_3$ 634.29; encontrado: 634.29 $(M+H)^+$. HRMS: Análisis calculado para $C_{36}H_{37}FN_7O_3$ 634.2942; encontrado: 634.2948 $(M+H)^+$.
D24	((1S)-1-(((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 Preparado a partir de la entrada D18 (en lugar de 152j-27) usando condiciones experimentales resumidas en el ejemplo 152k-1.	t_R = 1.89 min, (95%) EMBR: Análisis calculado para $C_{33}H_{39}FN_7O_3$ 600.31; encontrado: 600.32 $(M+H)^+$. HRMS: Análisis calculado para $C_{33}H_{39}FN_7O_3$ 600.3098; encontrado: 600.3121 $(M+H)^+$.

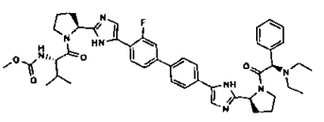
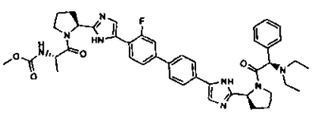
D25	(1R)-N,N-dietil-2-((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletanamina	 Preparado a partir de la entrada D17 (en lugar de 152j-27) usando condiciones experimentales resumidas en el ejemplo 152k-1.	t_R = 1.72 min, (90%) EMBR: Análisis calculado para $C_{38}H_{43}FN_7O$ 632.35; encontrado: 632.36 $(M+H)^+$. HRMS: Análisis calculado para $C_{38}H_{43}FN_7O$ 632.3513; encontrado: 632.3527 $(M+H)^+$.
D26	((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 Preparado a partir de la entrada D20 (en lugar de 152j-27) usando condiciones experimentales resumidas en el ejemplo 152k-1.	t_R = 1.96 min, (95%) EMBR: Análisis calculado para $C_{33}H_{38}F_2N_7O_3$ 618.30; encontrado: 618.31 $(M+H)^+$. HRMS: Análisis calculado para $C_{33}H_{38}F_2N_7O_3$ 618.3004; encontrado: 618.3024 $(M+H)^+$.

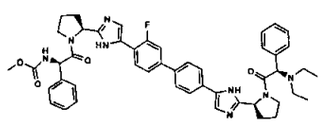
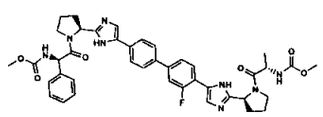
D27	((1R)-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) carbamato de metilo	 Preparado a partir de la entrada D19 (en lugar de 152j-27) usando condiciones experimentales resumidas en el ejemplo 152k-1.	t_R = 1.63 min, (95%) EMBR: Análisis calculado para $C_{36}H_{36}F_2N_7O_3$ 652.28; encontrado: 652.29 $(M+H)^+$. HRMS: Análisis calculado para $C_{36}H_{36}F_2N_7O_3$ 652.2848; encontrado: 652.2858 $(M+H)^+$.
D28	5,5'-(4-metoxi-3,4'-bifenildiil)bis(2-((2S)-2-pirrolidinil)-1H-imidazol)	 Preparado a partir de la entrada D9 (en lugar de 152j-27) usando condiciones experimentales resumidas en el ejemplo 152k-1.	t_R = 1.53 min, (98.2%) EMBR: Análisis calculado para $C_{27}H_{31}N_6O$ 455.26; encontrado: 455.26 $(M+H)^+$. HRMS: Análisis calculado para $C_{27}H_{31}N_6O$ 455.2559; encontrado: 455.2576 $(M+H)^+$.

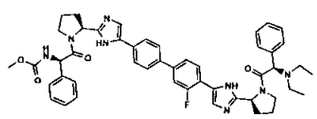
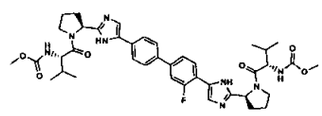
D29	5,5'-(3-fluoro-4,4'-bifenildiil)bis(2-((2S)-2-pirrolidinil)-1H-imidazol) tetraacetato	 Preparado a partir de la entrada 10 (en lugar de 152j-27) usando condiciones experimentales resumidas en el ejemplo 152k-1.	t_R = 1.55 min, (95%) EMBR: Análisis calculado para $C_{26}H_{28}FN_6$ 443.24; encontrado: 443.24 $(M+H)^+$. HRMS: Análisis calculado para $C_{26}H_{28}FN_6$ 443.2359; encontrado: 443.2371 $(M+H)^+$.
D30		 Preparado a partir de la entrada D12 (en lugar de 152j-27) usando condiciones experimentales resumidas en el ejemplo 152k-1.	t_R = 1.72 min, (77.5%) EMBR: Análisis calculado para $C_{26}H_{27}F_2N_6$ 461.23; encontrado: 461.25 $(M+H)^+$. HRMS: Análisis calculado para $C_{26}H_{27}F_2N_6$ 461.2265; encontrado: 461.2272 $(M+H)^+$.

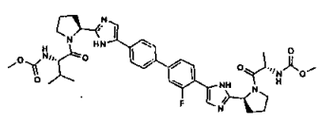
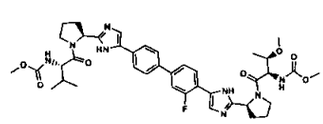
D31	5,5'-(2,5-difluoro-4,4'-bifenildiil)bis(2-((2S)-2-pirrolidinil)-1H-imidazol)	 Preparado a partir de la entrada D11 (en lugar de 152j-27) usando condiciones experimentales resumidas en el ejemplo 152k-1.	t_R = 1.67 min, (95%) EMBR: Análisis calculado para $C_{26}H_{27}F_2N_6$ 461.23; encontrado: 461.23 $(M+H)^+$. HRMS: Análisis calculado para $C_{26}H_{27}F_2N_6$ 461.2265; encontrado: 461.2287 $(M+H)^+$.
D32	2-(3-fluoro-4-(2-((2S)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-5-(2-((2S)-2-pirrolidinil)-1H-imidazol-5-il)pirimidina	 Preparado a partir de la entrada D13 (en lugar de 152j-27) usando condiciones experimentales resumidas en el ejemplo 152k-1.	t_R = 1.63 min, (95%) EMBR: Análisis calculado para $C_{24}H_{26}FN_8$ 445.23; encontrado: 445.23 $(M+H)^+$. HRMS: Análisis calculado para $C_{24}H_{26}FN_8$ 445.2264; encontrado: 445.2268 $(M+H)^+$.

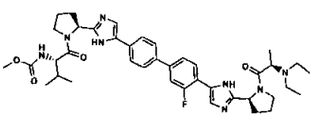
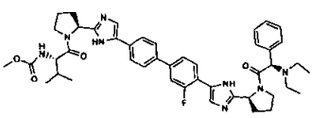
D33	(1R,1'R)-2,2'-((4-metoxi-3,4'-bifenildiil)bis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(N,N-dimetil-2-oxo-1-feniletanamina)	 Preparado a partir de la entrada D28 (en lugar de 148e) y Extremo-1 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.71 min, (95%) EMBR: Análisis calculado para $C_{47}H_{53}N_8O_3$ 777.42; encontrado: 777.41 $(M+H)^+$. HRMS: Análisis calculado para $C_{47}H_{53}N_8O_3$ 777.4241; encontrado: 777.4254 $(M+H)^+$.
D34	((4-metoxi-3,4'-bifenildiil)bis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etanediil)))biscarbamato de dimetilo	 Preparado a partir de la entrada D28 (en lugar de 148e) y Extremo-4 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 2.09 min, (95%) EMBR: Análisis calculado para $C_{47}H_{49}N_8O_7$ 837.37; encontrado: 837.34 $(M+H)^+$. HRMS: Análisis calculado para $C_{47}H_{49}N_8O_7$ 837.3724; encontrado: 837.3690 $(M+H)^+$.

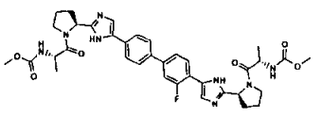
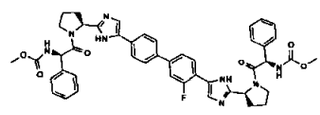
D35	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-3-fluoro-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 Preparado a partir de la entrada D25 (en lugar de 148e) y Extremo-51 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.85 min, (97.2%) EMBR: Análisis calculado para $C_{45}H_{54}FN_8O_4$ 789.43; encontrado: 789.43 $(M+H)^+$. HRMS: Análisis calculado para $C_{45}H_{54}FN_8O_4$ 789.4252; encontrado: 789.4225 $(M+H)^+$.
D36	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-3-fluoro-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	 Preparado a partir de la entrada D25 (en lugar de 148e) y Extremo-52 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.76 min, (97.9%) EMBR: Análisis calculado para $C_{43}H_{50}FN_8O_4$ 761.39; encontrado: 761.26 $(M+H)^+$. HRMS: Análisis calculado para $C_{43}H_{50}FN_8O_4$ 761.3939; encontrado: 761.3967 $(M+H)^+$.

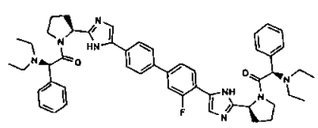
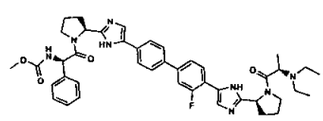
D37	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-3-fluoro-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Preparado a partir de la entrada D25 (en lugar de 148e) y Extremo-4 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.90 min, (98.6%) EMBR: Análisis calculado para $C_{48}H_{52}FN_8O_4$ 823.41; encontrado: 823.42 $(M+H)^+$. HRMS: Análisis calculado para $C_{48}H_{52}FN_8O_4$ 823.4096; encontrado: 823.4102 $(M+H)^+$.
D38	((1R)-2-((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Preparado a partir de la entrada D23 (en lugar de 148e) y Extremo-52 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.89 min, (98.2%) EMBR: Análisis calculado para $C_{47}H_{49}N_8O_7$ 763.34; encontrado: 763.32 $(M+H)^+$. HRMS: Análisis calculado para $C_{41}H_{44}FN_8O_6$ 763.3368; encontrado: 763.3358 $(M+H)^+$.

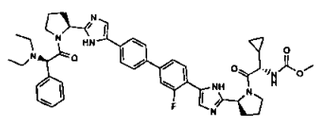
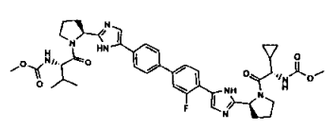
D39	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-3'-fluoro-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Preparado a partir de la entrada D23 (en lugar de 148e) y Extremo-2 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.88 min, (98.7%) EMBR: Análisis calculado para $C_{48}H_{52}FN_8O_4$ 823.41; encontrado: 823.39 $(M+H)^+$. HRMS: Análisis calculado para $C_{48}H_{52}FN_8O_4$ 823.4096; encontrado: 823.4127 $(M+H)^+$.
D40	((1S)-1-(((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-1-((2S)-2-((metoxi carbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 Preparado a partir de la entrada D29 (en lugar de 148e) y Extremo-51 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.97 min, (98.4%) EMBR: Análisis calculado para $C_{40}H_{50}FN_8O_6$ 757.38; encontrado: 757.32 $(M+H)^+$. HRMS: Análisis calculado para $C_{40}H_{50}FN_8O_6$ 757.3837; encontrado: 757.3815 $(M+H)^+$.

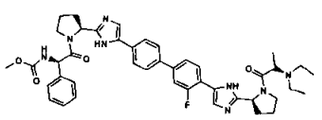
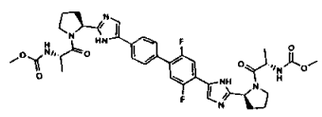
D41	((1S)-1-(((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 Preparado a partir de la entrada D24 (en lugar de 148e) y Extremo-52 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.82 min, (95.0%) EMBR: Análisis calculado para $C_{38}H_{46}FN_8O_6$ 729.35; encontrado: 729.29 $(M+H)^+$. HRMS: Análisis calculado para $C_{38}H_{46}FN_8O_6$ 729.3524; encontrado: 729.3523 $(M+H)^+$.
D42	((1S,2R)-1-(((2S)-2-(5-(3-fluoro-4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metoxipropil) carbamato de metilo	 Preparado a partir de la entrada D24 (en lugar de 148e) y Extremo-86 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.91 min, (94.0%) EMBR: Análisis calculado para $C_{40}H_{50}FN_8O_7$ 773.38; encontrado: 773.31 $(M+H)^+$. HRMS: Análisis calculado para $C_{40}H_{50}FN_8O_7$ 773.3786; encontrado: 773.3759 $(M+H)^+$.

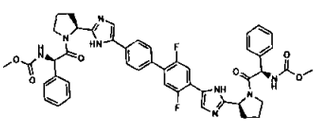
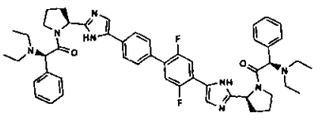
D43	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dietil-D-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-3'-fluoro-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 Preparado a partir de la entrada D24 (en lugar de 148e) y Extremo-69b usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.72 min, (97.6%) EMBR: Análisis calculado para $C_{40}H_{52}FN_8O_4$ 727.41; encontrado: 727.35 $(M+H)^+$. HRMS: Análisis calculado para $C_{40}H_{52}FN_8O_4$ 727.4096; encontrado: 727.4091 $(M+H)^+$.
D44	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-3'-fluoro-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 Preparado a partir de la entrada D24 (en lugar de 148e) y Extremo-2 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.83 min, (96.9%) EMBR: Análisis calculado para $C_{45}H_{54}FN_8O_4$ 789.43; encontrado: 789.36 $(M+H)^+$. HRMS: Análisis calculado para $C_{45}H_{54}FN_8O_4$ 789.4252; encontrado: 789.4225 $(M+H)^+$.

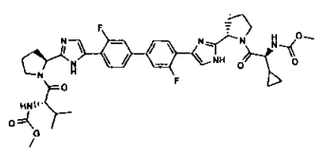
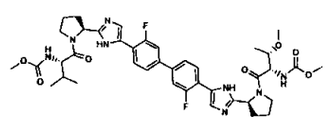
D45	((1S)-2-((2S)-2-(5-(3'-fluoro-4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	 Preparado a partir de la entrada D29 (en lugar de 148e) y Extremo-52 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.69 min, (97.7%) EMER: Análisis calculado para for $C_{36}H_{42}FN_8O_6$ 701.32; encontrado: 701.30 $(M+H)^+$. HRMS: Análisis calculado para $C_{36}H_{42}FN_8O_6$ 701.3222; encontrado: 701.3211 $(M+H)^+$.
D46	((3-fluoro-4,4'-bifenildiil)bis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etanediil)))biscarbamato de dimetilo	 Preparado a partir de la entrada D29 (en lugar de 148e) y Extremo-4 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 2.05 min, (99.9%) EMER: Análisis calculado para for $C_{46}H_{46}FN_8O_6$ 825.35; encontrado: 825.35 $(M+H)^+$. HRMS: Análisis calculado para $C_{46}H_{46}FN_8O_6$ 825.3524; encontrado: 825.3522 $(M+H)^+$.

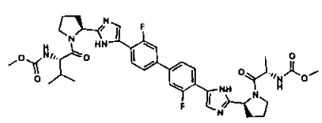
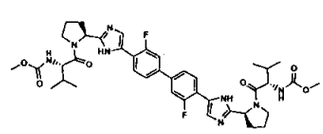
D47	(1R,1'R)-2,2'-((3-fluoro-4,4'-bifenildiil)bis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(N,N-dietil-2-oxo-1-feniletanamina)	 Preparado a partir de la entrada D29 (en lugar de 148e) y Extremo-2 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.72 min, (99.5%) EMBR: Análisis calculado para for $C_{50}H_{58}FN_8O_2$ 821.47; encontrado: 821.44 $(M+H)^+$. HRMS: Análisis calculado para $C_{50}H_{58}FN_8O_2$ 821.4667; encontrado: 821.4636 $(M+H)^+$.
D48	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dietil-D-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-3'-fluoro-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Preparado a partir de la entrada D23 (en lugar de 148e) y Extremo-69b usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.76min, (99.7%) EMBR: Análisis calculado para $C_{43}H_{50}FN_8O_4$ 761.39; encontrado: 761.27 $(M+H)^+$. HRMS: Análisis calculado para $C_{43}H_{50}FN_8O_4$ 761.3939; encontrado: 761.3952 $(M+H)^+$.

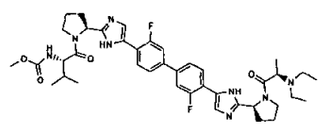
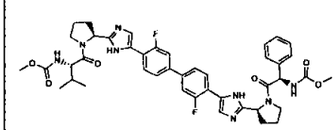
D49	((1S)-1-ciclopropil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-3-fluoro-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo	 Preparado a partir de la entrada D25 (en lugar de 148e) y Extremo-54b usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.92 min, (98.7%) EMBR: Análisis calculado para $C_{45}H_{52}FN_8O_4$ 787.41; encontrado: 787.36 $(M+H)^+$. HRMS: Análisis calculado para $C_{45}H_{52}FN_8O_4$ 787.4096; encontrado: 787.4074 $(M+H)^+$.
D50	((1S)-1-ciclopropil-2-((2S)-2-(5-(3-fluoro-4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo	 Preparado a partir de la entrada D24 (en lugar de 148e) y Extremo-54b usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.94 min, (99.0%) EMBR: Análisis calculado para $C_{40}H_{48}F_2N_8O_7$ 755.37; encontrado: 755.32 $(M+H)^+$. HRMS: Análisis calculado para $C_{40}H_{48}FN_8O_6$ 755.3681; encontrado: 755.3670 $(M+H)^+$.

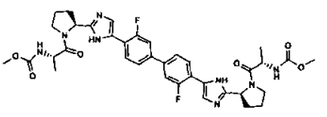
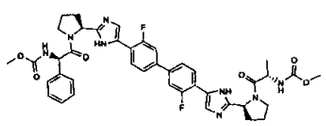
D51	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dietil-D-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-3'-fluoro-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Preparado a partir de la entrada D23 (en lugar de 148e) y Extremo-69b usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.92 min, (98.3%) EMBR: Análisis calculado para $C_{43}H_{50}FN_8O_4$ 761.39; encontrado: 761.35 $(M+H)^+$. HRMS: Análisis calculado para $C_{43}H_{50}FN_8O_4$ 761.3939; encontrado: 761.3956 $(M+H)^+$.
D52	((1S)-2-((2S)-2-(5-(2',5'-difluoro-4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	 Preparado a partir de la entrada D31 (en lugar de 148e) y Extremo-52 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.69 min, (99.2%) EMBR: Análisis calculado para $C_{36}H_{41}F_2N_8O_6$ 719.31; encontrado: 719.29 $(M+H)^+$. HRMS: Análisis calculado para $C_{36}H_{41}F_2N_8O_6$ 719.3117; encontrado: 719.3109 $(M+H)^+$.

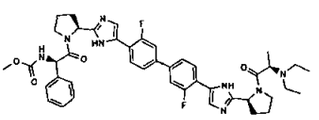
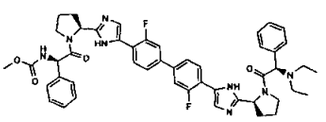
D53	((2,5-difluoro-4,4'-bifenildiil)bis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etanediil)))biscarbamato de dimetilo	 Preparado a partir de la entrada D31 (en lugar de 148e) y Extremo-4 usando condiciones experimentales resumidas en el ejemplo 148 de 10889PSP.	t_R = 2.08 min, (100.0%) EMBR: Análisis calculado para $C_{46}H_{45}F_2N_8O_6$ 843.34; encontrado: 843.34 $(M+H)^+$. HRMS: Análisis calculado para $C_{46}H_{45}F_2N_8O_6$ 843.3430; encontrado: 843.3458 $(M+H)^+$.
D54	(1R,1'R)-2,2'-((2,5-difluoro-4,4'-bifenildiil)bis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(N,N-dietil-2-oxo-1-feniletanamina)	 Preparado a partir de la entrada D31 (en lugar de 148e) y Extremo-2 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.76 min, (99.8%) EMBR: Análisis calculado para $C_{50}H_{57}F_2N_8O_2$ 839.46; encontrado: 839.43 $(M+H)^+$. HRMS: Análisis calculado para $C_{50}H_{57}F_2N_8O_2$ 839.4573; encontrado: 839.4585 $(M+H)^+$.

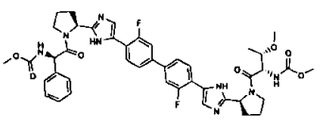
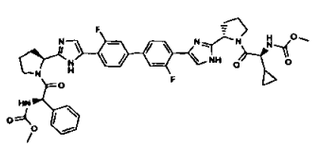
D55	((1S)-1-ciclopropil-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo	 Preparado a partir de la entrada D26 (en lugar de 148e) y Extremo-54b usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.93 min, (98.5%) EMBR: Análisis calculado para $C_{40}H_{47}F_2N_8O_6$ 773.36; encontrado: 773.31 $(M+H)^+$. HRMS: Análisis calculado para $C_{40}H_{47}F_2N_8O_6$ 773.3567; encontrado: 773.3587 $(M+H)^+$.
D56	((1S,2R)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metoxipropil)carbamato de metilo	 Preparado a partir de la entrada D26 (en lugar de 148e) y Extremo-86 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 2.00 min, (98.0%) EMBR: Análisis calculado para $C_{40}H_{49}F_2N_8O_7$ 791.37; encontrado: 791.32 $(M+H)^+$. HRMS: Análisis calculado para $C_{40}H_{49}F_2N_8O_7$ 791.3692; encontrado: 791.3682 $(M+H)^+$.

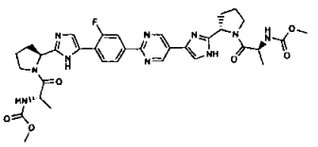
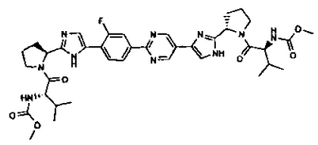
D57	((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 Preparado a partir de la entrada D26 (en lugar de 148e) y Extremo-52 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.86 min, (95.6%) EMBR: Análisis calculado para $C_{38}H_{45}F_2N_8O_6$ 747.34; encontrado: 747.30 $(M+H)^+$. HRMS: Análisis calculado para $C_{38}H_{45}F_2N_8O_6$ 747.3430; encontrado: 747.3425 $(M+H)^+$.
D58	((1S)-1-(((2S)-2-(5-(3,3'-difluoro-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	 Preparado a partir de la entrada D26 (en lugar de 148e) y Extremo-51 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 2.02 min, (96.3%) EMBR: Análisis calculado para $C_{40}H_{49}F_2N_8O_6$ 775.37; encontrado: 775.31 $(M+H)^+$. HRMS: Análisis calculado para $C_{40}H_{49}F_2N_8O_6$ 775.3743; encontrado: 775.37.34 $(M+H)^+$.

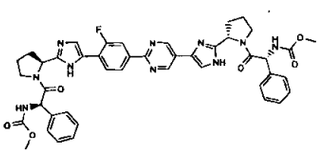
D59	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dietil-D-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-3,3'-difluoro-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 Preparado a partir de la entrada D26 (en lugar de 148e) y Extremo-69b usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.78 min, (98.2%) EMBR: Análisis calculado para $C_{40}H_{51}F_2N_8O_4$ 745.40; encontrado: 745.34 $(M+H)^+$. HRMS: Análisis calculado para $C_{40}H_{51}F_2N_8O_4$ 745.4001; encontrado: 745.4008 $(M+H)^+$.
D60	((1S)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 Preparado a partir de la entrada D26 (en lugar de 148e) y Extremo-4 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 2.08 min, (99.1%) EMBR: Análisis calculado para $C_{43}H_{47}F_2N_8O_6$ 809.36; encontrado: 809.29 $(M+H)^+$. HRMS: Análisis calculado para $C_{43}H_{47}F_2N_8O_6$ 809.3587; encontrado: 809.3568 $(M+H)^+$.

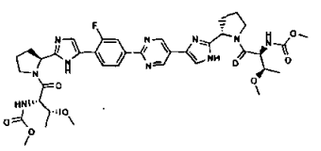
D61	((1S)-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	 Preparado a partir de la entrada D30 (en lugar de 148e) y Extremo-52 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.71min, (94.3%) EMBR: Análisis calculado para $C_{36}H_{41}F_2N_8O_6$ 719.31; encontrado: 719.19 $(M+H)^+$. HRMS: Análisis calculado para $C_{36}H_{41}F_2N_8O_6$ 719.3117; encontrado: 719.3115 $(M+H)^+$.
D62	((1R)-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Preparado a partir de la entrada D27 (en lugar de 148e) y Extremo-52 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.94 min, (98.3%) EMBR: Análisis calculado para $C_{41}H_{43}F_2N_8O_6$ 781.33; encontrado: 781.26 $(M+H)^+$. HRMS: Análisis calculado para $C_{41}H_{43}F_2N_8O_6$ 781.3274; encontrado: 781.3264 $(M+H)^+$.

D63	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dietil-D-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-3,3'-difluoro-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Preparado a partir de la entrada D27 (en lugar de 148e) y Extremo-69b usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.44 min, (99.0%) EMBR: Análisis calculado para $C_{43}H_{49}F_2N_8O_4$ 779.38; encontrado: 779.32 $(M+H)^+$. HRMS: Análisis calculado para $C_{43}H_{49}F_2N_8O_4$ 779.3845; encontrado: 779.3842 $(M+H)^+$.
D64	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-3,3'-difluoro-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Preparado a partir de la entrada D27 (en lugar de 148e) y Extremo-2 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.94 min, (95.3%) EMBR: Análisis calculado para $C_{48}H_{51}F_2N_8O_4$ 841.40; encontrado: 841.33 $(M+H)^+$. HRMS: Análisis calculado para $C_{48}H_{51}F_2N_8O_4$ 841.4001; encontrado: 841.3991 $(M+H)^+$.

D65	((1S,2R)-1-(((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metoxipropil) carbamato bis(trifluoro acetato) de metilo	 Preparado a partir de la entrada D27 (en lugar de 148e) y Extremo-86 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 2.00 min, (96.2%) EMBR: Análisis calculado para $C_{43}H_{47}F_2N_8O_7$, 825.35; encontrado: 825.28 $(M+H)^+$. HRMS: Análisis calculado para $C_{43}H_{47}F_2N_8O_7$, 825.3536; encontrado: 825.3527 $(M+H)^+$.
D66	((1S)-1-ciclopropil-2-((2S)-2-(5-(3,3'-difluoro-4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo	 Preparado a partir de la entrada D27 (en lugar de 148e) y Extremo-54b usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 2.01 min, (99.5%) EMBR: Análisis calculado para $C_{43}H_{45}F_2N_8O_6$ 807.34; encontrado: 807.29 $(M+H)^+$. HRMS: Análisis calculado para $C_{43}H_{45}F_2N_8O_6$ 807.3430; encontrado: 807.3409 $(M+H)^+$.

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 a partir de la entrada D32 (en lugar de 148e) y Extremo-52 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.58 min, (91.1%) EMBR: Análisis calculado para $C_{34}H_{40}FN_{10}O_6$ 703.31; encontrado: 703.27 $(M+H)^+$. HRMS: Análisis calculado 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)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo	 Preparado a partir de la entrada D32 (en lugar de 148e) y Extremo-51 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.95 min, (99.3%) EMBR: Análisis calculado para $C_{36}H_{48}FN_{10}O_6$ 759.37; encontrado: 759.30 $(M+H)^+$. HRMS: Análisis calculado para $C_{36}H_{48}FN_{10}O_6$ 759.3742; encontrado: 759.3715 $(M+H)^+$.

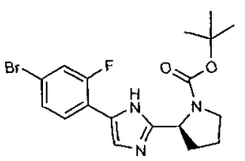
D69	((1R)-2-((2S)-2-(5-(2-(3-fluoro-4-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)fenil)-5-pirimidinil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 Preparado a partir de la entrada D32 (en lugar de 148e) y Extremo-4 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 2.05 min, (99.3%) EMBR: Análisis calculado para $C_{44}H_{44}FN_{10}O_6$ 827.34; encontrado: 827.27 $(M+H)^+$. HRMS: Análisis calculado 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 a partir de la entrada D32 (en lugar de 148e) y Extremo-86 usando condiciones experimentales resumidas en el ejemplo 148.	t_R = 1.79 min, (93.0%) EMBR: Análisis calculado para $C_{38}H_{48}FN_{10}O_8$ 791.36; encontrado: 791.31 $(M+H)^+$. HRMS: Análisis calculado para $C_{38}H_{48}FN_{10}O_8$ 791.3641; encontrado: 791.3636 $(M+H)^+$.

**Condiciones LCMS: Phenomenex-Luna 4.6 x 50 mm S10, 0 hasta 100%B durante 3 min, 4 min tiempo de paro, 4 mL/min, 220nm, A: 10% MeOH-90%H2O - 0.1% TFA; B: 90% MeOH-10%H2O-0.1% TFA

Ejemplo D5.

2-(5-(4-bromo-2-fluorofenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-tert-butilo



D5

El bromo (0.54 mL, 10.6 mmol) se le agregó gota a gota a una solución fría (0°C) de 4-bromo-2-fluoroacetofenona (2.30 g, 10.6 mmol) en dioxano (80 mL) y tetrahidrofurano (80 mL). La mezcla se agitó durante 1h a 0°C y se calentó a temperatura ambiente durante 15h. La mezcla se diluyó con acetato de etilo, se lavó con una solución de $NaHCO_3$ saturado, 5% solución de tiosulfato de sodio y salmuera previo al secado (Na_2SO_4). La 2-Bromo-1-(4-bromo-2-fluorofenil)etanona (D1) se aisló como una película incolora la cual se solidificó durante concentración adicional bajo alto vacío. Este sólido se disolvió en acetonitrilo anhidro (50 mL) y se trató con N-Boc-L-prolina (2.28 g, 10.6 mmol) y diisopropiletilamina (1.85 mL, 10.6 mmol). Después de agitarse durante 3h a temperatura ambiente, el solvente se removió in vacuo y el residuo se dividió en acetato de etilo y agua. La fase orgánica se lavó con ácido clorhídrico 0.1N, solución de $NaHCO_3$ saturado y salmuera previó al secado (Na_2SO_4), filtración, y concentración. El residuo se tomó en

xilenos (50 mL) y se trató hasta NH_4OAc sólido (4.1 g, 53.0 mmol). La mezcla se calentó a 140°C durante 2 hr en un matraz de extremo de rosca de pared gruesa antes esto se enfrió a temperatura ambiente, se diluyó con acetato de etilo y se lavó con solución de $NaHCO_3$ saturado y salmuera previó al secado (Na_2SO_4) y concentración. La purificación del residuo por cromatografía instantánea Biotage™ en gel de sílice (65M Columna, preequilibrada con 16%B durante 1800 mL seguido por gradiente de elución con 16%B hasta 16%B durante 450 mL, 16%B hasta 50%B durante 2199 ml y finalmente 50%B hasta 100%B durante 2199 mL) proporciono el compuesto del título (D5) (3.61 g, 83%) como un aceite color caramelo/café. Una porción pequeña (40 mg) del compuesto del título se purificó además por HPLC preparativa (20%B hasta 100%B durante 14 min en donde B es 10mM NH_4OAc en 10:90 H_2O/ACN y A es 10 mM NH_4OAc en 95:5 H_2O/CAN usando una columna Phenomenex-Gemini 30 x 100 mm S10 con flujo a 40 mL/min) para proporcionar 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).

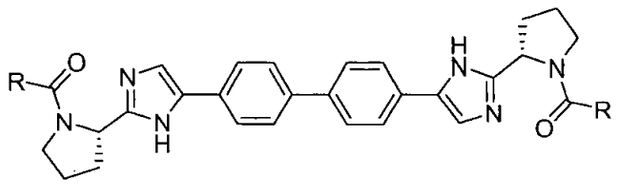
HPLC Phenomenex LUNA C-18 4.6 x 50 mm, 0 hasta 100% B durante 3 minutos, tiempo de espera 1 minuto, A = 90%

agua, 10% metanol, 0.1% TFA, B = 10% agua, 90% metanol, 0.1% TFA, TR = 2.27 min, 95% índice de homogeneidad.

EMBR: Análisis calculado para $C_{18}H_{22}BrFN_3O_2$ 410.09 y 412.09; encontrado: 410.08 y 412.08 $(M+H)^+$.

HRMS: Análisis calculado para $C_{18}H_{22}BrFN_3O_2$ 410.0879; encontrado: 410.0893 $(M+H)^+$.

Ejemplos M1-M27



El ejemplo M1-M27 se prepararon a partir de 1e y los ácidos respectivos usando el método descrito por el ejemplo 1. Los productos se prepararon como sales TFA, a menos de que se indique de otra manera. Las condiciones CL fueron como sigue:

Condición 1

Columna = Phenomenex-Luna 3.0X 50 mm S10

Inicio %B = 0

Final %B = 100

Tiempo de Gradiente = 2 min

Tiempo de paro = 3 min

Relación de flujo = 4 mL/min

Longitud de onda = 220 nm

Solvente A = 0.1% TFA en 10% metanol/90%H_2O

Solvente B = 0.1% TFA en 90% metanol/10% H_2O

Condición 2

Columna = Phenomenex-Luna 4.6X50 mm S10

Inicio %B = 0

Final %B = 100

Tiempo de Gradiente = 2 min

Tiempo de paro = 3 min

Relación de flujo = 5 mL/min

Longitud de onda = 220 nm

Solvente A = 0.1% TFA en 10% metanol/90%H_2O

Solvente B = 0.1% TFA en 90% metanol/10% H_2O

Condición 3

Columna = HPLC XTERRA C18 3.0 x 50mm S7

Inicio %B = 0

Final %B = 100

Tiempo de Gradiente = 3 min

Tiempo de paro = 4 min

Relación de flujo = 4 mL/min

Longitud de onda = 220 nm

Solvente A = 0.1% TFA en 10% metanol/90%H_2O

Solvente B = 0.1% TFA en 90% metanol/10% H_2O

Condición M1

Columna: Luna 4.6X 50 mm S10

Inicio %B = 0

Final %B = 100

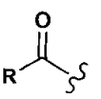
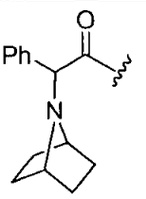
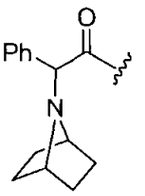
Tiempo de Gradiente = 3 min

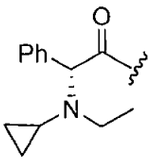
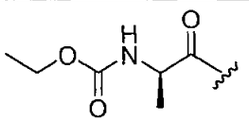
Tiempo de paro = 4 min

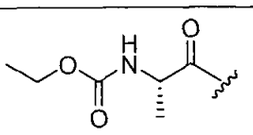
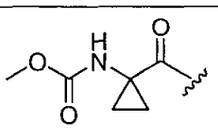
Relación de flujo = 4 mL/min

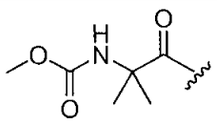
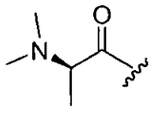
Solvente A: = 95% H_2O: 5% CH_3CN, 10 mm acetato de amonio

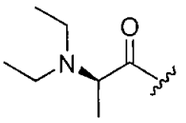
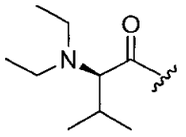
Solvente B: = 5% H_2O: 95% CH_3CN; 10 mm acetato de amonio

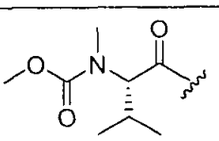
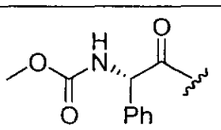
Ejemplo	Nombre del Compuesto	 (Fuente)	TR (LC-Cond.); % índice de homogeneidad; Datos EM; ^{1}H RMN datos
M1	7,7'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil(2-oxo-1-fenil-2,1-etanediil)))bis(7-azabiciclo[2.2.1]heptano)	 (Extremo-77a)	1.04 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{54}H_{59}N_8O_2$: 851.48; encontrado 851.55; HRMS: Análisis calculado para $[M+H]^+$ $C_{54}H_{59}N_8O_2$: 851.4761; encontrado 851.4780
M2	7,7'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil(2-oxo-1-fenil-2,1-etanediil)))bis(7-azabiciclo[2.2.1]heptano)	 (Extremo-77b)	1.13 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{54}H_{59}N_8O_2$: 851.48; encontrado 851.57; HRMS: Análisis calculado para $[M+H]^+$ $C_{54}H_{59}N_8O_2$: 851.4761; encontrado 851.4792

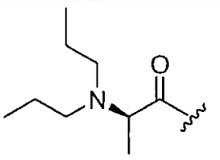
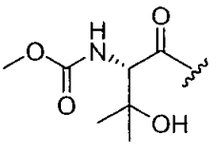
M3	N,N'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etanediil)))bis(N-etilciclopropanamina)	 (Extremo-78)	1.13 min (Cond. 1); >95%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{52}H_{59}N_8O_2$: 827.48; encontrado 827.69; HRMS: Análisis calculado para $[M+H]^+$ $C_{52}H_{59}N_8O_2$: 827.4761; encontrado 827.4782
M4	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(etoxicarbonil)-D-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de etilo	 (Extremo-59a)	1.20 min (Cond. 1); >97%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.36; encontrado 711.46; HRMS: Análisis calculado para $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.3619; encontrado 711.3638

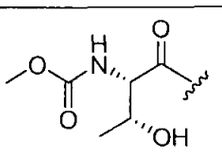
M5	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(etoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de etilo	 (Extremo-59b)	1.16 min (Cond. 1); 97%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.36; encontrado 711.48; HRMS: Análisis calculado para $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.3619; encontrado 711.3621
M6	(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiilcarbonil-1,1-ciclopropanediil)) biscarbamato de dimetilo	 (Extremo-60)	1.12 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{43}N_8O_6$: 707.33; encontrado 707.45; HRMS: Análisis calculado para $[M+H]^+$ $C_{38}H_{43}N_8O_6$: 707.3306; encontrado 707.3309

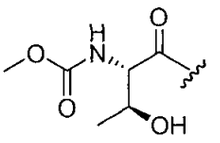
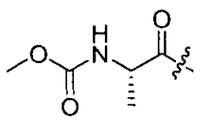
M7	(2-((2S)-2-(5-(4'-(2-((2S)-1-(2-((metoxicarbonil)amino)-2-metilpropanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1,1-dimetil-2-oxoetil)carbamato de metilo	 (Extremo-61)	1.21 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.36; encontrado 711.53; HRMS: Análisis calculado para $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.3619; encontrado 711.3652
M8	(2R,2'R)-1,1'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(N,N-dimetil-1-oxo-2-propanamina)	 (Extremo-83)	0.91 min (Cond. 1); >80%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{36}H_{47}N_8O_2$: 623.38; encontrado 623.46; HRMS: Análisis calculado para $[M+H]^+$ $C_{36}H_{47}N_8O_2$: 623.3822; encontrado 623.3819

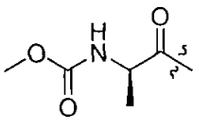
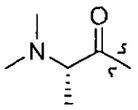
M9	(2R,2'R)-1,1'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(N,N-dietil-1-oxo-2-propanamina)	 (Extremo-69a)	1.00 min (Cond. 1); >95%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{55}N_8O_2$: 623.38; encontrado 679.67; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{55}N_8O_2$: 679.4448; encontrado 679.4432
M10	(2R,2'R)-1,1'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(N,N-dietil-3-metil-1-oxo-2-butanamina)	 (Extremo-72)	1.03 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{63}N_8O_2$: 735.51; encontrado 735.76; HRMS: Análisis calculado para $[M+H]^+$ $C_{44}H_{63}N_8O_2$: 735.5074; encontrado 735.5060

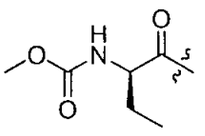
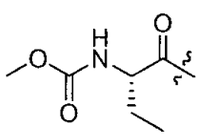
M11	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)(metil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)metilcarbamato de metilo	 (Extremo-62)	1.46 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{55}N_8O_2$: 767.42; encontrado 767.38; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{55}N_8O_2$: 767.4245; encontrado 767.4252
M12	(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1S)-2-oxo-1-fenil-2,1-etanediil)))bis carbamato de dimetilo	 (Extremo-82)	1.32 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{46}H_{47}N_8O_6$: 807.36; encontrado 807.32; HRMS: Análisis calculado para $[M+H]^+$ $C_{46}H_{47}N_8O_6$: 807.3619; encontrado 807.3651

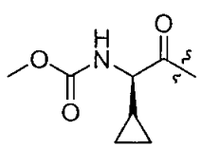
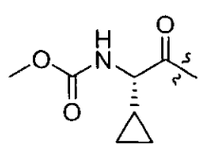
M13	N,N'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((2R)-1-oxo-1,2-propanediil)))bis(N-propil-1-propanamina)	 (Extremo-70a)	1.09 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{63}N_8O_2$: 735.51; encontrado 735.46; HRMS: Análisis calculado para $[M+H]^+$ $C_{44}H_{63}N_8O_2$: 735.5074; encontrado 735.5063
M14	((1S)-2-hidroxi-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-hidroxi-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	 (Extremo-65)	1.13 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{51}N_8O_8$: 771.38; encontrado 771.21

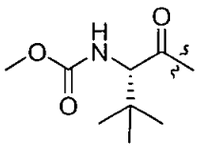
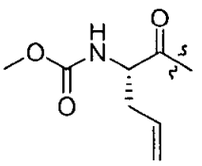
M15	((1S,2R)-2-hidroxi-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-3-hidroxi-2-((metoxicarbonil)amino)butanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo	 (Extremo-66)	1.10 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{47}N_8O_8$: 743.35; encontrado 743.23; ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz), ~14.5 (br s, 4H), 8.15 (s, 2H), 7.97 (d, J = 8.5, 4H), 7.89 (d, J = 8.4, 4H), 7.10/7.05 (dos traslapado d, J = 8.0, 8.4, 1.82H), 6.57 (app br s, 0.18H), 5.78 (br d, J = 7.9, 0.18H), 5.16 (m, 1.82H), 4.27 (dd, J = 8.0, 5.3, 1.82H), 4.10 (m, 0.18H), 3.96-3.81 (m, 6H), 3.55 (s, 5.46H), 3.37 (s, 0.54H), 2.41 (m, 2H), 2.17-2.00 (m, 6H), 1.10 (d, J = 6.3, 0.54H), 1.04 (d, J = 6.3, 5.46H).

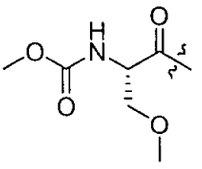
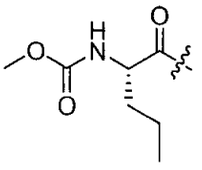
M16	((1S,2S)-2-hidroxi-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S,3S)-3-hidroxi-2-((metoxicarbonil)amino)butanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo	 (Extremo-67)	1.11 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{47}N_8O_8$: 743.35; encontrado 743.23
M17	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	 (Extremo-52)	1.64 min (Cond. 2); 99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{36}H_{43}N_8O_6$: 683.33; encontrado 683.30; HRMS: Análisis calculado para $[M+H]^+$ $C_{36}H_{43}N_8O_6$: 683.3306; encontrado 683.3305.

M18	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-D-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	 (Extremo-85)	1.70 min (Cond. 2); 97%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{36}H_{43}N_8O_6$: 683.33; encontrado 683.32; HRMS: Análisis calculado para $[M+H]^+$ $C_{36}H_{43}N_8O_6$: 683.3306; encontrado 683.3318.
M19	(2S,2'S)-1,1'-(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil))bis(N,N-dimetil-1-oxo-2-propanamina)	 (Extremo-13)	1.43 min (Cond. 2); >99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{36}H_{47}N_8O_2$: 623.38; encontrado 623.43; HRMS: Análisis calculado para $[M+H]^+$ $C_{36}H_{47}N_8O_2$: 623.3822; encontrado 623.3837.

M20	(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((2R)-1-oxo-1,2-butanodiil)))bis carbamato de dimetilo	 (Extremo-53a)	1.82 min (Cond.2); >99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.36; encontrado: 711.35; HRMS: Análisis calculado para $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.3619; encontrado 711.3649.
M21	(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((2S)-1-oxo-1,2-butanodiil)))bis carbamato de dimetilo	 (Extremo-53b)	1.81 min (Cond.2); >99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.36; encontrado 711.35; HRMS: Análisis calculado para $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.3619; encontrado 711.3643.

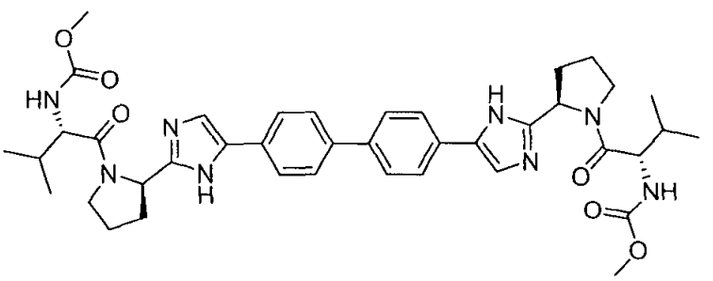
M22	(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1R)-1-ciclopropil-2-oxo-2,1-etanediil)))bis carbamato de dimetilo	 (Extremo-54a)	1.83 min (Cond. 2); >99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.36; encontrado 735.44; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.3619; encontrado: 735.3614.
M23	(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((1S)-1-ciclopropil-2-oxo-2,1-etanediil)))bis carbamato de dimetilo	 (Extremo-54b)	1.81 min (Cond. 2); >99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.36; encontrado 735.43; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.3619; encontrado 735.3651.

M24	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3,3-dimetilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2,2-dimetilpropil) carbamato de metilo		2.11 min (Cond. 2); >99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{55}N_8O_6$: 767.42; encontrado 767.58; HRMS: Análisis calculado para $C_{42}H_{55}N_8O_6$: 767.4245; encontrado 767.4230.
M25	(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2S)-2,1-pirrolidindiil((4S)-5-oxo-1-pentene-5,4-diil)))bis carbamato de dimetilo	 (Extremo-55)	1.91 min (Cond. 2); 98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.36; encontrado 735.47; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.3619; encontrado 735.3630.

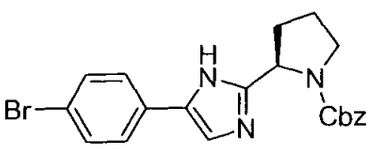
M26	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-seril)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-(metoximetil)-2-oxoetil)carbamato de metilo	 (Extremo-56)	1.72 min (Cond. 2); 97%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{47}N_8O_8$: 743.35; encontrado 743.49; HRMS: Análisis calculado para $[M+H]^+$ $C_{38}H_{47}N_8O_8$: 743.3517; encontrado 743.3489.
M27	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)pentanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)butil)carbamato de metilo	 (Extremo-57)	1.98 min (Cond. 2); 98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.39; encontrado 739.52; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.3932; encontrado 739.3904.

Ejemplo M28

((1S)-1-(((2R)-2-(5-(4'-(2-((2R)-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

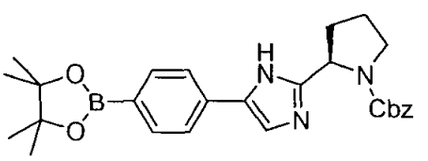


Ejemplo M28, Extremo a



El Bromo M28a se preparó a partir de D-Prolina de conformidad al procedimiento descrito por su enantiomero 28b.

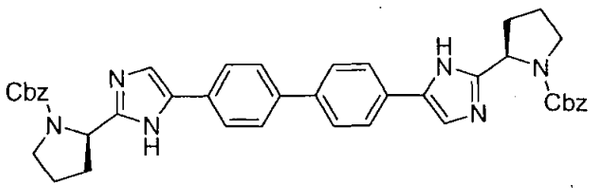
Ejemplo M28, Extremo b



El éster de boronato M28b se preparó a partir de bromo M28a de conformidad al procedimiento descrito por el intermediario 1c. LC: TR = 1.57 min (Cond. 1); LC/MS: Análisis calculado para $[M+H]^+$ $C_{27}H_{33}BN_3O_4$: 474.26; encontrado

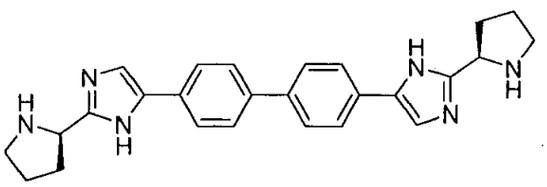
474.24.

Ejemplo M28, Extremo c



El bifenilo M28c se preparó a partir de bromo M28a y boronato M28b de conformidad al procedimiento descrito por el intermediario 1d. LC: TR = 1.43 min (Cond. 1); LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{41}N_6O_4$: 693.32; encontrado 693.38.

Ejemplo M28, Extremo d



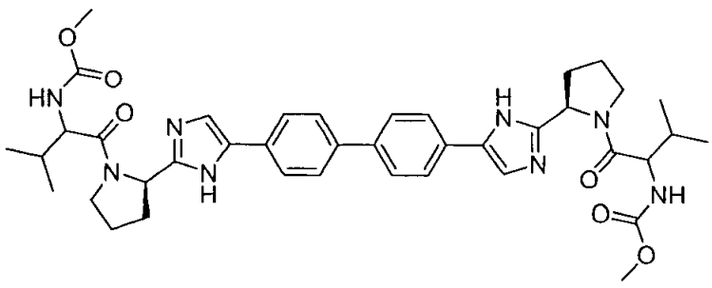
La pirrolidina M28d se preparó a partir de carbamato M28c de conformidad al procedimiento descrito por el intermediario 28d. ^{1}H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 11.83 (br s, 2H), 7.80 (d, J = 8.3, 4H), 7.66 (d, J = 8.3, 4H), 7.46 (br s, 2H), 4.16 (app t, J = 7.2, 2H), 3.00-2.94 (m, 2H), 2.88-2.82 (m, 2H), 2.10-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.82-1.66 (m, 4H). [Nota: en la región entre 3.2-2.6 ppm esto es una señal de línea base amplia

que se cree que es aquella de la pirrolidina NH]. CL: TR = 1.02 min (Cond. 1); LC/MS: Análisis calculado para $[M+H]^+$ $C_{26}H_{29}N_6$: 425.25; encontrado 425.27.

Ejemplo M28

El ejemplo M28 se preparó como la sal TFA del intermediario M28d y Extremo-51 de conformidad al procedimiento descrito por el ejemplo 1. CL: TR = 1.33 min (Cond. 1); 96% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.32; encontrado 739.43; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.3932; encontrado 739.3907.

Ejemplo M28-1



La sal TFA del ejemplo M28-1 se preparó como una mezcla de tres estereoisómeros del intermediario M28d y versión racémica del extremo-51 de conformidad al procedimiento descrito por el ejemplo 1. Los tres picos con un tiempo de retención de 21.74 min, 22.62 min, y 23.40 min, y que exhiben el peso molecular correcto, se observaron cuando la muestra se analizó bajo la siguiente

condición:

Waters Acquity HPLC con Micromass ZQ MS (sonda de electrorocío) y detección Waters 2996 PDA. (detección UV @ 315nm)

Columna: Acquity UPLC; BEH C18; 1.7um; 100 X 2.1 mm ID; (a aproximadamente 30C)

Fase móvil A: agua, 25 mM acetato de amonio a pH=5

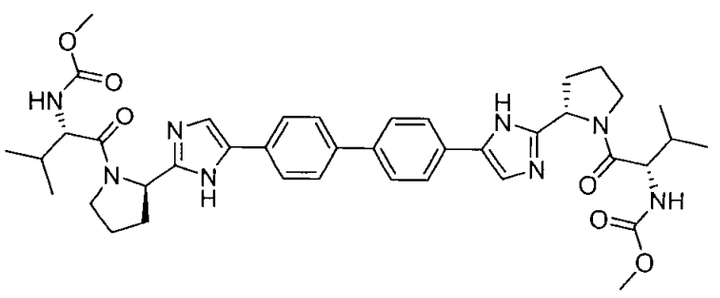
Fase móvil B: acetonitrilo

Relación de flujo: 0.50 ml/min

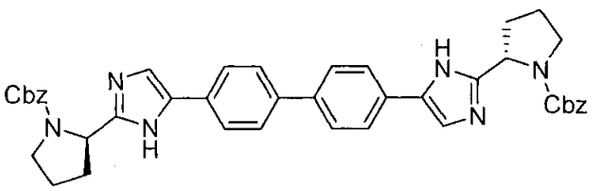
10-50%B	0-35.0 min
50-98%B	35.0-45.0min
Esperar 98%B	45.0-48.0 min
98%B-100%B	48.0-48.5min
Esperar 100%B	48.5-50.0min

Ejemplo M28-2

((1S)-1-(((2S)-2-(5-(4'-(2-((2R)-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

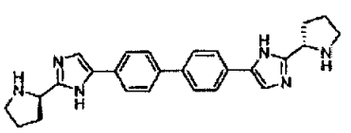


Ejemplo M28-2, Extremo a



El carbamato M28-2a se preparó a partir de éster de boronato M28b y bromo 28b de conformidad al procedimiento descrito por el intermediario 1d. ^{1}H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.25/12.01/11.93 (tres br s, 2H), 7.86-6.98 (m, 20H), 5.13-4.88 (m, 6H), 3.63 (m, 2H), 3.47 (m, 2H), 2.35-1.84 (M, 8H). CL: TR = 1.46 min (Cond. 1); LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{41}N_6O_4$: 693.32; encontrado 693.34.

Ejemplo M28-2, Extremo b



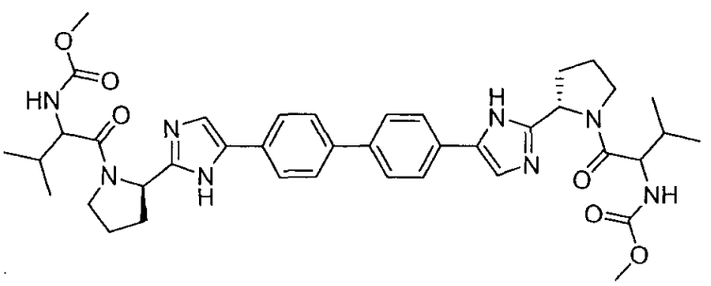
La pirrolidina M28-2b se preparó a partir de carbamato M28-2a de conformidad al procedimiento descrito por el intermediario 28d. ^{1}H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 11.84 (br s, 2H), 7.80 (d, J = 8.3, 4H), 7.66 (d, J = 8.3, 4H), 7.46 (br s, 2H), 4.87 (m, 0.05H), 4.16 (app t, J = 7.2, 1.95H), 3.00-2.94 (m, 2H), 2.88-2.82 (m, 2H), 2.10-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.82-1.66 (m, 4H). [Nota: en la

región entre ~3.1-2.6 ppm esto es una señal de línea base amplia que se cree que es aquella de la pirrolidina NH]. CL: TR = 0.96 min (Cond. 1); LC/MS: Análisis calculado para $[M+H]^+$ $C_{26}H_{29}N_6$: 425.25; encontrado 425.28.

Ejemplo M28-2

El ejemplo M28-2 se preparó como la sal TFA del intermediario M28-2b y Extremo-51 de conformidad al procedimiento descrito por el ejemplo 1. CL: TR = 1.96 minutos (Cond. 2); 98% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{51}N_8O_6$ 739.39; encontrado 739.47.

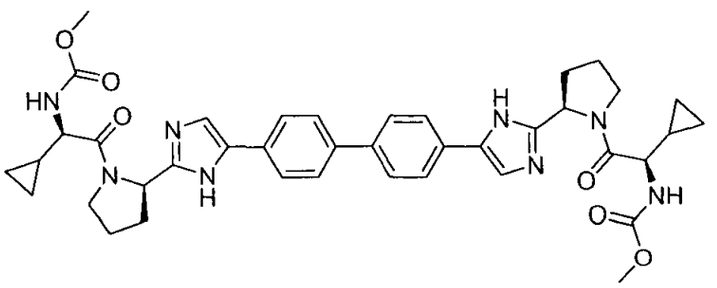
Ejemplo M28-3



La sal TFA del ejemplo M28-3 se preparó como una mezcla de cuatro estereisómeros del intermediario M28-2b y versión racémica del extremo-51 de conformidad al procedimiento descrito por el ejemplo 1. Los tres picos con un tiempo de retención de 21.28 min, 22.19 min, y 23.01 min, y que exhiben el peso molecular correcto, se observaron cundo la muestra se analizó bajo la condición LC/MS descrita por el ejemplo M28-1.

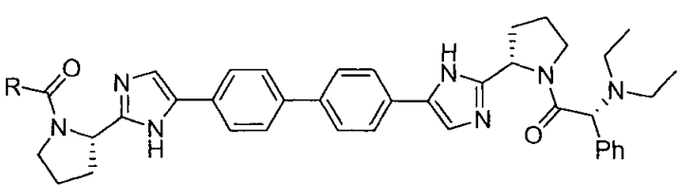
Ejemplo M29

(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(2R)-2,1-pirrolidindiil((1R)-1-ciclopropil-2-oxo-2,1-etanediil)))biscarbamato de dimetilo

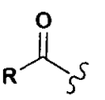
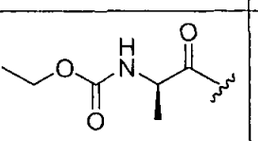
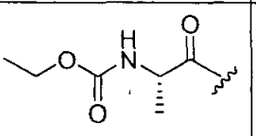


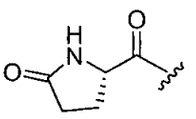
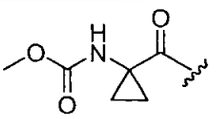
El ejemplo M29 se preparó como la sal TFA del intermediario M28d y Extremo-54a de conformidad al procedimiento descrito por el ejemplo 1. CL: TR = 1.21 min (Cond. 1); >98% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.36; encontrado 735.42; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.3619; encontrado 735.3598.

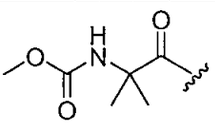
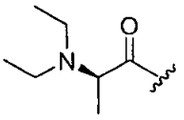
Ejemplo M30-M62

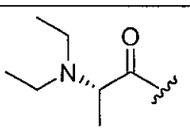
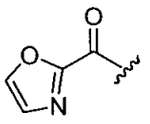


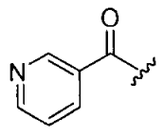
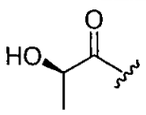
El ejemplo M30-M62 se prepararon como la sal TFAs a partir de CJ-24 y los extremos respectivas usando el mismo método descrito por el ejemplo 28.

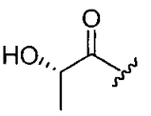
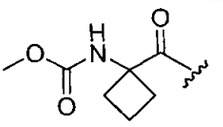
Ejemplo	Nombre del Compuesto	 (Fuente)	RT (LC-Cond.); % índice de homogeneidad; Datos EM
M30	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de etilo	 (Extremo-59a)	1.13 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.42; encontrado 757.50; HRMS: Análisis calculado para $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.4190; encontrado 757.4181
M31	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de etilo	 (Extremo-59b)	1.07 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.42; encontrado 757.55; HRMS: Análisis calculado para $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.4190; encontrado 757.4225

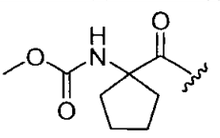
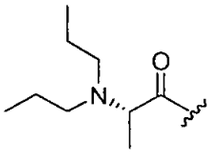
M32	(5S)-5-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-pirrolidinona		1.02 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{49}N_8O_3$: 725.39; encontrado 725.48; HRMS: Análisis calculado para $[M+H]^+$ $C_{43}H_{49}N_8O_3$: 725.3928; encontrado 725.3926
M33	(1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)ciclo propil)carbamato de metilo	 (Extremo-60)	1.12 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{51}N_8O_4$: 755.40; encontrado 755.61; HRMS: Análisis calculado para $[M+H]^+$ $C_{44}H_{51}N_8O_4$: 755.4033; encontrado 755.4066

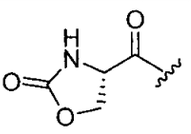
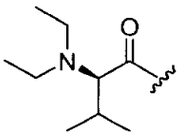
M34	(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1,1-dimetil-2-oxoetil)carbamato de metilo	 (Extremo-61)	1.16 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.42; encontrado 757.63; HRMS: Análisis calculado para $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.4190; encontrado 757.4164
M35	(2R)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dietil-1-oxo-2-propanamina	 (Extremo-69a)	1.06 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{45}H_{57}N_8O_2$: 741.46; encontrado 741.64; HRMS: Análisis calculado para $[M+H]^+$ $C_{45}H_{57}N_8O_2$: 741.4604; encontrado 741.4597

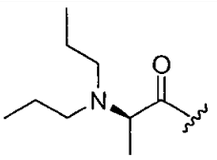
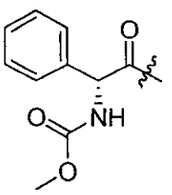
M36	(2S)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dietil-1-oxo-2-propanamina	 (Extremo-69b)	1.04 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{45}H_{57}N_8O_2$: 741.46; encontrado 741.63; HRMS: Análisis calculado para $[M+H]^+$ $C_{45}H_{57}N_8O_2$: 741.4604; encontrado 741.4581
M37	(1R)-N,N-dietil-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-2-ilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletanamina		1.11 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{45}N_8O_3$: 709.36; encontrado 709.51; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{45}N_8O_2$: 709.3615; encontrado 709.3615

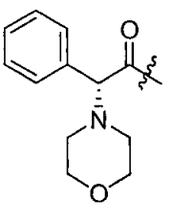
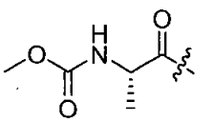
M38	(1R)-N,N-dietil-2-oxo-1-fenil-2-((2S)-2-(5-(4'-(2-((2S)-1-(3-piridinilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) etanamina		1.09 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{47}N_8O_2$: 719.38; encontrado 719.51; HRMS: Análisis calculado para $[M+H]^+$ $C_{44}H_{47}N_8O_2$: 719.3822; encontrado 719.3829
M39	(2R)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-oxo-2-propanol		1.09 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{48}N_7O_3$: 686.38; encontrado 686.58; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{48}N_7O_3$: 686.3819; encontrado 686.3843

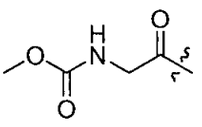
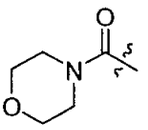
M40	(2S)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-oxo-2-propanol		1.09 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{48}N_7O_3$: 686.38; encontrado 686.57; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{48}N_7O_3$: 686.3819; encontrado 686.3832
M41	(1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)ciclobutil)carbamato de metilo	 (Extremo-64)	1.19 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 769.42; encontrado 769.66; HRMS: Análisis calculado para $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 769.419; encontrado 769.4155

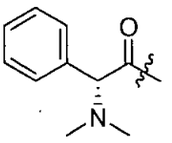
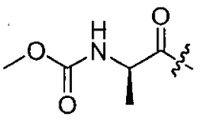
M42	(1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)ciclo pentil)carbamato de metilo	 (Extremo-63)	1.25 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{46}H_{55}N_8O_4$: 783.43; encontrado 783.69; HRMS: Análisis calculado para $[M+H]^+$ $C_{46}H_{55}N_8O_4$: 783.4346; encontrado 783.4357
M43	N-((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)-N-propil-1-propanamina	 (Extremo-70b)	1.10 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{47}H_{61}N_8O_2$: 769.49; encontrado 769.69; HRMS: Análisis calculado para $[M+H]^+$ $C_{47}H_{61}N_8O_2$: 769.4917; encontrado 769.4925

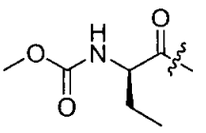
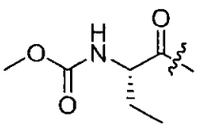
M44	(4S)-4-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-1,3-oxazolidin-2-ona	 (Extremo-81)	1.08 min (Cond.1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.37; encontrado 727.56; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{47}N_8O_4$: 727.3720; encontrado 727.3740
M45	(2R)-1-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dietil-3-metil-1-oxo-2-butanamina	 (Extremo-72)	1.08 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{47}H_{61}N_8O_2$: 769.49; encontrado 769.73; HRMS: Análisis calculado para $[M+H]^+$ $C_{47}H_{61}N_8O_2$: 769.4917; encontrado 769.4898

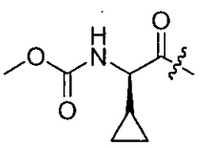
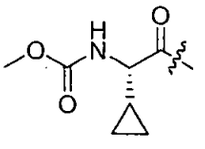
M46	N-((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)-N-propil-1-propanamina	 (Extremo-70a)	1.12 min (Cond.1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{47}H_{61}N_8O_2$: 769.49; encontrado 769.45; HRMS: Análisis calculado para $[M+H]^+$ $C_{47}H_{61}N_8O_2$: 769.4917; encontrado 769.4915
M47	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 (Extremo-4)	1.85 min (Cond.2); 97%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{48}H_{53}N_8O_4$: 805.42; encontrado 805.4; HRMS: Análisis calculado para $[M+H]^+$: $C_{48}H_{53}N_8O_4$ 805.4190; encontrado 805.4196.

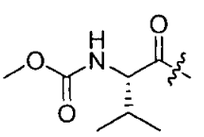
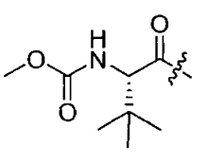
M48	(1R)-N,N-dietil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(4-morfolinil)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletanamina	 (Extremo-6)	1.69 min (Cond. 2); 98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{50}H_{57}N_8O_3$: 817.45; encontrado 817.48; HRMS: Análisis calculado para $[M+H]^+$ $C_{50}H_{57}N_8O_3$: 817.4554; encontrado 817.4589.
M49	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	 (Extremo-52)	1.67 min (Cond. 2); 92%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.40; encontrado 743.42; HRMS: Análisis calculado para $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.4033; encontrado 743.4053.

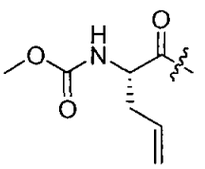
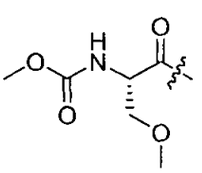
M50	(2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo		1.63 min (Cond. 2); 99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{49}N_8O_4$: 729.39; encontrado 729.39; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{49}N_8O_4$: 729.3877; encontrado 729.3888.
M51	(1R)-N,N-dietil-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-morfolinilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletanamina		1.67 min (Cond.2); 99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{51}N_8O_3$: 727.41; encontrado 727.40; HRMS: Análisis calculado para $[M+H]^+$ $C_{43}H_{51}N_8O_3$: 727.4084; encontrado 727.4117.

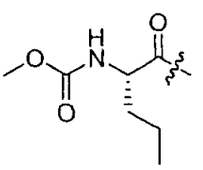
M52	(1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina	 (Extremo-1)	1.65 min (Cond. 2); 92%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{48}H_{55}N_8O_2$: 775.44; encontrado 775.48; HRMS: Análisis calculado para $[M+H]^+$ $C_{48}H_{55}N_8O_2$: 775.4448; encontrado 775.4433.
M53	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	 (Extremo-85)	1.68 min (Cond.2); 98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.40; encontrado 743.42; HRMS: Análisis calculado para $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.4033; encontrado 743.4055.

M54	((1R)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)propil) carbamato de metilo	 (Extremo-53a)	1.78 min; (Cond. 2); >99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.42; encontrado 757.42; HRMS: Análisis calculado para $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.4190; encontrado 757.4216.
M55	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)propil) carbamato de metilo	 (Extremo-53b)	1.74 min (Cond. 2); >99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.42; encontrado 757.41; HRMS: Análisis calculado para $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.4190; encontrado 757.4212 .

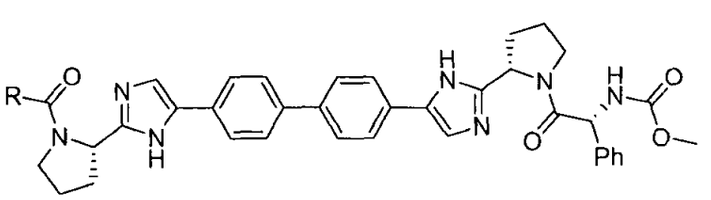
M56	((1R)-1-ciclopropil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo	 (Extremo-54a)	1.74 min (Cond. 2); >99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 769.42; encontrado 769.52; HRMS: Análisis calculado para $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 769.4190; encontrado 769.4188.
M57	((1S)-1-ciclopropil-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo	 (Extremo-54b)	1.72 min (Cond. 2); >99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 769.42; encontrado 769.53; HRMS: Análisis calculado para $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 769.4190; encontrado 769.4218.

M58	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 (Extremo-51)	1.76 min (Cond. 2); >99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{45}H_{59}N_8O_4$: 771.43; encontrado 771.54; HRMS: Análisis calculado para $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 771.4346; encontrado 771.4379.
M59	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2,2-dimetilpropil) carbamato de metilo		1.92 min (Cond. 2); 99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{46}H_{57}N_8O_6$: 785.45; encontrado 785.63; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{57}N_8O_4$: 785.4503; encontrado 785.4515.

M60	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-3-buten-1-il)carbamato de metilo	 (Extremo-55)	1.81 min (Cond.2); 99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 769.42; encontrado 769.55; HRMS: Análisis calculado para $[M+H]^+$ $C_{45}H_{53}N_8O_4$: 769.4190; encontrado 769.4157.
M61	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-(metoximetil)-2-oxoetil)carbamato de metilo	 (Extremo-56)	1.73 min (Cond. 2); 99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{53}N_8O_5$: 773.41; encontrado 773.55; HRMS: Análisis calculado para $[M+H]^+$ $C_{44}H_{53}N_8O_5$: 773.4139; encontrado 773.4107.

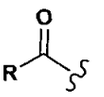
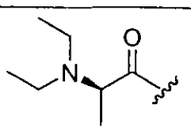
M62	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)butil)carbamato de metilo	 (Extremo-57)	1.73 min (Cond. 2); 99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{45}H_{55}N_8O_4$: 771.43; encontrado 771.56 $(M+H)^+$; HRMS: Análisis calculado para $[M+H]^+$ $C_{45}H_{55}N_8O_4$: 771.4346; encontrado 771.4315.

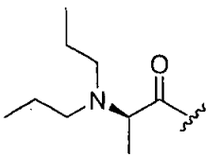
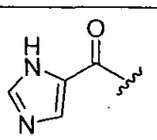
Ejemplo M63-M66

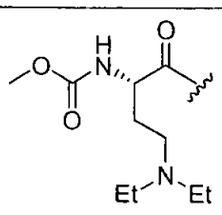


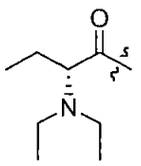
El ejemplo M63-M66x se prepararon a partir de 28f y los ácidos respectivos usando el método descrito por el ejemplo

28. Los productos se prepararon como la sal TFA a menos de que se indique de otra manera.

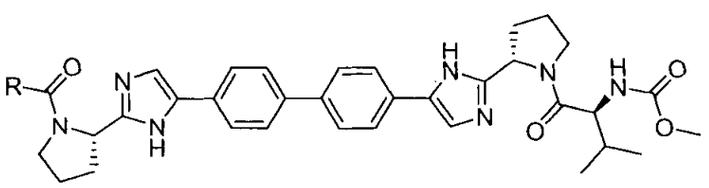
Ejemplo	Nombre del Compuesto	 (Fuente)	TR (CL-Cond.); % índice de homogeneidad; Datos EM
M63	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dietil-D-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 (Extremo-69a)	1.17 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.40; encontrado 743.41; HRMS: Análisis calculado para $[M+H]^+$ $C_{43}H_{51}N_8O_4$: 743.4033; encontrado 743.4017

M64	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropil-D-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 (Extremo-70a)	1.22 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{45}H_{55}N_8O_4$: 771.43; encontrado 771.39; HRMS: Análisis calculado para $[M+H]^+$ $C_{45}H_{55}N_8O_4$: 771.4346; encontrado 771.4361
M65	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-5-ilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.15 min (Cond. 1); >90%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{40}N_9O_4$: 710.32; encontrado 710.31; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{40}N_9O_4$: 710.3203; encontrado 710.3180

M66a & M66b	M66a: ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-(4-(dietilamino)-2-((metoxicarbonil)amino)butanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo	 (Extremo-76)	Dos fracciones enriquecidas con uno de los dos compuestos que exhiben datos de espectros muy similares se aislaron. M66a: 1.19 min (Cond. 1); 97%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{46}H_{56}N_9O_6$: 830.44; encontrado 830.39 M66b: 1.21 min (Cond. 1); >97%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{46}H_{56}N_9O_6$: 830.44; encontrado 830.39; HRMS: Análisis calculado para $[M+H]^+$ $C_{46}H_{56}N_9O_6$: 830.4354; encontrado 830.4316

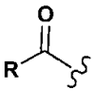
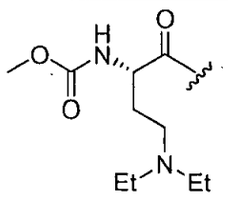
	M66x (AcOH)	((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino)butanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo		1.80 minutos (Cond.2); (98%); LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{53}N_8O_4$ 757.42; encontrado 757.48; HRMS: Análisis calculado para $[M+H]^+$ $C_{44}H_{53}N_8O_4$: 757.4190; encontrado 757.4156

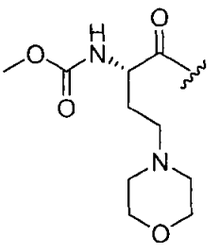
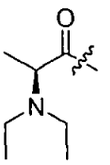
Ejemplo M67-M91

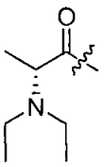
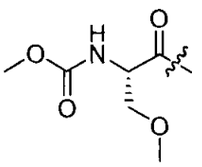


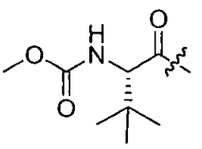
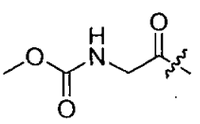
El ejemplo M67-M91y se prepararon a partir de 28d y los ácidos respectivos usando el método descrito por el ejemplo 28. Los productos finales se prepararon como la sal TFA, a

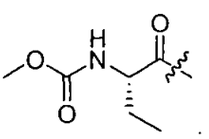
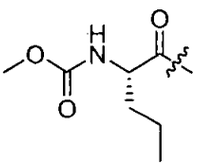
menos de que se indique de otra manera.

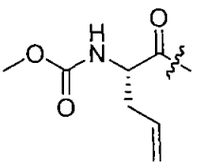
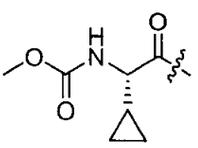
Ejemplo	Nombre del Compuesto	 (Fuente)	TR (CL-Cond.); % índice de homogeneidad; Datos EM
M67a & M67b	M67a: ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(4-(dietilamino)-2-((metoxicarbonil) amino)butanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 (Extremo-76)	Dos fracciones enriquecidas con uno de dos compuestos que exhiben datos de datos de espectros muy similares se aislaron M67a: 1.16 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{59}N_9O_6$: 796.45; encontrado 796.40 M67b: 1.17 min (Cond. 1); >96%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{59}N_9O_6$: 796.45; encontrado 796.40; HRMS: Análisis calculado para $[M+H]^+$ $C_{43}H_{59}N_9O_6$: 796.4510; encontrado 796.4537

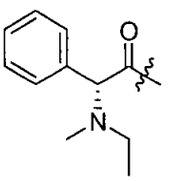
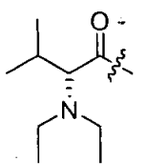
M68 (.AcOH)	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-3-(4-morfolinil)propil)carbamato de metilo	 (Extremo-79)	1.10 min (Cond. 1); >96%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{56}N_9O_7$: 810.43; encontrado 810.44; HRMS: Análisis calculado para $[M+H]^+$ $C_{43}H_{56}N_9O_7$: 810.4303; encontrado 810.4333
M69	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dietil-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 (Extremo-69b)	1.72 min (Cond. 2); 98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{53}N_8O_4$: 709.42; encontrado 709.56; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{53}N_8O_4$: 709.4190; encontrado 709.4219.

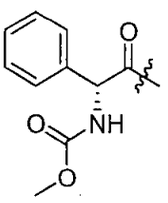
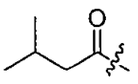
M70	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dietil-D-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 (Extremo-69a)	1.75 min (Cond. 2); 99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{53}N_8O_4$: 709.42; encontrado 709.55; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{53}N_8O_4$: 709.4190; encontrado 709.4184.
M71	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-(metoximetil)-2-oxoetil)carbamato de metilo	 (Extremo-56)	1.81 min (Cond. 2); 97%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{39}H_{49}N_8O_7$: 741.37; encontrado 741.48; HRMS: Análisis calculado para $[M+H]^+$ $C_{39}H_{49}N_8O_7$: 741.3724; encontrado 741.3738.

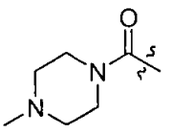
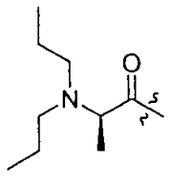
M72	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3,3-dimetilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo		2.07 min (Cond. 2); 97%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{53}N_8O_6$: 753.41; encontrado 753.53; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{53}N_8O_6$: 753.4088; encontrado 753.4111.
M73	(2-((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo		1.80 min (Cond. 2); 97%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{37}H_{45}N_8O_6$: 697.35; encontrado 697.32; HRMS: Análisis calculado para $[M+H]^+$ $C_{37}H_{45}N_8O_6$: 697.3462; encontrado 697.3443.

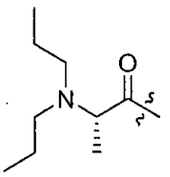
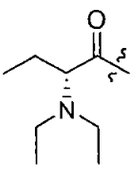
M74	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)butanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil) carbamato de metilo	 (Extremo-53b)	1.90 min (Cond. 2); 98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{39}H_{49}N_8O_6$: 725.37; encontrado 725.36; HRMS: Análisis calculado para $[M+H]^+$ $C_{39}H_{49}N_8O_6$: 725.3775; encontrado 725.3742.
M75	((1S)-1-(((2S)-2-(5-(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)butil) carbamato de metilo	 (Extremo-57)	1.96 min (Cond. 2); 98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.39; encontrado 739.37; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.3932; encontrado 739.3953.

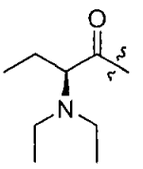
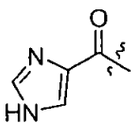
M76	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-3-buten-1-il)carbamato de metilo	 (Extremo-55)	1.91 min (Cond. 2); 98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{49}N_8O_6$: 737.38; encontrado 737.38; HRMS: Anal. Calcd. $C_{40}H_{49}N_8O_6$: 737.3775; encontrado 737.3744.
M77	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-ciclopropil-2-((metoxicarbonil)amino)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo	 (Extremo-54b)	1.90 min (Cond. 2); 98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{49}N_8O_6$ 737.38; encontrado 737.34; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{49}N_8O_6$ 737.3775; encontrado 737.3764.

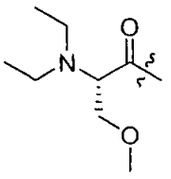
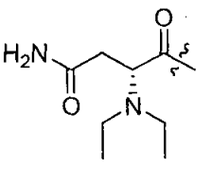
M78	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(etil(metil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 (Extremo-3)	1.82 min (Cond. 2); 98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{53}N_8O_4$ 757.42; encontrado 757.42; HRMS: Análisis calculado para $[M+H]^+$ $C_{44}H_{53}N_8O_4$ 757.4190; encontrado 757.4188.
M79	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dietil-D-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 (Extremo-72)	1.78 min (Cond. 2); 94%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{57}N_8O_4$ 737.45; encontrado 737.45; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{57}N_8O_4$ 737.4503; encontrado 737.4488.

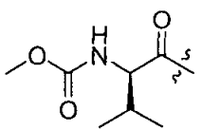
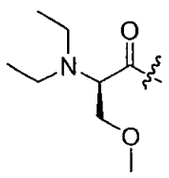
M80	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil) carbamato de metilo	 (Extremo-4)	2.05 min (Cond. 2); 99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{49}N_8O_6$ 773.37; encontrado 773.40; HRMS: Análisis calculado para $[M+H]^+$ $C_{43}H_{49}N_8O_6$ 773.375; encontrado: 773.3759.
M81	((1S)-2-metil-1-(((2S)-2-(5-(4'-(2-((2S)-1-(3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil) carbamato de metilo		2.05 min (Cond. 2); 99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{48}N_7O_4$ 666.38; encontrado 666.37; HRMS: Análisis calculado para $[M+H]^+$ $C_{38}H_{48}N_7O_4$ 666.3768; encontrado 666.3785.

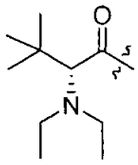
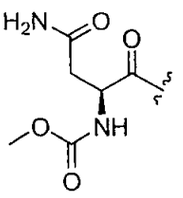
M82	((1S)-2-metil-1-(((2S)-2-(5-(4'-(2-((2S)-1-((4-metil-1-piperazinil)carbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)propil) carbamato de metilo		1.75 min (Cond. 2); 98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{39}H_{50}N_9O_4$ 708.40; encontrado 708.38; HRMS: Análisis calculado para $[M+H]^+$ $C_{39}H_{50}N_9O_4$ 708.3986; encontrado 708.3974.
M83	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropil-D-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 (Extremo-70a)	1.81 min (Cond. 2); 98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{57}N_8O_4$ 737.45; encontrado 737.47; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{57}N_8O_4$ 737.4503; encontrado 737.4480.

M84	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropil-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 (Extremo-70b)	1.78 min (Cond. 2); 99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{57}N_8O_4$ 737.45; encontrado 737.47; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{57}N_8O_4$ 737.4503; encontrado 737.4491 .
M85	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dietilamino) butanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 (Extremo-71a)	1.76 min (Cond. 2); 98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{55}N_8O_4$ 723.43; encontrado 723.47; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{55}N_8O_4$ 723.4346; encontrado 723.4335 .

M86	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-(dietilamino) butanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 (Extremo-71b)	1.73 min (Cond. 2); 98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{55}N_8O_4$ 723.43; encontrado 723.47; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{55}N_8O_4$ 723.4346; encontrado 723.4343.
M87	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(1H-imidazol-4-ilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo		1.67 min (Cond. 2); 99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{37}H_{42}N_9O_4$ 676.34; encontrado 676.45; HRMS: Análisis calculado para $[M+H]^+$ $C_{37}H_{42}N_9O_4$ 676.3360; encontrado 676.3344.

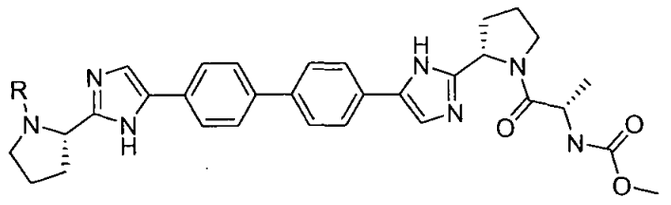
M88	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dietil-O-metil-L-seril)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 (Extremo-73)	1.67 min (Cond. 2); 97%; LCMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{55}N_8O_5$ 739.43; encontrado 739.54; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{55}N_8O_5$ 739.4295; encontrado 739.4327.
M89	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N^2,N^2-dietil-D-asparaginil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 (Extremo-74)	1.76 min (Cond. 2); 97%; LCMS: Análisis calculado para for $[M+H]^+$ $C_{41}H_{54}N_9O_5$ 752.42; encontrado 752.43; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{54}N_9O_5$ 752.4248; encontrado 752.4263.

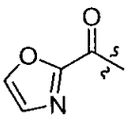
M90	((1S)-1-(((2S)-2-(5-(4'-(2-((2R)-1-((2R)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 (Extremo-84)	2.00 min (Cond. 2); 98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{51}N_8O_6$ 739.39; encontrado 739.46; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{51}N_8O_6$ 739.3932; encontrado 739.3901.
M91	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dietil-O-metil-D-seril)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo	 (Extremo-75)	1.73 min (Cond. 2); 99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{55}N_8O_5$ 739.43; encontrado 739.39; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{55}N_8O_5$ 739.4295; encontrado 739.4277.

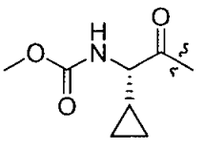
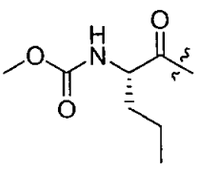
M91x	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dietil-3-metil-D-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo		1.78 minutos (Cond. 2); (97%); LC/MS: Análisis calculado para $[M+H]^+$ $C_{43}H_{59}N_8O_4$ 751.47; encontrado 751.50; HRMS: Análisis calculado para $[M+H]^+$ $C_{43}H_{59}N_8O_4$: 751.4659; encontrado: 751.4648.
M91y	((1S)-3-amino-1-(((2S)-2-(5-(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)-3-oxopropil) carbamato (sin nombre preferido) de metilo	 (Extremo-58)	1.92 min (Cond. 2); (>97%); LC/MS: Análisis calculado para $[M+H]^+$ $C_{39}H_{48}N_9O_7$ 754.37; encontrado 754.42; HRMS: Análisis calculado para $[M+H]^+$ $C_{39}H_{48}N_9O_7$: 754.3677; encontrado: 754.3676.

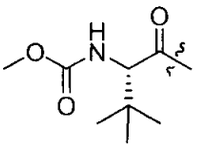
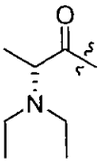
Ejemplo M92-M103

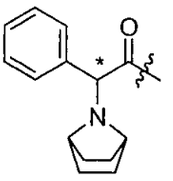
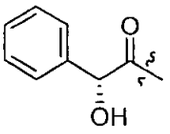
El ejemplo M92-M103 se prepararon a partir de 28d y los ácidos respectivos usando el método descrito por el ejemplo 28. Los productos finales se prepararon como la sal TFA, a menos de que se indique de otra manera.

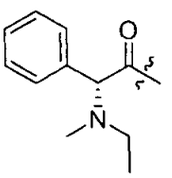
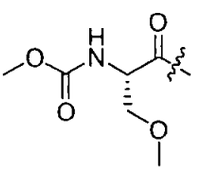


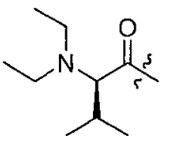
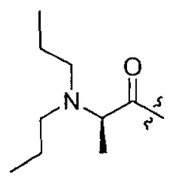
Ej.	Nombre del Compuesto	R (Fuente)	Datos Analíticos
M92	((1S)-1-metil-2-((2S)-2-(5-(4'-(2-((2S)-1-(1,3-oxazol-2-ilcarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo		1.70 min (Cond. 2); 95%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{35}H_{37}N_8O_5$ 649.29; encontrado 649.41; HRMS: Análisis calculado para $[M+H]^+$ $C_{35}H_{37}N_8O_5$ 649.2887; encontrado 649.2867

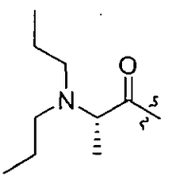
M93	((1S)-1-ciclopropil-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxoetil)carbamato de metilo	 (Extremo-54b)	1.76 min (Cond. 2); 98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{45}N_8O_6$ 709.35; encontrado 709.50; HRMS: Análisis calculado para $[M+H]^+$ $C_{38}H_{45}N_8O_6$ 709.3462; encontrado 709.3478
M94	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)propanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)butil)carbamato de metilo	 (Extremo-57)	1.84 min (Cond. 2); 99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{47}N_8O_6$ 711.36; encontrado 711.54; HRMS: Análisis calculado para $[M+H]^+$ $C_{38}H_{47}N_8O_6$ 711.3619; encontrado 711.3590.

M95	((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2,2-dimetilpropil) carbamato de metilo		1.91 min (Cond. 2); 99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{39}H_{49}N_8O_6$ 725.37; encontrado 725.54; HRMS: Análisis calculado para $[M+H]^+$ $C_{39}H_{49}N_8O_6$ 725.3775; encontrado 725.3809.
M96	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dietil-D-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	 (Extremo-69a)	1.61 min (Cond. 2); 99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{49}N_8O_4$ 681.39; encontrado 681.54; HRMS: Análisis calculado para $[M+H]^+$ $C_{38}H_{49}N_8O_4$ 681.3877; encontrado 681.3867.

M97	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(7-azabiciclo[2.2.1]hept-7-il(fenil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	 (Extremo-77b)	1.72 min (Cond. 2); 98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{45}H_{51}N_8O_4$ 767.40; encontrado 767.59; HRMS: Análisis calculado para $[M+H]^+$ $C_{45}H_{51}N_8O_4$ 767.4033; encontrado 767.4067.
M98	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-hidroxi-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo		1.80 min (Cond. 2); 99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{39}H_{42}N_7O_5$ 688.32; encontrado 688.48; HRMS: Análisis calculado para $[M+H]^+$ $C_{39}H_{42}N_7O_5$ 688.3247; encontrado 688.3263.

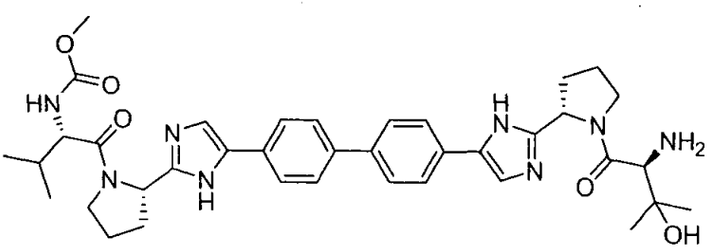
M99	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(etil(metil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	 (Extremo-3)	1.70 min (Cond. 2); 99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{49}N_8O_4$ 729.39; encontrado 729.56; HRMS: Análisis calculado para $[M+H]^+$ $C_{42}H_{49}N_8O_4$ 729.3877; encontrado 729.3887.
M100	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-(metoximetil)-2-oxoetil)carbamato de metilo	 (Extremo-56)	1.75 min (Cond. 2); 99%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{37}H_{45}N_8O_7$ 713.34; encontrado 713.34; HRMS: Análisis calculado para $[M+H]^+$ $C_{37}H_{45}N_8O_7$ 713.3411; encontrado 713.3386.

M101	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dietil-D-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	 (Extremo-72)	1.66 min (Cond. 2); 94%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{53}N_8O_4$ 709.42; encontrado: 709.42; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{53}N_8O_4$ 709.4190; encontrado 709.4166.
M102	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropil-D-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	 (Extremo-70a)	1.71 min (Cond. 2); 98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{53}N_8O_4$ 709.42; encontrado 709.48; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{53}N_8O_4$ 709.4190; encontrado 709.4191.

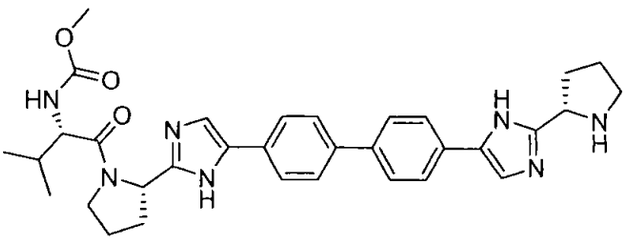
M103	((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N,N-dipropil-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo	 (Extremo-70b)	1.66 min (Cond. 2); 98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{53}N_8O_4$ 709.42; encontrado 709.42; HRMS: Análisis calculado para $[M+H]^+$ $C_{40}H_{53}N_8O_4$ 709.4190; encontrado 709.4198.

Ejemplo M104

((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-(3-hidroxi-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo



Ejemplo M104, Extremo a



La pirrolidina M104a se preparó del intermediario 28d y Extremo-51 de conformidad al procedimiento descrito por la síntesis de la pirrolidina 28f.

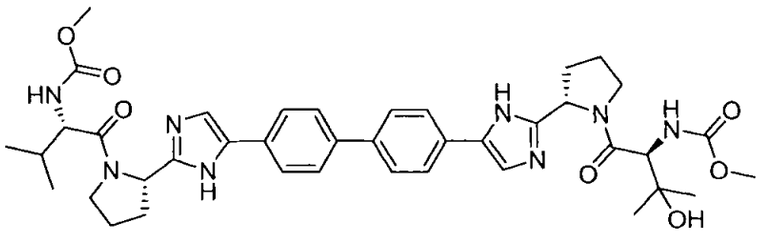
Ejemplo M104

El HATU (96.3 mg, 0.253 mmol) se le agregó a una solución DMF (5.0 mL) de pirrolidina M104a (150 mg, 0.217 mmol), ácido (S)-2-(tert-butoxicarbonilamino)-3-hidroxi-3-metilbutanoico (65.8 mg, 0.282 mmol) y i-Pr_2EtN (180 uL, 1.03 mmol), y la mezcla de reacción se agitó a condición del ambiente durante 35 min. El componente volátil se removió in vacuo, y el residuo se purificó con HPLC de fase invsera ($MeOH/H_2O/TFA$), y las fracciones se concentraron in vacuo. El residuo resultante se trató con 25% TFA/CH_2Cl_2 (6.0 mL) y se agitó durante 3.25 hr. El componente volátil se removió in vacuo y el residuo se hizó base libre (MCX; Lavado MeOH; elución 2.0 M $NH_3/MeOH$) para proporcionar el ejemplo M104 como una espuma blanca opaca (107 mg). CL (Cond. 2): TR = 1.03 min; >95%

índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{49}N_8O_5$ = 697.38; encontrado 697.28.

Ejemplo M105

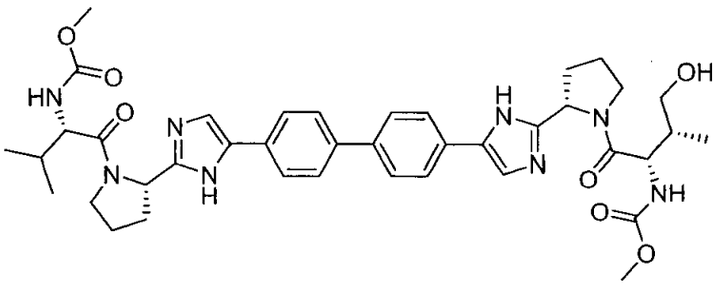
((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-3-hidroxi-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo



El cloroformiato de metilo (20 µL, 0.258 mmol) se le agregó a una solución THF (2.0 mL) del ejemplo M104 (82.9 mg, 0.119 mmol) y i-Pr_2EtN (50 uL, 0.287 mmol) y se agitó durante 65 min. La mezcla luego se trató con 2.0 M NH_3/MeOH (3 mL), se agitó durante 2.75 hr, y el componente volátil se removió in vacuo. El residuo resultante se purificó con HPLC de fase inversa (MeOH/H_2O/TFA) para proporcionar la sal TFA del ejemplo M105 como una espuma blanca (64.1 mg). CL (Cond. 2): TR = 1.17 min; >98% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{51}N_8O_7$ = 755.39; encontrado 755.25.

Ejemplo M106

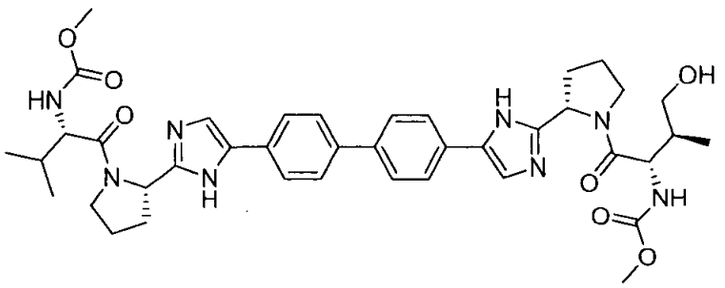
((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S,3R)-4-hidroxi-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo



El HATU (69 mg, 0.181 mmol) se le agregó a una solución DMF (3.0 mL) de pirrolidina M104a (101 mg, 0.173 mmol), Extremo-80b (55.9 mg, ~0.183 mmol) y i-Pr_2EtN (90 µL, 0.515 mmol), y la mezcla de reacción se agitó a condición del ambiente durante 70 min. El componente volátil se removió in vacuo y el residuo se purificó con HPLC de fase inversa (H_2O/MeOH/TFA) para recuperar el dominio de señal. La fracción colectada se permitió mantener a una condición del ambiente durante algunas horas y luego el componente volátil se removió in vacuo, en cuyo tiempo la destilación total del producto de acoplamiento se llevo a cabo. El producto resultante se sometió a HPLC de purificación de fase inversa (ACN/H_2O/NH_4OAc) para proporcionar el ejemplo M106 como una espuma blanca opaca (32.2 mg). CL (Cond. 2): TR = 1.19 min; >95% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{51}N_8O_7$ = 755.39; encontrado 755.85.

Ejemplo M107

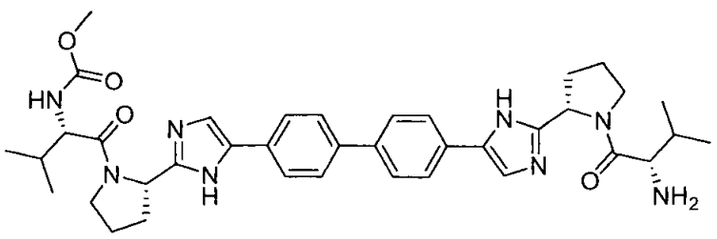
((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S,3S)-4-hidroxi-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo



El ejemplo M107 se preparó a partir de pirrolidina M104a y Extremo-80a de conformidad al procedimiento descrito por la síntesis del ejemplo M106. CL (Cond. 2): TR = 1.20 min; ~95% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{51}N_8O_7$ = 755.39; encontrado 755.78.

Ejemplo M108

((1S)-2-metil-1-(((2S)-2-(5-(4'-(2-((2S)-1-L-valil-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo



El HATU (70.1 mg, 0.184 mmol) se le agregó a una

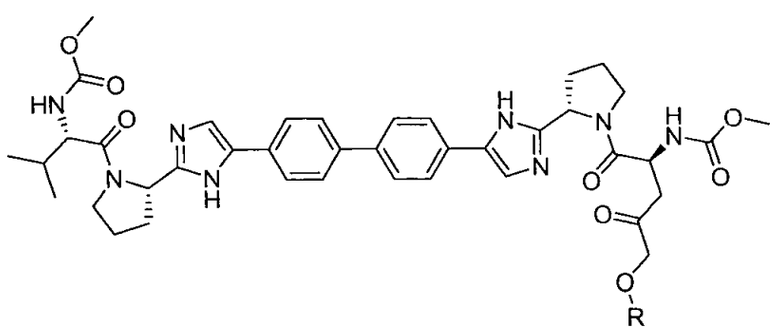
solución DMF (3.0 mL) de pirrolidina M104a (100.7 mg, 0.173 mmol), (L)-Boc-Valina (49.6 mg, 0.228 mmol) y i-Pr_2EtN (70 uL, 0.40 mmol), y la mezcla de reacción se agitó a condición del ambiente durante 65 min. El componente volátil se removió in vacuo y el residuo se purificó con Biotage (60-100% EtOAc/hexanos) para proporcionar 116.6 mg del producto de acoplamiento.

El producto de arriba (112 mg) se trató con 25% TFA/CH_2Cl_2 (2 mL) y la mezcla de reacción se agitó durante 6 hr. El componente volátil se removió in vacuo y el material crudo se purificó con una combinación de resina MCX (Lavado MeOH; elución 2.0 M NH_3/MeOH) y HPLC de fase inversa (H_2O/MeOH/TFA) para proporcionar la sal TFA del ejemplo M108 como una espuma blanca (98.5 mg). CL (Cond. 2): TR = 1.14 min; >98% índice de homogeneidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{49}N_8O_4$ = 681.39; encontrado 681.36. HRMS Calculado para $[M+H]^+$ $C_{38}H_{49}N_8O_4$: 681.3877; encontrado 681.3865.

Ejemplo M109 (R = Bn) & M110 (R = Me)

M109: (3S)-3-((metoxicarbonil)amino)-4-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-4-oxobutanoato de bencilo

M110: (3S)-3-((metoxicarbonil)amino)-4-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-4-oxobutanoato de metilo

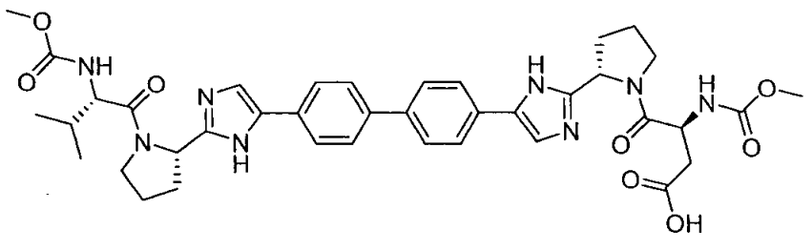


El HATU (109 mg, 0.287 mmol) se le agregó a una solución DMF (1.5 ml) de pirrolidina M104a (151 mg, 0.260 mmol), Extremo-68 (109 mg, 387 mmol), y i-Pr_2EtN (100 µl, 0.574 mmol), y la mezcla de reacción se agitó a condición del ambiente durante 3 hr. El componente volátil se removió in vacuo y el material crudo se purificó con una combinación de resina MCX (Lavado MeOH; elución 2.0 M NH_3/MeOH) y HPLC de fase inversa (H_2O/MeOH/TFA) para proporcionar la sal TFA del ejemplo M109 (88.0 mg) y ejemplo M110 (90.2 mg). El ejemplo M109: CL (Cond. 2): TR = 2.16; 97% índice de homogenicidad;

LC/MS: Análisis calculado para $[M+H]^+$ $C_{46}H_{53}N_8O_8$: 845.40; encontrado 845.51. HRMS Calculado para $[M+H]^+$ $C_{46}H_{53}N_8O_8$: 845.3986; encontrado 845.3983. El ejemplo M110: LC (Cond. 2): TR = 1.92; 97% índice de homogenicidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{49}N_8O_4$: 769.47; encontrado 769.46. HRMS Calculado para $[M+H]^+$ $C_{40}H_{49}N_8O_4$: 769.3673; encontrado 769.3682.

Ejemplo M111

Ácido (3S)-3-((metoxicarbonil)amino)-4-((2S)-2-(5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-4-oxobutanoico

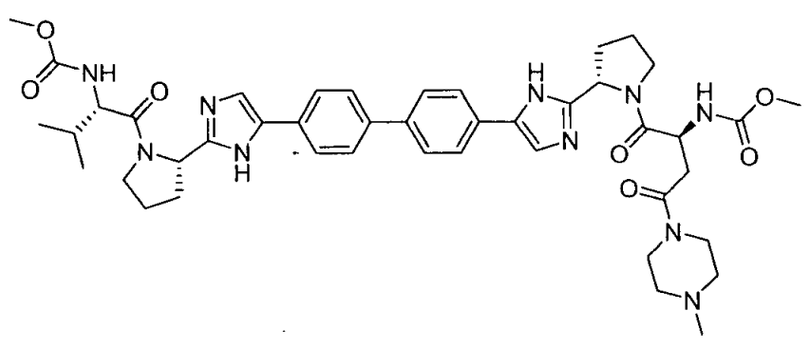


Una mezcla del ejemplo M109 (69.7 mg, 0.082 mmol) y 10% Pd/C (10 mg) en metanol (5 ml) se agitó a temperatura ambiente bajo un globo de H_2 durante 1.5 h. La reacción se filtró a través de tierra diatomácea (Celite®) y se concentró in vacuo, y el material resultante se purificó con HPLC de fase inversa (H_2O/MeOH/TFA) para proporcionar la sal TFA del ejemplo M111 como una espuma blanca opaca (54.0 mg). CL (Cond. 2): TR = 1.18; 99% índice de homogenicidad; LC/MS:

Análisis calculado para $[M+H]^+$ $C_{39}H_{47}N_8O_8$: 755.35; encontrado 755.32. HRMS Calculado para $[M+H]^+$ $C_{39}H_{47}N_8O_8$: 755.3517; encontrado 755.3525.

Ejemplo M112

((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-4-(4-metil-1-piperazinil)-4-oxobutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

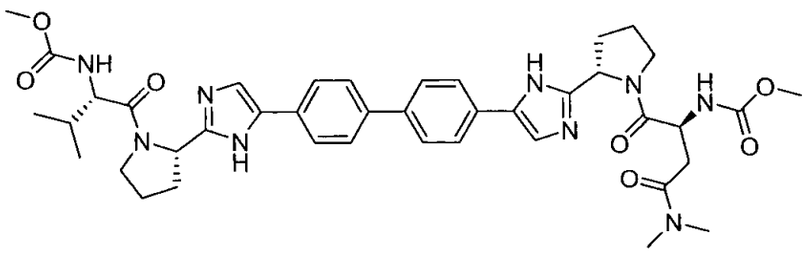


El HATU (30.6 mg, 0.080 mmol) se le agregó a una solución DMF (1.5 ml) del ejemplo M111 (55.3 mg, 0.0733 mmol), N-metil piperazina (11.0 mg, 0.11 mmol) y i-Pr_2EtN (25 µl, 0.14 mmol), y la mezcla de reacción se agitó a condición del ambiente durante 1.5 h. Todos los componentes volátiles se removieron in vacuo, y el residuo se purificó con una combinación de resina MCX y HPLC de fase inversa (H_2O/MeOH/TFA) para proporcionar la sal TFA del ejemplo M112 como una espuma blanca opaca (51.4 mg). CL (Cond. 2): TR

= 1.75; 91% índice de homogenicidad; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{57}N_{10}O_7$: 837.44; encontrado 837.59. HRMS Calculado para $[M+H]^+$ $C_{44}H_{57}N_{10}O_7$: 837.4412; encontrado 837.4453.

Ejemplo M113

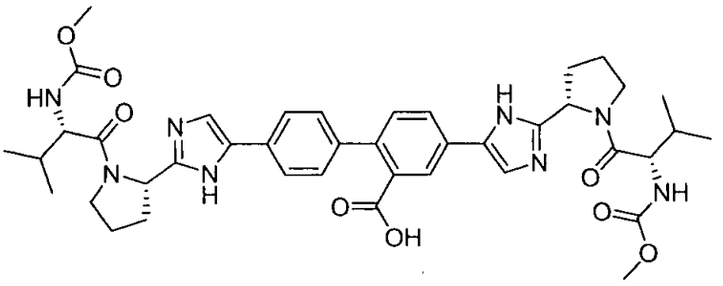
((1S)-3-(dimetilamino)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-3-oxopropil)carbamato de metilo



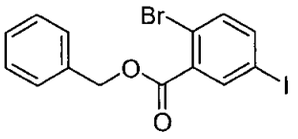
El ejemplo M118 se preparó a partir del ejemplo M111 y $Me_2N.HCl$ de conformidad al procedimiento descrito por el ejemplo M112. CL (Cond. 2): TR = 1.89; 99% índice de homogenicidad. LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{52}N_9O_7$: 782.40; encontrado 782.47. HRMS Calculado para $[M+H]^+$ $C_{41}H_{52}N_9O_7$: 782.3990; encontrado 782.4008.

Ejemplo M114

Ácido 4,4'-bis(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-5-il)-2-bifenilcarboxílico



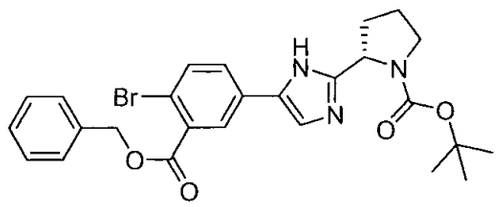
Ejemplo M114, Extremo a



El DMF (20 mL) se le agregó a una mezcla de $KHCO_3$ (1.84g, 18.4 mmol) y ácido 2-bromo-5-yodobenzoico (4.99 g, 15.3 mmol) y la mezcla resultante se agitó durante 15 min. El bromuro de bencilo (2.4 mL, 20.2 mmol) se le agregó gota a gota durante 5 min y se continuó agitando a condición del ambiente durante ~20 hr. Más del componente volátil se removió in vacuo y el residuo se dividió entre CH_2Cl_2 (50 mL) y agua (50 mL), y el extremo orgánica se lavó con agua (50 mL), se secó ($MgSO_4$), se filtró, y se concentró. El material crudo resultante se purificó con cromatografía instantánea (7% EtOAc/hexanos) para proporcionar éster M114a como un aceite viscoso incoloro (6.01 g). ^1H 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),

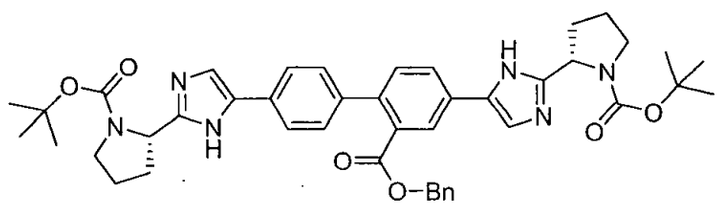
7.53 (d, J = 8.4, 1H), 7.48 (m, 2H), 7.43-7.34 (m, 3H), 5.34 (s, 2H). CL (Cond. 1): TR = 2.1 min; LC/MS: Análisis calculado para $[M+Na]^+$ $C_{14}H_{10}BrINaO_2$: 438.88; encontrado 438.83.

Ejemplo M114, Extremo b-d



El éster M114a elaboró el éster M114d por emplear un protocolo de tres Extremos empleado en la síntesis del bromo 121c a partir de 1-bromo-4-yodo-2-metilbenceno. M114d: ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.04/11.97 (br s, 1H), 8.12 (d, J = 2.0, 0.92H), 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). CL (Cond. 1): TR = 1.66 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{26}H_{29}BrN_3O_4$: 526.13; encontrado 526.16.

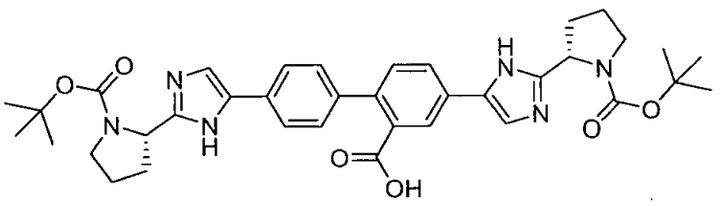
Ejemplo M114, Extremo e



El éster M114e se preparó a partir del bromo M114d y boronato 1c de conformidad a 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 (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 (dos s, 18H). CL (Cond. 1): TR = 1.54 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{51}N_6O_6$: 759.39; encontrado 759.63.

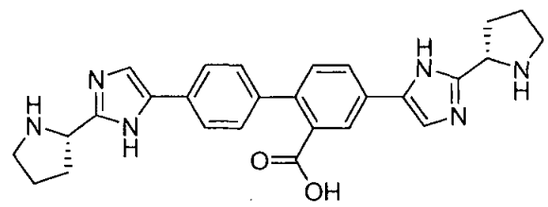
Ejemplo M114, Extremo f



Una mezcla de éster de bencilo M114e (1.005 g, 1.325 mmol) y 10% Pd/C (236 mg) en MeOH (20 mL) se agitó bajo un globo de H_2 durante 5 hr. La mezcla de reacción luego se trató 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 sometió a un rotoevaporador para proporcionar el ácido M114f (840 mg), contamidado con Ph_3PO el cual se llevo a cabo a partir de la Extremo de acoplamiento Suzuki. ^1H RMN (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, traslapado con señal de agua) 2.27-1.84

(m, 8H), 1.41/1.16 (dos s, 18H). CL (Cond. 1): TR = 1.37 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{37}H_{45}N_6O_6$: 669.34; encontrado 669.53.

Ejemplo M114, Extremo g



El 4N HCl/dioxano (8.0 mL) y CH_2Cl_2 (2.0 mL) se agregaron secuencialmente al carbamato M114f (417 mg, 0.623 mmol), la mezcla se agitó vigorosamente 5.5 hr, y luego el componente volátil se removió in vacuo para proporcionar la sal HCl (.4x) de pirrolidina M114g (487 mg), contaminada con impureza de Ph_3PO. ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz) después del 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). CL (Cond. 1): TR = 0.92 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{27}H_{29}N_6O_2$: 469.24; encontrado 469.31.

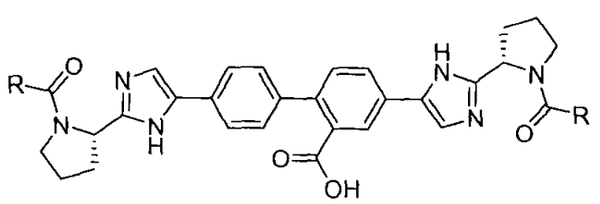
Ejemplo M114

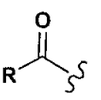
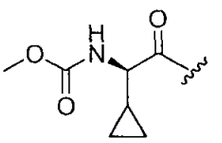
El HATU (79.9 mg, 0.21 mmol) se le agregó a una solución DMF (3.0 mL) de pirrolidina M114g.4HCl (80

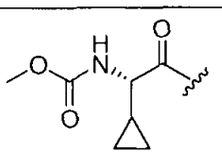
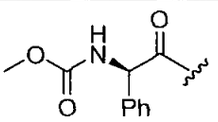
mg, 0.13 mmol), Extremo-51 (92.4 mg, 0.527 mmol) y i-Pr_2EtN (160 µL, 0.919 mmol), y la mezcla de reacción se agitó a condición del ambiente durante 2 hr. El componente volátil se removió in vacuo y el residuo se purificó con una combinación de MCX (lavado MeOH; elución 2.0 M NH_3/MeOH) y HPLC de fase inversa ($CH_3CN/H_2O/$ NH_4OAc) para proporcionar la sal del ácido acético del ejemplo M114. CL (Cond. 1): TR = 1.20 min; >98 índice de homogeneidad. LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{51}N_8O_8$: 783.38; encontrado 783.34. HRMS Calculado para $[M+H]^+$ $C_{41}H_{51}N_8O_8$: 783.3830; encontrado 783.3793.

Ejemplo M115-M116

Los ejemplos M115-M116 se prepararon usando el mismo método como se describe por el ejemplo M114 y por substituir los ácidos apropiados para el extremo-51. Los productos se aislaron como ya sea el ácido acético o sal TFA dependiendo en la naturaleza de la fase móvil de la Extremo de purificación HPLC.

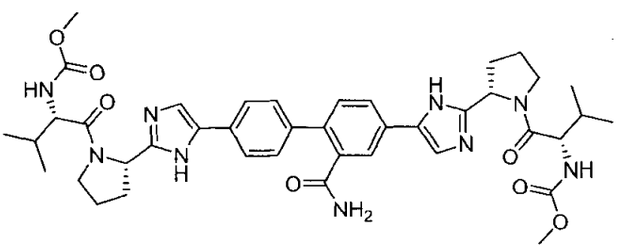


Ejemplo	Nombre del Compuesto	 (Fuente)	TR (LC-Cond.); % índice de homogeneidad; Datos EM
M115 (AcOH)	Ácido 4,4'-bis(2-((2S)-1-((2R)-2-ciclopropil-2-((metoxi carbonil)amino)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-bifenil carboxílico	 (Extremo-54a)	1.17 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{47}N_8O_8$: 779.35; encontrado 779.33; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{47}N_8O_8$: 779.3517; encontrado 779.3498

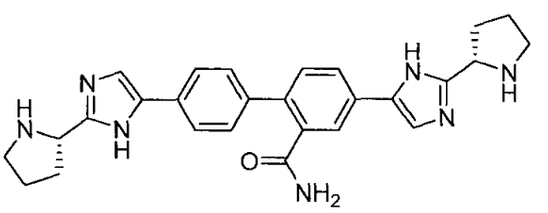
M116 (2.TFA)	Ácido 4,4'-bis(2-((2S)-1-((2S)-2-ciclopropil-2-((metoxicarbonil)amino)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-bifenil carboxílico	 (Extremo-54b)	1.13 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{47}N_8O_8$: 779.35; encontrado 779.33; HRMS: Análisis calculado para $[M+H]^+$ $C_{41}H_{47}N_8O_8$: 779.3517; encontrado 779.3551
M117 (2.TFA)	Ácido 4,4'-bis(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-5-il)-2-bifenil carboxílico	 (Extremo-4)	1.29 min (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{47}H_{47}N_8O_8$: 851.35; encontrado 851.33; HRMS: Análisis calculado para $[M+H]^+$ $C_{47}H_{47}N_8O_8$: 851.3517; encontrado 851.3480

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, Extremo a



El Et_3N (300 µL, 2.15 mmol) se le agregó a una mezcla del ácido 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) en DMF (8.0 mL) y se agitó durante 17 hr a condición de ambiante. La mezcla de reacción se filtró a través de 0.45 µm de filtro, el componente volátil se removió in vacuo y el residuo se dividió entre CH_2Cl_2 y agua. El extremo orgánica se concentró y el material crudo resultante se purificó con HPLC de fase inversa ($MeOH/H_2O/TFA$).

El producto de arriba se trató con 25% TFA/CH_2Cl_2 (4.0 mL) y la mezcla de reacción se agitó durante 2.5 hr a condición de ambiante. El componente volátil se removió in vacuo y el residuo se hizó base libre

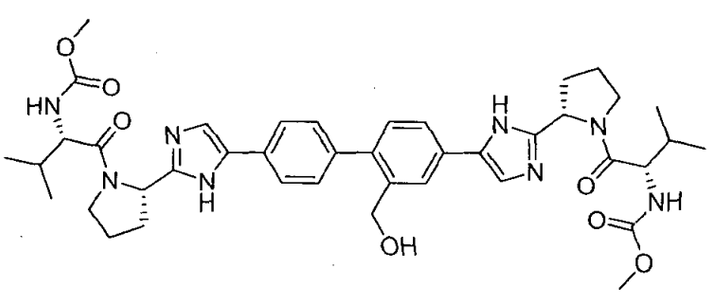
(MCX; Lavado MeOH; 2.0 M NH_3/MeOH elución) para proporcionar la amida M118a (67.2 mg). ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 11.83 (br s, 2H), 7.81-7.80 (m, 2H), 7.73 (d, J = 8.3, 2H), 7.65 (br s, 1H), 7.52 (br S, 1H), 7.44 (br s, 1H), 7.41 (d, J = 8.3, 2H), 7.36 (d, J = 8.3, 1H), 7.31 (br s, 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). CL (Cond. 1): TR = 0.89 min; >95 índice de homogeneidad. LC/MS: Análisis calculado para $[M+H]^+$ $C_{27}H_{30}N_7O$: 468.25; encontrado 468.24.

Ejemplo M118

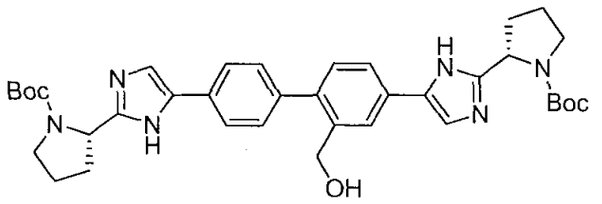
La sal TFA del ejemplo M118 se preparó del intermediario M118a y Extremo-51 de conformidad al procedimiento descrito por el ejemplo 1. CL (Cond. 1): TR = 1.16 min; 97% índice de homogeneidad. LC/MS: Análisis calculado para $[M+H]^+$ $C_{41}H_{52}N_9O_7$: 782.40; encontrado 782.40. HRMS: Análisis calculado 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

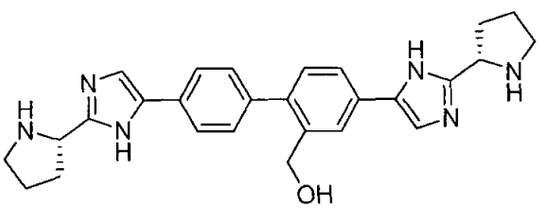


Ejemplo M119, Extremo a



El DIBAL-H (8.0 mL de 1.0 M/CH_2Cl_2, 8.0 mmol) se le agregó gota a gota a una solución CH_2Cl_2 fría de agua con hielo (20 mL) de éster de bencilo M114e (1.216 g, 1.60 mmol), y la mezcla de reacción se agitó durante 1 hr y DIBAL-H adicional (0.5 mL de 1.0 M/CH_2Cl_2, 0.5 mmol) se le agregó y se continuó agitando durante ~2.5 hr. La reacción se apagó con exceso de solución NH_4Cl saturada y la mezcla se diluyó con agua y se extrajo con CH_2Cl_2 (3x). La fase orgánica combinada se secó ($MgSO_4$), se filtró, y se concentró in vacuo. El material crudo resultante se purificó con Biotage (100 g gel de sílice; 2-6% MeOH/EtOAc) para proporcionar el alcohol M119a como una espuma blanca opaca (610 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). CL (Cond. 1): TR = 1.36 min. LC/MS: Análisis calculado para $[M+H]^+$ $C_{37}H_{47}N_6O_5$: 655.36; encontrado 655.34.

Ejemplo M119, Extremo b



El 25% TFA/CH_2Cl_2 (3.0 mL) se le agregó al carbamato M119a (105 mg, 0.160 mmol) y la mezcla se agitó a condición del ambiente durante 4.5 hr. El componente volátil se removió in vacuo y el residuo se hizó base libre (MCX; Lavado MeOH; elución 2.0 M NH3/MeOH) para proporcionar la pirrolidina M119b, contaminada con su derivado trifluoroacetilado de regioquímica desconocida. La muestra se disolvió en MeOH (1.5 mL) y se trató con 1.0 M NaOH/H_2O (300 µL, 0.3 mmol) y la mezcla se agitó durante 2.75 hr. Esto luego se sometió directamente a purificación MCX (Lavado MeOH; 2.0 M NH_3/MeOH elución) para proporcionar M119b como una película de sólido blanco (63.8 mg). ^{1}H 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; esto es una señal de línea base amplia en esta región a partir de la NH pirrolidina que no se incluye en la integración), 2.10-2.01 (m, 2H), 1.94-1.85 (m, 2H), 1.83-1.67 (m, 4H). CL (Cond.1): TR = 0.78 min. LC/MS: Análisis

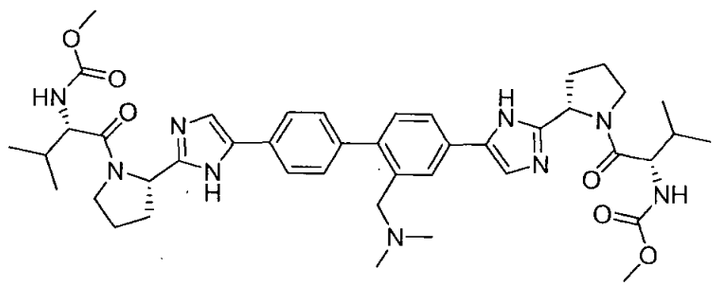
calculado para $[M+H]^+$ $C_{27}H_{31}N_6O$: 455.26; encontrado 455.27.

Ejemplo M119

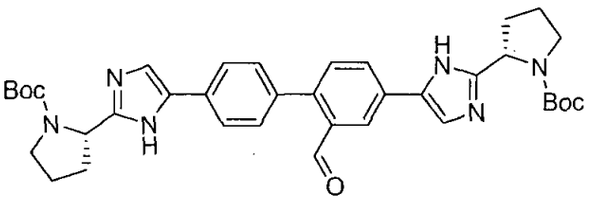
El ejemplo M119 se preparó a partir de M119b y Extremo-51 de conformidad al procedimiento descrito por el ejemplo 1, con la excepción de que la HPLC de fase inversa con el sistema de solvente $ACN/H_2O/NH_4OAC$ se emplea para la Extremo de purificación. CL (Cond. 1): TR = 1.15 min; 98% índice de homogeneidad. LC/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

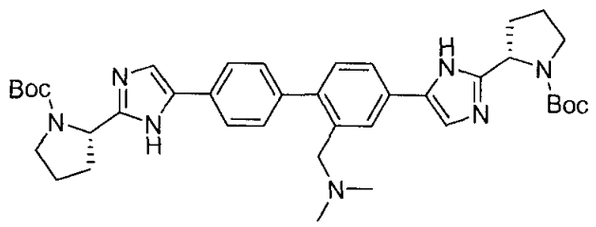


Ejemplo M120, Extremo a



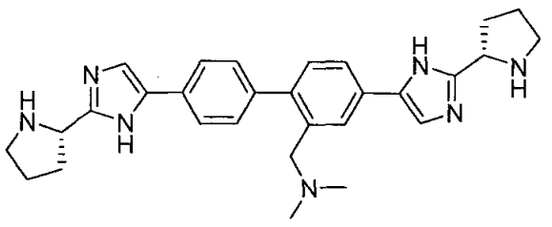
El CH_2Cl_2 (6.0 mL) se le agregó a una mezcla de alcohol M119a (501 mg, 0.765 mmol), TPAP (29.1, 0.083 mmol) y N-óxido de 4-metilmorfolina (135.8 mg, 1.159 mmol), y la mezcla heterogénea resultante se agitó vigorosamente a condición del ambiente durante 14.5 hr. El TPAP adicional (11.0 mg, 0.031 mmol) y N-óxido de 4-metilmorfolina (39 mg, 0.33 mmol) se agregaron y se continuaron agitando durante 24 horas adicionales. La mezcla se filtró a través de tierra diatomácea (Celite®), el filtrado se sometió a un rotoevaporador y el material crudo resultante se purificó con Biotage (2% MeOH/EtOAc) para proporcionar el aldehído M120a como un aceite viscoro amarillo (195.6 mg). CL (Cond. 1): TR = 1.37 min. LC/MS: Análisis calculado para $[M+H]^+$ $C_{37}H_{45}N_6O_5$: 653.35; encontrado 653.40.

Ejemplo M120, Extremo b



El $NaCNBH_3$ (33 mg, 0.50 mmol) se le agregó en lote a una solución MeOH (3.0 mL) del aldehído M120a (195.6 mg, 0.30 mmol) y Me_2NH (200 µL de solución 40% en H_2O), y la mezcla de reacción se agitó durante 4 hr. El componente volátil se removió in vacuo y el residuo se purificó con a cromatografía instantánea (la muestra se cargó como una malla de gel de sílice; 3-15% $MeOH/CH_2Cl_2$) para proporcionar la amina M120b como una espuma blanca opaca (120 mg). CL (Cond. 1): TR = 1.32 min. LC/MS: Análisis calculado para $[M+H]^+$ $C_{39}H_{52}N_7O_4$: 682.41; encontrado 682.42.

Ejemplo M120, Extremo c



El carbamato M120b se convirtió a M120c empleando el protocolo descrito por la preparación del 1e a partir del 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, 1.90H), ~3.3 (señal de Me_2NCH_2 traslapado con aquel de agua), 3.01-2.94 (m, 2H), 2.89-2.83 (m, 2H), 2.10 (s, 6H), 2.10-2.01 (m,

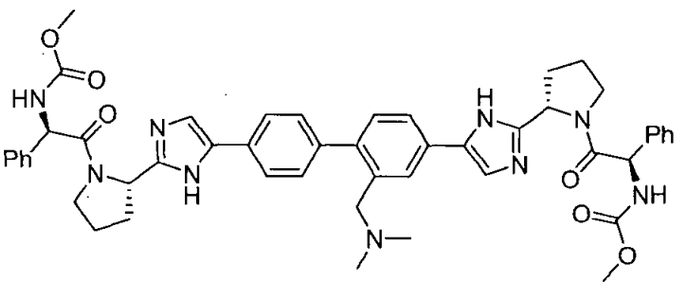
2H), 1.94-1.85 (m, 2H), 1.81-1.67 (m, 4H). CL (Cond. 1): TR = 0.79 min. LC/MS: Análisis calculado para $[M+H]^+$ $C_{29}H_{36}N_7$: 482.30; encontrado 482.35.

Ejemplo M120

La sal TFA del ejemplo M120 se preparó a partir de pirrolidina M120c y Extremo-51 de conformidad al procedimiento descrito por el ejemplo 1. CL (Cond. 1): TR = 1.06 min; 96% 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-etanediil)))biscarbamato de dimetilo

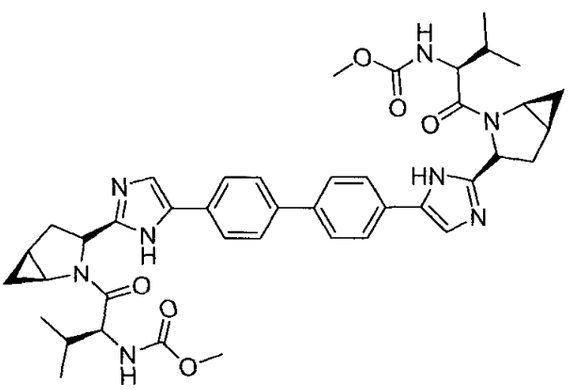


La sal TFA del ejemplo M121 se preparó a partir de M120c y Extremo-4 de conformidad al procedimiento descrito por el ejemplo 1. CL (Cond. 1): TR = 1.15 min; >98% índice de homogeneidad. LC/MS: Análisis calculado

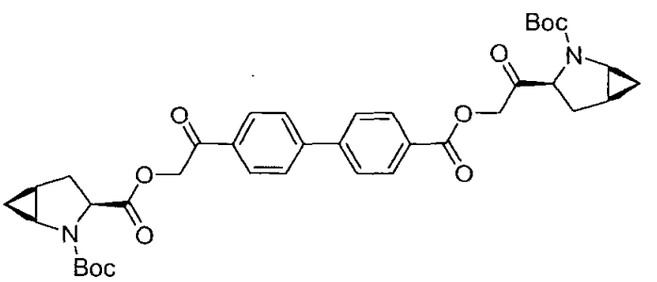
para $[M+H]^+$ $C_{49}H_{54}N_9O_6$: 796.45; encontrado 864.46. HRMS: Análisis calculado para $[M+H]^+$ $C_{49}H_{54}N_9O_6$: 864.4197; encontrado 864.4222.

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



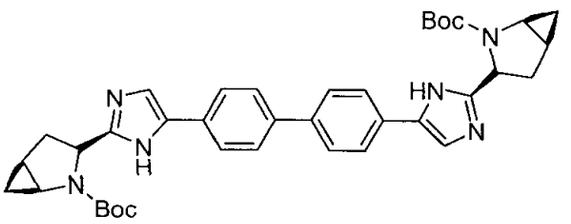
Ejemplo M122, Extremo a



La diisopropil etilamina (1.81 mL, 10.4 mmol) se agregó lentamente a una solución acetonitrilo (20 mL) de ácido (1S,3S,5S)-2-(tert-butoxicarbonil)-2-azabiciclo[3.1.0]hexano-

3-carboxílico (2.36 g, 10.4 mmol) y (2-(4'-(2-bromoacetil)bifenil-4-il)-2-oxoetil)bromo (2.0 g, 5.05 mmol), y la mezcla de reacción se agitó a condiciones ambientales durante 16 hr. El solvente se evaporó y el residuo se dividió entre acetato de etilo y agua (1:1, 40 mL cada uno). El extremo orgánica se lavó con $NaHCO_3$ saturado (2 x 10 mL), salmuera, se secó (Na_2SO_4), se filtró, y se concentró in vacuo para proporcionar el cetoéster M122a (3.58 g) como un aceite color ámbar viscoso, el cual se solidificó durante el 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). CL (Cond. 1): TR = 1.70 min; LC/MS: el ión molecular no tiene es escogido.

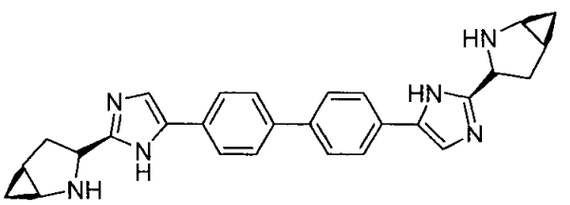
Ejemplo M122, Extremo b



El acetato de amonio (2.89 g, 37.5 mmol) se le agregó a una solución de tolueno (20 mL), cetoéster M122a (2.58 g, 3.75 mmol), y la mezcla resultante se calentó a 120°C durante 4.5 hr, mientras se hizo azeotropa con el agua que se formó con una preparación Dean-Stark. La mezcla de

reacción se enfrió a temperatura ambiente y el componente volátil se removió in vacuo. La solución de $NaHCO_3$ saturado (10 mL) se le agregó al sólido y la mezcla se agitó durante 30 min, y el sólido se filtró, se secó in vacuo y se sometió a purificación Biotage (28-100% EtOAc/hexanos) para proporcionar el imidazol M122b como sólido amarillo ligero (0.6 g). CL (Cond. 1): TR = 1.52 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{45}N_6O_4$: 649.35; encontrado 649.78.

Ejemplo M122, Extremo c



El 4 N HCl en dioxano (5 mL) se le agregó a una solución de dioxano fría de agua con hielo (16 mL) de carbamato M122b (0.8 g, 1.2 mmol), el baño de agua con hielo se removió y la mezcla se agitó a condición del ambiente durante 4 hr. Los pedazos grandes del sólido que se formó durante la reacción se rompieron con una espátula. El removido del componente volátil in vacuo proporciono la pirrolidina M122c (.4 HCl) como sólido amarillo (0.73 g). ^1H RMN (DMSO-d_6, δ =

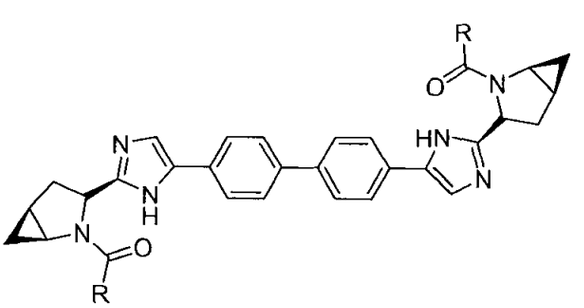
2.5 ppm, 400 MHz): δ 7.90 (d, J = 8.3, 4H), 7.84 (br s, 2H), 7.79 (d, J = 8.3, 4H), 5.24 (m, 2H), 3.38 (m, 2H), 2.71 (m, 2H), ~2.50 (2H, traslapado con la señal de solvente), 1.93 (m, 2H), 1.38 (m, 2H), 0.96 (m, 2H). CL (Cond. 1): TR = 1.03 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{28}H_{29}N_6$: 449.25; encontrado 449.59.

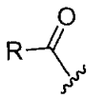
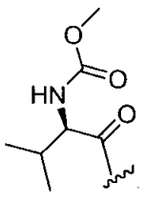
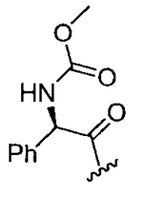
Ejemplo M122

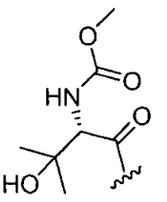
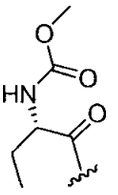
La sal TFA del ejemplo M122 se preparó a partir de M122c y Extremo-51 de conformidad al procedimiento descrito por el ejemplo 1. CL (Cond. 1): TR = 1.34 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{51}N_8O_6$: 763.39; encontrado 763.73.

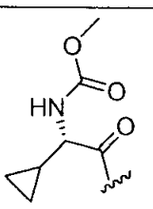
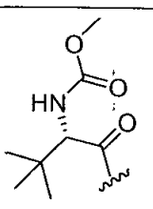
Ejemplo M123-M130

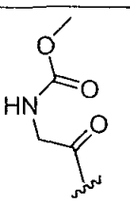
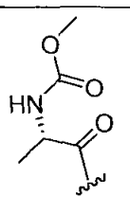
El ejemplo M123-M130 se prepararon de conformidad al procedimiento descrito por el ejemplo M122. El ejemplo M123-M129 se prepararon como la sal TFA, en donde como en el Ejemplo M130 se preparó como una base libre.



Ejemplo	Nombre del Compuesto	 (Fuente)	TR (CL-Cond.); % índice de homogeneidad; Datos EM
M123	((1R)-1-(((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2R)-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	 (Extremo-84)	1.372 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{51}N_8O_6$: 763.39; encontrado 763.73
M124	(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(1S,3S,5S)-2-azabiciclo[3.1.0]hexano-3,2-diil((1R)-2-oxo-1-fenil-2,1-etanediil)))biscarbamato de dimetilo	 (Extremo-4)	2.28 minutos (Cond. M1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{48}H_{47}N_6O_6$: 831.36; encontrado 831.36

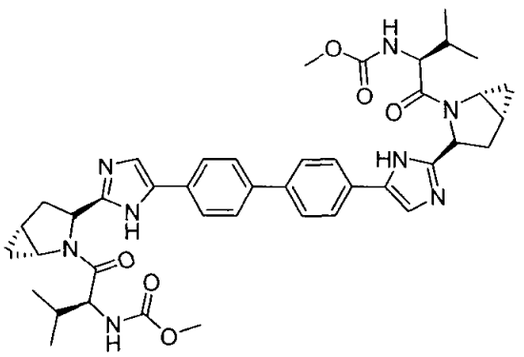
M125	((1S)-2-hidroxi-1-(((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2S)-3-hidroxi-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo	 (Extremo-65)	1.76 minutos (Cond. M1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{51}N_8O_8$: 795.38; encontrado 795.37
M126	(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(1S,3S,5S)-2-azabiciclo[3.1.0]hexano-3,2-diil((2S)-1-oxo-1,2-butanodiil)))biscarbamato de dimetilo	 (Extremo-53b)	1.25 minutos (Cond.1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.36; encontrado 735.68

M127	(4,4'-bifenildiilbis(1H-imidazol-5,2-diil(1S,3S,5S)-2-azabiciclo[3.1.0]hexano-3,2-diil((1S)-1-ciclopropil-2-oxo-2,1-etanediil)))biscarbamato de dimetilo	 (Extremo-54b)	1.27 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{47}N_8O_6$: 759.36; encontrado 759.72
M128	((1S)-1-(((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-((2S)-2-((metoxicarbonil)amino)-3,3-dimetilbutanoil)-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)-2,2-dimetilpropil)carbamato de metilo		2.48 minutos (Cond. M1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{44}H_{55}N_8O_6$: 791.42; encontrado 791.41

M129	(2-((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-(((metoxicarbonil)amino)acetil)-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)-2-oxoetil)carbamato de metilo		1.10 minutos (Cond.1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{36}H_{39}N_8O_6$: 679.74; encontrado 679.77
M130	((1S)-2-((1S,3S,5S)-3-(5-(4'-(2-((1S,3S,5S)-2-(N-(metoxicarbonil)-L-alanil)-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)-1-metil-2-oxoetil)carbamato de metilo	 (Extremo-52)	1.16 minutos (Cond. 1); >98%; LC/MS: Análisis calculado para $[M+H]^+$ $C_{38}H_{43}N_8O_6$: 707.33; encontrado 707.69

Ejemplo M131

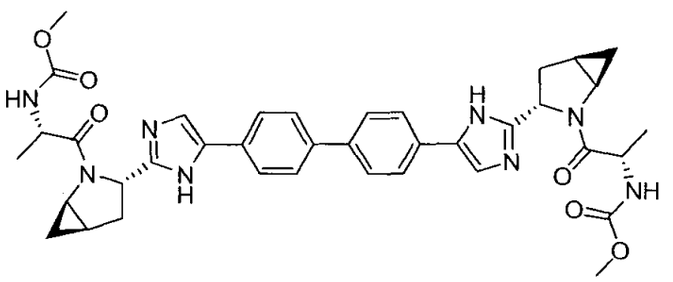
((1S)-1-(((1R,3R,5R)-3-(5-(4'-(2-((1R,3R,5R)-2-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo



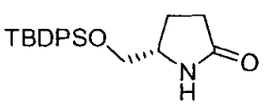
El ejemplo M131 se preparó de conformidad al procedimiento descrito por su diastereómero del ejemplo M122 partiendo a partir del ácido (1R,3S,5R)-2-(tert-butoxicarbonil)-2-azabiciclo[3.1.0]hexano-3-carboxílico, el cual se volvió a sintetizar por emplear un protocolo de literatura (Hanessian et al., Angew. Chem., Int. Ed. Engl. 1997, 36, 1881-1884). CL (Cond. I): TR = 1.273 min; LC/MS: Análisis calculado para $[M+H]^+$ $C_{42}H_{50}N_8O_6$: 763.39; encontrado 763.94.

Ejemplo M132

((1S)-2-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-(N-(metoxicarbonil)-L-alanil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-1-metil-2-oxoetil)carbamato de metilo



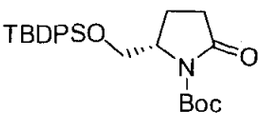
Ejemplo M132, Extremo a



A una solución de (*S*)-5-(hidroximetil)pirrolidin-2-ona (10 g, 87 mmol) en CH_2Cl_2 (50 mL) se agregó *tert*-butilclorodifenilsilano (25.6 g, 93 mmol), trietilamina (12.1 mL, 87 mmol) y DMAP (1.06 g, 8.7 mmol). La mezcla se agitó a temperatura ambiente durante 5 horas, se trató con CH_2Cl_2 (50 mL) y se lavó con agua (50 mL). La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró *in vacuo*. El producto crudo se purificó con una cromatografía instantánea (30 hasta 100% de EtOAc/hexanos) para proporcionar éter

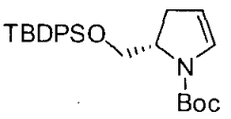
M132a como aceite incoloro (22.7 g, 74% de rendimiento). ^{1}H RMN (DMSO-d_6, δ = 2.50, 400 MHz): 7.69 (br s, 1H), 7.64-7.61 (m, 4H), 7.50-7.42 (m, 6H), 3.67-3.62 (m, 1H), 3.58-3.51 (m, 2H), 2.24-2.04 (m, 3H), 1.89-1.78 (m, 1H), 1.00 (s, 9H).

Ejemplo M132, Extremo b



Di-*tert*-butil dicarbonato (28.0 g, 128 mmol) se agregó lentamente a una solución enfriada (hielo/agua) CH_2Cl_2 (120 mL) de éter M132a (22.7 g, 64.2 mmol), trietilamina (8.95 mL, 64.2 mmol), y DMAP (7.84 g, 64.2 mmol). Al final de la adición, el baño de enfriado se removió y agitó continuamente a condición de ambiente durante 20 horas. El componente volátil se removió *in vacuo*, y el material crudo se sometió a una cromatografía instantánea (20 hasta 50% EtOAc/de hexanos) para proporcionar carbamato M132b como sólido blanco opaco (29 g, 99% de rendimiento). ^{1}H RMN (DMSO-d_6, δ = 2.50, 400 MHz): 7.61-7.54 (m, 4H), 7.50-7.38 (m, 6H), 4.19-4.16 (m, 1H), 3.90 (dd, J = 10.4, 3.6, 1H), 3.68 (dd, J = 10.4, 2.1, 1H), 2.68-2.58 (m, 1H), 2.40-2.33 (m, 1H), 2.22-2.12 (m, 1H), 2.01-1.96 (m, 1H), 1.35 (s, 9H), 0.97 (s, 9H).

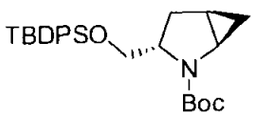
Ejemplo M132, Extremo c



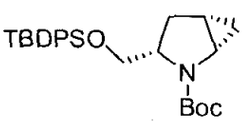
Un matraz de tres cuellos equipado con un termómetro y una entrada de nitrógeno se cargó con carbamato M132b (10.054 g, 22.16 mmol) y tolueno (36 mL), y disminuyendo en -55°C el baño de enfriado. Cuando la temperatura interna de la mezcla alcanzó ~ -50°C, Superhidruro (23 mL de 1.0 M en THF, 23.00 mmol) se agregó gota a gota durante 30 minutos mientras se mantiene la temperatura interna entre -50 y -45°C, y se agitó durante 35 minutos mientras se mantiene la temperatura entre -50 y -45 °C. Se agregó Base Hunig (16.5 mL, 94 mmol) gota a gota durante 10 minutos. Luego se agregó DMAP (34 mg, 0.278 mmol) en un baño, seguido por la adición de anhídrido trifluoroacético (3.6 mL, 25.5 mmol) durante 15 minutos, mientras se mantiene la temperatura interna entre -50 y -45°C. El baño se removió 10 minutos después, y la mezcla de reacción se agitó durante 14 horas mientras se permite que se descongele a temperatura ambiente. Luego se diluyó con tolueno (15 mL), se enfrió con un baño de hielo-agua, y se trató lentamente con agua (55 mL) durante 5 minutos. Al final de la adición, las fases se separaron, y la capa orgánica se lavó con agua (50 mL, 2x) y luego se concentró

in vacuo. El material crudo se purificó con una cromatografía instantánea (5% EtOAc/hexanos) para proporcionar carbamato M132c como un aceite viscoso incoloro (7.947 g, 82%). ^{1}H RMN (DMSO-d_6, δ= 2.50, 400 MHz): 7.62-7.58 (m, 4H), 7.49-7.40 (m, 6H), 6.47 (br m, 1H), 5.07-5.01 (br m, 1H), 4.18 (br m, 1H), 3.89 (br m, 0.48H), 3.69 (br m, 1.52 H), 2.90-2.60 (br m, 2H), 1.40/1.26 (dos s traslapados, 9H), 0.98 (s, 9H).

Ejemplo M132, Extremo d



M132d-i

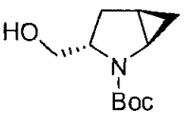


M132d-ii

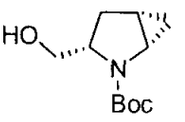
Dietilzinc (19 mL de ~1.1 M en tolueno, 20.90 mmol) se agregó gota a gota durante 15 minutos hasta una solución (-30°C) de toleuno (27 mL) de carbamato M132c (3.94 g, 9.0 mmol). Luego cloroyodometano (97%, estabilizado sobre cobre; 3 mL, 41.2 mmol) se agregó gota a gota durante 10 minutos, y se agita mientras se mantiene el baño a temperatura alrededor de -25°C durante 1 hora y alrededor de -21°C durante 18.5 horas. La reacción luego se abrió al aire y se apagó por una adición lenta de 50% de solución $NaHCO_3$ saturada (40 mL), y luego se removió del baño de enfriado y se agitó a condición de ambiente durante 20 minutos. Se filtró a través de un papel filtro

y la torta blanca se lavó con 50 mL de tolueno. La fase orgánica del filtrado se separó, y se lavó con agua (40 mL, 2x), se secó ($MgSO_4$), se filtró, y se concentró *in vacuo*. El material crudo resultante se purificó con un sistema Biotage (350 g gel de sílice; la muestra se cargó con 7% de EtOAc/hexanos; se eluyó con 7-20% de EtOAc/hexanos) para proporcionar metanopirrolidina M132d como un aceite viscoso incoloro, principalmente como el isómero trans (3.691 g, 90.7%). [Nota: la relación trans/cis exacta no se ha determinado aún en esta Extremo]. ^1H RMN (DMSO-d_6, δ = 2.50, 400 MHz) de M132d-i: 7.62-7.60 (m, 4H), 7.49-7.40 (m, 6H), 3.76 (br m, 1H), 3.67 (br m, 2H), 3.11-3.07 (m, 1H), 2.23 (br m, 1H), 2.03 (br m, 1H), 1.56-1.50 (m, 1H), 1.33 (br s, 9H), 1.00 (s, 9H), 0.80-0.75 (m, 1H), 0.30 (br m, 1H).

Ejemplo M132, Extremo e



M132e-i

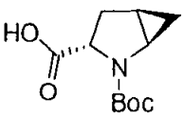


M132e-ii

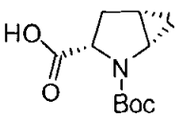
Se agregó TBAF (7.27 mL de 1.0 M en THF, 7.27 mmol) gota a gota durante 5 minutos a una solución THF (30 mL) del éter M132d (3.13 g, 6.93 mmol) y la mezcla se agitó a condición ambiente durante 4.75 horas. Después se trató con solución NH_4Cl saturada (5 mL), más del componente

volátil se removió *in vacuo*, y el residuo se dividió entre CH_2Cl_2 (70 mL) y 50% de solución NH_4Cl saturada (30 mL). La fase acuosa se extrajo con CH_2Cl_2 (30 mL), y la fase orgánica combinada se secó ($MgSO_4$), se filtró, se concentró *in vacuo*, y luego se expuso a alto vacío durante la noche. El material crudo resultante se purificó con un Biotage (40-50% EtOAc/hexanos) para proporcionar alcohol M132e como aceite incoloro, principalmente como el isómero trans, contaminado con residuos de impurezas Rf inferiores (1.39 g, 94%). [Nota: la relación trans/cis exacta no se ha determinado aún en esta Extremo]. ^1H RMN (DMSO-d_6, δ = 2.50, 400 MHz) de M132e-i: 4.70 (app t, J = 5.7, 1H), 3.62-3.56 (m, 1H), 3.49-3.44 (m, 1H), 3.33-3.27 (m, 1H), 3.08-3.04 (m, 1H), 2.07 (br m, 1H), 1.93-1.87 (m, 1H), 1.51-144 (m, 1H), 1.40 (s, 9H), 0.76-0.71 (m, 1H), 0.26 (br m, 1H).

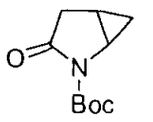
Ejemplo M132, Extremo f



M132f-i



M132f-ii



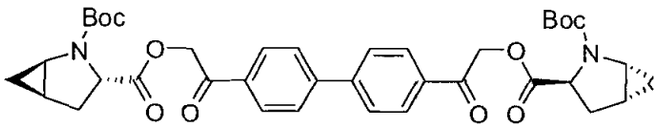
M132f-iii

Una semi-solución de $NaIO_4$ (6.46 g, 30.2 mmol) en H_2O (31 mL) se agregó a CH_3CN (20 mL) y CCl_4 (20 mL) la solución de alcohol M132e (2.15 g, 10.08 mmol) preparado

arriba, y $RuCl_3$ (0.044 g, 0.212 mmol) se agregó inmediatamente y la mezcla de reacción heterogenea se agitó vigorosamente durante 75 minutos. La mezcla de reacción se diluyó H_2O (60 mL) y se extrajo con CH_2Cl_2 (50 mL, 3x). La fase orgánica combinada se trató con 1 mL CH_3OH, se permitió reposar durante alrededor de 5 minutos, y luego se filtró a través de una almohadilla de tierra diatomácea (Celite®). La almohadilla se lavó con CH_2Cl_2 (50 mL), y el filtrado se colocó en un rotoevaporador para proporcionar un sólido color carbón vegetal ligero. ^1H RMN del material crudo indicado en una relación 1.00:0.04:0.18 mol entre ácido *trans* M132f-i: ácido *cis* presumido M132f-ii: producto lateral M132f-iii. El material crudo se disolvió en EtOAc (~10 mL) con calentamiento, y se permitió reposar a condición ambiente con sembrado. Alrededor de 15 minutos en la fase enfriada, se observó una formación de cristal rápido. Alrededor 1 hora después, hexanos (~6 mL) se agregó y la mezcla se refrigeró durante la noche (no parece que el compuesto adicional se ha precipitado). La mezcla se filtró y se lavó con hexanos/EtOAc enfriado con hielo/agua (relación 2:1; 20 mL) y se secó bajo alto vacío para proporcionar la primera cosecha de ácido M132f-i (cristales blancos opacos, 1.222 g). El lícor madre se colocó en un rotoevaporador, y el residuo se

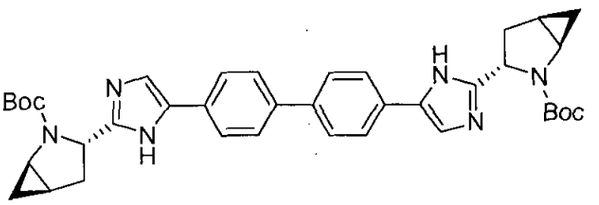
disolvió en ~3 ml de EtOAc (con calentamiento), se permitió reposar a condición de ambiente durante 1 hora, y luego 3 mL hexanos se agregó y se almacenó en un refrigerador durante ~15 horas. Una segunda cosecha de ácido M132f-i (cristales grises, 0.133 g) se recuperó similarmente. ^{1}H RMN (DMSO-d_6, δ = 2.50, 400 MHz): 12.46 (br s, 1H), 3.88 (br m, 1H), 3.27 (br m, 1H; parcialmente traslapado con la señal de agua), 2.28 (br m, 1H), 2.08 (br m, 1H), 1.56 (br m, 1H), 1.40/1.34 (dos br s traslapados, 9H), 0.73-0.68 (m, 1H), 0.46-0.43 (m, 1H). Rotación óptica (10 mg/mL de $CHCl_3$): $[\alpha]_D$ = -216 para la primera cosecha y -212 para la segunda cosecha.

Ejemplo M132, Extremo g



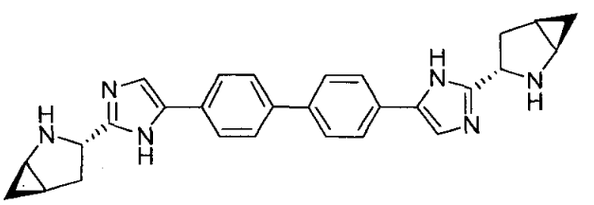
El cetoéster M132g se preparó de ácido M132f-i y 1,1'-(bifenil-4,4'-diil)bis(2-bromoetanona) al emplear el procedimiento descrito para la preparación de cetoéster M122a. CL (Cond. I): TR = 2.09 minutos. LC/MS: análisis calculado para $[M+H-Boc]^+$ $C_{33}H_{37}N_2O_8$: 589.26; encontrado 589.29.

Ejemplo M132, Extremo h



El carbamato M132h se preparó de cetoéster M132g de acuerdo al procedimiento descrito para la preparación de imidazol 1b de cetoamida 1a, con la excepción de que 20 mol equiv de NH_4OAc se empleó para la ciclización térmica, y que CH_2Cl_2 se empleó durante la Extremo de trabajo. CL (Cond. I): TR = 1.48 minutos. LC/MS: análisis calculado para $[M+H]^+$ $C_{38}H_{45}N_6O_4$: 649.35; encontrado 649.40.

Ejemplo M132, Extremo i

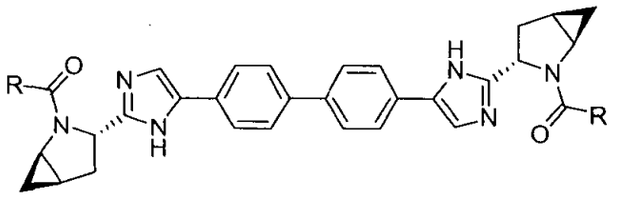


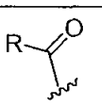
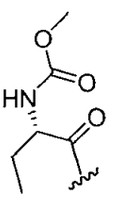
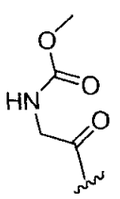
La pirrolidina M132i (HCl .4) se preparó de carbamato M132h de acuerdo al procedimiento descrito para la preparación de pirrolidina M122c. El material crudo se sometió a Extremo de acilación posterior sin purificación. ^1H RMN (DMSO-d_6, δ = 2.50, 400 MHz): 10.5-10.0 (señal br, no integradable), 8.02 (s, 2H), 7.95 (d, J = 8.6, 4H), 7.85 (d, J = 8.3, 4H), 4.75

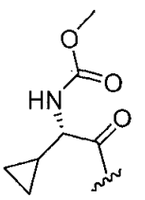
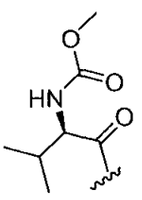
(m, 2H), 3.43 (m, 2H), 2.67-2.50 (m, 4H), 1.95 (m, 2H), 1.11 (m, 2H), 0.86 (m, 2H). TR = 1.00 minutos. LC/MS: análisis calculado para $[M+H]^+$ C28H20N6: 449.25; encontrado 49.27.

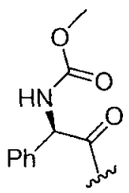
Ejemplo M132

El ejemplo M132, junto con sus análogos del Ejemplo M133-M137 resaltados en la tabla a continuación, se prepararon como sales TFA de pirrolidina M132i (HCl .4) al emplear el procedimiento descrito para la síntesis del Ejemplo M122 y ácidos apropiados. El ejemplo M132: CL (Cond. I): TR = 1.14 min; >95% de índice de homogeneidad. LC/MS: análisis calculado para $[M+H]^+$ $C_{38}H_{43}N_8O_6$: 707.33; encontrado 707.43.



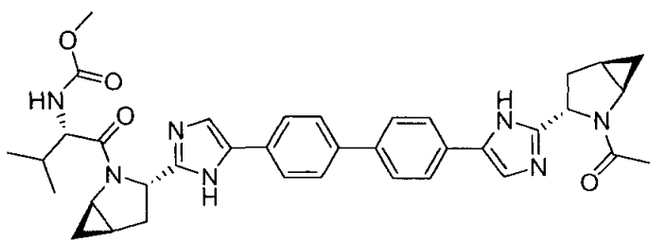
Ejemplo	*Nombre del compuesto*		*TR (CL-Cond.); % de índice de homogeneidad; Datos EM*
M133	(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0] hexan-3,2-diil((2S)-1-oxo-1,2-butanediil))) biscarbamato de dimetilo		1.22 minutos (Cond. I); >98%; LC/MS: análisis calculado para $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.36; encontrado 735.48
M134	(2-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-(((metoxicarbonil) amino)acetil)-2-azabiciclo[3.1.0] hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0] hex-2-il)-2-oxoetil)carbamato de metilo		1.12 minutos (Cond. I); >98%; LC/MS: análisis calculado para $[M+H]^+$ $C_{36}H_{39}N_8O_6$: 679.30; encontrado 679.38

M135	(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3,2-diil((1S)-1-ciclopropil-2-oxo-2,1-etandiil))) biscarbamato de dimetilo		1.25 minutos (Cond. I); >98%; LC/MS: análisis calculado para $[M+H]^+$ $C_{42}H_{47}N_8O_6$: 759.36; encontrado 759.45
M136	((1R)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2R)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo		1.34 minutos (Cond. I); >98%; LC/MS: análisis calculado para $[M+H]^+$ $C_{42}H_{50}N_8O_6$: 763.39; encontrado 763.46

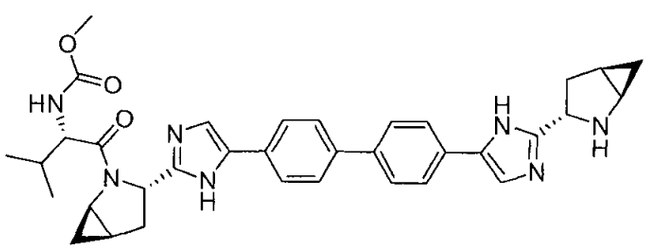
M137	(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0] hexan-3,2-diil((1R)-2-oxo-1-fenil-2,1-etandiil))) biscarbamato de dimetilo		1.38 minutos (Cond. I); >98%; LC/MS: análisis calculado para $[M+H]^+$ $C_{48}H_{47}N_8O_6$: 831.36; encontrado 831.37

Ejemplo M138

((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-acetil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de metilo



Ejemplo M138, Extremo a



A una mezcla espesa de pirrolidina M132i (HCl .4) (0.3 g, 0.32 mmol) en DMF (4 mL), el ácido (*S*)-2-(metoxicarbonilamino)-3-metilbutanoico (97 mg, 0.55 mmol) e *i*-Pr_2EtN (0.26 mL, 1.5 mmol) se agregaron. Después la mezcla se volvió una solución transparente, HATU (0.2 g, 0.53 mmol) se agregó, y se agitó a temperatura ambiente durante 3 horas. El componente volátil se removió *in vacuo*, y el residuo resultante (el cual fue una mezcla de material de partida, y productos mono- y bis-acilados) se disolvió en metanol y se purificó con una HPLC de fase inversa (CH_3OH/H_2O/TFA) para aislar la sal TFA de pirrolidina M138a como espuma blanca (80 mg). CL (Cond. I): TR = 1.17 minutos. LC/MS: análisis calculado para $[M+H]^+$ $C_{35}H_{40}N_7O_3$: 606.32; encontrado 606.36.

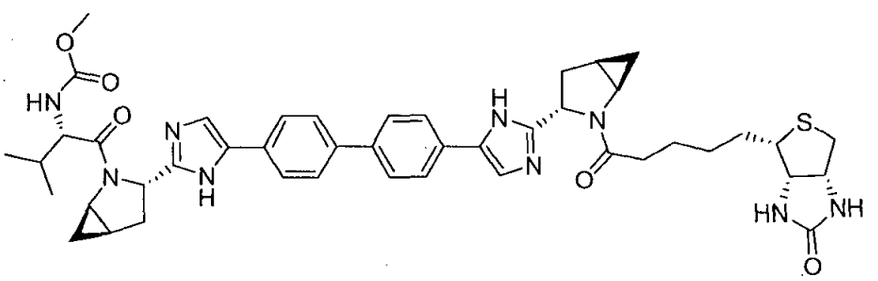
Ejemplo M138

El ácido acético (7.6 mg, 0.13 mmol), *i*-Pr_2EtN (32 mg, 0.25 mmol), y HATU (53 mg, 0.14 mmol) se agregaron secuencialmente a una solución DMF (2 mL) de la sal TFA de pirrolidina M138a (40 mg, 0.04 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 3 horas. El componente volátil se removió *in vacuo*, y el residuo se disolvió en metanol y se purificó con una HPLC de fase inversa (CH_3OH/H_2O/TFA) para proporcionar la sal TFA del Ejemplo M138 como espuma blanca (8 mg). CL (Cond. I): TR = 1.20 min; >95% de índice de homogeneidad. LC/MS: análisis

calculado para $[M+H]^+$ $C_{37}H_{42}N_7O_4$: 648.33; encontrado 648.36.

Ejemplo M139

((1S)-2-metil-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-(5-((3aS,4S,6aR)-2-oxohexahidro-1H-tieno[3,4-d]imidazol-4-il)pentanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil-2-metilpropil)carbamato de metilo

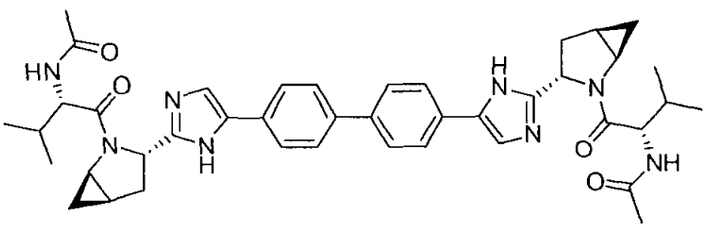


Se agregó HATU (53 mg) a una mezcla de la sal TFA de pirrolidina M138a (40 mg, 0.042 mmol), *d*-Biotin (10.3 mg, 0.042 mmol) e *i*-Pr_2EtN (0.044 mL, 0.253 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 3 horas. El componente volátil se removió *in vacuo*, y el residuo se disolvió en metanol y se purificó con una HPLC de fase inversa (CH_3OH/H_2O/TFA) para proporcionar la sal TFA del Ejemplo M139 como un sólido amarillo ligero (7 mg). CL (Cond. I): TR = 1.28 min; >95% de índice de homogeneidad. LC/MS: análisis calculado para

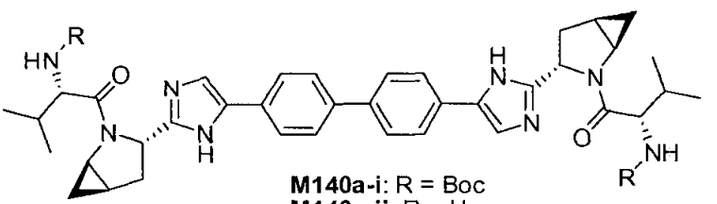
$[M+H]^+$ $C_{45}H_{54}N_9O_5S$: 832.40; encontrado 832.34.

Ejemplo M140

N-((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-acetamido-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)acetamida



Ejemplo M140, Extremo a



M140a-i: R = Boc
M140a-ii: R = H

Se agregó HATU (852 mg, 2.24 mmol) a una solución DMF (20 mL) de pirrolidina M132i (HCL .4) (650 mg, 1.09 mmol), Boc-*L*-Valina (523 mg, 2.41 mmol), *i*-Pr_2EtN (1.15 mL, 6.56 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 1 hora. El componente volátil se removió *in vacuo*, y el crudo se disolvió en CH_3OH y se purificó con una HPLC de fase inversa (CH_3OH/H_2O/TFA) para proporcionar 0.96 g de producto acilado. Una porción del producto (0.72 g) se disolvió en CH_2Cl_2 (4 mL), se trató con TFA (0.26 mL, 3.35

mmol), y la mezcla resultante se agitó a condición de ambiente durante 4 horas. El componente volátil se removió *in vacuo* para proporcionar la sal TFA de M140a-ii, *((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-((tert-butoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de tert-butilo*, el cual se usó en la siguiente Extremo sin purificación. CL (Cond. I): TR = 0.93 minutos. LC/MS: análisis calculado para $[M+H]^+$ $C_{38}H_{47}N_8O_2$: 647.38; encontrado 647.26.

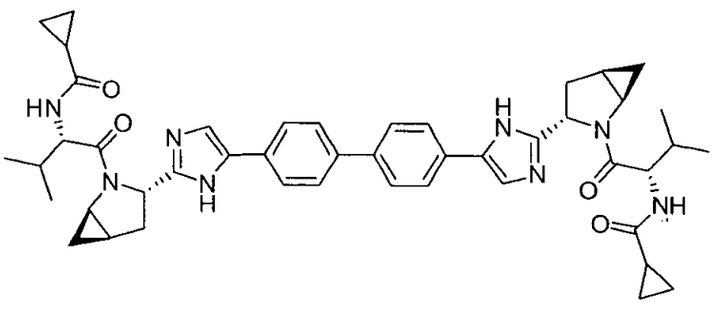
La forma de base libre de carbamato M140a-i se puede aislar a la Extremo de acoplamiento como sigue: la fracción HPLC se neutralizó con exceso de NH_3/CH_3OH 2.0 N, el componente volátil se removió *in vacuo* y el residuo se dividió entre CH_2Cl_2 y ~5% de solución $NaHCO_3$ saturada. La capa orgánica se secó (Na_2SO4), se filtró, y se concentró *in vacuo* para proporcionar M140a-i, *(2S)-1-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-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)-3-metil-1-oxo-2-butanamina*, como una espuma amarillo ligero. CL (Cond. I): TR = 1.64 min; >95% de índice de homogeneidad. LC/MS: análisis calculado para $[M+H]^+$ $C_{48}H_{63}N_8O_6$: 847.49; encontrado 847.54.

Ejemplo M140

El anhídrido acético (21 mg, 0.204 mmol) e *i*-Pr_2EtN (0.083 mL, 0.476 mmol) se agregaron secuencialmente a una solución DMF (3 mL) de la sal TFA de M140a-ii (75 mg, 0.068 mmol), y la mezcla de reacción se agitó a condición ambiente hasta completarse, como se determina por análisis LC/MS. El componente volátil se removió *in vacuo*, y el residuo se disolvió en CH_3OH y se sometió a una HPLC de fase inversa (CH_3OH/H_2O/TFA) para proporcionar la sal TFA del Ejemplo M140 como espuma blanca (35 mg). CL (Cond. I): TR = 1.18 min; >98% de índice de homogeneidad. LC/MS: análisis calculado para $[M+H]^+$ $C_{42}H_{51}N_8O_4$: 731.40; encontrado 731.34.

Ejemplo M141

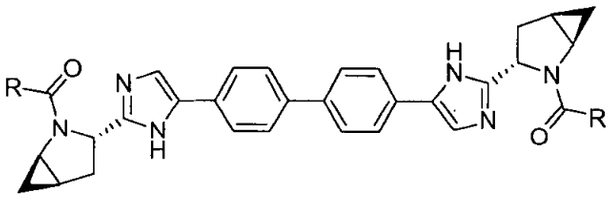
N-((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-((ciclopropilcarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)ciclopropancarbamato

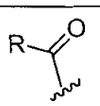
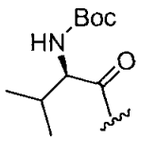
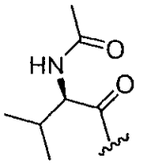


El ejemplo M141 se preparó como una sal TFA de amina M140a-ii (sal TFA) y ácido ciclopropancarboxílico de acuerdo al procedimiento de acoplamiento descrito para la síntesis de carbamato de M140a-i. CL (Cond. I): TR = 1.33 min; >95% de índice de homogeneidad. LC/MS: análisis calculado para $[M+H]^+$ $C_{46}H_{55}N_8O_4$: 783.42; encontrado 783.36.

Ejemplo M142-M143

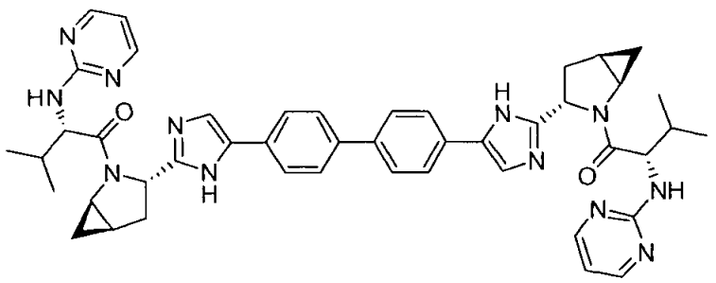
El ejemplo M142 (base libre) y el Ejemplo M143 (sal TFA) se prepararon al emplear los procedimientos descritos para la síntesis del Ejemplo M140 y materiales apropiados.



Ejemplo	*Nombre del compuesto*		*TR (CL-Cond.); % de índice de homogeneidad; Datos EM*
M142	((1R)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2R)-2-((tert-butoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)carbamato de tert-butilo		1.65 minutos (Cond. I); >98%; LC/MS: análisis calculado para $[M+H]^+$ $C_{48}H_{63}N_8O_6$: 847.49; encontrado 847.54
M143	N-((1R)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2R)-2-acetamido-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilpropil)acetamida		1.26 minutos (Cond. I); >98%; LC/MS: análisis calculado para $[M+H]^+$ $C_{42}H_{51}N_8O_4$: 731.40; encontrado 731.34

Ejemplo M144

N,N'-(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0]hexan-3,2-diil((2S)-3-metil-1-oxo-1,2-butandiil)))di(2-pirimidinamina)



Una mezcla de la sal TFA de amina M140a-ii (75 mg, 0.068 mmol), 2-bromopirimidina (32.4 mg, 0.204 mmol), e *i*-Pr_2EtN (0.048 mL, 0.272 mmol) en DMSO (0.2 mL)/tolueno (1.2 mL) se calentó a 90°C durante 20 horas. Se agregó 2-bromopirimidina adicional (32.4 mg, 0.204 mmol) y se calentó continuamente durante 8 horas. Más del componente volátil se removió *in vacuo* y el residuo se purificó dos veces por un sistema HPLC de fase inversa, (CH_3OH/H_2O/TFA) seguido por (ACN/H_2O/TFA), para proporcionar la sal TFA del Ejemplo M144, contaminado con impurezas menores no conocidas, como una espuma amarilla (10 mg). TR = 20.9 minutos (ver el método CL detallado a continuación); >95% de índice de homogeneidad. LC/MS: análisis calculado para $[M+H]^+$ $C_{46}H_{51}N_{12}O$: 803.43; encontrado 803.70.

Métodos detallados para análisis del Ejemplo M144:

Instrumento: Waters Acquity HPLC con detección Waters PDA UV-Vis y Waters SQ MS (sonda ESCI)

Columna: Waters Acquity BEH C18; 1.7um ; 150 X 2.1 mm ID; (a 35C)

Fase móvil A: agua/acetonitrilo (97.5/2.5) con formiato de amonio 5 mM; 0.05% de ácido formico a pH 3.3

Fase móvil B: : Acetonitrilo/agua (97.5/2.5) con formiato de amonio 5 mM; 0.05% de ácido formico

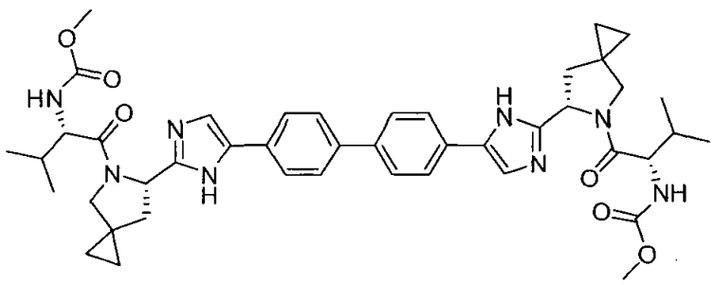
Flujo: 0.35 ml/min

Esperar 10%B	0-1min
10-35%B	1-20 min
35-98%B	20-32 min
Esperar 98%	32-35 min
98-10%B	35- 35.5 min
espera 10%B	35.5-40.0 min

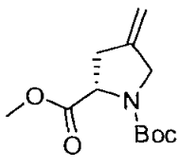
detección UV: @ 260 nm

Ejemplo M145

((1S)-1-(((6S)-6-(4-(4'-(2-((6S)-5-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-azaspiro[2.4]hept-6-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-5-azaspiro[2.4]hept-5-il)carbonil)-2-metilpropil)carbamato de metilo



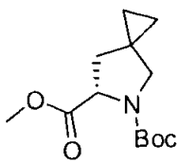
Ejemplo M145, Extremo a



Se agregó $TMSCHN_2$ (3.63 mL de 2.0 M/éter, 7.26 mmol) se agregó gota a gota a una solución CH_3OH (33 mL)/benceno (33 mL) de 4-metilenpirrolidin-1,2-dicarboxilato de (*S*)-1-*tert*-butilo (1.5 g, 6.60 mmol), y la mezcla de reacción se agitó a condición de ambiente durante 3.5 horas. La eliminación del componente volátil *in vacuo* proporcionó éster M145a como un aceite color canela (1.57 g). ^1H RMN ($CDCl_3$, δ = 7.26 ppm, 500 MHz): 5.01-4.98 (m, 2H), 4.50-4.48 (m, 0.5H), 4.39-4.37 (m, 0.5H), 4.07-4.04 (m, 2H),

3.71 (s, 3H), 3.01-2.87 (m, 1H), 2.66-2.55 (m, 1H), 1.46/1.41 (dos s traslapados, 9H).

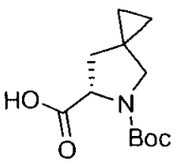
Ejemplo M145, Extremo b



Se agregó dietilzinc (5.65 mL de 1.1 M en tolueno, 6.22 mmol) gota a gota durante 20 minutos hasta enfriarse (-22 °C) tolueno (4 mL) solución de éster M145a (0.50 g, 2.07 mmol). Se agregó cloroyodometano (0.90 mL, 12.4 mmol) gota a gota durante 10 minutos, y la mezcla de reacción se agitó a -22°C durante 18 horas. La reacción se apagó con solución saturada de $NaHCO_3$ (ac.) (5 mL) a temperatura similar y luego se permitió descongelarse a temperatura ambiente. La mezcla se filtró, y el precipitado se lavó con EtOAc (100 mL). Las capas del filtrado se separaron, y la fase orgánica se secó ($MgSO_4$), se filtró, y se concentró *in vacuo*. El material crudo resultante se purificó con un Biotage (10-20% EtOAc/hexanos) para proporcionar éster M145b como aceite incoloro (0.139 g). ^1H RMN ($CDCl_3$, δ = 7.26 ppm, 500 MHz): 4.47-4.44 (m, 0.5H), 4.47-4.34 (m, 0.5H), 3.73 (s, 3H), 3.39-3.27 (m, 2H), 2.25-2.18 (m, 1H), 1.86-1.84 (m, 0.5H), 1.78-1.75 (m, 0.5H), 1.44/1.40 (dos s traslapados, 9H), 0.63-0.48 (m, 4H). CL (Cond. II): TR = 2.26 minutos. LC/MS: análisis calculado para $[M+Na]^+$

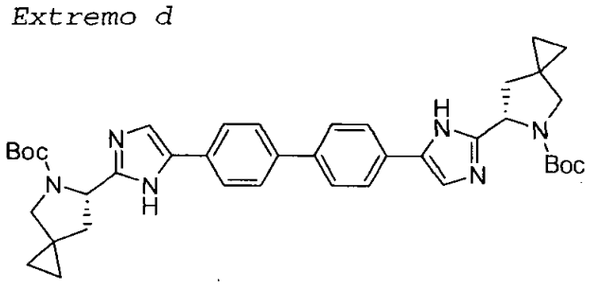
$C_{12}H_{19}NNaO_4$: 264.12; encontrado 264.22.

Ejemplo M145, Extremo c



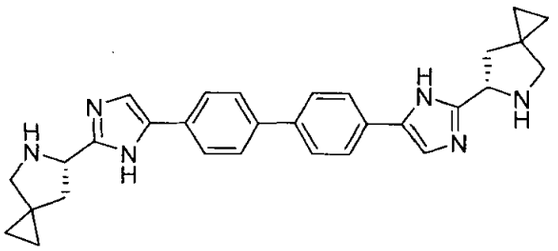
Una solución de agua (0.61 mL) de LiOH (0.016 g, 0.65 mmol) se agregó a una solución de etanol (1.2 mL) de éster M145b (0.139 g, 0.544 mmol), y la mezcla de reacción se agitó a condición de ambiente durante 19 horas. El componente volátil se removió *in vacuo*, y el residuo se disolvió en agua (5 mL), enfriada (hielo/agua), acidificada a una región pH de 3.0 con HCl 1N (ac.), y luego se extrajo con EtOAc (50 mL, 3x). La capa orgánica combinada se secó ($MgSO_4$), se filtró, y se concentró *in vacuo* para proporcionar ácido M145c como aceite viscoso el cual se solidificó hasta reposarse (0.129 g). ^1H RMN ($CDCl_3$, δ = 7.26 ppm, 500 MHz): 4.48-4.40 (m, 1H), 3.55-3.05 (m, 2H), 2.37-1.87 (m, 2H), 1.47/1.44 (dos s traslapados, 9H), 0.78-0.50 (m, 4H). CL (Cond. II): TR = 2.26 minutos. LC/MS: análisis calculado para $[M+Na]^+$ $C_{12}H_{19}NNaO_4$: 264.12; encontrado 264.22.

Ejemplo M145, Extremo d



El carbamato M145d se preparó a partir de ácido M145c y 1,1'-(bifenil-4,4'-diil)bis(2-bromoetanona) y empleando el procedimiento general descrito para la síntesis de M122b con la excepción de que la Extremo de ciclización de cetoéster se condujo bajo condiciones de microondas (140°C; 90 min). CL (Cond. II): TR = 2.54 minutos. LC/MS: análisis calculado para $[M+H]^+$ $C_{40}H_{49}N_6O_4$: 677.38; encontrado 677.45.

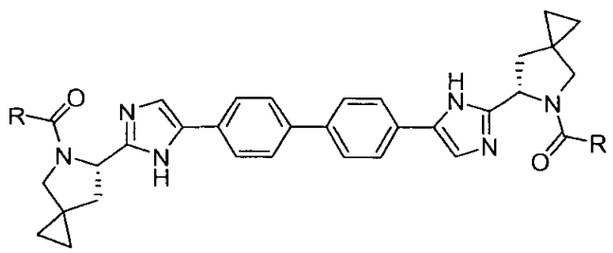
Ejemplo M145, Extremo e

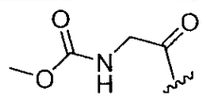
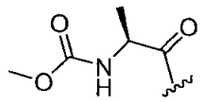


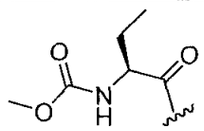
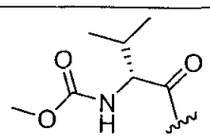
Se agregó 25% de TFA/CH_2Cl_2 (5.3 mL) al carbamato M145d (0.718 g, 1.06 mmol) y la mezcla resultante se agitó a condición de ambiente durante 5 horas. El componente volátil se removió *in vacuo*, y el residuo se hizó básico libre con MCX (6 g, lavado CH_3OH; 1:1 $CHCl_3/NH_3$ 2 N/elusión CH_3OH) para proporcionar pirrolidina M145e como un sólido amarillo ligero (406 mg). ^1H RMN (DMSO-d_6, d = 2.5 ppm, 500 MHz): 11.89 (br s, 2H), 7.82 (d, J = 7.9, 4H), 7.67 (d, J = 7.9, 4H), 7.50 (br s, 2H), 4.37 (m, 2H), 2.92 (app d, J = 9.8, 2H), 2.81 (app d, J = 10.1, 2H), 2.09-2.05 (m, 2H), 1.98-1.94 (m, 2H), 0.62-0.49 (m, 8H). CL (Cond. II): TR = 1.75 minutos. LC/MS: análisis calculado para $[M+H]^+$ $C_{30}H_{33}N_6$: 477.28; encontrado 477.35.

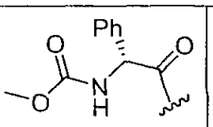
Ejemplo M145

El ejemplo M145, junto con sus análogos del Ejemplo M146-M147 resaltados en la tabla a continuación, se prepararon como sales TFA iniciando de pirrolidina M145 y ácidos apropiados, al emplear la condición de acoplamiento HATU general resumida por el Ejemplo-1, con la excepción de que la mezcla de reacción se diluyó con CH_3OH y se sometió directamente a una purificación de HPLC de fase inversa (CH_3OH/H_2O/TFA). Ejemplo M145: CL (Cond. II), TR = 2.27 min); >95% de índice de homogeneidad. LC/MS: análisis calculado para $[M+H]^+ = C_{44}H_{55}N_8O_6$: 791.42; encontrado 791.44.



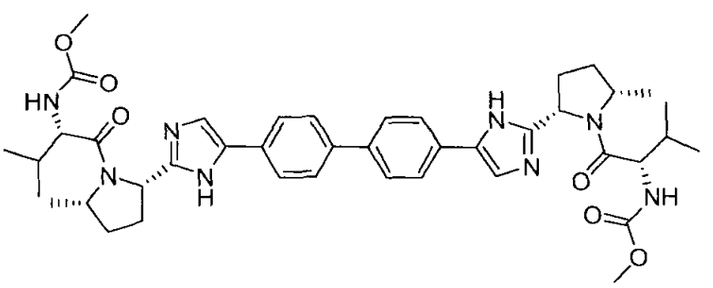
Ejemplo	*Nombre del Compuesto*		*TR (CL-Cond.); % de índice de homogeneidad; Datos EM*
M146	(2-((6S)-6-(4-(4'-(2-((6S)-5-(((metoxicarbonil)amino) acetil)-5-azaspiro[2.4]hept-6-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-5-azaespiro[2.4]hept-5-il)-2-oxoetil)carbamato de metilo		1.97 minutos (Cond. II); >95%; LC/MS: análisis calculado para $[M+H]^+$ $C_{38}H_{43}N_8O_6$: 707.33; encontrado 707.36
M147	((1S)-2-((6S)-6-(4-(4'-(2-((6S)-5-(N-(metoxicarbonil)-L-alanil)-5-azaespiro[2.4]hept-6-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-5-azaspiro[2.4]hept-5-il)-1-metil-2-oxoetil) carbamato de metilo		2.01 minutos (Cond. II); >95%; LC/MS: análisis calculado para $[M+H]^+$ $C_{40}H_{47}N_8O_6$: 735.36; encontrado 735.41

M148	(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(6S)-5-azaspiro[2.4]heptan-6,5-diil((2S)-1-oxo-1,2-butanediil))) biscarbamato de dimetilo		2.14 minutos (Cond. II); >95%; LC/MS: análisis calculado para $[M+H]^+$ $C_{42}H_{51}N_8O_6$: 763.39; encontrado 763.46
M149	((1R)-1-(((6S)-6-(4-(4'-(2-((6S)-5-((2R)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-azaespiro[2.4]hept-6-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-5-azaespiro[2.4]hept-5-il)carbonil)-2-metilpropil)carbamato de metilo		2.44 minutos (Cond. II); >95%; LC/MS: análisis calculado para $[M+H]^+$ $C_{44}H_{55}N_8O_6$: 791.42; encontrado 791.44

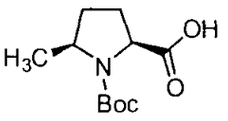
M150	(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(6S)-5-azaspiro[2.4]heptan-6,5-diil((1R)-2-oxo-1-fenil-2,1-etandiil)))biscarbamato de dimetilo		2.52 minutos (Cond. II); >95%; LC/MS: análisis calculado para $[M+H]^+$ $C_{50}H_{51}N_8O_6$: 859.39; encontrado 859.42

Ejemplo M151

((1S)-1-(((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo

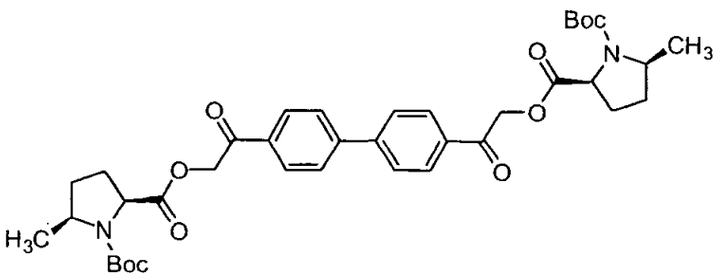


Ejemplo M151, Extremo a



El compuesto del título se sintetizó de acuerdo a un protocolo de literatura (*J. Med. Chem.*, 2006, *49*, 3520) con las siguientes modificaciones de purificación: el material crudo (2.7 g) se volvió a cristalizar de EtOAc/hexanos a temperatura ambiente para proporcionar ácido M151a como un cristal blanco (2.2 g). ^{1}H RMN ($CDCl_3$, δ = 7.24 ppm, 400 MHz): 4.32 (br m, 1H), 3.89 (br m, 1H), 2.40 (br m, 1H), 2.00 (m, 2H), 1.65 (m, 1H), 1.45 (s, 9H), 1.20 (d, J = 5.6, 3H). CL (Cond. I): TR = 1.40 minutos. LC/MS: análisis calculado para $[M+Na]^+$ $C_{11}H_{20}NO_4Na$: 252.12; encontrado 252.21.

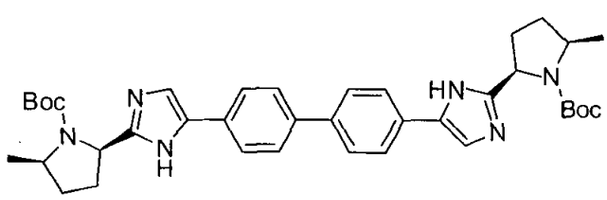
Ejemplo M151, Extremo b



A una mezcla de ácido M151a y 1,1'-(bifenil-4,4'-diil)bis(2-bromoetanona) (1.85 g, 4.66 mmol) en acetonitrilo (50 mL), *i*-Pr_2EtN (1.24 g, 9.6 mmol) se agregó

gota a gota, y la reacción se agitó a temperatura ambiente durante 7 hr. El componente volátil se removió *in vacuo* y el residuo se dividió entre acetato de etilo y agua (1:1, 100 mL). La capa orgánica se separó y se lavó con $NaHCO_3$ saturado y salmuera, se secó (Na_2SO_4), se filtró, y se concentró *in vacuo* para proporcionar cetoéster M151b como espuma blanca (3.19 g), el cual se usó en la siguiente Extremo sin purificación. ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 8.10 (d, J = 8.5, 4H), 7.95 (d, J= 8.5, 4H), 5.70-5.50 (br m, 4H), 4.40 (br m, 2H), 3.90 (br m, 2H), 2.25 (m, 2H), 2.15 (m, 4H), 1.60 (m, 2H), 1.41 (s, 8H), 1.39 (s, 10H), 1.20 (m, 6H). CL (Cond. I): TR = 2.15 minutos. LC/MS: no se observa el ión precursor.

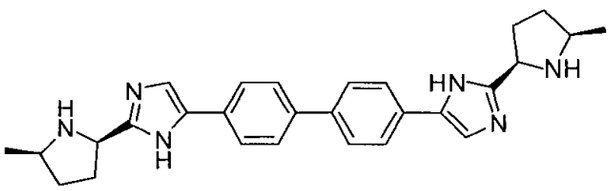
Ejemplo M151, Extremo c



Una mezcla de cetoéster M151b (2.94 g, 4.24 mmol) y acetato de amonio (6.54 g, 85 mmol) en xileno (40 mL) se calentó en un tubo sellado a 140°C durante 2 horas. El componente volátil se removió *in vacuo* y el residuo se dividió entre CH_2Cl_2 (100 mL) y agua (50 mL). La capa orgánica se lavó con $NaHCO_3$ saturado (20 mL), se secó (Na_2SO_4), se concentró *in vacuo*. El material crudo

resultante se purificó con un Biotage (0-100% EtOAc/hexanos) para proporcionar imidazol M151c como sólido café ligero (1.72 g). CL (Cond. I): TR = 1.03 minutos. LC/MS: análisis calculado para $[M+H]^+$ $C_{38}H_{49}N_6O_4$: 653.37; encontrado 653.40.

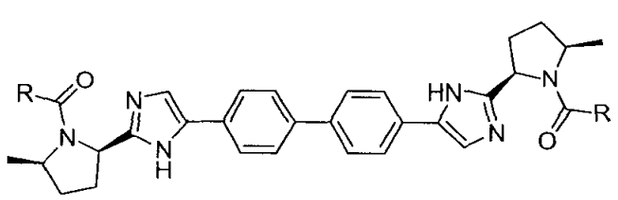
Ejemplo M151, Extremo d

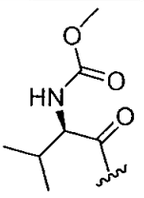
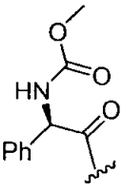


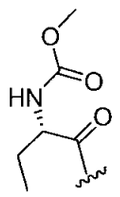
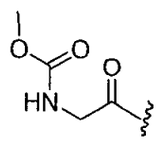
Se agregó HCl 4 N en dioxano (14 mL, 56 mmol) gota a gota a una solución de dioxano (70 mL) de carbamato M151c (1.72 g, 2.63 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 4 horas. La eliminación del componente volátil *in vacuo* proporcionó la sal HCl de pirrolidina M151d como un sólido amarillo (1.58 g). ^1H RMN (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 9.85 (br s, 1H), 8.80 (br s, 1H), 7.89 (d, J = 8.3, 4H), 7.77 (s, 2H), 7.75 (d, J = 8.6, 4H), 4.70 (br m, 2H), 3.75 (br m, 2H), 2.45-2.35 (m, 4H), 2.25 (m, 2H), 1.75 (m, 2H), 1.50 (d, J = 6.6, 6H). CL (Cond. I): TR = 1.03 minutos. LC/MS: análisis calculado para $[M+H]^+$ $C_{28}H_{33}N_6$: 453.28; encontrado 453.28.

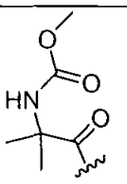
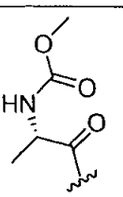
Ejemplo M151

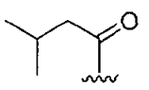
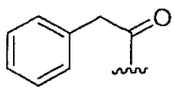
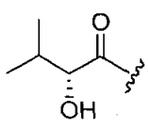
El ejemplo M151, junto con sus análogos del Ejemplo M152-M161 resaltados en la tabla a continuación, se prepararon como sales TFA iniciando de pirrolidina M151d y ácidos apropiados, al emplear la condición de acoplamiento HATU general resumida por el Ejemplo-1, con la excepción de que la mezcla de reacción se diluyó con CH_3OH y se sometió directamente a una purificación de HPLC de fase inversa (CH_3OH/H_2O/TFA). Ejemplo M151: CL (Cond. I): TR = 1.41 min; >95% de índice de homogeneidad. LC/MS: análisis calculado para $[M+H]^+$ $C_{42}H_{55}N_8O_6$: 767.42; encontrado 767.40.

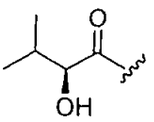


Ejemplo	*Nombre del Compuesto*		*TR (LC-Cond.); % de índice de homogeneidad; datos EM*
M152	((1R)-1-(((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-((2R)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo		1.38 minutos (Cond. I); >98%; LC/MS: análisis calculado para $[M+H]^+$ $C_{42}H_{55}N_8O_6$: 767.42; encontrado 767.33
M153	(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((2S,5S)-5-metil-2,1-pirrolidindiil)((1R)-2-oxo-1-fenil-2,1-etandiil)))biscarbamato de dimetilo		1.46 minutos (Cond. I); >98%; LC/MS: análisis calculado para $[M+H]^+$ $C_{48}H_{51}N_8O_6$: 835.39; encontrado 835.31

M154	(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((2S,5S)-5-metil-2,1-pirrolidindiil)((2S)-1-oxo-1,2-butandiil))) biscarbamato de dimetilo		1.27 minutos (Cond. I); >98%; LC/MS: análisis calculado para $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.39; encontrado 739.28
M155	(2-((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-(((metoxicarbonil)amino)acetil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)-2-oxoetil)carbamato de metilo		1.19 minutos (Cond. I); >98%; LC/MS: análisis calculado para $[M+H]^+$ $C_{36}H_{43}N_8O_6$: 683.33; encontrado 683.32

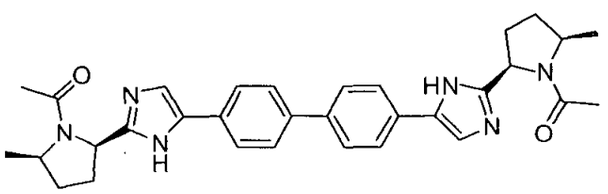
M156	(2-((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-(2-((metoxicarbonil)amino)-2-metilpropanoil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)-1,1-dimetil-2-oxoetil)carbamato de metilo		1.33 minutos (Cond. I); >98%; LC/MS: análisis calculado para $[M+H]^+$ $C_{40}H_{51}N_8O_6$: 739.39; encontrado 739.28
M157	((1S)-2-((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-(N-(metoxicarbonil)-L-alanil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo		1.21 minutos (Cond. I); >98%; LC/MS: análisis calculado para $[M+H]^+$ $C_{38}H_{47}N_8O_6$: 711.36; encontrado 711.23

M158	4,4'-(4,4'-bifenildiil)bis(2-((2S,5S)-5-metil-1-(3-metilbutanoil)-2-pirrolidinil)-1H-imidazol)		1.42 minutos (Cond. I); >98%; LC/MS: análisis calculado para $[M+H]^+$ $C_{38}H_{49}N_6O_2$: 621.39; encontrado 621.28
M159	4,4'-(4,4'-bifenildiil)bis(2-((2S,5S)-5-metil-1-(fenilacetil)-2-pirrolidinil)-1H-imidazol)		1.46 minutos (Cond. I); >98%; LC/MS: análisis calculado para $[M+H]^+$ $C_{44}H_{45}N_6O_2$: 689.36; encontrado 689.26
M160	(2R,2'R)-1,1'-(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((2S,5S)-5-metil-2,1-pirrolidindiil)))bis(3-metil-1-oxo-2-butanol)		1.27 minutos (Cond. I); >98%; LC/MS: análisis calculado para $[M+H]^+$ $C_{38}H_{49}N_6O_4$: 653.38; encontrado 653.27

M161	(2S,2'S)-1,1'-(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((2S,5S)-5-metil-2,1-pirrolidindiil)))bis(3-metil-1-oxo-2-butanol)		1.267 minutos (Cond. I); >98%; LC/MS: análisis calculado para $[M+H]^+$ $C_{38}H_{49}N_6O_4$: 653.38; encontrado 653.34

Ejemplo M162

2-((2S,5S)-1-acetil-5-metil-2-pirrolidinil)-4-(4'-(2-((2S,5S)-1-acetil-5-metil-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol

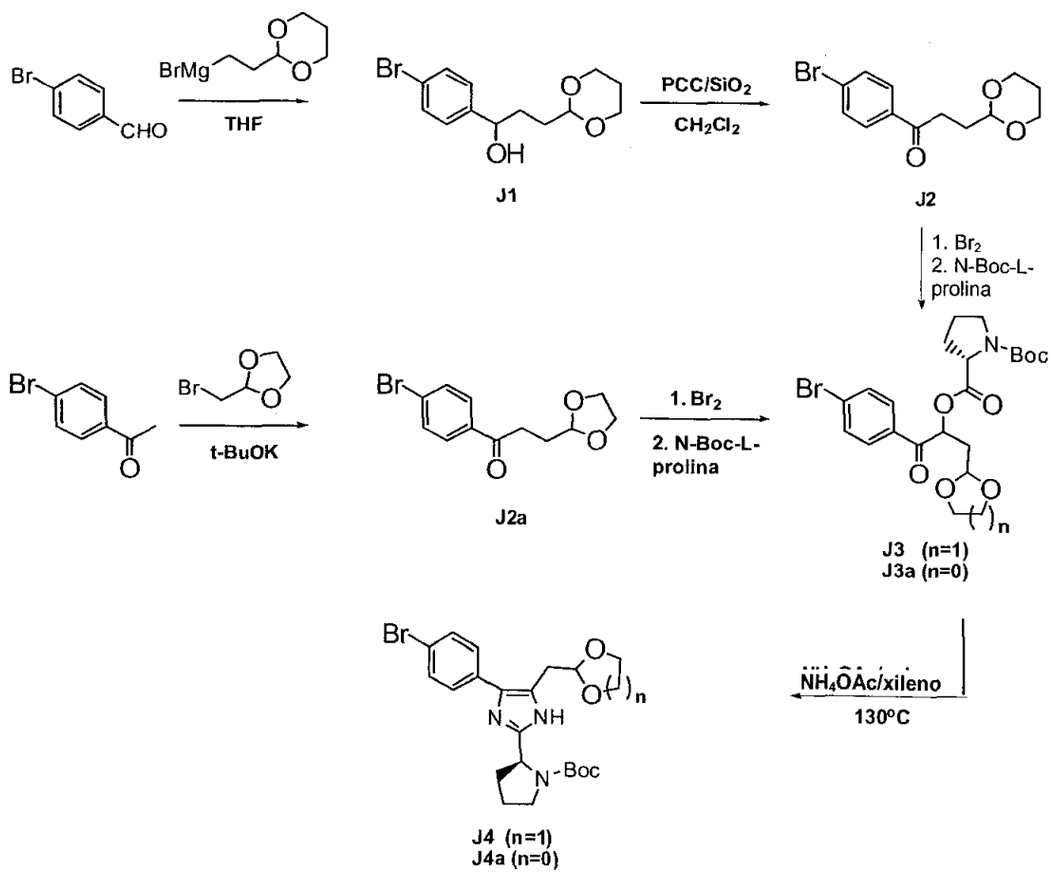


Se agregaron anhídrido acético (38.4 mg, 0.376 mmol) y *i*-Pr_2EtN (0.153 mL, 0.877 mmol) a una solución DMF (3 mL) de la sal HCl de pirrolidina M151d (75 mg, 0.125 mmol), y la mezcla se agitó a temperatura ambiente durante 2 horas. El componente volátil se removió *in vacuo*, y el

residuo se disolvió en CH_3OH y se purificó con una HPLC de fase inversa (CH_3OH/H_2O/TFA) para proporcionar la sal TFA de M162 como una espuma blanca (55 mg). CL (Cond. I): TR = 1.13 min; >95% de índice de homogeneidad. LC/MS: análisis calculado para $[M+H]^+$ $C_{32}H_{37}N_6O_2$: 537.30 ; encontrado 537.21.

Ejemplo J1-J14.f y E1-E5m

Esquema de reacción sintético 1



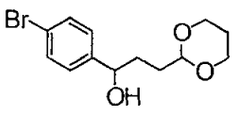
Condiciones LCMS 1: Phenomenex-Luna 4.6 x 50 mm S10, 0 hasta 100%B durante 2 min, 3 min tiempo de paro, 4 mL/min,

220nm, A: 10% CH_3OH-90%H2O - 0.1% TFA; B: 90% CH_3OH-10%H2O-0.1% TFA.

Condiciones LCMS 2: Phenomenex-Luna 4.6 x 50 mm S10, 0 hasta 100%B durante 3 min, 4 min tiempo de paro, 4 mL/min, 220nm, A: 10% CH_3OH-90%H2O - 0.1% TFA; B: 90% CH_3OH-10%H2O-0.1% TFA.

Condiciones LCMS 3: Luna 4.6 x 30 mm C18, 0 hasta 100%B durante 2 min, 3 min tiempo de paro, 5 mL/min, 220nm, A: 5% Acetonitrilo-90%H2O - 10 Mm NH_4OAc; B: 90% Acetonitrilo - 10%H2O-0.1% 10 Mm NH_4OAc.

Referencia: *J.Org.Chem.* (1992) 57,1784.

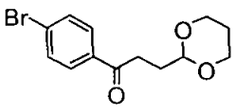


J1

108 mL de bromuro de (1,3-dioxan-2-iletil)magnesio (0.5M) se agregó a una solución de 4-bromobenzaldehído (10g, 54.0 mmol) en THF (350 mL) a -78°C bajo nitrógeno y se agitó durante 2 horas antes de calentar hasta 0°C. La reacción se apagó con solución NH_4Cl saturado, se diluyó con dietil éter y se lavó con salmuera. El producto crudo se cargó (CH_2Cl_2) a un cartucho de gel de sílice Biotage 40M; gradiente de elución 15 - 100% B sobre 750 mL (A = Hexanos; B = acetato de etilo) para dar el Ejemplo J1, 1-(4-bromofenil)-3-(1,3-dioxan-2-il)propan-1-ol (rendimiento cuantitativo). ^1H RMN (500 MHz, $CDCl_3$) δ 7.44 (d, J = 8.5

Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 4.70-4.66 (m, 1H), 4.57 (t, *J* = 4.9 Hz, 1H), 4.12-4.19 (m, 2H), 3.76 (tt, *J* = 11.9, 2.7 Hz, 2H), 2.87 (d, *J* = 3.7 Hz, 1H), 2.12-2.03 (m, 1H), 1.86-1.87 (m, 2H), 1.74-1.68 (m, 2H), 1.36-1.32 (m, 1H). TR = 1.8 minutos (condición 1); EMBR: Ión precursor no evidente.

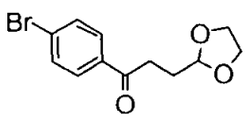
Referencia: *JOC* (1989) *54* 5387.



J2

El PCC (8.16g, 59.8 mmol) se mezcló con 9 g SiO_2 y molido (matraz y mango de matraz) y se suspendión en diclorometano (360 mL). A la suspensión se agregó en una porción el Ejemplo J1, 1-(4-bromofenil)-3-(1,3-dioxan-2-il)propan-1-ol (9g, 29.9 mmol) se disolvió en 5 mL del mismo solvente. La mezcla de reacción se agitó durante 2 horas un filtrado a través de celite (se enjuagó con (CH_2Cl_2). Después de concentrar el residuo se cargó (CH_2Cl_2) a un cartucho de gel de sílice Biotage 40 M. Gradiente de elución 15-70% B sobre 750 mL mL (A = Hexanos; B = acetato de etilo) da el Ejemplo J2, 1-(4-bromofenil)-3-(1,3-dioxan-2-il)propan-1-ona 7.7 g (86 %). ^{1}H RMN (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.7 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H), 4.65 (t, *J* = 4.9 Hz, 1H), 4.09-4.06 (m, 2H), 3.74 (dt, *J* = 11.0, 2.4 Hz, 2H), 3.06 (t, *J* = 7.3 Hz, 2H), 2.07-2.01 (m, 3H), 1.35-1.31 (m, 1H). LCMS:

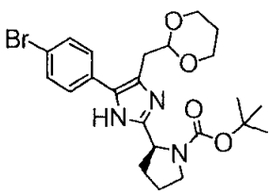
TR = 1.9 minutos (condición 1); C13H15BrO3 Calculado: 299; encontrado: 299 $(M+H)^+$.



J2a

El *tert*-butóxido de potasio (15 mL, 1M en THF) se agregó gota a gota a una solución de 1-(4-bromofenil)etanona (3 g, 15.07 mmol) en DMSO (60 mL) a 0°C y se agitó durante 30 min bajo nitrógeno. El enolato se puso por cánulo en una solución de 2-(bromometil)-1,3-dioxolano (2.52 g, 15.07 mmol) en DMSO (10 mL) a 0°C y la reacción se permite calentar hasta 24°C y se agitó 6 horas. El concentrado para remover el solvente (evaporación rotatoria de alto vacío) y se cargó (CH_2Cl_2) del residuo a un cartucho de gel de sílice Biotage 40 (M) y gradiente de elución 5-35% B sobre 1 L (A = Hexanos; B = acetato de etilo) da el Ejemplo J2a, 1-(4-bromofenil)-3-(1,3-dioxolan-2-il)propan-1-ona 327 mg (7.6%) y 571 mg de un producto de adición bis. ^1H RMN (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 4.97 (t, *J* = 4.3 Hz, 1H), 3.96-3.94 (m, 2H), 3.87-3.84 (m, 2H), 3.08-3.05 (m, 2H), 2.15-2.11 (m, 2H).

Referencia: Bromination *JACS* (1952) *74* 6263. Displacement/Cyclization *J.Med.Chem.* (2001) *44* 2990.

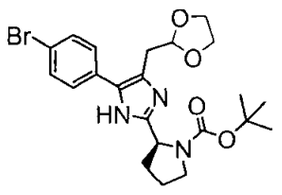


J4

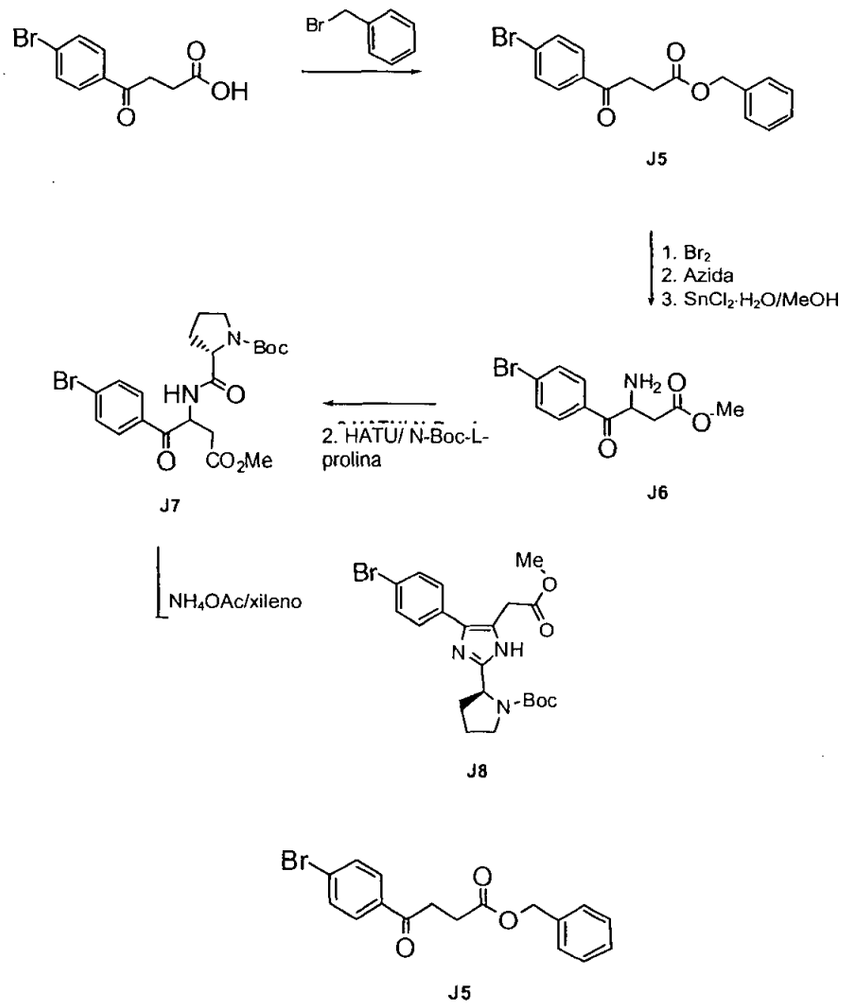
El bromuro (1.3 mL, 25.2 mmol) se agregó a una solución del Ejemplo J2, 1-(4-bromofenil)-3-(1,3-dioxan-2-il)propan-1-ona (7.7g, 25.7 mmol) en dietil éter (60 mL) y 1,4-dioxano (40 mL) y la solución se agitó 30 min a 24°C (hasta que el CCD indica que la reacción se completa). El solvente se removió por evaporación rotatoria y el residuo se tomó en acetonitrilo (350 mL). La (S)-N-Boc-Prolina (5.54g, 25.7 mmol) se agregó seguido por la adición gota a gota de base Hunig (8.5 mL, 51.5 mmol) y la reacción se agitó 6 horas antes de concentrarse. El producto crudo se tomó en CH_2Cl_2 y se cargó a un cartucho de gel de sílice Biotage 40 (M). Gradiente de elución 15 - 100% B sobre 1 L (A = hexanos; B = acetato de etilo) da el Ejemplo J3, 2-(1-(4-bromofenil)-3-(1,3-dioxan-2-il)-1-oxopropan-2-il) 1-*tert*-butil pirrolidin-1,2-dicarboxilato 13 g (100%).). TR = 2.2 minutos (condición 1); LCMS: Análisis. C23H30BrNO7 Calculado. 534; encontrado: 534 $(M+Na)^+$.

El acetato de amonio (6.45 g, 107 mmol) se agregó

a una solución del Ejemplo J3, 2-(1-(4-bromofenil)-3-(1,3-dioxan-2-il)-1-oxopropan-2-il) 1-*tert*-butil pirrolidin-1,2-dicarboxilato (5.5 g, 10.7 mmol) en xileno (120 mL) y se agitó durante 3 horas a 130°C en un recipiente a presión de 500 mL con extremo de rosca. Después de enfriarse, la mezcla de reacción se diluyó con acetato de etilo (600 mL) y se lavó con $NaHCO_3$ saturado y salmuera antes de concentrarse por evaporación rotatoria bajo alto vacío. El producto crudo se tomó en CH_2Cl_2 y se cargó a un cartucho de gel de sílice Biotage 40 (M). Gradiente de elución 15 - 100% B sobre 2 L (A = CH_2Cl_2; B = acetato de etilo) da el Ejemplo J4, 2-(4-((1,3-dioxan-2-il)metil)-5-(4-bromofenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*tert*-butilo 2.22 g (40%). ^1H RMN (500 MHz, $CDCl_3$) δ 7.46 (s, 4H), 4.94-4.92 (m, 1H), 4.77 (t, J = 4.9 Hz, 1H), 4.15-4.12 (m, 2H), 3.81-3.75 (m, 2H), 3.3-3.37 (m, 2H), 3.0-2.90 (m, 2H), 2.10-2.05 (m, 4H), 1.94-1.91 (m, 1H), 1.49 (s, 9H) 1.36-1.34 (m, 1H). TR = 1.8 minutos (condición 1); HRMS: Análisis C23H30BrN3O4 Calculado. 492.1492; encontrado: 492.1505 $(M+H)^+$.

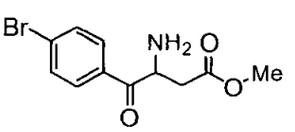
J4a Derivado del ejemplo J2a		TR = 1.68 min, (Cond 1) HRMS: análisis calculado para $C_{22}H_{29}BrN_3O_4$ 478.1336; encontrado: 478.1356 $(M+H)^+$.

Esquema de reacción sintético 2



El bromuro de bencilo (9.98 g, 58.3 mmol) se agregó a

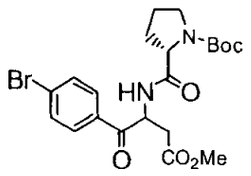
una solución de ácido 4-(4-bromofenil)-4-oxobutanoico (15.0 g, 58.3 mmol) y K_2CO_3 (3.5 g, 58.3 mmol) en DMF (300 mL) y se agitó durante 18 horas. La mezcla de reacción se dividió entre agua (200 mL) y acetato de etilo (500 mL). La solución $NaHCO_3$ saturada (20 mL) se agregó y la capa acuosa se extrajo con acetato de etilo (2x) y las capas orgánicas combinadas se lavaron con salmuera y se secaron y filtraron. La concentración da el Ejemplo J5, 4-(4-bromofenil)-4-oxobutanoato de bencilo 16 g (79%) el cual se usó sin purificación adicional. ^1H RMN (500 MHz, $CDCl_3$) δ 7.83 (d, J = 8.6 Hz, 2H), 7.61 (d, J = 8.5 Hz, 2H), 7.35-7.34 (m, 5H), 5.14 (s, 2H), 3.27 (t, J = 6.7 Hz, 2H), 2.81 (t, J = 6.7 Hz, 2H). HRMS: Análisis C17H16BrNO3 Calculado. 347.0277; encontrado: 347.0283 $(M+H)^+$.



J6

El bromuro (2.5 mL, 46.1 mmol) se agregó a una solución del Ejemplo J5, 4-(4-bromofenil)-4-oxobutanoato de bencilo (16 g, 46.1 mmol) en éter (200 mL) y 1,4-Dioxano (50 mL) y la solución se agitó durante 6 horas antes de concentrarse por evaporación rotatoria y se tomó en acetonitrilo (450 mL). La azida de sodio (3.0 g, 46.1 mmol) se agregó y la mezcla de reacción se agitó 18 horas.

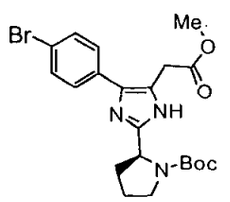
El solvente se removió hasta concentración y el residuo se tomó en acetato de etilo y se lavó con agua, salmuera, se secó Na_2SO_4, y se filtró. La concentración da 3-azido-4-(4-bromofenil)-4-oxobutanoato de bencilo 17g (95%) el cual se llevó a cabo adelante sin purificación adicional. El cloruro de estaño (II) deshidratado (24.9 g, 131 mmol) se agregó a una solución de 3-azido-4-(4-bromofenil)-4-oxobutanoato de bencilo (17 g, 43.8 mmol) en CH_3OH (550 mL) y se agitó durante 14 horas a 65°C. La reacción se concentró por evaporación rotatoria y se secó bajo alto vacío durante 18 horas para dar una mezcla de bencilo y Ejemplo J6, 3-amino-4-(4-bromofenil)-4-oxobutanoato de metilo, (transesterificación ha ocurrido) y se lleva a cabo adelante con purificación. TR = 1.3 minutos (condición 1); LCMS: Análisis C11H12BrNO3 Calculado 286.0; encontrado: 286.14 $(M+H)^+$.



J7

El HATU (10.5 g, 27.6 mmol) se agregó a una solución del Ejemplo J6, 3-amino-4-(4-bromofenil)-4-oxobutanoato de metilo (10 g, 27.6 mmol), (S)-N-Boc-prolina (7.13 g, 33.1 mmol), y base Hunig (45 mL, 276 mmol) en DMF (150 mL) y se agitó durante 18 horas a 24°C. La reacción se diluyó con

acetato de etilo (2 vol) y H2O (1/4 vol) y $NaHCO_3$ saturado (1/8 vol). Se filtró a través de tierra diatomácea (Celite®) para remover las sales de estaño. Se extrajo la capa acuosa (2x) con acetato de etilo, y se concentró el orgánico combinado para remover los solventes (alto vacío en evaporador rotatorio). El residuo se sometió a una cromatografía en gel de sílice corta para remover los sub-productos, y el producto crudo resultante se cargó (CH_2Cl_2) en un carticho de gel de sílice Biotage 65 (M). Gradiente de elución 15 - 70% B sobre 2 L (A = Hexanos; B = acetato de etilo) da una banda menor polar de 2-(4-(benciloxi)-1-(4-bromofenil)-1,4-dioxobutan-2-ilcarbamoil)pirrolidin-1-carboxilato de (2S)-*tert*-butilo 1.35 g (8.7%) y más polar el Ejemplo J7, 2-(4-(metoxi)-1-(4-bromofenil)-1,4-dioxobutan-2-ilcarbamoil)pirrolidin-1-carboxilato de (2S)-*tert*-butilo 7.6 g (49%). TR = 2.0 minutos (condición 1); LCMS: Análisis C21H27BrN2O6 Calculado 383; encontrado: 383 (M-Boc).

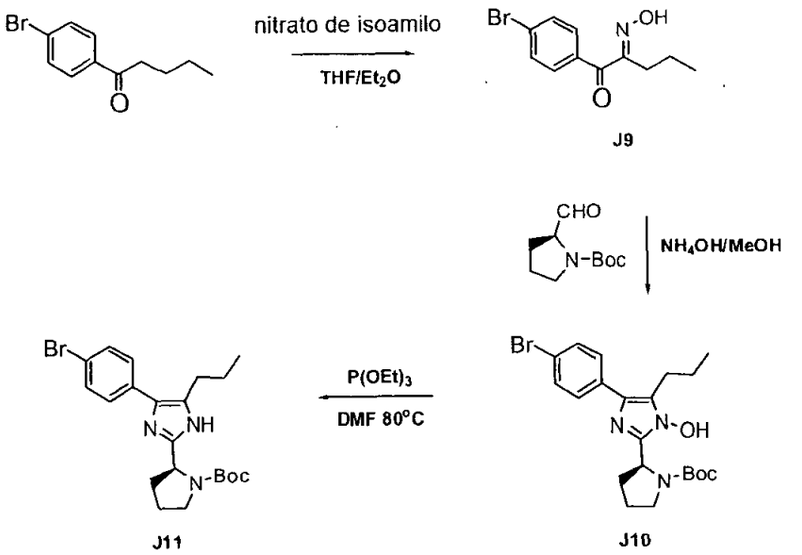


J8

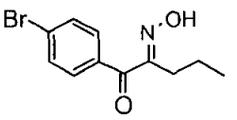
El acetato de amonio (9.4 g, 157 mmol) se agregó a una solución del Ejemplo J7, 2-(4-(metoxi)-1-(4-

bromofenil)-1,4-dioxobutan-2-ilcarbamoil)pirrolidin-1-carboxilato de (2S)-*tert*-butilo (7.6 g, 15.7 mmol) en xileno (80 mL) y se agitó durante 4 horas a 140°C en un recipiente a presión de 150 mL con extremo de rosca. Después de enfriarse, la mezcla de reacción se diluyó con acetato de etilo y se lavó con $NaHCO_3$ saturado y salmuera antes de concentrarse por evaporación rotatoria bajo alto vacío. El producto crudo se tomó en CH_2Cl_2 y se cargó a un cartucho de gel de sílicoe Biotage 40 (M). Gradiente de elución 15 - 100% B sobre 2 L (A = CH_2Cl_2; B = acetato de etilo) da el Ejemplo J8, 2-(4-(4-bromofenil)-5-(2-metoxi-2-oxoetil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*tert*-butilo 3.38 g (46%). ^1H RMN (500 MHz, DMSO-d_6) δ 7.54 (s, 4H), 4.83-4.73 (m, 1H), 3.81 (br. s, 1H), 3.62 (s, 3H), 3.53-3.51 (m, 1H), 3.38-3.31 (m, 2H), 2.25-2.15 (m, 1H), 1.99-1.83 (m, 3H), 1.41/1.16 (s, 9H). TR = 1.6 minutos (Condición 1). LCMS: análisis calculado para C21H26BrN3O4 464.11; encontrado: 464.40 $(M+H)^+$.

Esquema de reacción sintético 3



Referencia: *J.Med.Chem.*(84), *27*, 20. *Syn. Lett.* (2004) 2315.

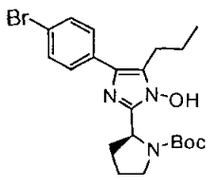


J9

El HCl concentrado (40 mL) se agregó gota a gota a una solución de 1-(4-bromofenil)pentan-1-ona (4.68g, 19.41 mmol) y nitrito de sodio (4.02 g, 58.2 mmol) en THF (80 ml) a 0°C y se permitió calentar hasta temperatura ambiente y se agitó 18 horas. La mezcla de reacción se diluyó con dietil éter y la fase orgánica se lavó con $NaHCO_3$ saturado y salmuera. La concentración da (Z)-1-(4-bromofenil)-2-(hidroxiimino)pentan-1-ona 3.1g (33%) como un aceite el cual se usó sin purificación adicional.). TR = 2.1 min, (Condición 1) LCMS:

análisis calculado para C11H12BrN1O2 270.01; encontrado: 270.15 $(M+H)^+$.

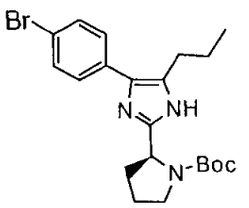
Referencia: *Bioorg. Med.Chem.Lett* (2002) 1009.



J10

El hidróxido de amonio al 28% (15 mL) se agregó a una solución de (Z)-1-(4-bromofenil)-2-(hidroxiimino)pentan-1-ona (1.5g, 5.55 mmol) y (S)-N-BOC-prolinal (1.1g, 5.55 mmol) en metanol (60 mL) y se agitó durante 18 horas a 24°C. La mezcla de reacción se dividió entre CH_2Cl_2 y agua y la fase orgánica se concentró y aplicó (CH_2Cl_2) a una columna de gel de sílice Biotage 40 (M). Gradiente de elución, 5-100%, sobre 1L (A = Hexanos; B = acetato de etilo) da 2-(4-(4-bromofenil)hidroxi-5-propil-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*tert-butilo* (863 mg, 34.5% de rendimiento). ^1H RMN (500 MHz, DMSO-d_6) δ 7.54 (m, 4H), 5.0-4.88 (m, 1H), 3.53-3.41 (m, 1H), 3.41-3.36 (m, 1H), 2.72 (t, *J* = 7.0 Hz, 2H), 2.24-2.03 (m, 2H), 1.96-1.91 (m, 1H), 1.89-1.81 (m, 1H), 1.60 (h, *J* = 7.6 Hz, 2H), 1.39/1.17 (s, 9H). 0.92 (t, *J* = 7.0 Hz, 3H). TR = 1.9 min, (Condición 1) LCMS: análisis calculado para C21H28BrN3O3 450.13; encontrado: 450.33 $(M+H)^+$.

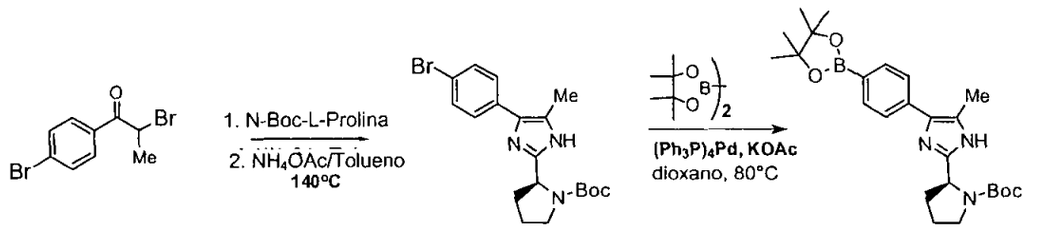
Referencia: *Chem. Pharm. Bull.* (1994) *42*, 560.



J11

El trietil fosfito (0.9 mL, 5.33 mmol) se agregó a una solución de 2-(4-(4-bromofenil)hidroxi-5-propil-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*tert-butilo* (800 mg, 1.776 mmol) en DMF (2 mL) y se agitó durante 18 horas a 80°C. Agregando segundo unos 0.8 mL y la reacción se continuó unas 8 horas adicionales, enfriando, y tomando en acetato de etilo (400 mL) y lavando con agua y salmuera. Aplicado en CH_2Cl_2 a una columna de gel de sílice Biotage 25 (M). Gradiente de elución, 15-100%, sobre 750 mL (A = Hexanos; B = acetato de etilo) da 2-(4-(4-bromofenil)-5-propil-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*tert-butilo* 585 mg (76%). ^{1}H RMN (500 MHz, DMSO-d_6) δ 7.55-7.53 (m, 4H), 4.80-4.69 (m, 1H), 3.53-3.51 (m, 1H), 3.38-3.32 (m, 1H), 2.71 (t, *J* = 7.0 Hz, 2H), 2.24-2.11 (m, 1H), 2.0-1.79 (m, 1H), 1.89-1.79 (m, 2H), 1.63-1.59 (m, 2H), 1.41/1.17 (s, 9H). 0.91 (t, *J* = 7.6 Hz, 3H). TR = 1.8 min, (Condición 1) EMBR: Análisis calculado para C21H28BrN3O2 434.14; encontrado: 434.0 $(M+H)^+$.

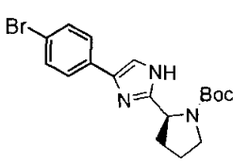
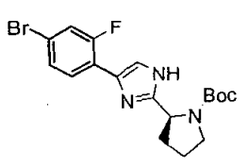
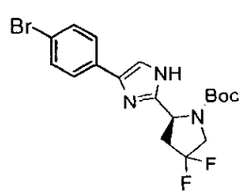
Esquema de reacción sintético 4

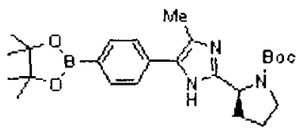


A una mezcla de 2,4'-dibromopropiofenona (4.96 g, 0.017 mol) y N-Boc-L-prolina (4.09 g, 0.019 mol) en CH_3CN seco (75 mL) se agregó DIEA (3.30 mL, 0.019 mol) y la mezcla se agitó a temperatura ambiente bajo Ar durante 16 horas. La mezcla luego se concentró bajo presión reducida y el concentrado se dividió con CH_2Cl_2-10% $NaHCO_3$ saturado. La fase orgánica se lavó (salmuera), se secó (Na_2SO_4), se filtró, y se concentró para dar el éster prolina (7.28 g, >100%) como una goma incolora la cual se usó como tal en la siguiente Extremo. LCMS: análisis calculado para C19H24BrNO5: 426; encontrado: 426 $(M+H)^+$.

Una mezcla del éster de prolina (0.435 g, 1.0 mmol) y acetato de amonio (0.308 g, 4.0 mmol) en tolueno (5 mL) se calentó a 140°C (temperatura del baño) en un tubo sellado durante 5 horas. La mezcla de reacción enfriada se evaporó y el residuo se procesó por cromatografía (SiO_2/acetato de etilo-hexano, 3:2) para dar el Ejemplo E1 (0.320 g, 79%) como una espuma casi incolora. ^1H RMN (400 MHz, $CDCl_3$) δ 7.53 (s, 4H), 4.98 (m, 0.3H), 4.87 (m, 0.7H), 3.65 (m,

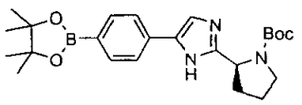
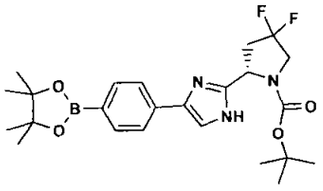
1H), 3.4-3.6 (m, 1H), 2.50 (s, 3H), 2.32 (m, 1H), 2.13 (m, 2H), 1.94 (m, 1H), 1.47 (s, 3H), 1.31 (s, 6H). LCMS: análisis calculado para C19H24BrN3O2: 405, 407; encontrado: 406, 408 $(M+H)^+$.

E1a		TR = 1.71 min (condición 1); LCMS: análisis calculado para $C_{18}H_{23}BrN_3O_2$: 392.10; encontrado 391.96 [M+H]+
E1b		TR = 2.27 min, (Cond 2) EMBR: análisis calculado para $C_{18}H_{22}BrFN_3O_2$ 410.09 y 412.09; encontrado: 410.08 y 412.08 $(M+H)^+$.
E1c		TR = 2.19 min, (Cond 2) LCMS: análisis calculado para $C_{18}H_{21}BrF_2N_3O_2$ 428.08 y 430.08; encontrado: 428.07 y 430.07 $(M+H)^+$.

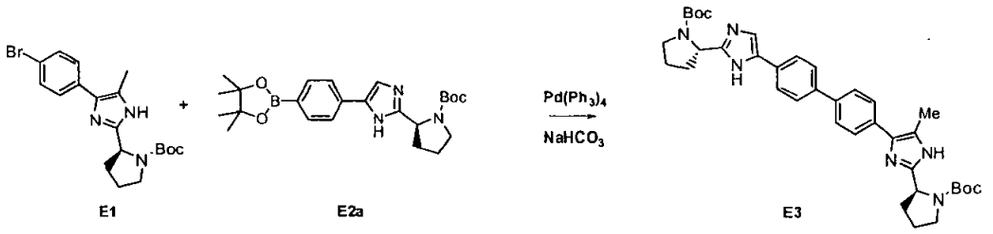


E2

Una mezcla del Ejemplo E1, 2-(4-(4-bromofenil)-5-metil-1H-imidazol-2-il)-pirrolidin-1-carboxilato de (S)-*tert-butilo* (1.568 g, 3.86 mmol), bis(pinacolato)diboro (2.058 g, 8.10 mmol) y acetato de potasio (0.947 g, 9.65 mmol) en dioxano (25 mL) se purgó con una corriente de Ar burbujeada durante 10 min y luego $(Ph_3P)_4Pd$ (0.223 g, 0.19 mmol) se agregó y se purgó con Ar se continuó durante otros 10 min. El recipiente de reacción luego se selló y se calentó a 80°C (temperatura del baño) durante 18 horas. La mezcla enfriada se diluyó con diclorometano y luego se lavó (H_2O, salmuera), se secó (Na_2SO_4), se filtró, y se concentró. El residuo se trituró con acetato de etilo y el sólido resultante se filtró, se lavó con un poco de acetato de etilo y se secó in vacuo para dar el compuesto del título (cuantitativo) como un sólido. Se usó como tal en la siguiente Extremo sin purificación adicional. ^{1}HRMN (400 MHz, DMSO-d_6) δ 11.93 (br s, 0.3H), 11.71 (br s, 0.7H), 7.65 (br s, 4H), 4.79 (m, 0.4H), 4.69 (m, 0.6H), 3.52 (m, 1H), 3.36 (m, 2H), 2.38 (s, 3H), 1.78-2.26 (m, 4H), 1.41 (s, 4H), 1.30 (s, 10H), 1.17 (m, 6H). LCMS: análisis calculado para C25H36BN3O4: 453; encontrado: 454 $(M+H)^+$.

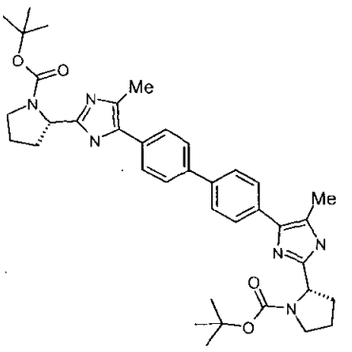
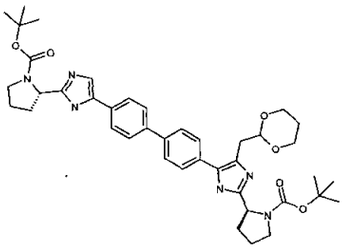
E2a		TR = 1.64 min (condi 1); LCMS: análisis calculado para C24H35BN3O4: 440.27; encontrado 440.23. [M+H]+
E2b		TR = 2.44 min, (Cond 2) LCMS: análisis calculado para C24H33BF2N3O4 476.25; encontrado: 476.51 $(M+H)^+$.

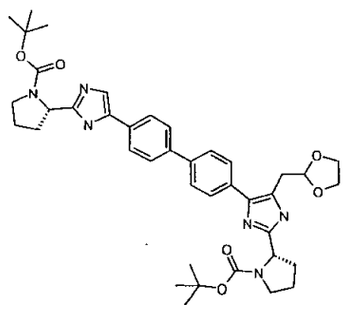
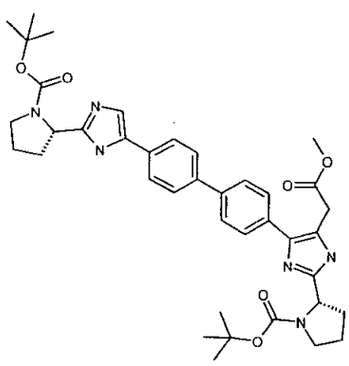
Esquema de reacción sintético 5

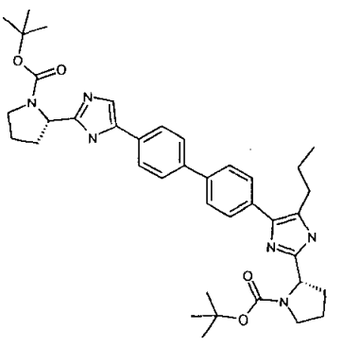
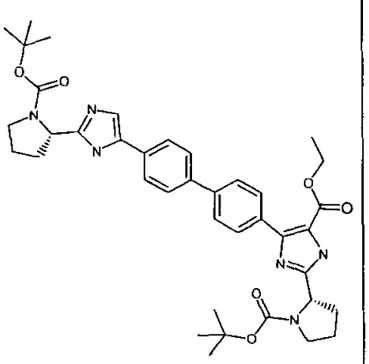


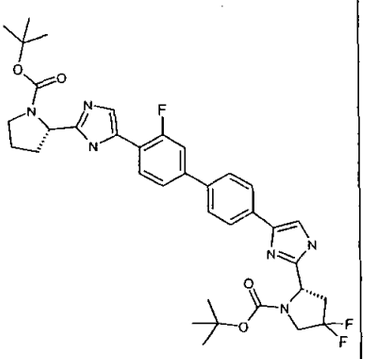
Una mezcla del Ejemplo E1, 2-(4-(4-bromofenil)-5-metil-1H-imidazol-2-il)-pirrolidin-1-carboxilato de (S)-*tert-butilo* (0.682 g, 1.68 mmol), Ejemplo E2a, 2-(4-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-*tert-butilo* (0.764 g, 1.74 mmol) y $NaHCO_3$ (0.465 g, 5.53 mmol) en una mezcla de DME (20 mL) y H_2O (5 mL) se purgó con una

corriente de Ar burbujeada durante 10 min. A esta mezcla se agregó $(Ph_3P)_4Pd$ (0.091 g, 0.08 mmol) y se purgó con Ar se continuo durante otros 10 min. El recipiente de reacción luego se selló y se calentó a 80°C (temperatura del baño) durante 18 horas. La mezcla enfriada se concentró bajo presión reducida y el concentrado se diluyó con acetato de etilo y se lavó con H_2O. La fase acuosa se volvió a extraer con acetato de etilo y la fase orgánica combinada se lavó (salmuera), se secó (Na_2SO_4), se filtró, y se concentró para dar una goma. El residuo se procesó por cromatografía (SiO_2/acetato de etilo-hexano, 7:3) para dar el Ejemplo E3 (0.592 g, 59%) como una espuma. ^{1}HRMN (400 MHz, $CDCl_3$) δ 7.37-7.88 (m, 8H), 7.27 (s, 1H), 5.10 (t, J = 7.65 Hz, 2H), 3.45 (m, 4H), 3.00 (m, 2H), 2.44 (s, 3H), 2.20 (br s, 4H), 1.99 (m, 2H), 1.53 (s, 18H). LCMS: análisis calculado para C37H46N6O4: 638; encontrado: 639 $(M+H)^+$.

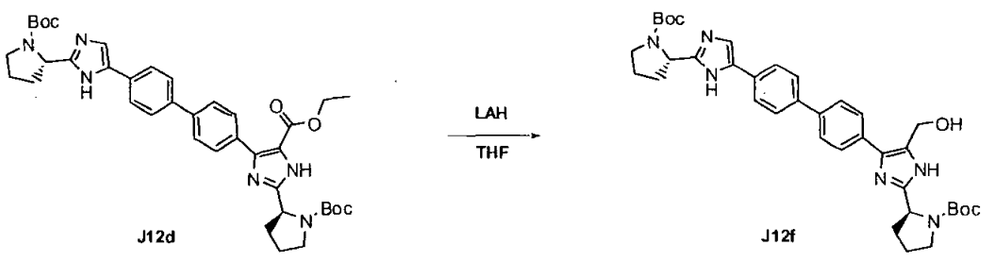
E3a Derivado del ejemplo E2 y E3			LCMS: análisis calculado para C38H48N6O4 :652; encontrado : 653 $(M+H)^+$.
J12 Derivado del ejemplo E2a y J4	(2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-4-(1,3-dioxan-2-ilmetil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidin carboxilato de tert-butilo		TR = 1.65 min, (cond 3) HRMS: análisis calculado para $C_{41}H_{53}N_6O_6$ 725.4021; encontrado : 725.4026 $(M+H)^+$.

J12a Derivado del ejemplo E2a y J4a	(2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-4-(1,3-dioxolan-2-ilmetil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidin carboxilato de tert-butilo		TR = 1.62 min, (cond 1) HRMS: análisis calculado para $C_{40}H_{51}N_6O_6$ 711.3865; encontrado: 711.3874 $(M+H)^+$.
J12b Derivado del ejemplo E2a y J8	(2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-5-(2-metoxi-2-oxoetil)-1H-imidazol-2-il)-1-pirrolidin carboxilato de tert-butilo		TR = 1.72 min, (cond 1) HRMS: análisis calculado para $C_{39}H_{48}N_6O_6$ 697.3087; encontrado: 697.3721 $(M+H)^+$.

J12c Derivado del ejemplo E2a y J11	(2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-5-propil-1H-imidazol-2-il)-1-pirrolidin carboxilato de tert-butilo		TR = 1.72 min, (cond 1) LCMS: análisis calculado para $C_{39}H_{50}N_6O_4$ 667.40; encontrado : 667.30 $(M+H)^+$.
J12d	2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-5-(4'-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-4-carboxilato de etilo		TR = 1.70 min, (95%) (Cond 2); LRMS: análisis calculado para C38H47N6O6 683.36; encontrado : 683.42 $(M+H)^+$

J12e Derivado del ejemplo E2b y E1b	(2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-3'-fluoro-4-bifenilil)-1H-imidazol-2-il)-4,4-difluoro-1-pirrolidin carboxilato de tert-butilo		TR = 2.24 min, (cond 2) LCMS: análisis calculado para $C_{36}H_{42}F_3N_6O_4$ 679.32; encontrado: 679.57 $(M+H)^+$.

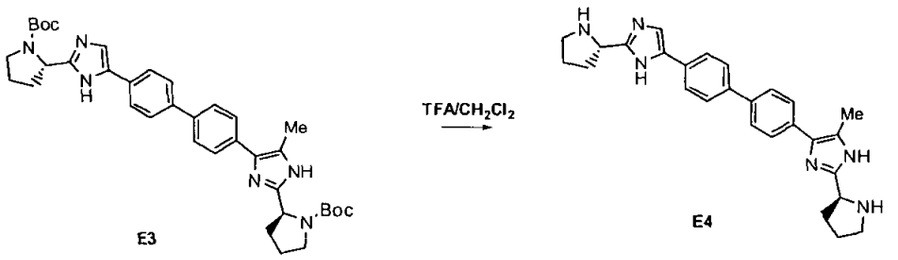
Esquema de reacción sintético 6



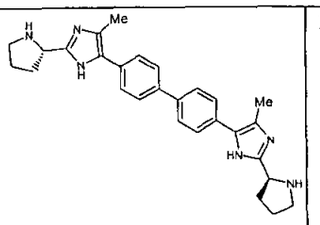
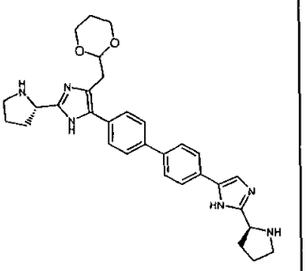
El LAH (0.7 mL, 1M en THF) se agregó a una solución del Ejemplo J12d, (466 mg, 0.669 mmol) en THF (50 mL) y se agitó a 0°C durante 1.5 horas antes se permitió calentar lentamente hasta temperatura ambiente. Después de 3 horas la reacción se apagó con agua (0.4 mL), 15% de NaOH (0.4 mL) y agua (0.4 mL) y las sales de aluminio se removieron por filtración. Las sales se enjuagaron con THF, los filtrados combinados se concentraron, y el residuo se cargó (CH_2Cl_2) a un cartucho de

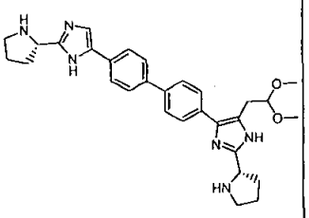
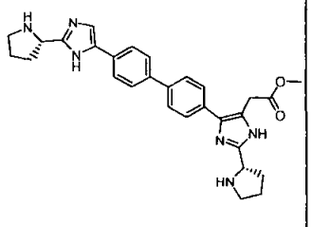
gel de sílice Biotage 25 (S) y se eluye el gradiente 15-100% sobre solvente 1L (A = CH_2Cl_2; B = 10% CH_3OH/acetato de etilo) para dar el Ejemplo J12f, (2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-4-(hidroximetil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidincarboxilato de tert-butilo, 88 mg (20%) además para recuperar J12d y sobre reducción. TR = 1.7 minutos (Condición 1); LCMS análisis calculado para C37H46N6O5 665.36; encontrado: 665.46 $(M+H)^+$.

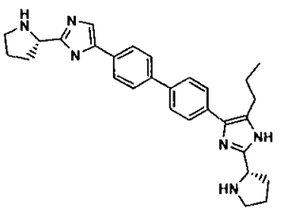
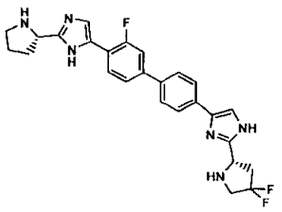
Esquema de reacción sintético 7

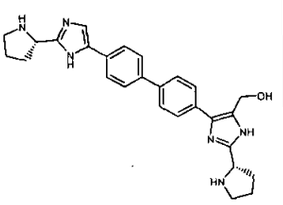


Una solución del Ejemplo E3 (0.240 g, 0.376 mmol) en 5 mL de TFA-CH_2Cl_2 (4:1) se agitó a temperatura ambiente durante 2 horas y luego los volátiles se removieron bajo presión reducida. La goma resultante se tomó en un volumen mínimo de CH_3OH y se adsorbió en un carticho MCX LP (6 g, pre-condicionado con CH_3OH). El cartucho se lavó con CH_3OH y luego se eluye con NH_3 2M en CH_3OH. Las fracciones que contienen el producto se combinaron y se evaporaron para dar el E4 (cuantitativo) como uan goma la cual se usó como tal en la siguiente Extremo. LCMS: análisis calculado para C27H30N6: 438; encontrado: 439 $(M+H)^+$.

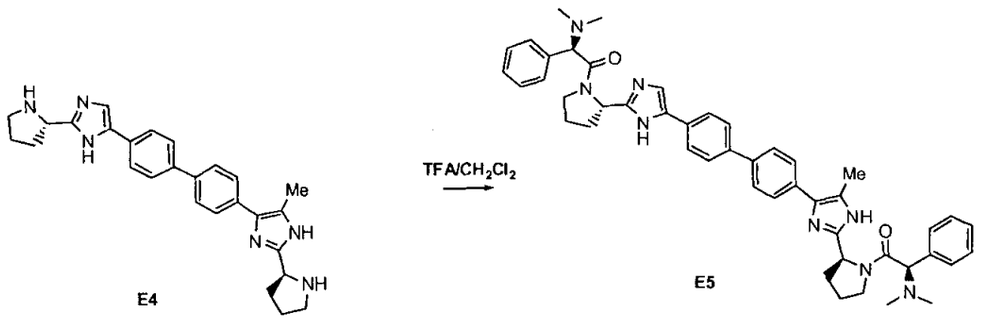
E4a			LCMS: análisis calculado para $C_{28}H_{32}N_6$: 452; encontrado: 453 $(M+H)^+$.	
J13 Derivado del ejemplo J12			TR = 1.18 min, (cond 1) LCMS: análisis calculado para $C_{31}H_{36}N_6O_2$ 525.29; encontrado: 525.31 $(M+H)^+$.	Preparado usando condiciones de experimento del ejemplo 152k-1.

J13a Derivado del ejemplo J12a			TR = 1.14 min, (cond 1) LCMS: análisis calculado para $C_{30}H_{36}N_6O_2$ 513.29; encontrado: 513.42 $(M+H)^+$.	Preparado usando condiciones de experimento en el ejemplo 152k-1.
J13b Derivado del ejemplo J12b			TR = 1.19 min, (cond 1) LCMS: análisis calculado para $C_{29}H_{32}N_6O_2$ 497.26; encontrado: 497.48 $(M+H)^+$.	Preparado usando condiciones de experimento en el ejemplo 152k-1.

J13c Derivado del ejemplo J12c			TR = 1.26 min, (cond 1) LCMS: análisis calculado para $C_{39}H_{50}N_6O_4$ 467.28; encontrado: 467.55 $(M+H)^+$.	Preparado usando condiciones de experimento del ejemplo 152k-1.
J13e Derivado del ejemplo J12e	2-((2S)-4,4-difluoro-2-pirrolidinil)-4-(3'-fluoro-4'-(2-((2S)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol		TR = 1.77 min, (Cond 2) LCMS: análisis calculado para $C_{26}H_{26}F_3N6_8$ 479.22; encontrado: 479.39 $(M+H)^+$.	Preparado usando condiciones de experimento del ejemplo 152k-1.

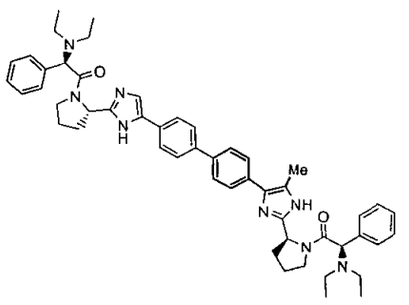
J13f Derivado del ejemplo J12f			TR = 1.02 min, (cond 1) LCMS: análisis calculado para $C_{27}H_{30}N_6O$ 455.25; encontrado: 455.47 $(M+H)^+$.	Preparado usando condiciones de experimento del ejemplo 152k-1.

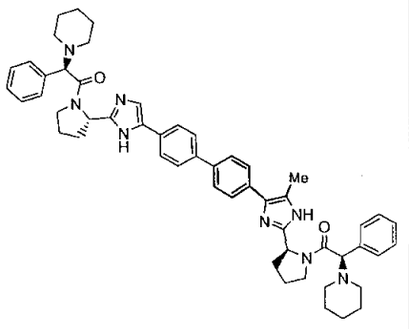
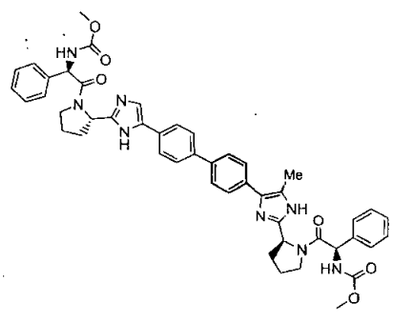
Esquema de reacción sintético 8

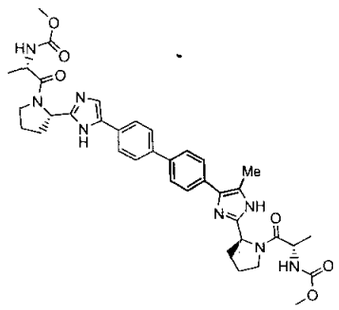
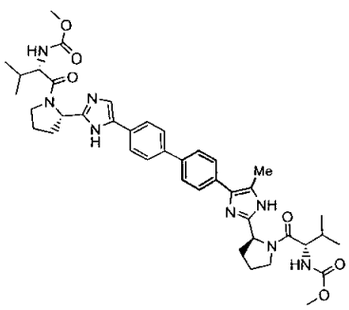


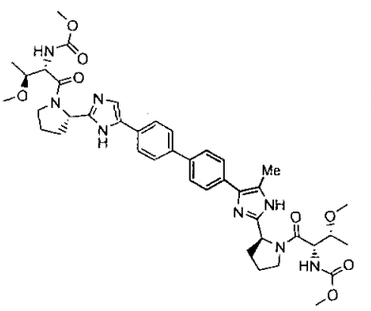
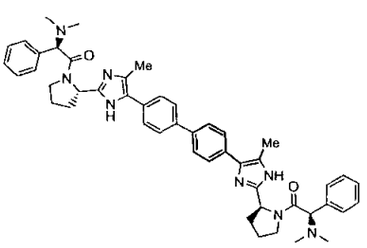
Una solución de clorohidrato del ácido (R)-2-(dimetilamino)-2-fenilacético (0.047 g, 0.220 mmol), HATU (0.084 g, 0.220 mmol) y DIEA (0.17 mL, 0.70 mmol) en DMF seco (1 mL) se agitó a temperatura ambiente durante 5 min y luego una solución de E4 (0.041 g, 0.094 mmol) en DMF seco (0.5 mL) se agregó. La mezcla se agitó a temperatura ambiente durante 18 horas y luego se apagó con AcOH (0.2 mL) y unas pocas gotas de TFA. Esta solución se sometió directamente a HPLC to preparativa (C-18/CH_3CN-H2O+0.1% TFA) para dar la sal TFA del Ejemplo E5, (1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-

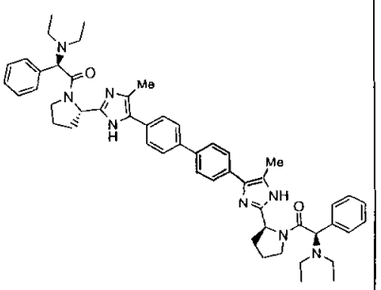
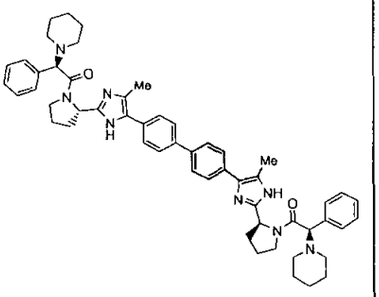
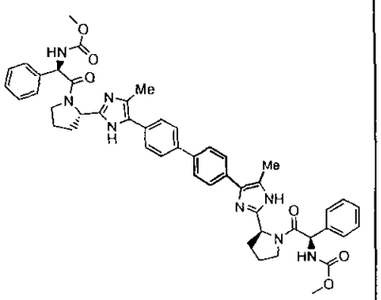
((2R)-2-(dimetilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-5-metil-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dimetil-2-oxo-1-feniletanamina (0.011 g, 10%) como un sólido blanco. ^{1}HRMN (400 MHz, CH_3OH-d_4) δ 7.80-7.93 (m, 6H), 7.71-7.74 (m, 2H), 7.50-7.67 (m, 10H), 5.37-5.51 (m, 2H), 5.30 (m, 2H), 4.04 (br s, 3H), 3.00-3.13 (m, 4H), 2.81 (br s, 8H), 2.55 (s, 2H), 2.49 (s, 1H), 2.36 (m, 2H), 2.12-2.25 (m, 5H), 1.96 (br s, 2H). LCMS: análisis calculado para C47H52N8O2: 760; encontrado: 761 $(M+H)^+$.

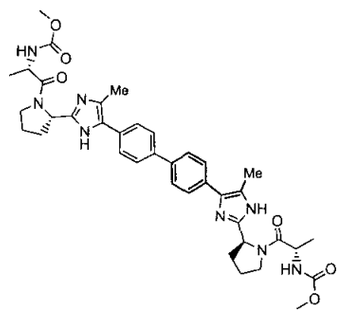
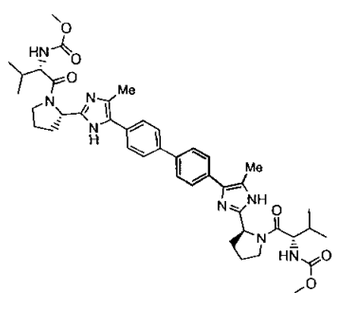
E5a Derivado del ejemplo E4	(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-5-metil-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dietil-2-oxo-1-feniletanamina		LCMS: análisis calculado para $C_{51}H_{60}N_8O_2$: 816; encontrado: 817 $(M+H)^+$.

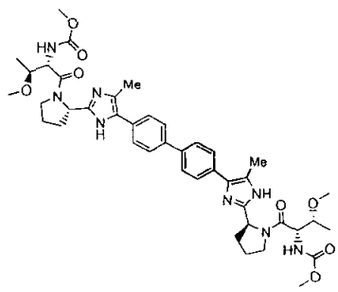
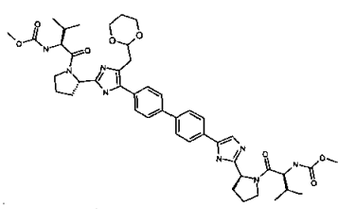
E5b Derivado del ejemplo E4	1-((1R)-2-((2S)-2-(4-(4'-(4-metil-2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) piperidina		LCMS: análisis calculado para $C_{53}H_{60}N_8O_2$: 840; encontrado: 841 $(M+H)^+$.
E5c Derivado del ejemplo E4	((1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-((metoxicarbonil) amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-5-metil-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil) carbamato de metilo		LCMS: análisis calculado para $C_{47}H_{48}N_8O_6$: 820; encontrado: 821 $(M+H)^+$.

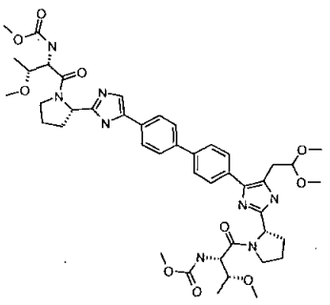
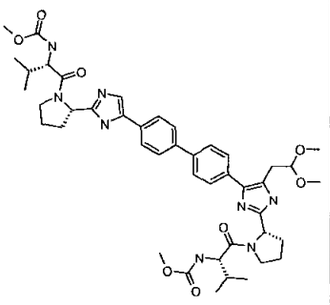
E5d Derivado del ejemplo E4	((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-4-metil-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil) carbamato de metilo		LCMS: análisis calculado para $C_{37}H_{44}N_8O_6$: 696; encontrado: 697 $(M+H)^+$.
E5e Derivado del ejemplo E4	((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil) amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-5-metil-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil) carbamato de metilo		LCMS: análisis calculado para $C_{41}H_{52}N_8O_6$: 752; encontrado: 753 $(M+H)^+$.

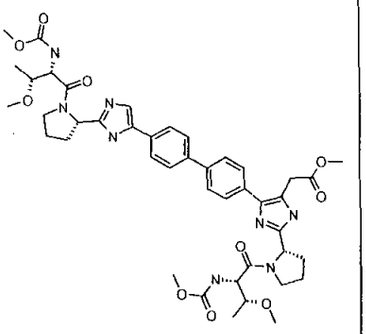
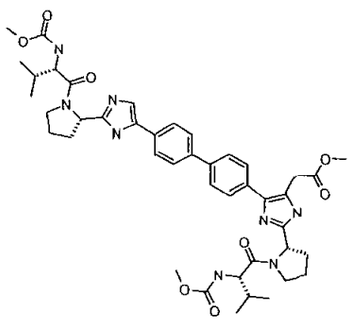
E5f Derivado del ejemplo E4	((1S,2R)-2-metoxi-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-treonil)-2-pirrolidinil)-4-metil-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)propil) carbamato de metilo		LCMS: análisis calculado para $C_{41}H_{52}N_8O_8$: 784; encontrado: 785 $(M+H)^+$.
E5g Derivado del ejemplo E4a	(1R,1'R)-2,2'-(4,4'-bifenildiilbis((4-metil-1H-imidazol-5,2-diil)(2S)-2,1-pirrolidindiil))bis (N,N-dimetil-2-oxo-1-feniletanamina)		LCMS: análisis calculado para $C_{48}H_{54}N_8O_2$: 774; encontrado: 775 $(M+H)^+$.

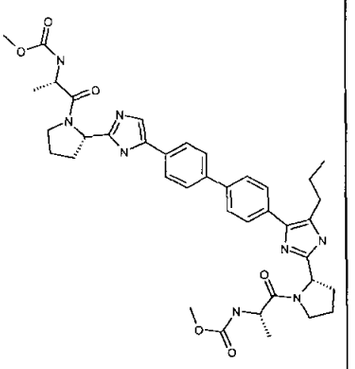
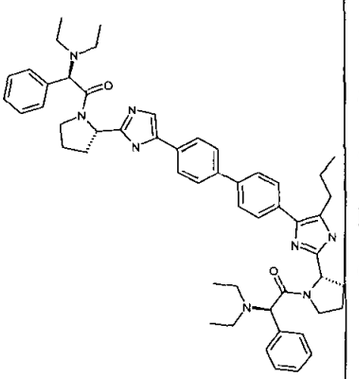
E5h Derivado del ejemplo E4a	(1R,1'R)-2,2'-(4,4'-bifenildiilbis((4-metil-1H-imidazol-5,2-diil)(2S)-2,1-pirrolidindiil))bis(N,N-dietil-2-oxo-1-feniletanamina)		LCMS: análisis calculado para $C_{52}H_{62}N_8O_2$: 830; encontrado: 831 $(M+H)^+$.
E5i Derivado del ejemplo E4a	1,1'-(4,4'-bifenildiilbis((4-metil-1H-imidazol-5,2-diil)(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))dipiperidina		LCMS: análisis calculado para C54H62N8O2: 854; encontrado: 855 $(M+H)^+$.
E5j Derivado del ejemplo E4a	(4,4'-bifenildiilbis((4-metil-1H-imidazol-5,2-diil)(2S)-2,1-pirrolidindiil((1R)-2-oxo-1-fenil-2,1-etandiil)))biscarbamato de dimetilo		LCMS: análisis calculado para C48H50N8O6: 834; encontrado: 835 $(M+H)^+$.

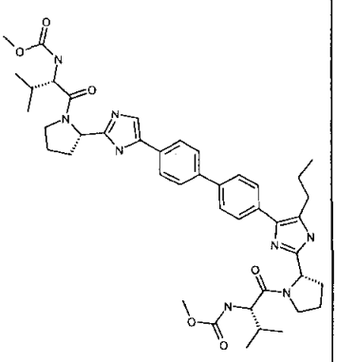
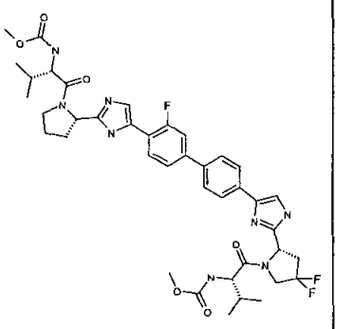
E5k Derivado del ejemplo E4a	((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-5-metil-1H-imidazol-4-il)-4-bifenilil)-5-metil-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo		LCMS: análisis calculado para C38H46N8O6: 710; encontrado: 711 $(M+H)^+$.
E5l Derivado del ejemplo E4a	((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil) amino)-3-metilbutanoil)-2-pirrolidinil)-4-metil-1H-imidazol-5-il)-4-bifenilil)-5-metil-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo		LCMS: análisis calculado para C42H54N8O6: 766; encontrado: 767 $(M+H)^+$.

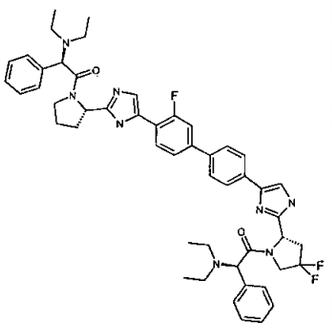
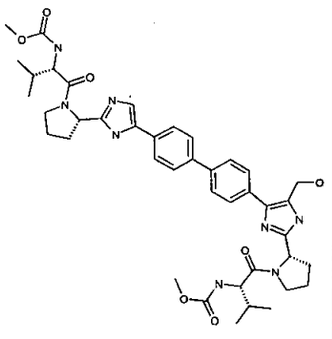
E5m Derivado del ejemplo E4a	((1S,2R)-2-metoxi-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-treonil)-2-pirrolidinil)-5-metil-1H-imidazol-4-il)-4-bifenilil)-5-metil-1H-imidazol-2-il)-1-pirrolidinil) carbonil)propil) carbamato de metilo		LCMS: análisis calculado para C42H54N8O8: 798; encontrado: 799 $(M+H)^+$.
J14 Derivado del ejemplo J13	((1S)-1-(((2S)-2-(4-(1,3-dioxan-2-ilmetil)-5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil) amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil)carbamato de metilo		TR = 1.37 min, (Cond 1); HRMS: análisis calculado para $C_{45}H_{58}N_8O_9$ 839.4450; encontrado: 839.4456 $(M+H)^+$.

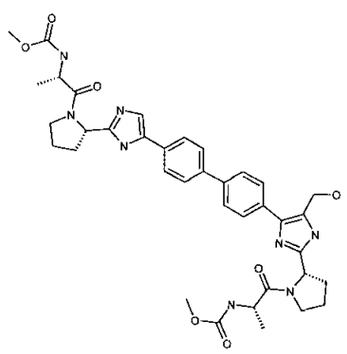
J14a Derivado del ejemplo J13a	((1S,2R)-1-(((2S)-2-(4-(2,2-dimetoxietil)-5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-treonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metoxipropil) carbamato de metilo		TR = 1.44 min, (Cond 1); HRMS: análisis calculado para $C_{44}H_{58}N_8O_{10}$ 859.4349; encontrado: 859.4352 $(M+H)^+$.
RJ14a.1 Derivado del ejemplo J13a	(1S)-1-(((2S)-2-(4-(2,2-dimetoxietil)-5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil) amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo		TR = 1.44 min, (Cond 1); HRMS: análisis calculado para $C_{44}H_{58}N_8O_8$ 827.4450; encontrado: 827.4449 $(M+H)^+$.

J14b Derivado del ejemplo J13b	(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-treonil)-2-pirrolidinil)-4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-treonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-5-il)acetato de metilo		HRMS: análisis calculado para $C_{43}H_{54}N_8O_{10}$ 843.4036; encontrado: 843.4046 $(M+H)^+$.
J14b.1 Derivado del ejemplo J13b	(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-5-il)acetato de metilo		TR = 1.42 min, (Cond 1); HRMS: análisis calculado para $C_{43}H_{54}N_8O_8$ 811.4137; encontrado: 811.4154 $(M+H)^+$.

J14c Derivado del ejemplo J13c	((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-4-propil-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo		TR = 1.42 min, (Cond 1); HRMS: análisis calculado para $C_{39}H_{49}N_8O_6$ 725.3775; encontrado: 725.3758 $(M+H)^+$.
J14c.1 Derivado del ejemplo J13c	(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-5-propil-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dietil-2-oxo-1-feniletanamina		RT = 1.39 min, (Cond 1); HRMS: análisis calculado para $C_{53}H_{65}N_8O_2$ 845.5225; encontrado: 845.5207 $(M+H)^+$.

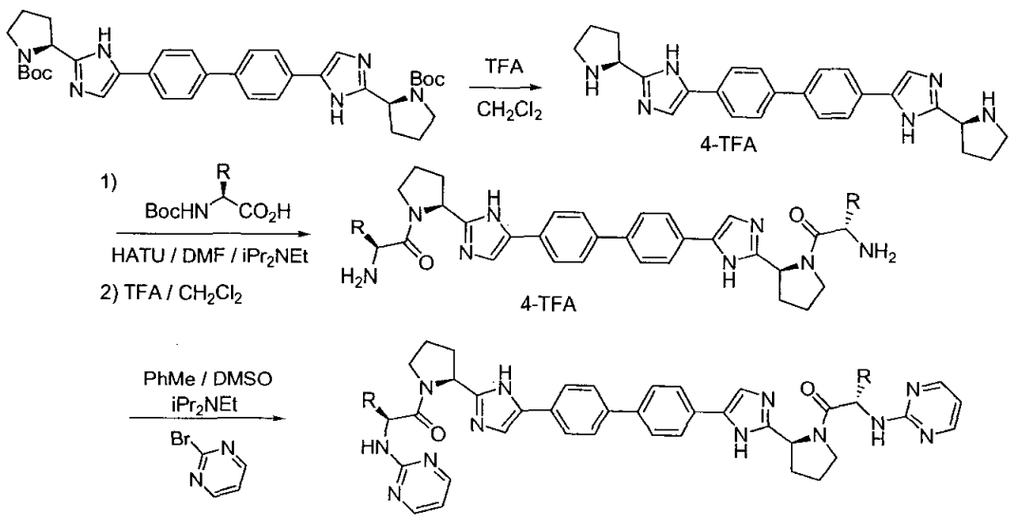
J14c.2 Derivado del ejemplo J13c	((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil) amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-5-propil-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil) carbamato de metilo		TR = 1.59 min, (Cond 1); HRMS: análisis calculado para $C_{43}H_{57}N_8O_6$ 781.4317; encontrado: 781.4377 $(M+H)^+$.
J14e Derivado del ejemplo J13e	((1S)-1-(((2S)-4,4-difluoro-2-(4-(3'-fluoro-4'-(2-((2S)-1-((2S)-2-((metoxicarbonil) amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilpropil)carbamato de metilo		TR = 1.99 min, (Cond 2) HRMS: análisis calculado para $C_{40}H_{48}F_3N_8O_6$ 793.3643; encontrado: 793.3653 $(M+H)^+$.

J14e.1 Derivado del ejemplo J13e	(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-4,4-difluoro-2-pirrolidinil)-1H-imidazol-4-il)-3-fluoro-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dietil-2-oxo-1-feniletanamina		TR = 1.79 min, (Cond 2) HRMS: análisis calculado para $C_{50}H_{56}F_3N_8O_2$ 857.4473; encontrado: 857.4478 $(M+H)^+$.
J14f Derivado del ejemplo J13f	((1S)-1-(((2S)-2-(4-(hidroximetil)-5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil) amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil) carbonil)-2-metilpropil)carbamato de metilo		RT = 1.40 min, (Cond 1); HRMS: análisis calculado para $C_{41}H_{53}N_8O_7$ 769.4037; encontrado: 769.4020 $(M+H)^+$.

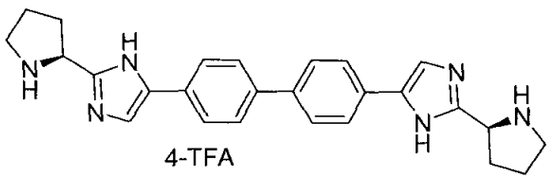
J14f.1 Derivado del ejemplo J13f	((1S)-2-((2S)-2-(4-(4'-(4-(hidroximetil)-2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo		TR = 1.21 min, (Cond 1); HRMS: análisis calculado para $C_{37}H_{45}N_8O_7$ 713.3411; encontrado: 713.3391 $(M+H)^+$.

Sección PY

Esquema de reacción 1

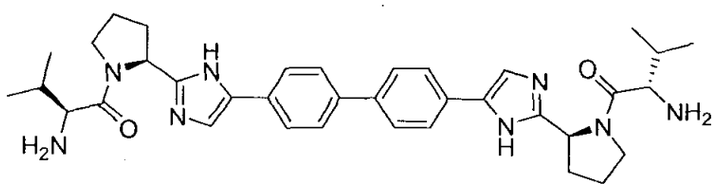


Ejemplo PY1. Sal del ácido trifluoroacético 4,4'-bis(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)bifenilo



A una solución de 2,2'-(5,5'-(bifenil-4,4'-diil)bis(1H-imidazol-5,2-diil))dipirrolidin-1-carboxilato de (2S,2'S)-tert-butilo (2.61 g, 4.18 mmol) en CH_2Cl_2 (25 mL) se agregó TFA (12 mL) y la mezcla se permitió agitar a temperatura ambiente. Después de permitir que la reacción se agitara durante 2 horas se concentró hasta secado *in vacuo*. El material se usó sin purificación adicional en las Extremos posteriores. LCMS: Análisis calculado para $C_{26}H_{28}N_6$: 424; encontrado: 425 $(M+H)^+$.

Ejemplo PY2. (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-(bifenil-4,4'-diil)bis(1H-imidazol-5,2-diil))bis(pirrolidin-2,1-diil))bis(2-amino-3-metilbutan-1-ona).

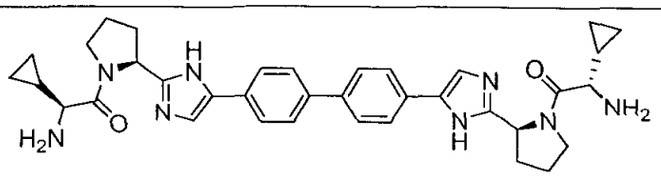
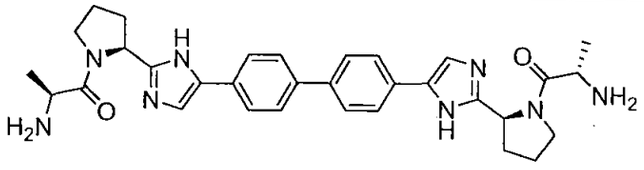


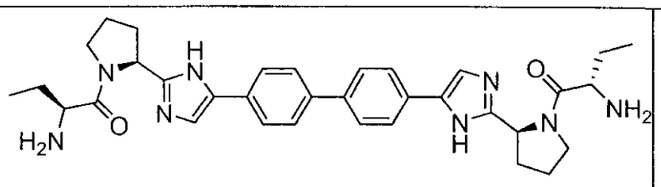
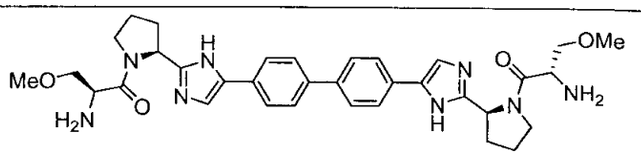
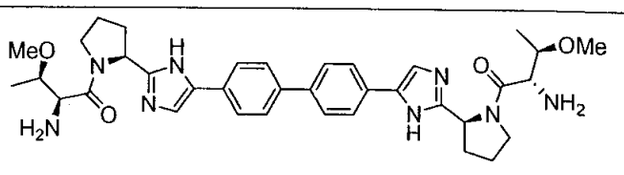
A una solución de 4,4'-bis(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)bifenil tetraquis(2,2,2-trifluoroacetato) (2.695 g, 3.06 mmol), ácido (S)-2-(tert-butoxicarbonilamino)-

3-metilbutanoico (1.60 g, 7.34 mmol) y DIEA (5.3 mL, 30.6 mmol) en DMF (15 mL) se agregó HATU (2.39 g, 6.27 mmol) y la mezcla se permitió agitar a temperatura ambiente durante 14 h. Se agregó MeOH (5 mL) y la mezcla se permitió agitar durante 4h. Luego se vació en ca. 150 mL de agua fría y se permitió reposar durante 20 min. El sólido se filtró y se secó bajo vacío durante la noche y luego se purificó por biotage (40+M, 0 hasta 25% MeOH en EtOAc) para dar una espuma café amarilla (1.76 g, 70%). ^{1}HRMN (300 MHz, DMSO-d_6) δ 12.11-12.17 (m, 1H), 11.76 (s, 1H), 7.73 - 7.94 (m, 4H), 7.62 - 7.70 (m, 4H), 7.49 (d, J = 1.8 Hz, 1H), 6.76 (d, J = 8.5 Hz, 1H), 5.06 (dd, J = 2.7, 6.3 Hz, 2H), 4.00 - 4.07 (m, 2H), 3.77 (s, br, 3H), 2.07 - 2.15 (m, 4H), 1.88 - 2.00 (m, 6H), 1.37 (s, 18H), 0.88 (d, J = 6.6 Hz, 6H), 0.82 (d, J = 6.6 Hz, 6H). LCMS: Análisis calculado para $C_{46}H_{62}N_8O_6$: 822; encontrado: 823 $(M+H)^+$. El material se suspendió en CH_2Cl_2 (15 mL) y TFA (6 mL) se agregó. Despues de agitar durante 2h los solventes se removieron *in vacuo* dando un sólido amarillo anaranjado. El sólido se dividió entre $NaHCO_3$ saturado y EtOAc sin embargo el material fue insoluble en EtOAc. Por lo tanto los volátiles se removieron *in vacuo* y el residuo se cargó en un cartucho de intercambio de cationes SCX y se eluyo con MeOH y luego NH_3 en MeOH (2M). Las fracciones apropiadas se concentraron *in vacuo* para dar una espuma amarilla (1.24 g, 65%). LCMS: Análisis calculado para $C_{36}H_{46}N_8O_2$: 622;

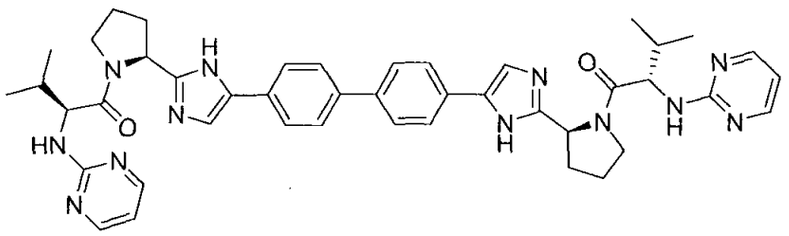
encontrado: 623 $(M+H)^+$. El material se usó como en las Extremos posteriores.

Lo siguiente se preparó similarmente. Se nota que en algunos casos la sal TFA obtenido de la desprotección Boc se llevo a cabo directamente adelante.

Ejemplo	*Estructura*	*Datos analíticos*
Ejemplo PY3		LCMS: análisis calculado para $C_{36}H_{42}N_8O_2$: 618; encontrado: 619 $(M+H)^+$.
Ejemplo PY4		LCMS: análisis calculado para $C_{32}H_{38}N_8O_2$: 566; encontrado: 567 $(M+H)^+$.

Ejemplo PY5		LCMS: análisis calculado para $C_{34}H_{42}N_8O_2$: 594; encontrado: 595 $(M+H)^+$.
Ejemplo PY6		LCMS: análisis calculado para $C_{34}H_{42}N_8O_4$: 626; encontrado: 627 $(M+H)^+$.
Ejemplo PY7		LCMS: análisis calculado para $C_{36}H_{42}N_8O_2$: 618; encontrado: 619 $(M+H)^+$.

Ejemplo PY8 (N,N'-(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(2S)-2,1-pirrolidindiil((2S)-3-metil-1-oxo-1,2-butandiil)))di(2-pirimidinamina)

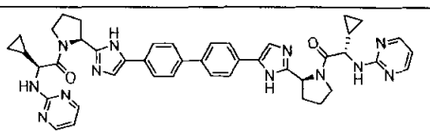


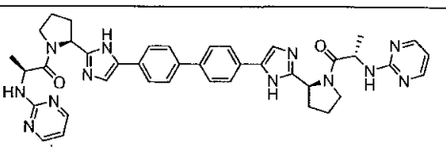
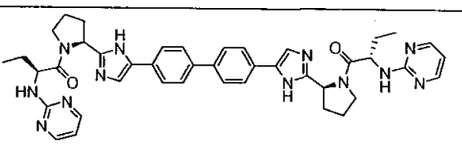
Una mezcla de (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-(bifenil-4,4'-diil)bis(1H-imidazol-5,2-diil))bis(pirrolidin-2,1-diil))bis(2-amino-3-metilbutan-1-ona) (222 mg, 0.36 mmol), 2-bromopirimidina (0.170 g, 1.07 mmol) e iPr_2NEt (0.25 mL, 1.432 mmol) en tolueno (3 mL) y DMSO (0.5 mL) se calentó a 90°C durante la noche. LCMS indica la reacción para incompletarse por lo tanto se continuo calentando durante unas 12 horas adicionales. Los volátiles se removieron *in vacuo* y el residuo se diluyó con MeOH y se purificó por HPLC prep (CH_3CN-H_2O-NH_4OAc). Las fracciones apropiadas se concentraron *in vacuo* y posteriormente se volvió a purificar por HPLC prep (CH_3CN-H_2O-TFA). Las fracciones apropiadas se absorbieron en un cartucho de resian de intercambio de cationes MCX (Oasis) y la resina se lavó con MeOH y se eluyó con NH3 2M en MeOH. El solvente se removió *in vacuo* y el residuo se liofilizó para dar un sólido incoloro (17.2 mg, 6%). ^{1}HRMN (300 MHz, DMSO-d_6) δ 12.15, 12.28 (s, 1H, rotámeros, relación 1:1), 8.28 (d, J = 4.8 Hz, 4H), 7.79

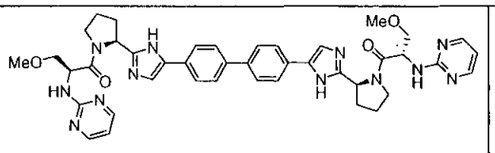
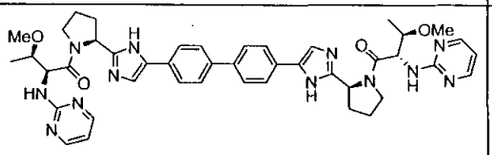
(app d, J = 8.1 Hz, 4H), 7.62 - 7.70 (m, 4H), 7.49 (d, J = 1.5 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 6.60 (t, J = 4.8 Hz, 2H), 5.05 (dd, J = 6.9, 4.0 Hz, 2H), 4.50 (app t, no resuelto dd, J = 8.5, 8.0 Hz, 2H), 3.98 - 4.06 (m, 2H), 3.78 - 3.85 (m, 2H), 1.98 - 2.23 (m, 10H), 0.96 (d, J= 6.6 Hz, 6H), 0.92 (d, J= 6.6 Hz, 6H). LCMS: análisis calculado para $C_{44}H_{50}N_{12}O_2$: 778; encontrado: 779 $(M+H)^+$.

Los siguientes se prepararon similarmente:

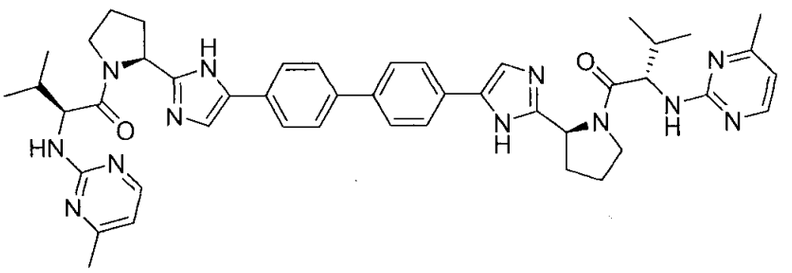
Se nota que en algunos casos la sal TFA obtenida de la desprotección Boc se llevo a cabo directamente adelante y uma cantidad apropiada de iPr_2NEt se agregó a la mezcla de reacción.

Nombre del compuesto	*Ejemplo*	*Estructura*	*Datos analíticos*
N,N'-(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(2S)-2,1-pirrolidindiil((1S)-1-ciclopropil-2-oxo-2,1-etandiil)))di(2-pirimidinamina)	*Ejemplo PY 9*		LCMS: análisis calculado para $C_{36}H_{42}N_8O_2$: 618; encontrado: 619 $(M+H)^+$.

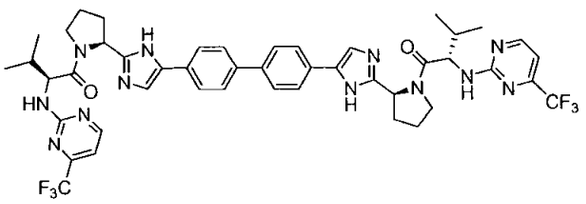
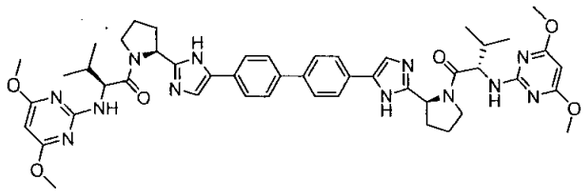
N,N'-(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(2S)-2,1-pirrolidindiil((2S)-1-oxo-1,2-propandiil)))di(2-pirimidinamina)	*Ejemplo PY10*		LCMS: análisis calculado para $C_{32}H_{38}N_8O_2$: 566; encontrado: 567 $(M+H)^+$.
N,N'-(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(2S)-2,1-pirrolidindiil((2S)-1-oxo-1,2-butandiil)))di(2-pirimidinamina)	*Ejemplo PY11*		LCMS: análisis calculado para $C_{34}H_{42}N_8O_2$: 594; encontrado: 595 $(M+H)^+$.

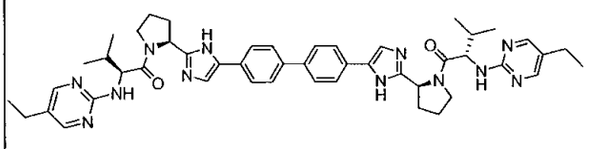
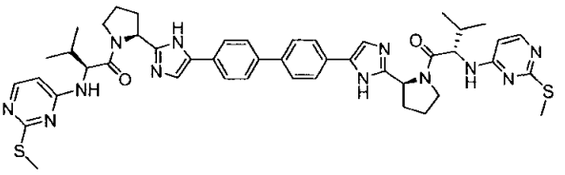
N,N'-(4,4'-bifenildiilbis (1H-imidazol-4,2-diil(2S)-2,1-pirrolidindiil ((2S)-3-metoxi-1-oxo-1,2-propandiil))) di(2-pirimidinamina)	*Ejemplo PY12*		LCMS: análisis calculado para $C_{34}H_{42}N_8O_4$: 626; encontrado: 627 $(M+H)^+$.
N,N'-(4,4'-bifenildiilbis (1H-imidazol-4,2-diil(2S)-2,1-pirrolidindiil ((2S,3R)-3-metoxi-1-oxo-1,2-butandiil))) di(2-pirimidinamina)	*Ejemplo PY13*		LCMS: análisis calculado para $C_{36}H_{42}N_8O_2$: 618; encontrado: 619 $(M+H)^+$.

Ejemplo PY14. (Método modificado)

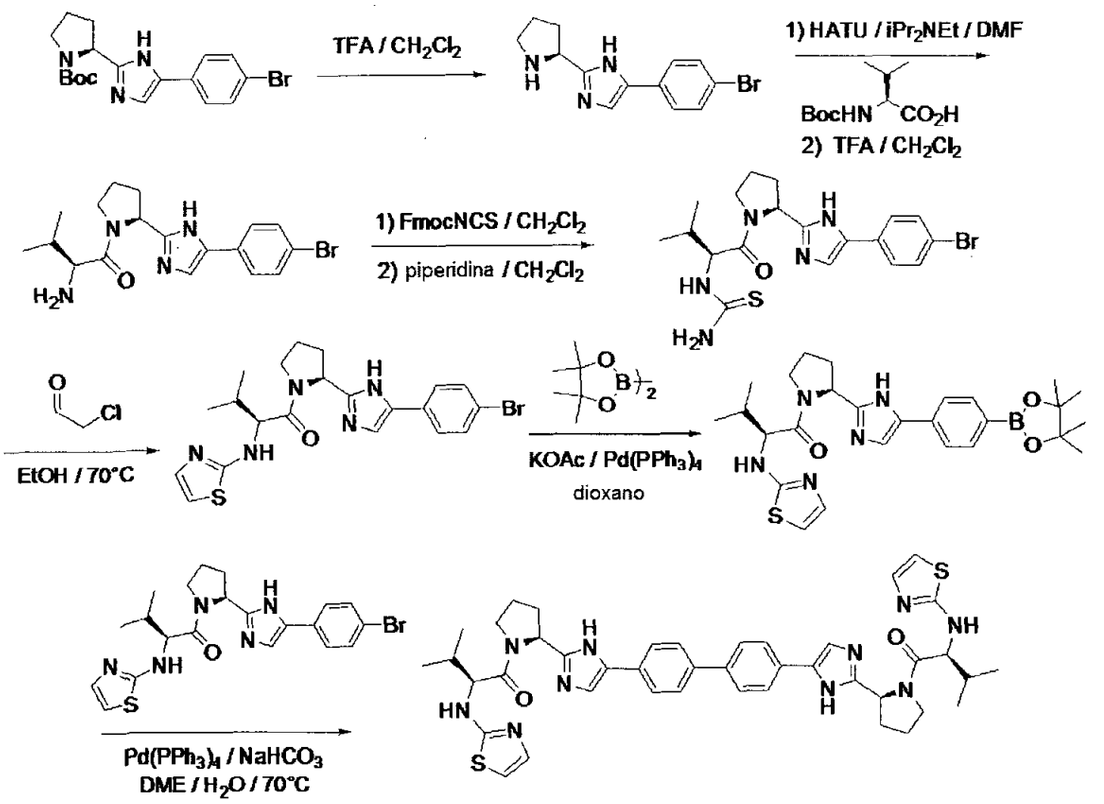


Una mezcla de (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-(bifenil-4,4'-diil)bis(1H-imidazol-5,2-diil))bis(pirrolidin-2,1-diil))bis(2-amino-3-metilbutan-1-ona) (50 mg, 0.080 mmol), 2-cloro-4-metilpirimidina (103 mg, 0.803 mmol), y DIPEA (0.140 mL, 0.803 mmol) en NMP (3 mL) se calentó en un tubo de sellado durante 4h a 140°C usando un Microondas. Los volátiles se removieron *in vacuo* y el residuo se diluyó con MeOH y se filtró a través de un cartucho Strata XC MCX. El cartucho se lavó con metanol. El compuesto se liberó del cartucho por lavado con una solución de 2M de amoniaco/Metanol. El filtrado se evaporó bajo presión reducida para dar un aceite anaranjado. El material crudo se purificó por HPLC (CH_3CN-H_2O-NH_4OAc). Las fracciones apropiadas se concentraron *in vacuo* y posteriormente se volvieron a purificar por HPLC prep (CH_3CN-H_2O-TFA). Las fracciones apropiadas se concentraron *in vacuo* para dar un sólido amarillo (21.5 mg, 31.9%). LCMS: análisis calculado para $C_{46}H_{54}N_{12}O_2$:807; encontrado: 807.5 $(M+H)^+$.

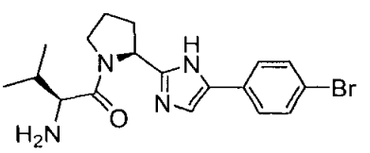
Ejemplo	Estructura	Datos analíticos
Ejemplo PY15		LCMS: Análisis calculado para $C_{46}H_{48}F_6N_6O_2$: 914; encontrado: 915.16 $(M+H)^+$.
Ejemplo PY16		LCMS: Análisis calculado para $C_{48}H_{58}N_{12}O_6$: 898; encontrado: $(M+H)^+$899.2 1.16

Ejemplo PY17		LCMS: Análisis calculado para $C_{48}H_{58}N_{12}O_2$:834; encontrado: $(M+H)^+$835.45.
Ejemplo PY18		LCMS: Análisis calculado para $C_{46}H_{54}N_{12}O_4S_2$:870; encontrado: $(M+H)^+$ 871.24.

Esquema de reacción 2



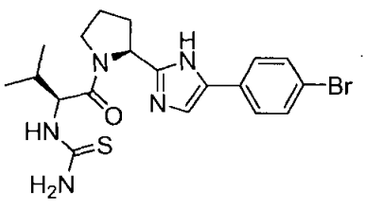
Ejemplo PY19. (S)-2-amino-1-((S)-2-(5-(4-bromofenil)-1H-imidazol-2-il)pirrolidin-1-il)-3-metilbutan-1-ona.



El compuesto del título se preparó de 2-(5-(4-bromofenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-tert-butilo y ácido (S)-2-amino-3-metilbutanoico por los procedimientos detallados en los ejemplos 1 y 2. ^{1}HRMN (300 MHz, DMSO-d_6) δ 11.73 (s, 1H), 7.68 (d, J = 5.9 Hz, 1H), 7.65

(d, J = 5.9 Hz, 1H), 7.46 - 7.58 (m, 3H), 5.14, 5.05 (dd, J = 7.0, 3.0 Hz, 1H, rotámeros, relación 1:1), 3.66 (app t, J = 6.5 Hz, 1H), 3.53 - 3.61 y 3.38 - 3.47 (m, 1H, rotámeros, relación 1:1), 3.28 (s, 2H), 1.70 - 2.21 (m, 6H), 0.75 - 0.88 (m, 6H). LCMS: Anal. Calcd. para $C_{18}H_{23}BrN_4O$: 390, 392; encontrado: 391, 393 $(M+H)^+$.

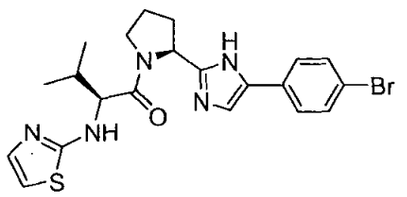
Ejemplo PY20. 1-((S)-1-((S)-2-(5-(4-bromofenil)-1H-imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2-il)tiourea.



A una solución de (S)-2-amino-1-((S)-2-(5-(4-bromofenil)-1H-imidazol-2-il)pirrolidin-1-il)-3-metilbutan-1-ona (1.530 g, 3.91 mmol) en CH_2Cl_2 (10 mL) se agregó carbonisotiocianatidato de O-(9H-fluoren-9-il)metilo (1.100 g, 3.91 mmol) como un sólido en una porción. La mezcla se permitión agitar a temperatura ambiente durante 12 h. Piperidina (2 mL) se agregó a la mezcla y esto se permitió agitar a temperatura ambiente durante 1 h. Una porción adicional de Piperidina (2 mL) se agregó y la solución se permitió agitar a 1 h. La solución se concentró hasta secarse y el residuo se purificó por cromatografía de columna (biotage, eluido con 5:4.5:0.5 hex:EtOAc:MeOH, y luego 5% MeOH en EtOAc). El compuesto del título como se obtiene como

un cristalino amarillo ligero (1.30 g, 74%). ^{1}HRMN (300 MHz, DMSO-d_6) δ 11.81 (s, H), 7.65 (d, J = 8.8 Hz), 7.63 - 7.71 (m, traslapado con pico previo, 2H total), 7.42 - 7.56 (m, 2H), 7.10 - 7.14 (m, 1H), 5.06 (dd, J = 7.0, 3.0 Hz, 1H), 4.94 (app t, J = 8.0 Hz, 1H), 4.72 - 4.76 y 4.56 - 4.62 (m, 1H, rotámeros, relación 1:1), 3.77 - 3.90 (m, 1H), 2.07 - 2.14 (m, 2H), 1.90 - 1.98 (m, 3H), 0.93 (d, J = 7.0 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H). LCMS: Análisis calculado para $C_{19}H_{24}BrN_5OS$: 449, 451; encontrado: 450, 452 $(M+H)^+$.

Ejemplo PY21. (S)-1-((S)-2-(5-(4-bromofenil)-1H-imidazol-2-il)pirrolidin-1-il)-3-metil-2-(tiazol-2-ilamino)butan-1-ona.

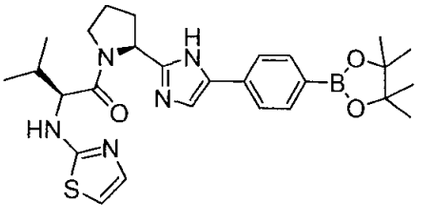


Una solución de 1-((S)-1-((S)-2-(5-(4-bromofenil)-1H-imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2-il)tiourea (1.29 g, 2.86 mmol) se disolvió en EtOH (50 mL) y 2-cloroacetaldehido (0.4 mL, 3.15 mmol) se agregó. La mezcla se calentó a 70°C durante la noche. Una porción adicional de 2-cloroacetaldehído (0.4 mL, 3.15 mmol) se agregó y se calentó continuamente durante 12 horas adicionales. La solución se concentró *in vacuo* y el residuo se purificó por cromatografía de columna (biotage), eluido con 50% EtOAc en hexanos y luego 10%

MeOH en EtOAc. El producto deseado se aisló como una espuma café-anaranjada (557.2 mg). LCMS (NH_4OAc) mostró ser suficientemente pura. Se eluye además con 100% MeOH dio una segunda fracción (980.8 mg) la cual se mostró para contener el producto por CCD (5:4.5:0.5 hex:EtOAc:MeOH). Esta segunda fracción de la columna se re-purificó para dar la espuma café ligeramente anaranjada (426.6 mg). Las dos fracciones se combinaron para proporcionar el compuesto del título como una espuma café-anaranjado (983.8 mg, 72%).

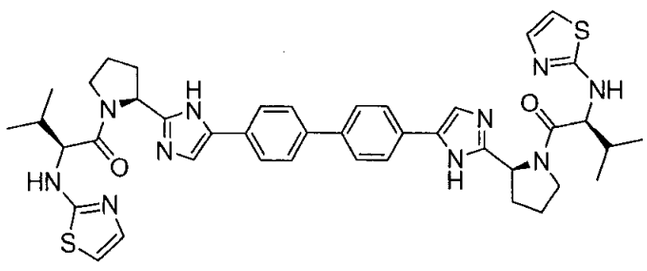
^{1}HRMN (300 MHz, CD_3OD) δ 7.57 (app d, J = 8.0 Hz, 2H), 7.47 (app d, J = 8.0 Hz, 2H), 7.32 (s, 1H), 6.98 (d, J = 3.6 Hz, 1H), 6.55 (d, J = 3.6 Hz, 1H), 5.32 - 5.35 and 5.10 - 5.15 (m, 1H, rotámeros, relación 1:3), 4.08 - 4.15 (m, 1H), 3.82 - 3.90 (m, 1H), 3.03 - 3.15 (m, 1H), 2.03 - 2.33 (m, 4H), 1.06 y 0.99 (d, J = 7.0 Hz, 3H, rotámeros relación 1:3), 1.04 y 0.94 (d, J = 7.0 Hz, 3H, rotámeros relación 1:3). LCMS: Análisis calculado para $C_{21}H_{24}BrN_5OS$: 473, 475; encontrado: 474, 476 $(M+H)^+$.

Ejemplo PY22. (S)-3-metil-1-((S)-2-(5-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1H-imidazol-2-il)pirrolidin-1-il)-2-(tiazol-2-ilamino)butan-1-ona.



Una mezcla de (S)-1-((S)-2-(5-(4-bromofenil)-1H-imidazol-2-il)pirrolidin-1-il)-3-metil-2-(tiazol-2-ilamino)butan-1-ona (87.5 mg, 0.184 mmol), 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (141 mg, 0.553 mmol), acetato de potasio (91 mg, 0.922 mmol) y $Pd(Ph_3P)_4$ (21.31 mg, 0.018 mmol) se suspendió en dioxano y se desgasificó por burbujeo N_2 a través de la mezcla. Esto luego se calentó a 85°C. Después de calentarse durante 4 h la mezcla se concentró y se purificó por pasarse a través de una almohadilla de gel de sílice eluido con 1:1 hex:EtOAc, y luego EtOAc (puro) para dar el producto deseado proporcionado como una película amarilla ligera (101 mg). LCMS (CH_3CN-H_2O-NH_4OAc) muestra que el producto se contaminó con ca. 10% PPh_3O. El material se usó como es en las Extremos subsecuentes. LCMS: Anal. Calcd. para $C_{27}H_{36}BN_5O_3S$: 521; encontrado: 522 $(M+H)^+$.

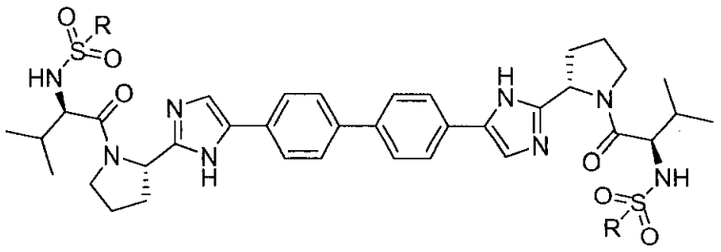
Ejemplo PY23. (N,N'-(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(2S)-2,1-pirrolidinediil((2S)-3-metil-1-oxo-1,2-butanediil)))bis(1,3-tiazol-2-amina)



Una mezcla de (S)-3-metil-1-((S)-2-(5-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1H-imidazol-2-il)pirrolidin-1-il)-2-(tiazol-2-ilamino)butan-1-ona (275 mg, 0.527 mmol), (S)-1-((S)-2-(5-(4-bromofenil)-1H-imidazol-2-il)pirrolidin-1-il)-3-metil-2-(tiazol-2-ilamino)butan-1-ona (250 mg, 0.527 mmol), $NaHCO_3$ (133 mg, 1.582 mmol) y $Pd(Ph_3P)_4$ (60.9 mg, 0.053 mmol) en DME (3 mL) y agua (1 mL) se desgasificó por pasar una corriente de N_2 a través de la mezcla. El recipiente se selló y la reacción se calentó a 80°C durante la noche. La mezcla de reacción se diluyó con H_2O y se extrajo con EtOAc que contiene ca. 5% MeOH (X3). Las capas orgánicas combinadas se concentraron, se disolvieron en MeOH y se cargaron en un cartucho MCX. El cartucho se lavó con MeOH y luego NH_3 en MeOH (2M). Las fracciones apropiadas se concentraron *in vacuo* y el residuo se purificó por HPLC prep (CH_3CN-H_2O-NH_4OAc). El material se purificó por cromatografía de columna (biotage) eluido con 0 hasta 20% MeOH en EtOAc. La purificación adicional por HPLC prep (CH_3CN-H_2O-NH_4OAc) se permitió por liofilización para proporcionar el compuesto del título como un sólido incoloro (6.9 mg, 2%). ^{1}HRMN (300 MHz, DMSO-d_6) δ 13.41 (s, 1H), 11.75 (s, 2H), 7.75 - 7.80 (m, 4H), 7.68 - 7.71 (m, 4H), 7.49 (s, 2H), 6.99 (d, J = 3.7 Hz, 2H), 6.57 (d, J = 3.7 Hz, 2H), 5.34 - 5.36 (m, 1H), 5.07 (app dd, J = 3.7, 7.0Hz, 2H), 4.42 (t, J = 8.4 Hz, 2H), 3.98 - 4.05 (m, 2H), 3.79 - 3.85 (m, 2H), 3.44

- 3.56 (m, 1H), 1.97 - 2.21 (m, 8H), 1.01 y 0.95 (d, J = 7.0 Hz, 6H, rotámeros, relación 1:3), 0.99 y 0.92 (d, J = 7.0 Hz, 6H, rotámeros, relación 1:3). LCMS: Anal. Calcd. para $C_{42}H_{48}N_{10}O_2S_2$: 788; encontrado: 789 $(M+H)^+$.

Ejemplos FY1-FY3



Los ejemplos FY1-FY3 se prepararon de conformidad a los protocolos descritos por la síntesis del ejemplo F66 y por emplear los materiales apropiados.

Condición LC/MS:

Columna: Phenomenex 10u 3.0 X 50 mm

% de inicio B = 0

% final B = 100

Tiempo de gradiente = 3min

Intervalo de flujo = 4 mL/Min

Longitud de onda = 220

Solvente A = 10% MeOH - 90% H_2O - 0.1% TFA

Solvente B = 90% MeOH - 10% H_2O - 0.1% TFA

Ejemplo	*R*	*TR (Cond. CL es nota como arriba); % de índice de homogeneidad; Datos EM*
FY1		2.03 min; > 95%; LC/MS: análisis calculado para $[M+H]^+$ $C_{38}H_{51}N_8O_6S_2$ 779.34; encontrado: 779.72
FY2		2.19 min; > 95%; LC/MS: análisis calculado para $[M+H]^+$ $C_{40}H_{55}N_8O_6$ S_2 807.37; encontrado: 807.78
FY3		2.24 min; > 95%; LC/MS: análisis calculado para $[M+H]^+$ $C_{42}H_{55}N_8O_6$ S_2 831.37; encontrado: 832.02

ACTIVIDAD BIOLOGICA

Un ensayo de replicón de HCV se utilizó en la presente descripción, y se preparó, condujo y validó como se describe en propiedad común con PCT/US2006/022197 y en O'Boyle et. Al. Antimicrob Agents Chemother. 2005 Abr; 49(4):1346-53.

Las células de replicón 1b-377-neo de HCV se usaron para probar el compuesto descrito actualmente en serie así como células

resistentes al compuesto A debido a una mutación Y2065H en NS5A (descrita en la Solicitud PCT/US2006/022197). Los compuestos probados se determinaron para tener más de 10 veces menos actividad inhibidora en células resistentes al compuesto A de células tipo silvestre indicando una relación de mecanismo de acción entre las dos series de compuesto. De esta manera, los compuestos de la presente descripción pueden ser efectivos para inhibir la función de la proteína NS5A del HCV y se entiende como que son efectivas en combinaciones como se describe previamente en la Soliticud PCT/US2006/022197 y en propiedad común con WO/04014852. Además, los compuestos de la presente descripción pueden ser efectivos contra el genotipo 1b de HCV. Deberá también entenderse que los compuestos de la presente descripción pueden inhibir genotipos múltiples de HCV. La tabla 2 muestra los valores EC50 de los compuestos representativos de la presente descripción contra el genotipo 1b de HCV. En una modalidad los compuestos de la presente descripción son activos contra los genotipos 1a, 1b, 2a, 2b, 3a, 4a, y 5a. Los intervalos EC50 contra HCV 1b son como siguen: A = 1-10 μM; B = 100-999 nM; C = 1-99 nM; y D = 10-999 pM.

Los compuestos de la presente descripción pueden inhibir la HCV por mecanismos en adición a o diferente de la inhibición NS5A. En una modalidad los compuestos de la presente descripción inhiben el replicón de HCV y en otra modalidad los compuestos de la presente descripción inhiben NS5A.

Tabla 2

Ejemplo	Intervalo
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	Intervalo
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	Intervalo
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	Intervalo
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	Intervalo
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	Intervalo
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 1 Diastereómero	D
LS27 2 Diastereómero	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 Diaestereómeros	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
cj-84	D
cj-85	D
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
cj-113	D
cj-114	D
cj-115	D
cj-116	D
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
J21	D
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

M131	D
M132	D
M133	D
M134	C
M135	D
M136	C

M137	D
M138	D
M139	D
M140	D
M140a-ii	C
M140a-i	C

M141	C
M142	C
M143	C
M144	D
M145	D
M146	D

M147	D
M148	D
M149	C
M150	D
M151	D
M152	
M153	D
M154	D
M155	C
M156	C
M157	D
M158	C
M159	D
M160	C

M161	C
M162	C
E5	D
E5a	D
E5b	D
E5c	D
E5d	D
E5e	D
E5f	D
E5g	D
E5h	D
E5i	D
E5j	D
E5k	D

E5l	D
E5m	D
J14	D
J14a	D
J14a.1	D
J14b	D
J14b.1	D
J14c	D
J14c.1	D
J14c.2	D
J14e	D
J14e.1	D
J14f	D
J14f.1	C

Será evidente para alguien experto en la técnica que la presente descripción no se limita a los ejemplos ilustrativos anteriores, y que puede ser una modalidad en otras formas específicas sin alejarse de los atributos esenciales de los mismos. Se desea por lo tanto que los ejemplos sean considerados en todos los aspectos como se ilustra y no que no sean restrictivos, se hace referencia a las reivindicaciones anexas, en vez de los ejemplos anteriores, y todos los cambios llegarán sin el significado y intervalo de equivalencia de las reivindicaciones son por lo tanto serán pretendidos para abarcar la presente.

Los compuestos de la presente descripción pueden inhibir el HCV por mecanismos en adición a o diferente a la inhibición NS5A. En una modalidad los compuestos de la presente descripción inhiben el replicón HCV y en otra modalidad los compuestos de la presente descripción inhiben NS5A. Los compuestos de la presente descripción pueden inhibir los genotipos múltiples de HCV.

REIVINDICACIONES

1. Un compuesto caracterizado porque se selecciona de ((1S)-2-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-(N-(metoxicarbonil)-L-alanil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-1-metil-2-oxoetil)carbamato de metilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0]hexano-3,2-diil((2S)-1-oxo-1,2-butanodiil)))biscarbamato de dimetilo;

(2-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-(((metoxicarbonil)amino)acetil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)-2-oxoetil) carbamato de metilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0]hexano-3,2-diil((1S)-1-ciclopropil-2-oxo-2,1-etanediil)))biscarbamato de dimetilo;

((1R)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2R)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilopropil)carbamato de metilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0]hexano-3,2-diil((1R)-2-oxo-1-fenil-2,1-etanediil)))biscarbamato de dimetilo;

((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-acetil-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilopropil)carbamato de metilo;

((1S)-2-metil-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-(5-((3aS,4S,6aR)-2-oxohexahidro-1H-tieno[3,4-d]imidazol-4-il)pentanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil-2-metilopropil)carbamato de metilo;

N-((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-acetamido-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilopropil)acetamide;

((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-((tert-butoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilopropil)carbamato de tert-butilo;

(2S)-1-((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-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)-3-metil-1-oxo-2-butanamina;

N-((1S)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2S)-2-((ciclopropilcarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-

imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilopropil)ciclopropanocarbamato;

((1R)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2R)-2-((tert-butoxicarbonil)amino)-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilopropil)carbamato de tert-butilo;

N-((1R)-1-(((1R,3S,5R)-3-(4-(4'-(2-((1R,3S,5R)-2-((2R)-2-acetamido-3-metilbutanoil)-2-azabiciclo[3.1.0]hex-3-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-2-azabiciclo[3.1.0]hex-2-il)carbonil)-2-metilopropil)acetamide;

N,N'-(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(1R,3S,5R)-2-azabiciclo[3.1.0]hexano-3,2-diil((2S)-3-metil-1-oxo-1,2-butanodiil)))di(2-pirimidinamina);

((1S)-1-(((6S)-6-(4-(4'-(2-((6S)-5-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-azaspiro[2.4]hept-6-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-5-azaspiro[2.4]hept-5-il)carbonil)-2-metilopropil)carbamato de metilo;

((1S)-1-(((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)carbonil)-2-metilopropil)carbamato de metilo;

(2-((6S)-6-(4-(4'-(2-((6S)-5-

(((metoxicarbonil)amino)acetil)-5-azaspiro[2.4]hept-6-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-5-azaspiro[2.4]hept-5-il)-2-oxoetil)carbamato de metilo;

((1S)-2-((6S)-6-(4-(4'-(2-((6S)-5-(N-(metoxicarbonil)-L-alanil)-5-azaspiro[2.4]hept-6-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-5-azaspiro[2.4]hept-5-il)-1-metil-2-oxoetil)carbamato de metilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(6S)-5-azaspiro[2.4]heptano-6,5-diil((2S)-1-oxo-1,2-butanodiil)))biscarbamato de dimetilo;

((1R)-1-(((6S)-6-(4-(4'-(2-((6S)-5-((2R)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-azaspiro[2.4]hept-6-il)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-5-azaspiro[2.4]hept-5-il)carbonil)-2-metilopropil)carbamato de metilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(6S)-5-azaspiro[2.4]heptano-6,5-diil((1R)-2-oxo-1-fenil-2,1-etanediil)))biscarbamato de dimetilo;

((1R)-1-(((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-((2R)-2-((metoxicarbonil)amino)-3-metilbutanoil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)carbonil)-2-metilopropil)carbamato de metilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((2S,5S)-5-metil-2,1-pirrolidinediil)((1R)-2-oxo-1-fenil-2,1-

etanediil)))biscarbamato de dimetilo;

(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((2S,5S)-5-metil-2,1-pirrolidinediil)((2S)-1-oxo-1,2-butanodiil)))biscarbamato de dimetilo;

(2-((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-(((metoxicarbonil)amino)acetil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)-2-oxoetil)carbamato de metilo;

(2-((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-(2-((metoxicarbonil)amino)-2-metilopropanoil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)-1,1-dimetil-2-oxoetil)carbamato de metilo;

((1S)-2-((2S,5S)-2-(4-(4'-(2-((2S,5S)-1-(N-(metoxicarbonil)-L-alanil)-5-metil-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-5-metil-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo;

4,4'-(4,4'-bifenildiil)bis(2-((2S,5S)-5-metil-1-(3-metilbutanoil)-2-pirrolidinil)-1H-imidazol);

4,4'-(4,4'-bifenildiil)bis(2-((2S,5S)-5-metil-1-(fenilacetil)-2-pirrolidinil)-1H-imidazol);

(2R,2'R)-1,1'-(4,4'-bifenildiilbis(1H-imidazol-4,2-diil((2S,5S)-5-metil-2,1-pirrolidinediil)))bis(3-metil-1-oxo-2-butanol);

(2S,2'S)-1,1'-(4,4'-bifenildiilbis(1H-imidazol-4,2-

diil((2S,5S)-5-metil-2,1-pirrolidinediil))bis(3-metil-1-oxo-2-butanol);

2-((2S,5S)-1-acetil-5-metil-2-pirrolidinil)-4-(4'-(2-((2S,5S)-1-acetil-5-metil-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol;

(2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-4-(1,3-dioxan-2-ilmetilo)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidincarboxilato de tert-butilo;

(2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-4-(1,3-dioxolan-2-ilmetilo)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidincarboxilato de tert-butilo;

(2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-5-(2-metoxi-2-oxoetil)-1H-imidazol-2-il)-1-pirrolidincarboxilato de tert-butilo;

(2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-5-propil-1H-imidazol-2-il)-1-pirrolidincarboxilato de tert-butilo;

2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-5-(4'-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-4-carboxilato de etilo;

(2S)-2-(4-(4'-(2-((2S)-1-(tert-butoxicarbonil)-2-pirrolidinil)-1H-imidazol-4-il)-3'-fluoro-4-bifenilil)-1H-

imidazol-2-il)-4,4-difluoro-1-pirrolidincarboxilato de tert-butilo;

2-((2S)-4,4-difluoro-2-pirrolidinil)-4-(3'-fluoro-4'-(2-((2S)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol;

(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-5-metil-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dietil-2-oxo-1-feniletanamina;

1-((1R)-2-((2S)-2-(4-(4'-(4-metil-2-((2S)-1-((2R)-2-fenil-2-(1-piperidinil)acetil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)piperidina;

((1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-((metoxicarbonil)amino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-5-metil-1H-imidazol-2-il)-1-pirrolidinil)-2-oxo-1-feniletil)carbamato de metilo;

((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-4-metil-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo;

((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-5-metil-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilopropil)carbamato de metilo;

((1S,2R)-2-metoxi-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-treonil)-2-pirrolidinil)-4-metil-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo;

(1R,1'R)-2,2'-(4,4'-bifenildiilbis((4-metil-1H-imidazol-5,2-diil)(2S)-2,1-pirrolidinediil))bis(N,N-dimetil-2-oxo-1-feniletanamina);

(1R,1'R)-2,2'-(4,4'-bifenildiilbis((4-metil-1H-imidazol-5,2-diil)(2S)-2,1-pirrolidinediil))bis(N,N-dietil-2-oxo-1-feniletanamina);

1,1'-(4,4'-bifenildiilbis((4-metil-1H-imidazol-5,2-diil)(2S)-2,1-pirrolidinediil((1R)-2-oxo-1-fenil-2,1-etanediil)))dipiperidina;

(4,4'-bifenildiilbis((4-metil-1H-imidazol-5,2-diil)(2S)-2,1-pirrolidinediil((1R)-2-oxo-1-fenil-2,1-etanediil)))biscarbamato de dimetilo;

((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-5-metil-1H-imidazol-4-il)-4-bifenilil)-5-metil-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo;

((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-4-metil-1H-imidazol-5-il)-4-bifenilil)-5-metil-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilopropil)carbamato de metilo;

((1S,2R)-2-metoxi-1-(((2S)-2-(4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-treonil)-2-pirrolidinil)-5-metil-1H-imidazol-4-il)-4-bifenilil)-5-metil-1H-imidazol-2-il)-1-pirrolidinil)carbonil)propil)carbamato de metilo;

((1S)-1-(((2S)-2-(4-(1,3-dioxan-2-ilmetilo)-5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilopropil)carbamato de metilo;

((1S,2R)-1-(((2S)-2-(4-(2,2-dimetoxietil)-5-(4'-(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-treonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metoxipropil)carbamato de metilo;

((1S)-1-(((2S)-2-(4-(2,2-dimetoxietil)-5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilopropil)carbamato de metilo;

(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-treonil)-2-pirrolidinil)-4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-O-metil-L-treonil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-5-il)acetato de metilo;

(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-pirrolidinil)-4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-valil)-2-

pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-5-il)acetato de metilo;

((1S)-2-((2S)-2-(4-(4'-(2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-4-propil-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo;

(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-5-propil-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dietil-2-oxo-1-feniletanamina;

((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-5-propil-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilopropil)carbamato de metilo;

((1S)-1-(((2S)-4,4-difluoro-2-(4-(3'-fluoro-4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilopropil)carbamato de metilo;

(1R)-2-((2S)-2-(4-(4'-(2-((2S)-1-((2R)-2-(dietilamino)-2-fenilacetil)-4,4-difluoro-2-pirrolidinil)-1H-imidazol-4-il)-3-fluoro-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-N,N-dietil-2-oxo-1-feniletanamina;

((1S)-1-(((2S)-2-(4-(hidroximetilo)-5-(4'-(2-((2S)-1-((2S)-2-((metoxicarbonil)amino)-3-metilbutanoil)-2-

pirrolidinil)-1H-imidazol-4-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)carbonil)-2-metilopropil)carbamato de metilo;

((1S)-2-((2S)-2-(4-(4'-(4-(hidroximetil)-2-((2S)-1-(N-(metoxicarbonil)-L-alanil)-2-pirrolidinil)-1H-imidazol-5-il)-4-bifenilil)-1H-imidazol-2-il)-1-pirrolidinil)-1-metil-2-oxoetil)carbamato de metilo;

(N,N'-(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil((2S)-3-metil-1-oxo-1,2-butanodiil)))di(2-pirimidinamina);

N,N'-(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil((1S)-1-ciclopropil-2-oxo-2,1-etanediil)))di(2-pirimidinamina);

N,N'-(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil((2S)-1-oxo-1,2-propanodiil)))di(2-pirimidinamina);

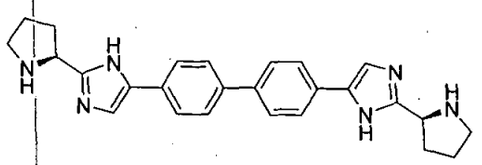
N,N'-(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil((2S)-1-oxo-1,2-butanodiil)))di(2-pirimidinamina);

N,N'-(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil((2S)-3-metoxi-1-oxo-1,2-propanodiil)))di(2-pirimidinamina); y

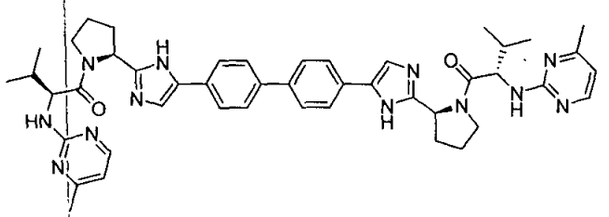
N,N'-(4,4'-bifenildiilbis(1H-imidazol-4,2-diil(2S)-2,1-pirrolidinadiil((2S,3R)-3-metoxi-1-oxo-1,2-butanodiil)))di(2-pirimidinamina);

o una sal farmacéuticamente aceptable del mismo.

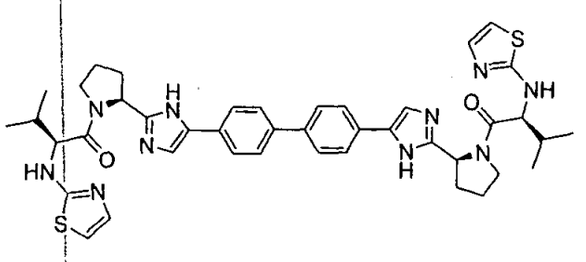
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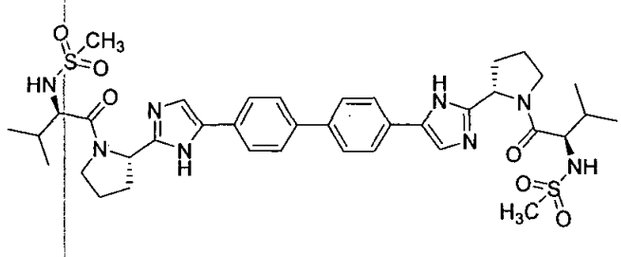
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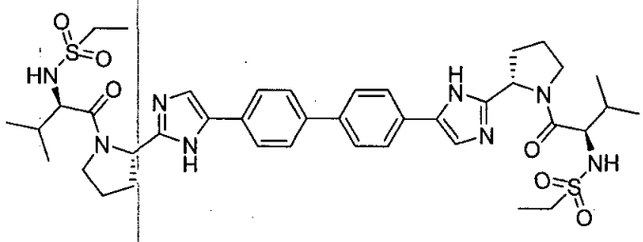
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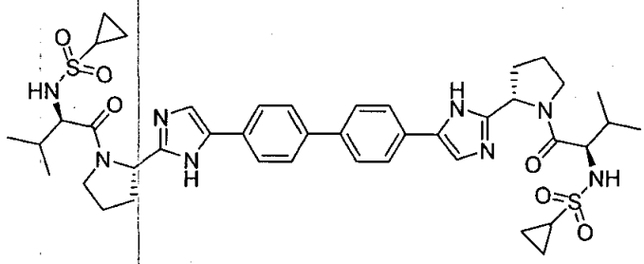
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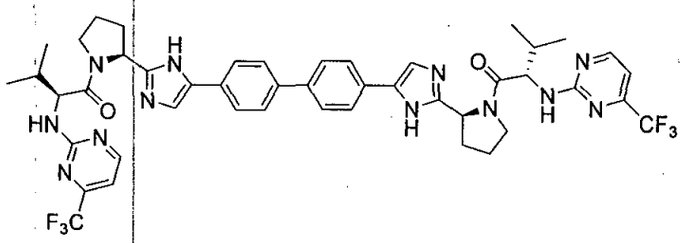
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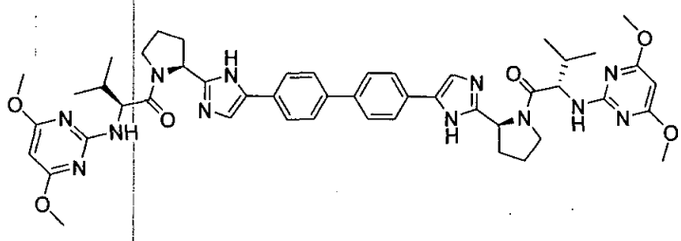
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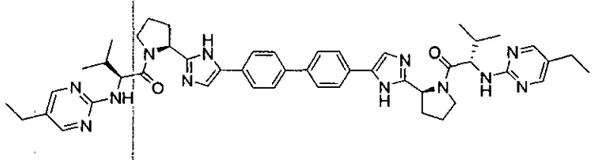
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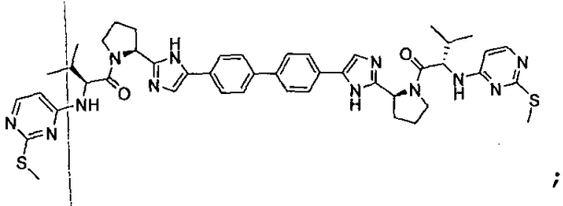
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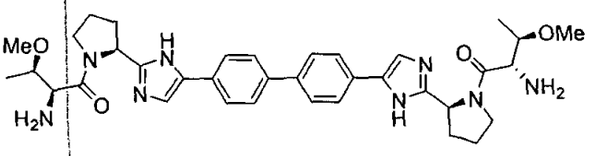
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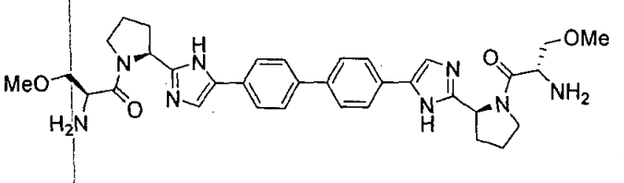
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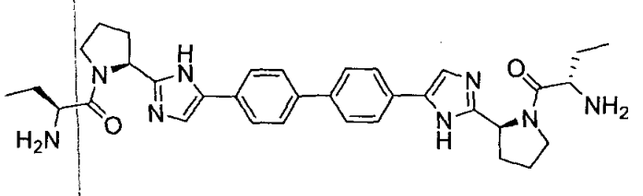
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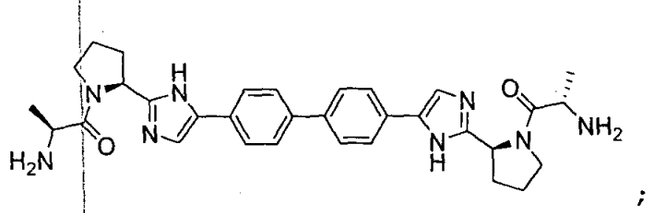
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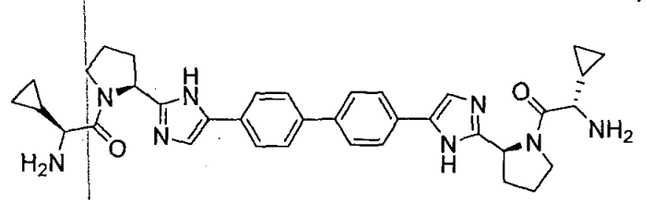
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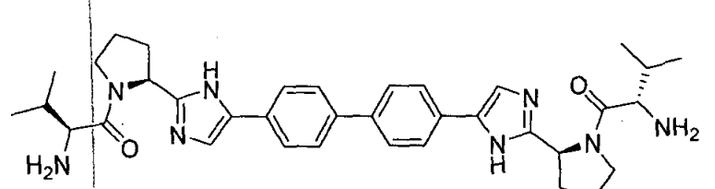
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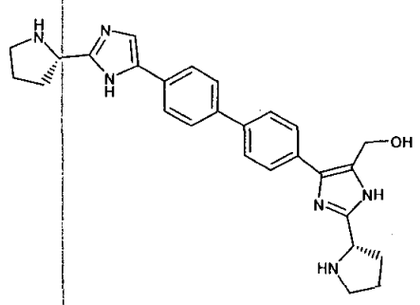
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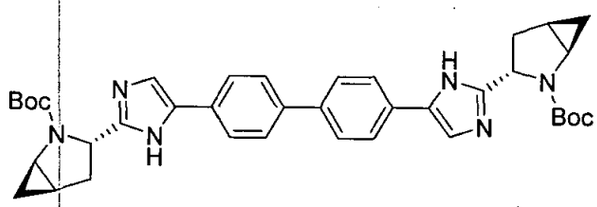
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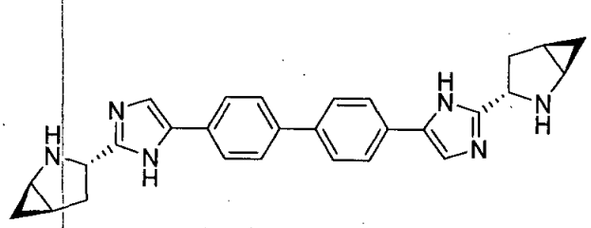
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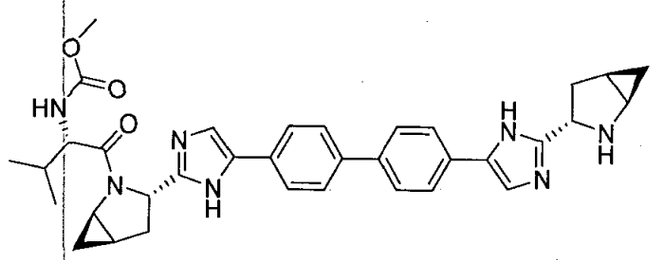
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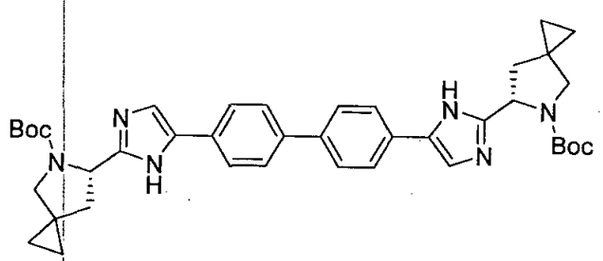
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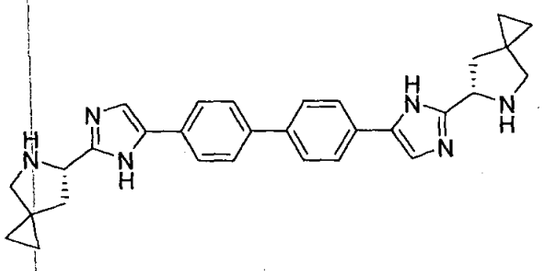
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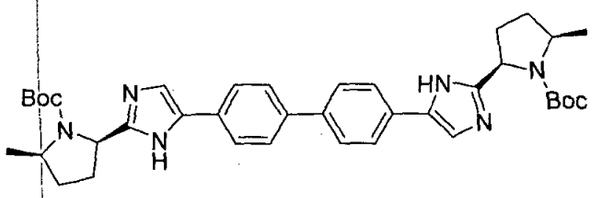
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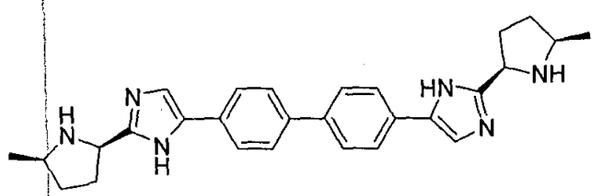
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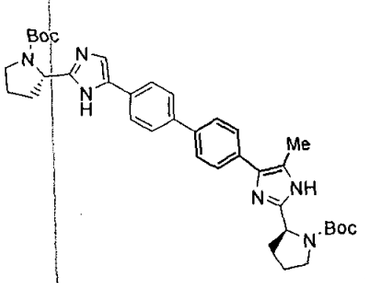
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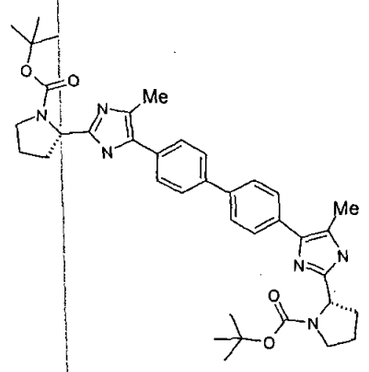
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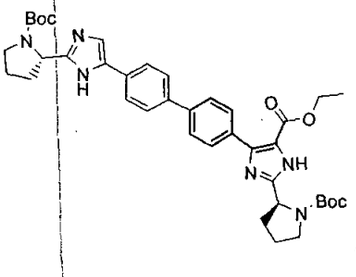
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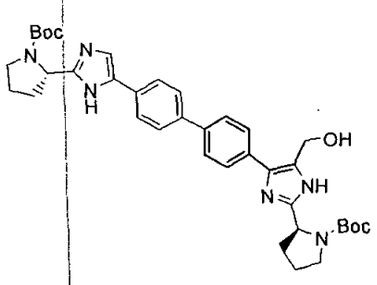
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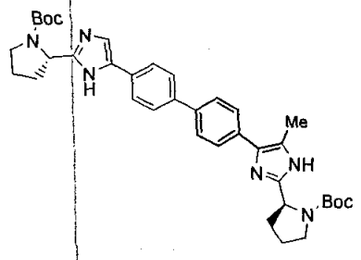
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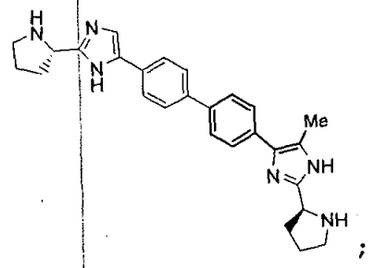
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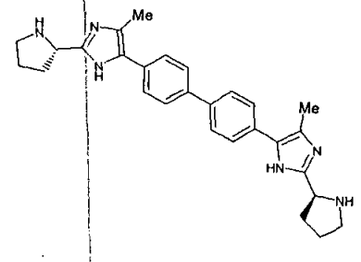
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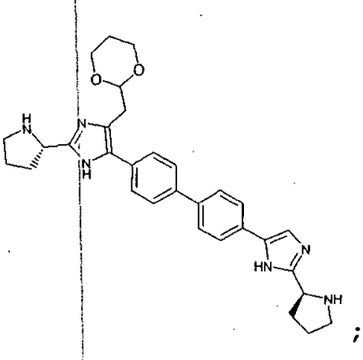
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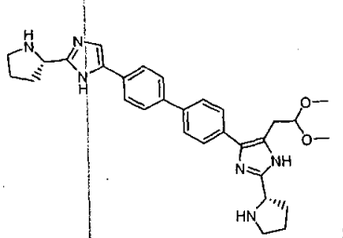

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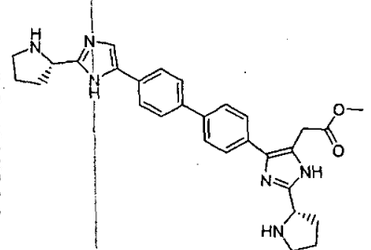
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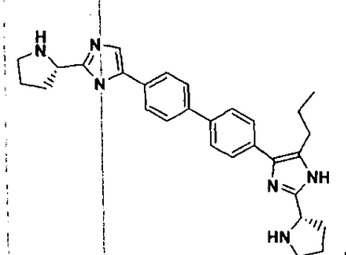

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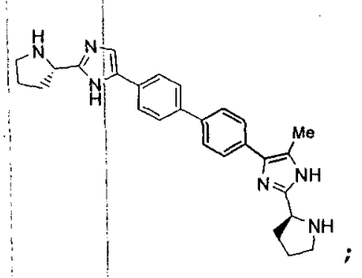
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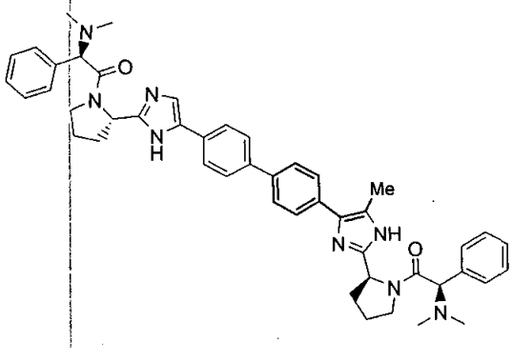

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o una sal farmacéuticamente aceptable del mismo.

3. Una composición, caracterizada porque comprende un 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 además comprende 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 del interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A, e interferón tau linfoblastoide.

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 aumenta el desarrollo de una respuesta de células T auxiliar de tipo 1, ARN interferente, ARN anti-sentido, Imiquimod, ribavirina, un inhibidor de inosina 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 del HCV, serina proteasa del HCV, polimerasa del HCV, helicasa del HCV, proteína NS4B del HCV, entrada del HCV, ensamble del HCV, salida del HCV, proteína NS5A del HCV, e IMPDH para el tratamiento de una infección por HCV.

9. Una composición, caracterizada porque comprende un 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 además comprende uno o dos compuestos adicionales que tienen 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 del

interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A, e interferón tau linfoblastoide.

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 aumenta el desarrollo de una respuesta de célula T auxiliar de tipo 1, ARN interferente, ARN anti-sentido, Imiquimod, ribavirina, un inhibidor de inosina 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 del HCV, serina proteasa del HCV, polimerasa del HCV, helicasa del HCV, proteína NS4B del HCV, entrada del HCV, ensamble del HCV, salida del HCV, proteína NS5A del HCV, e IMPDH para el tratamiento contra una infección por HCV.

15. Un método para tratar una infección de HCV en un paciente, caracterizado porque comprende administrar al paciente una cantidad terapéuticamente efectiva de un compuesto de conformidad con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo.

16. El método de conformidad con la reivindicación 15,

caracterizado además porque comprende administrar uno o dos compuestos adicionales que tienen actividad anti-HCV previo a, después de 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 del interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A, e interferón tau linfoblastoide.

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, interleucina 12, un compuesto que aumenta el desarrollo de una respuesta de célula T auxiliar de tipo 1, ARN interferente, ARN anti-sentido, Imiquimod, ribavirina, un inhibidor de inosina 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 del HCV, serina

proteasa del HCV, polimerasa del HCV, helicasa del HCV, proteína NS4B del HCV, entrada del HCV, ensamble del HCV, salida del HCV, proteína NS5A del HCV, e IMPDH para el tratamiento contra una infección por HCV.

21. Un método para tratar una infección HCV en un paciente, caracterizado porque comprende administrar al paciente una cantidad terapéuticamente efectiva de un compuesto de conformidad con la reivindicación 2, o una sal farmacéuticamente aceptable del mismo.

22. El método de conformidad con la reivindicación 21, caracterizado además porque comprende administrar uno o dos compuestos adicionales que tienen actividad anti-HCV previo a, después de 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 del interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A, e interferón tau linfoblastoide.

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, interleucina 12, un compuesto que aumenta el desarrollo de una respuesta de célula T auxiliar tipo 1, ARN interferente, ARN anti-sentido, Imiquimod, ribavirina, un inhibidor de inosina 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 del HCV, serina proteasa del HCV, polimerasa del HCV, helicasa del HCV, proteína NS4B del HCV, entrada del HCV, ensamble del HCV, salida del HCV, proteína NS5A del HCV, e IMPDH para el tratamiento contra una infección por HCV.

RESUMEN DE LA INVENCIÓN

La presente descripción se refiere a compuestos, composiciones y métodos para el tratamiento de la infección por virus de hepatitis C (HCV). También se describen composiciones farmacéuticas que contienen tales compuestos y métodos para usar estos compuestos en el tratamiento de la infección por HCV.

POD-4002

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 Senior)

AUTENTICACIÓN DE COPIA DE DOCUMENTO ORIGINAL QUE PRESENTO EL ORDEN DE NOTARIA DE ESTE DESPACHO

10 6 AGO 2010

NOTARIO 33 DE BOGOTÁ

JAIME A. GARAVITO B
INTÉRPRETE OFICIAL

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

AUTENTICACIÓN COPIA DE ORIGINAL
NOTARIA 30 DE BOGOTÁ D.C.
06 AGO 2010

BOGDMS#82106

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

1915

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

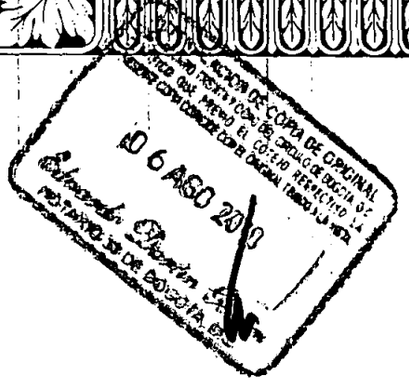
8. NO. A295716

9. SEAL/STAMP:

10. SIGNATURE

Bradley Abelow





BAKER & MCKENZIE

Raisbeck, Lara, Rodriguez & Rueda
Av. 82 No. 10 - 62 6th Floor
Bogotá, Colombia

NIT: 860.068.840-3
Tel: +57 1 634 1500
Fax: +57 1 376 2211
www.bakernet.com

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

AUTENTICADO ANTE EL CONSULADO DE COLOMBIA EN NUEVA JERSEY
COPIA FIEL TOMADA DEL ORIGINAL QUE HE TENIDO A LA VISTA
CERTIFICO QUE HABIENDO EL CITADO PRESENTADO LA
FIRMA QUE APARECE EN EL PRESENTE DOCUMENTO
10 6 AGO 2007
Eduardo Pombo Sánchez
NOTARIO 38 DE BOGOTÁ, 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

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
SALLY B. HANSEN
Notary Public of New Jersey
My Commission Expires June 6, 2010

10 AGO 2011

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 099269
	Solicitud internacional	PCT/US2008/053779
	Fecha inicio fase nacional	13/09/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	№ 12847

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, 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.

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 01 OCT. 2010
adpa11

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